

# ANNUAL REPORT

2015

— SCIENTIFIC SUPPLEMENT —



# KIDS are at the of everything we do

At the Telethon Kids Institute we are committed to research that makes a real difference.

We want every child to have the very best opportunity to enjoy a happy and healthy childhood.

Our team of almost 600 dedicated researchers and support staff are passionate about discovering causes, cures and treatments for the illnesses and diseases that target our kids and young people.

With top scientific minds and facilities, a reputation for being at the forefront of global child health research and a track record to prove it, Telethon Kids is world-class.

Yet we know that our work is even stronger when we work together. We are committed to collaboration. We create and facilitate connections with researchers, practitioners, service providers, our partners and the community, to maximise the potential in what we do and deliver tangible benefits to kids and families.

**Discover. Prevent. Cure.** Together, that's how we make a difference.

Find out more at  
[telethonkids.org.au](https://telethonkids.org.au)



# ABORIGINAL HEALTH AND WELLBEING

## Overview

The needs of Aboriginal children and families have always been in the forefront of the Institute's thinking and action and as such has featured in the restructure of the Institute and in particular in its governance and research development capacity. The endeavor here is to ensure that over time Aboriginal health research is a whole of Institute approach and that Aboriginal communities and organisations participate in all stages of the research process ultimately resulting in sustainable positive change in the health and wellbeing of Aboriginal children.

The Aboriginal Health and Wellbeing Group is supported by and comprised of the following in delivering on the aims and objectives of the Institute's Commitment to Aboriginal Children and Families (2013-2107) Statement consistent with the Working Together Strategic Plan (2013-2017).

## **ABORIGINAL CONSULTATIVE COMMITTEE ADVISING RESEARCH AND EVALUATION (ACCARE)**

### **Background**

As part of the Institute's strategic planning process that was conducted in 2013, a parallel strategic process was undertaken to ensure that the needs of Aboriginal families were considered. This parallel process was led by Emerita Professor Rhonda Marriott (Senior Aboriginal Researcher), Dr Michael Wright (Senior Aboriginal Researcher) and Glenn

Pearson (Manager Aboriginal Research Program) and supported by the Institute's Aboriginal Research Leadership Group.

The outcomes of these processes have led to the development of the *Institute's Working Together Strategic Plan (2013 -2017)* and the objectives of the Institute's *Commitment to Aboriginal Children and Families (2013-2017)* with a recommendation that ACCARE would be reconstituted as an advisory committee reporting directly to the Director Telethon Kids Institute – Professor Jonathan Carapetis.

With the exception of the Director the membership is now entirely comprised of Aboriginal people. These members have not been engage to represent their regions rather that they bring from across the State a vast range and much needed skills and experiences to assist in the Council's work.

*The ACCARE members are:*

- Kate George - Chair
- Rhonda Marriott
- June Oscar
- Josie Janz
- Ian Trust
- Darryl Kickett
- Jon Ford
- Jonathan Carapetis
- Glenn Pearson

The goal of ACCARE is:

*To provide high level advice to the Director around strategic directions and operational elements relating*

to Aboriginal health research at the Telethon Institute with the aim of ensuring facilitation, translation and application of research finding into policy and practice.

## **ABORIGINAL HEALTH RESEARCH FOCUS AREA STEERING COMMITTEE**

As part of the Institute's Working Together Strategic Plan a Research Focus Area Strategic Framework was developed to reflect four key areas of research of which Aboriginal Health was one. Under each RFA a Steering Committee was established and comprised of 10-15 senior researchers drawn from across the Institute, PMH and SPACH.

The purpose of each RFA Steering Committee is to facilitate the development and implementation of high quality collaborative research projects consistent with the Institute Strategic Plan and RFA research goals and to ensure our research makes a difference.

The Aboriginal Health RFA Steering Committee has acknowledged that it plays a dual role across the Institute in both promoting an increase in the numbers of Aboriginal health related research projects within the Aboriginal Health area as well as across the other three RFA's.

In 2014 the AHRFA Steering Committee held two Open Space Forums to create an opportunity for researchers to engage with the Aboriginal community. The outcomes of these forums will contribute to a deepening in the relationship between researchers and Aboriginal people to ensure that our research better reflects the needs of Aboriginal families as well as translates into positive change in

the health and wellbeing of these families. A third and final Open Space forum was held in 2015 to look at identifying a process to prioritise our research. The outcomes of all three Forums were analyzed to identify areas to inform an Open Space Action Plan.

This Action Plan was presented to the Elders who participated in the three Open Space Forums all of which will be actioned in 2016. Of these and of substantial interest to the Elders is the development of a protocols for conducting research in the Nyoongar community.

The Open Space Forum approach will be considered in further relationship building and consultation with other Aboriginal communities where the Institute is conducting research.

## **KULUNGA ABORIGINAL RESEARCH DEVELOPMENT UNIT (KARDU)**

The Telethon Kids Institute *Commitment to Aboriginal Children and Families* outlines a blueprint for action for the Institute to continue its work in Aboriginal health research and translate outcomes into positive sustainable change in the health and well-being of Aboriginal children and families. The Commitment outlines the following priorities:

- Aboriginal Governance for Ensuring a clear Aboriginal voice and influence
- Setting Research Priorities for Research that reflects the needs of Aboriginal families
- Aboriginal Employment and Career Development Strategy for Developing Aboriginal Staff and Students
- Research Development and Support



for Building Our Capacity to Do Research that Responds to the Needs of Aboriginal Families

- Showcase Projects for Demonstrating Our Best
- Funding Support for Aboriginal Research and Researchers for Investing in the Future
- Communication and Dissemination for Keeping Us Connected to Community

In relation to the priority of Research Development and Support, the Kulunga Aboriginal Research Development Unit (KARDU) has been established by the Institute with Glenn Pearson as Head of the Unit. He was joined by Kristen White - Program Manager (Kimberley and Pilbara), then Mara West and Isabelle Adams in June 2015 who jo share the Unit The key focus of the Unit is to facilitate research interest and opportunities that involve Aboriginal families and communities as well as building the capacity and development of Institute researchers working on Aboriginal projects.

The Unit has the following specific tasks in relation to its key focus:

- Establish and maintain relationships with Aboriginal Communities and the Aboriginal Community Controlled Services Sector.
- Support for Research Strategy Leaders and Other Researchers in Indigenous research methodologies, research design, relationship building with Aboriginal communities and sourcing personnel.
- Building the research capacity of Aboriginal and non-Aboriginal Researchers.

- Promote the development of Indigenous Knowledge and its application as a strategy to maximise research outcomes for researchers, Aboriginal families and their children.
- Take responsibility for the management of ACCARE, and the establishment and management of the Aboriginal Research Projects, Clearing House and Government Relations Forums.
- In partnership with the Communications and Development team, develop and present on a regular basis, a series of in-house training modules for research staff on conducting research in Aboriginal communities.

The following tasks have been undertaken in 2015:

- Operational Plan to guide the operations of the Unit completed
- Databases of Aboriginal communities and traditional owner groups and Aboriginal Community Controlled Services Organisations.
- Planning for Aboriginal Communication and Dissemination Strategy
- Information sessions for Aboriginal people and organisations
- Distribution of Institute Information packs to Aboriginal organisations
- Attendance at Aboriginal community events or site visits to Aboriginal organisations.
- Planning of specific content and activities for Aboriginal Community Participation in Health Research workshops.
- Attendance at Research Working Parties meetings
- Organisation of ACCARE meetings and minutes

- Planning for Aboriginal Research Projects Forums
- Planning for development of set of research protocols for conducting research in Aboriginal health.

## RESEARCH DEVELOPMENT AND SUPPORT

There are a number of research programs and projects at the Institute initiated to make a difference to the health and wellbeing of Aboriginal children and families and which in the future will come under the Aboriginal Health Research Focus Area. Some fall directly under KARDU, while others are managed under separate research groups and are discussed in more detail elsewhere and include:

- Alcohol and Pregnancy and Fetal Alcohol Spectrum Disorders Research Group
- Wesfarmers Centre for Vaccine and Infectious Disease
- Group A Streptococcus and Rheumatic Heart Disease Research Group
- Collaboration for Applied Research and Evaluation (CARE)

Additionally, KARDU has been actively working with researchers across the Institute to develop new programs of research that involve Aboriginal families and communities and in partnership with the Aboriginal Health Council of WA and the Rural Clinical School of WA to establish a research hub in Broome as the first site in creating the WA Aboriginal Health

Knowledge Network.

## WA ABORIGINAL HEALTH KNOWLEDGE NETWORK (WAAHKN)

Starting in 2011 the Telethon Kids Institute working in partnership with the Rural Clinical School of WA (RCSWA) and the Aboriginal Health Council of WA (AHCWA) commenced a joint process to establishing a WA Aboriginal Health Knowledge Network (the Network).

The original goal was to establish a Network comprised of four regional sites to facilitate key medical, research and training activities undertaken in partnership with Aboriginal communities.

Since that time the partnership group has continued to progress exploring the interest and funding to establish the Network. The Network aims to adequately resource Aboriginal communities to secure a stronger healthier future by influencing policy with evidence based research that is developed according to their own priorities and participation.

This model currently does not exist in Western Australia.

In fact much Aboriginal research continues to be determined and undertaken by those living outside of the communities and who are not the most affected by these issues. This has led to research, policies, programs and services that are not necessarily reflective of the priorities of Aboriginal communities and do not harness and support local knowledge and community control. A more sustainable approach is required that focuses on Aboriginal peoples'



inherent strengths and ability to identify the best ways to understand and improve their health outcomes and control the research process.

The importance accorded local knowledge, community engagement and participation are the key principles of the Network. It advocates that the suitability and relevance of any research agenda, and the effectiveness of any strategies and interventions must be aligned with and actively engage with Aboriginal people's knowledge and understanding of their communities' needs. Ultimately, the Network seeks to provide Aboriginal families with the means to participate in the entire research journey, so they benefit.

The West Australian Aboriginal Health Knowledge Network (the Network) is a partnership between key organisations whose aim is to improve the benefits that flow from Aboriginal families' participation in the research journey. The Network provides a framework for people to invest wisely in Aboriginal health research.

## **THE NETWORK - OBJECTIVES**

The Network will facilitate the development of research processes and research projects that bring together Aboriginal families, researchers and the policy makers together to;

- Build the capability of Aboriginal Research; Aboriginal and non-Aboriginal.
- Improve community ability to access and use all administrative related data i.e., education, housing, corrective services and health.
- Improve research capacity building; by giving people the opportunity to

acquire the skills to understand a range of scenarios.

- Broker cross-sectoral partnerships.
- Improve the way community influences Government policy planning and program implementation.

The Network is intended to be a system and infrastructure to support control of the local or regional Aboriginal health research. While the Network's 4 sites will not be a one size fits all model, it is anticipated that each will have:

- A local research advisory committee;
- Genuine partnerships with local Aboriginal community controlled health organisations;
- Research and training facilities supported by first class research and training expertise;
- A locally grown health research workforce established through immersion in all stages of research, skills development, training and mentoring;
- A community set research agenda;
- Established culturally secure research methodologies that translate at the local, regional and state level;
- Research infrastructure, to support and protect data collection; and,
- Capacity to draw upon and support national and international research collaborations.

Following discussions in 2014 and reconfirmed in 2015 Broome has been identified as the first site for the Network. It was agreed to co-locate the Broome hub with the Kimberley Aboriginal Medical Service and discussions have continued with a locally established working group which has included discussions with Lotterywest to help establish the Broome site.

## **ESTABLISHMENT OF PERMANENT ONGOING PRESENCE OF TELETHON KIDS IN THE KIMBERLEY**

Out of the discussions with the our partners and in particular the Kimberley Aboriginal Medical Services (KAMS) the Institute has commenced initial discussions and planning to establish a permanent ongoing presence in the Kimberley and in particular Broome. The aim of establishing a local presence is based upon an intention to be by invitation considered as part of the Kimberley group of organisations as well as providing a platform for Institute researchers as they undertake research in this region. The intention would to over time have local staff who would assist Institute researchers to establish relationships and networks with key organisations such as the Aboriginal Community Controlled Health Services. Additionally and as importantly these staff would ensure that all research was conducted in accord with Aboriginal community protocols. Discussions have commenced with several potential philanthropic donors to assist the Institute in taking this important and critical step.

## **PROPOSED MEMORANDUM OF AGREEMENT BETWEEN THE TELETHON KIDS INSTITUTE (TKI) AND THE KIMBERLEY ABORIGINAL MEDICAL SERVICE (KAMS)**

As part of the discussions with Kimberley Aboriginal Medical Service (KAMS) to establish the Broome site of the WAAHKN it has been agreed to establish a memorandum of agreement between the Telethon Kids Institute and the KAMS. The agreement to develop an MOU

between the two organisations will see the development of a common research agenda, to work collaboratively through the KAMS members services located across the Kimberley, investing local capacity building and to ensure that Aboriginal families and communities are the first beneficiary of the research.

2015 also saw the final year of the Institute's Aboriginal health and wellbeing flagship the NHMRC funded Centre for Excellence in Aboriginal Health and Wellbeing (CREAHW).

## **Research Projects**

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

The Centre for Research Excellence in Aboriginal Health and Wellbeing (CREAHW) is a collaborative research venture between seven research institutions and 10 Chief Investigators headed by Professor Fiona Stanley. The CREAHW brings the research strengths of each CI together in a cohesive program of community-based intervention research, well known both national and internationally, but with local relevance to Western Australia. It is being supported by the outstanding track record of the Institute working with government to inform policy and practice and build on past achievements by developing the next generation of Aboriginal health researchers and leadership among the CI team.

This was the last year of the CREAHW which officially ceased being funded by the NHMRC in October 2015.



## Highlights for 2015:

The CREAMH funded 2 international visits. One by Emeritus Professor Michael Chandler from the University of British Columbia, Canada and the other by A/Prof Angela Bowen from the University of Saskatoon, Canada and Prof Sally Kendall from the University of Hertfordshire, UK.

The Australian Government funded a national Aboriginal and Torres Strait Islander Suicide Prevention Evaluation Project (ATSISPEP) led by Chief Investigator Prof Pat Dudgeon. A/Prof Roz Walker is responsible for overseeing the project implementation and outcomes.

The Working Together: Aboriginal and Torres Strait Islander Mental Health and Wellbeing Principles and Practice was launched in Nedlands, June

## Investigators:

Prof Fiona Stanley, Prof Pat Dudgeon, Prof Dawn Bessarab, Prof Sandra Eades, Prof Rhonda Marriott, A/Prof Roz Walker,

Dr Juli Coffin, Dr Cheryl Kickett-Tucker, Dr Michael Wright and Glenn Pearson.

## Funding:

NHMRC Centre of Research Excellence grant 2010 – 2015.

The following projects were directly established through the CREAMH.

## LOOKING FORWARD: ABORIGINAL MENTAL HEALTH PROJECT

The Looking Forward Aboriginal Mental Health Project is a participatory action research project aimed at increasing access to and the responsiveness of the

mental health and drug and alcohol service system for Nyoongar families living in the south-east Perth metropolitan corridor (Armadale to Bentley), whose lives are affected by mental illness. A key outcome of the project is the development and implementation of a culturally secure systems change framework for mental health service delivery, which enhances the skills base of the mental health workforce by bringing them together with Nyoongar Elders so as to better respond to the mental health needs of Aboriginal families. The project uses Nyoongar cultural knowledge and protocols to inform the design and direction of the study along with the design and implementation of the framework for culturally secure service delivery.

A critical aspect of our research and knowledge exchange has been to tell the Nyoongar story of colonisation. In doing so, non-Aboriginal people are invited to (re)view past histories as complex and contested and thus shaped for the benefit of 'the coloniser'. When Elders tell of their own experiences of the impacts of colonisation, non-Aboriginal people witness a lived history rather than a written history. Such direct engagement cannot be taken lightly, for it is in these exchanges that service staff undertake profound shifts in their thinking, based on these firsthand accounts in response to colonising forces. In their telling, the Elders are effectively re-legitimising Nyoongar culture, by acknowledging past acts, so that decolonising processes can take hold. It is only then that Nyoongar people and non-Aboriginal people can truly come together to create a shared future.

## Plain Language summary

The Looking Forward Project aims to change the way mental health services and drug and alcohol support services respond to the needs of Nyoongar families living in the southeast Perth metropolitan region (i.e. Armadale to Bentley).

The Project team, in conjunction with Nyoongar Elders, has facilitated a number of events and activities to assist service providers to develop an understanding of and respect for Nyoongar culture and its centrality to mental health and wellbeing. These activities include damper and bush medicine making, storytelling, community days and walks on country. These have prepared services to work more openly and authentically with Nyoongar Elders, as they reflect on and reconfigure their own service structures and work practices to better meet the mental health needs and drug and alcohol concerns of Nyoongar families. Service providers are introduced to many concepts and experiences that, for most, are totally unfamiliar to their worldview. The experience for most has been profound.

## Funders of the project

Centre of Research Excellence in Aboriginal Health and Wellbeing, Telethon Kids Institute, Lotterywest, Western

Australian Mental Health Commission, Curtin University.

## Lead Investigator:

Michael Wright, PhD, Research Fellow (Curtin University) and Chief Investigator (CREAHW)

## NATIONAL ABORIGINAL AND TORRES STRAIT ISLANDER SUICIDE PREVENTION EVALUATION PROJECT (NATISPEP)

*Assoc. Prof Roz Walker*

The Project was undertaken by the School of Indigenous Studies at the University of Western Australia in partnership with the Telethon Kids Institute. Professor Pat Dudgeon from the School of Indigenous Studies at UWA led the Project and A/Prof Roz Walker from the Telethon Kids Institute oversaw the development of the evaluation. The project formally evaluated a range of existing Indigenous suicide prevention programs and services to enable the development of a much-needed evidence base for 'what works' in Aboriginal and Torres Strait Islander suicide prevention.

Rationale for the project was based on the premise that there is a need to develop an evaluation framework that can measure the effectiveness and appropriateness of the range of actions directed at addressing the complex issue of Aboriginal and Torres Strait Islander suicide, underpinned by understandings of suicide identified by communities and by international best practice.

The project objectives were informed by international models of best practice and Aboriginal and Torres Strait Islander community perspective and include:

- To evaluate Aboriginal and Torres Strait Islander suicide prevention services and programs.
- To identify Aboriginal and Torres Strait Islander community suicide prevention needs.

- To identify system-level change for Aboriginal and Torres Strait Islander suicide prevention.
- To inform the implementation of the National Aboriginal and Torres Strait Islander Suicide Prevention Strategy.

The project utilised a variety of methodologies including: a comprehensive review and analysis of all relevant literature, research and extensive community consultations; development of culturally appropriate frameworks to evaluate programs and services; application and analysis of national coronial data to highlight patterns and trends of suicide over time and between regions across Australia; and hosting a national summit on Aboriginal and Torres Strait Islander suicide prevention.

By the end of 2015 it was planned that the team completed the following project outcomes / outputs:

- Present a summary of work completed.
- Develop an evidence base of 'what works' in Aboriginal and Torres Strait Islander suicide prevention for individuals, families and communities.
- Establish recommendations for Aboriginal and Torres Strait Islander suicide prevention services and programs.
- Provide recommendations for systemic changes to prevent Aboriginal and Torres Strait Islander suicide.
- Provide recommendations for future action for Aboriginal and Torres Strait Islander suicide prevention at a national level to inform the National Strategy and develop a position paper.
- A national interactive consultation map and a spatial analysis map.

- Series of fact sheets.
- Produce a final report.

### Team Investigators

The project team at Telethon Kids Institute consisted of:

- A/Prof Roz Walker, Principal Investigator, Telethon Kids Institute/ Centre for Research Excellence in Aboriginal Health and Wellbeing (CREAHW)
- Prof Sven Silburn, Telethon Kids Institute and Menzies School of Health Research, Darwin
- Dr Clair Scrine, Senior Research Officer, Telethon Kids Institute, CREAHW
- Dr Carrington Shepherd, Research Fellow, Telethon Kids Institute, CREAHW
- Dr Brad Farrant, Telethon Kids Institute

### Lead Investigator

Associate Professor Roz Walker

### Funding

This was funded through the Commonwealth Government through the Department of Health.

## **PROMOTING POSITIVE PERINATAL MENTAL HEALTH, PARENTING, CULTURAL AND SPIRITUAL WELLBEING AND RESILIENCE IN ABORIGINAL PARENTS IN WESTERN AUSTRALIA**

*Rhonda Marriott, Fiona Stanley, Nicholas de Klerk, Roz Walker and Denise Groves.*

This project has made excellent progress in with conferences, publications and local capacity-building outcomes adding to the body of knowledge of Aboriginal research epistemology. This project has been given an extension by the ARC to February 2016.

The main study location for this project is Ieramagardu, located in Roebourne, Western Australia.

The collaborative qualitative methods used in this project have drawn on CPAR techniques to engage with Aboriginal people residing in the Pilbara region of WA. The use of this research method has achieved positive outcomes in working together to promote mental health, family strengths and to honour the place of culture. Parallel to this collaborative work is a sub-study applying a quantitative methodology (led by Fiona Stanley, Nick de Klerk and Roz Walker). The sub-study aims to address some important gaps in the evidence base in the area of Aboriginal health, with a focus on the perinatal period.

The work of the project has also enhanced the scholarly work and confidence of two CREAHW PhD students, Jayne Kotz and Ailsa Munns, whose work encompasses aspects of the project themes. Both students have presented their work at national conferences as well as submitting articles for publication and developing a strong profile in the field. In 2014 a culturally significant film was made titled, 'Mothering: Valuing Ngarda ways and culture' as part of the project activities in Ieramagardu. It will be launched in Perth in 2015.

Also in 2014, Rhonda and Jan Kapetas undertook to interview children and youth in Ieramagardu for the Commissioner for Children and Young People in WA. This will lead to further research questions on resilience in Aboriginal youth in 2015.

#### **Team Investigators:**

- Emerita Professor Rhonda Marriott, Murdoch University

- Professor Fiona Stanley (Patron), Telethon Kids Institute
- Associate Professor Roz Walker, Principal Investigator, Telethon Kids Institute
- Nicholas de Klerk
- Denise Groves

#### **Students:**

- Jayne Kotz
- Ailsa Munns

#### **Lead Investigator:**

- Emerita Professor Rhonda Marriott

#### **Funding:**

Australian Research Council

### **FAMILY ASSESSMENT TOOL, MILLIYA RUMURRA (MR), BROOME, WA**

*Professor Dawn Bessarab*

When looking at the health and social and mental wellbeing of MR clients the family assessment support tool (FAST) was developed to assist MR workers and clients to identify and engage with a family member/s or friend and invite them to participate in the client's treatment program.

The aim is to assist and enable the family member/friend to become a support person/mentor to help the client when they exit treatment. Including the family member/friend in the FAST program means they become familiar with what the client has learnt and are taught tools and strategies in partnership with the client that they can use to assist the client to stay Alcohol and Other Drug (AOD) free.



The FAST tool was designed and developed in collaboration with the MR staff, service provider stakeholders. The tool has been developed and is currently undergoing a series of evaluations to assess its effectiveness and usability. Staff have undergone training on how to use and apply the tool and are now implementing their work with new clients.

#### **Team Investigators:**

- Professor Dawn Bessarab, Director of, Centre for Aboriginal Medical and Dental Health (CAMDH), UWA

#### **Lead Investigator:**

- Professor Dawn Bessarab, Director of, Centre for Aboriginal Medical and Dental Health (CAMDH), UWA

#### **Funding :**

NHMRC

### **SOLID KIDS SOLID SCHOOLS (SKSS) – SOCIAL MARKETING THE PARENTS’ RESPONSE**

*Juli Coffin, Fiona Stanley, Lydia Hearn,  
Cheryl Kickett-Tucker and Roz Walker*

In 2014 the SKSS website was updated with more current information about the project. Juli created seven Solid Kids Infomercials around bullying and the future of our kids. These aired on all rural and mainstream TV channels over a period of six months. The poster series, Infomercials, Facebook campaign and the revamped website were all evaluated with parents/carers within the Yamaji region. In the evaluation the recall of the Infomercials was ranked the highest. This was explained by the recall rate of

the Infomercials which was exceptional due to using local identifiable talent. The preferred way for parents to receive information was through a Facebook campaign and TV with the least significant impact being from posters and booklets. Face-to-face was still the preferred way for communication around relationship issues. The link to these commercials and the Solid Kids page can all be found at [www.solidkids.net.au](http://www.solidkids.net.au).

#### **Team Investigators:**

- Dr Juli Coffin, Telethon Kids Institute and Geraldton Regional Aboriginal Medical Service (GRAMS), Geraldton
- Professor Fiona Stanley (Patron), Telethon Kids Institute
- Associate Professor, Cheryl Kickett-Tucker, Pindi Pindi, The National Research Centre for Aboriginal Children, Families and Community Midland, WA
- Associate Professor Roz Walker, Principal Investigator, Telethon Kids Institute
- Lydia Hearn

#### **Lead Investigator:**

- Dr Juli Coffin, Telethon Kids Institute and Geraldton Regional Aboriginal Medical Service (GRAMS), Geraldton

#### **Funding:**

NHMRC

## **INVESTIGATING ABORIGINAL WOMEN'S CULTURAL NEEDS FOR BIRTHING AND EVALUATING THE CULTURAL COMPETENCY, WORKFORCE AND EDUCATION NEEDS OF MIDWIVES.**

*Rhonda Marriott, Tracey Martin (Office of Nursing and Midwifery), Terri Barrett (Statewide Obstetric Support Unit), Roz Walker, Juli Coffin, Tracy Reibel (Telethon Kids Institute) & Fiona Stanley*

The philosophy of Birthing on Country is central to this four year NHMRC funded study based at the Centre for Aboriginal Research at Murdoch University, led by Professor Rhonda Marriott. We understand: Birthing on Country as ensuring a spiritual connection to the land for an Aboriginal mother and her baby.

Our research is driven by the belief that maternity services must ensure a culturally secure environment with culturally competent staff safeguarding the birthing woman's cultural rights, values and expectations and respecting her right to feel culturally safe. Much of our work in the past year has been about around intensively preparing a strong foundation before we enter into the data collection phases of the research.

Key activities for this year have included:

- Embedding our governance protocols and devising strategies to work more cohesively as a complex and diverse research team;
- Appointing Ms Janinne Gliddon, Senior Aboriginal Health Promotion Officer at King Edward Memorial Hospital as Chair of the Aboriginal Consultative Committee for the project;
- Focusing on promotion and community engagement activities (led by Alison

Gibson, Coordinator, Moort Boodjari Mia) including developing a Facebook page, developing promotional posters and brochures and planning future community engagement activities with a diversity of health and community organisations; and

- Recruiting three Aboriginal research assistants to conduct the yarning/ interviews with Aboriginal women, Elders and Senior Women. The research team members who will be involved in the interviewing have also completed a 'Yarning' methodology workshop with Dawn Bessarab.

Much of our preparatory work has also been around ensuring the Aboriginal cultural integrity of our approaches. This has included the organisation of a Nyoongar birthing workshop and two workshops about the meanings and interpretations of cultural security terminology. These activities have resulted in the forming of a cultural leadership group, which along with the Aboriginal Consultative Group will ensure that the conduct of the research is culturally secure.

### **Team Investigators:**

- Emerita Professor Rhonda Marriott\*, Murdoch University
- Dr Juli Coffin, Telethon Kids Institute and Geraldton Regional Aboriginal Medical Service (GRAMS), Geraldton
- Professor Fiona Stanley (Patron), Telethon Kids Institute
- Associate Professor Roz Walker, Principal Investigator, Telethon Kids Institute
- Tracey Martin (Office of Nursing and Midwifery)

- Terri Barrett (Statewide Obstetric Support Unit)

**Lead Investigator:**

- Emerita Professor Rhonda Marriott\*, Murdoch University

**Funding:**

NHMRC funded

**CULTURAL SECURITY FOR YAMAJI PEOPLE WITHIN REGIONAL HEALTH SERVICES**

*Associate Professor Juli Coffin*

Interviews were conducted and analysed in relation to the 'Coffin cultural security scale'. The health services interviewed were located in the Geraldton/Mid-west region. These included GRAMS (Geraldton Regional Aboriginal Medical Service), Medicare Local, WACHS (WA Country Health Service), St John Of God and the GP Division.

Each service was given feedback on the analysis and some have been able to incorporate it into their own reporting criteria. Feedback was provided to participants face-to-face, as well as in the form of a document they could use to record their findings. Since the audit, many health services have made significant changes. For example, the waiting room at the Accident and Emergency room in the regional hospital now has localised Aboriginal art featured on one of the main walls. (The artwork is on the front cover of this report).

**Team Investigators:**

- Dr Juli Coffin, Telethon Kids Institute and Geraldton Regional Aboriginal Medical Service (GRAMS), Geraldton

**Lead Investigator:**

- Dr Juli Coffin, Telethon Kids Institute and Geraldton Regional Aboriginal Medical Service (GRAMS), Geraldton

**Funding:**

NHMRC

**TOBACCO INTERVENTION - GAZEBO PROJECT**

*Associate Professor Juli Coffin*

Over the last year, 30 gazebos have been placed around the Geraldton and greater Midwest region across a multitude of public and privately owned homes and units.

At each gazebo location three canister samples were collected before gazebo erection, two weeks post gazebo erection and then six months later. The canisters were located in three positions in the household. The readings so far have been very positive and the project is awaiting final samples to be analysed. Juli has had positive feedback from people using their gazebos and appreciating that they now have a safe, comfortable and private space to smoke for themselves and visitors.

Participants of the gazebo project have also been given the Smokerlyser (an aid to assist people trying to stop smoking by monitoring their level of nicotine dependence) to use in the comfort of their own homes. This will measure if passive and direct smoking is reduced in

the household. An article will be published with all results including methodology and methods of engaging the community in the process.

Juli was approached by the West Australian newspaper to write a story about the tobacco project in Geraldton. Juli also created an Infomercial about the tobacco excise which was introduced in 2014. It was called 'What are you having for dinner?'

#### **Team Investigators:**

- Dr Juli Coffin, Telethon Kids Institute and Geraldton Regional Aboriginal Medical Service (GRAMS), Geraldton

#### **Lead Investigator:**

- Dr Juli Coffin, Telethon Kids Institute and Geraldton Regional Aboriginal Medical Service (GRAMS), Geraldton

#### **Funding:**

NHMRC, Healthways, Australian Government

## **MATERNAL CHILD HEALTH AND WELLBEING IN THE WESTERN DESERT**

*Associate Professor Roz Walker*

The goal of the community based work is to measurably improve the health of Aboriginal children in the Pilbara, in particular the Martu communities living in the Western Desert (including Jigalong, Parngurr, Punmu, Kunawarritji) and Newman.

The work in this area is ongoing. During 2014 the team comprising Roz Walker,

Clair Scrine and Carrington Shepherd worked in collaboration with a range of community partners to translate the results of the AEDI and other research data into tangible outcomes. A community based participatory action research process aims to foster genuine partnership and increase the resilience and empowerment of the families and service providers involved. The team have worked extensively with the Puntukurnu Aboriginal Medical Service and other key stakeholders and service providers in the region including the Jigalong community, the Aboriginal Independent Schools, Royal Life Saving Australia, World Vision and YMCA.

This work entails interconnected and mutually reinforcing place-based research focusing on child health issues of importance to the community. During that time there has been an increase in the coordination and integration of services, improved physical outcomes noted among young children at school, and increased understandings amongst mothers of the importance of good nutrition, hand hygiene and positive family attachments.

Clair Scrine has worked in collaboration with Roz Walker and Amanda Langridge in producing a report called Factors Influencing Maternal and Early Child Development for Martu Communities in the East Pilbara. The report has identified higher than average rates of low birth weight and premature babies who are at higher risk of poor health outcomes over the life course. Reasons include poor maternal nutrition and anaemia, low utilization and/or lack of access to antenatal and postnatal care, parenting capacity (particularly for teen mothers),



alcohol, drug and tobacco consumption during pregnancy, FASD and maternal mental health.

David Hendrickx has almost finalised his data collection across all Western Desert community clinics, which is providing a snapshot of the burden of infectious diseases in children up to 5 years old. His work to date shows that between 2007 and 2010, ear (20%), skin (21%) and respiratory infections (19%) were the most common reasons children in this age group presented to community clinics. This is important data, as it also provides compelling evidence to show that ear and skin infections are already evident in children as young as one month old. These infections contribute to low levels of readiness for school (i.e. hearing loss and language development delays), school engagement and achievement and are associated with chronic disease in adulthood.

**Team Investigators:**

- Associate Professor Roz Walker, Principal Investigator, Telethon Kids Institute
- Clair Scrine
- Carrington Shepherd
- Amanda Langridge

**Lead Investigator:**

- Associate Professor Roz Walker, Principal Investigator, Telethon Kids Institute

**Funding:**

BHP Billiton

## **IMPROVING CARE OF TYPE 2 DIABETES AMONG INDIGENOUS AUSTRALIANS**

*Professor Sandra Eades*

This major trial is in its final year with 18 participating Aboriginal Community Controlled Health Organisations (ACCHOs) in five different States and Territories. The nine services allocated to the intervention arm of the study will complete the intervention period on 30 June 2015. In the second half of 2015 final comparisons of the evidence practice gap for type 2 diabetes will be made between the 9 intervention and 9 control groups.

Sandra is participating in an evaluation of the 'Quit for New Life' program in NSW which aims to assist pregnant Aboriginal women and new mothers in the postnatal period to quit smoking.

Sandra is also collaborating with partners on two current NHMRC project grants with co-investigators from NSW, QLD, VIC and WA. She is also a CI on a further 4 project grants, 2 partnership grants and 1 partnership centre.

## **STRENGTHENING SOCIAL AND EMOTIONAL WELLBEING OF AUSTRALIAN ABORIGINAL PEOPLE**

*Associate Professor Cheryl Kickett-Tucker*

This project is an extension of A/Prof Kickett-Tucker's research on development of racial identity and related self-esteem of Aboriginal children, youths and adults using I-RISE (Indigenous Racial Identity and Social Esteem) measures across the lifespan.

In 2014, Daniel Christensen and Professor

David Lawrence joined the team and worked in consultation with project lead, Cheryl Kickett-Tucker to validate the I-RISE C and I-RISE Y. Cheryl also completed the I-RISE YC (5-7 years old) and prepared a preliminary report for the Bush School Project (led by Libby Lee Hammond-Murdoch University).

I-RISE was awarded a highly commended for the Communities Award for service or project in the metro-politan area during Children's Week which is funded by the Department of Local Government and Communities. As a result of the work with children and young people, Cheryl was invited as a member of the Aboriginal Reference Group for the Commissioner for Children and Young People.

The next stage of the I-RISE project has been planned with the development of an Australian Research Council (ARC) grant titled Cultural Learnings: Strengthening Aboriginal children's wellbeing and educational outcomes by connecting urban children to identity, culture, country and kin.

#### **Team Investigators:**

Dr Cheryl Kickett Tucker, Assoc Professor David Lawrence, Dr Daniel Christensen.

#### **Lead Investigator:**

- Dr Cheryl Kickett-Tucker

#### **Funding:**

NHMRC

The Aboriginal Health and Wellbeing Group through its research and networks also participates in the following with some emphasis on external committees, other research collaborations with community and within the industry. These are not exhaustive but provide examples of these other outcomes of our research.

## **External Committees**

### **National**

- **Prof Pat Dudgeon and Dr Juli Coffin, Prof Dawn Bessarab** - National Indigenous Research and Knowledges Network (NIRAKN) –are members of this group.
- **Prof Pat Dudgeon** is co-chair of the Aboriginal and Torres Strait Islander Mental Health and Suicide Prevention Advisory Group (ATSIMHSPAG).
- **Glenn Pearson** - Indigenous HealthInfonet Advisory Board
- **Glenn Pearson** - Australian Bureau of Statistics (ABS) National Aboriginal and Torres Strait Islander Round Table
- **Glenn Pearson and Roz Walker** - National Aboriginal Disability Researcher's Network.

## 2015 Success

### Invited Presentations

Investigators	Title	Conference	Location	Month
Fiona Stanley (invited speech)	Social inequalities in health and wellbeing: lessons from working with the Aboriginal population in Australia		Leuven, Belgium	4 February
Dawn Bessarab	World Social Work Day	Western Australian Social Work Organisation	UWA Club, Perth	18 March
Fiona Stanley	Science with a Soul: data to action for health child development-Clyde Hertzman Memorial Lecture	New Frontiers in Population Health toward Equity from the Start: Dialogue Series	Vancouver, Canada	28 April
Sandra Eades	Recent epidemiologic studies potential to contribute to improvements in the health of Australia's Aboriginal and Torres Strait Islanders	IEA World Congress of Epidemiology	Anchorage, Alaska	17-21 August
Rhonda Marriott	Congress of Aboriginal and Torres Strait Islander Nurses and Midwives (CATSINaM)		Perth	25
Dawn Bessarab	'Doing palliative care and being culturally safe and responsive in delivering services to Aboriginal people'	WA Palliative Care Conference	Perth	31 October
Pat Dudgeon	Back to the Future: Collective Reflexivities for Transformative Change	13th Trans-Tasman Community Psychology Conference	Perth	27-29 November





# ALCOHOL, PREGNANCY & FASD

## Alcohol, Pregnancy & FASD (AAPFASD)

### Overview

People with Fetal Alcohol Spectrum Disorders (FASD) have impairments that are permanent and negatively impact upon their development. FASD affects the ability to think, learn, focus attention and control behaviour and emotions. People with FASD may be impulsive and often have low self-esteem and mental health problems. Their impairments may also lead to socially unacceptable behaviour, alcohol and other drug use, and early interactions with police and the justice system.

It is important that everyone is aware of the harm that can be caused by alcohol on the developing baby. Our researchers are working with communities and stakeholders to develop prevention strategies; build the capacity of health professionals to diagnose FASD; raise awareness and recognition of FASD by people working in the justice system and develop workplace training programs; and implement programs that support children with FASD and their families.

### HIGHLIGHTS

Collaboration with communities and stakeholders is at the forefront of research

in the Alcohol Pregnancy & FASD Research Program.

Working with Aboriginal communities in the Kimberley, we have seen a reduction in the proportion of pregnant women drinking alcohol during pregnancy from approx. 65% in 2010 to 20% in 2015. The collaboration with communities has also seen an increase in people's awareness to more than 95%, that alcohol can harm the developing baby and it's not OK to drink while pregnant. Building on our model of community-led research, we were successful in receiving a National Health and Medical Research Council (NHMRC) grant to undertake work in prevention, diagnosis and support and therapy interventions the Pilbara region.

The Alert Program® was conducted at the Muludja School, with the school staff, parents and children providing positive feedback. The program was also successful in receiving funding from the 100 Women Foundation for a capacity building program for community researchers on the Alert Program® Study over the next two years.

Also working closely with stakeholders is the Banksia Hill FASD project team. This project commenced work assessing sentenced youth in Banksia Hill Juvenile Detention Centre and working with staff on workforce development. Another aspect of our work in the justice system was the release of FASD resources for justice professionals.

In late 2015 a collaboration of Australian researchers, including members of the Alcohol Pregnancy & FASD Research Program, were successful in gaining a NHMRC Centre of Research Excellence Grant 'Reducing the Effects of Antenatal Alcohol on Child Health'. This centre will commence in 2016.

## Research Projects

### Alert Program® Study

The Alert Program® Study: an evidence based program to improve self-regulation and executive functioning in primary school aged children with and without FASD in the Fitzroy Valley.

#### Names of investigators

CIA – Dr. James Fitzpatrick  
CIB – Prof. Karen Edmond  
CIC – Prof. Jane Latimer  
CID – Prof. Branko Celler  
CIE – Dr. Trevor Mazzucchelli  
CIF – Mr. Glenn Pearson  
CIG – Dr. Heather Carmichael Olsen  
CIH – Dr. Rochelle Watkins  
CIJ – Prof. John Boulton  
CII – Ms. Maureen Carter

#### Project background and aims of the project

The goal of this research is to develop, implement and evaluate a school curriculum version of the Alert Program® to improve impairments in self-regulation and executive functioning of children attending grades 1-6 in the Fitzroy Valley. In 2015, the first year of this project, a comprehensive formative process was undertaken in partnership with various

health, education and community stakeholder from the Fitzroy Valley. The formative process involved seven visits to the Fitzroy Valley and included working with the Kimberley Education Regional Office (KERO), the Marulu FASD Leadership Team, schools and the Kimberley Population Health Unit occupational therapists. Relationships were also formed between researchers, families and community representatives through a series of school visits, by running community barbecue and breakfast events, presenting information about the study at school conferences, community and service provider meeting, joining community networks and being visibly present on a regular basis within the community. This has also meant getting to know people outside of more formal situations by embracing the chance to be involved in activities like camping, fishing and cultural events with local community members. Regular communication and input into project design has also been facilitated by convening consumer reference group meetings, publishing a regular study newsletters and keeping in touch with key stakeholders by email and telephone.

Conducting a pilot study at a small remote community school enabled the team to trial all aspects of the Alert



Program® project and to gain valuable feedback from teachers, school support staff and families before finalising plans for the full study phase in 2016 and 2017. This included piloting research procedures, information and consent forms, the Alert Program® curriculum guide, resources and equipment, assessment tools and staffing processes. Investing time in community and consumer participation, as well as running a pilot study during the formative stage, has ensured the research design is not only rigorous but appropriate to the Fitzroy Valley context.



The employment of Aboriginal community members as community researchers on this project has been fundamental to researchers and community members developing a shared understanding and expectations for culturally and contextually sensitive research practices and processes. Locally employed community researchers have provided language and cultural support to both families participating in the research and to non-Aboriginal research staff. This two way research partnership has been central to the project being accepted by the community and to maximising participation from schools and families.

Additional funding has been received to enable locally based Aboriginal research staff to complete a Certificate II in Community Health Research between 2016 and 2017. By doing so, community researchers working on this project will develop the research skills to complement their existing expertise and knowledge which will enable them to seek employment across other research projects taking place in the Fitzroy Valley. This has already occurred in 2015 whereby Alert Program® Community Researchers were able to be employed on the Fitzroy Valley FASD Prevention research project that is also taking place through the Telethon Kids Institute.

### **Where to Next?**

Analysis of findings in 2018 will contribute to the basis for recommendations and preparation of guidelines for the use of the Alert Program® with children who have impairments in self-regulation and executive functioning in similar settings. The team also hopes to report on the importance of the formative process undertaken to inform and enhance the project and by doing so, hopefully influence similar projects to recognise the benefits of including community and consumer participation in program design, service delivery and research.

### **Plain Language summary**

While lots of children going to school in the Fitzroy Valley do well, some kids find school hard. They may have problems controlling their actions and mood which can affect their ability to learn in the classroom. This can be a big problem for children who have FASD. Primary schools

in the Fitzroy Valley are going to teach the Alert Program® in the classroom so students can learn to control their actions and mood. We call these skills “self-regulation”. We want to find out if teaching them the Alert Program® will help improve their learning and behaviour skills. This might help them to get better at remembering things, solving problems, paying attention, planning and organising themselves. These “executive functioning” skills are important for children to engage with the demands of school life. The Alert Program® teaches kids that their body is like a car engine. It can go into high speed, it can go into low speed and it can go into just right speed. The program teaches kids different ways they can change their engine speeds (level of alertness) by using ‘tools’ for their mouth, body, ear, eyes and hands to help them self-regulate and therefore learn more easily in the classroom. For example, a student could be feeling hyped up when they enter the classroom after recess (high gear). The teacher or Aboriginal and Islander Education Officer might teach the student to do some chair push-ups (heavy work) to shift their engine (level of alertness) into just right gear so they can concentrate on their spelling task when sitting at their desk.

### **Funders of the project**

NHMRC Project grant

### **External collaborators**

Nindilingarri Cultural Health Service, WA  
Fitzroy Valley primary schools, WA  
Department of Health, WA  
University of Washington, USA  
Therapy Works Inc., USA

### **3M FASD PREVENTION STRATEGY: MARULU, MASS MEDIA, MIDWIVES**

*James Fitzpatrick<sup>1</sup>, Maureen Carter<sup>2</sup>, June Oscar<sup>3</sup>, Rochelle Watkins<sup>1</sup>, Carol Bower<sup>1</sup>, Glenn Pearson<sup>1</sup>, Jonathan Carapetis<sup>1</sup>, Mike Daube<sup>2</sup>, Kaashifah Bruce<sup>1</sup>*

<sup>1</sup>*Telethon Kids Institute, The University of Western Australia, Perth, Australia*

<sup>2</sup>*Nindilingarri Cultural Health Services, Fitzroy Crossing, Australia*

<sup>3</sup>*Marninwarntikura Fitzroy Women’s Resource Centre, Fitzroy Crossing, Australia*

<sup>4</sup>*McCusker Centre for Action on Alcohol and Youth, Curtin University, Australia*

### **Project staff:**

*Kaashifah Bruce<sup>1</sup>, Martyn Symons<sup>1</sup>, Tracy Reibel<sup>1</sup>*

### **Project background and aims of the project: What happened in 2015**

The objective of the *FASD Prevention Strategy* is to implement and evaluate a community designed FASD prevention strategy for the Fitzroy Valley and surrounding communities that, if effective, can be translated to other settings in Western Australia. This overarching evidence-based and woman-centred Strategy was developed using a ‘Four Part Model of Prevention’ framework (Figure 1) and comprises three distinct but interrelated initiatives: the *Marulu FASD Prevention Strategy* in the Fitzroy Valley; a midwife screening/brief intervention strategy (Workforce Development Strategy); and a community-wide *media strategy*, with an initial focus on both Aboriginal and non-Aboriginal people in the Kimberley and Pilbara, as well as a health promotion strategy more broadly throughout Western Australia.



Figure 3 outlines the annual schedule of activities for the Strategy incorporating the intervention components.

### **Plain Language summary**

This program has three initiatives responding to high FASD prevalence rates in the Fitzroy Valley through a whole of community prevention strategy:

#### **Marulu:**

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

#### **Midwives:**

A workforce intervention up-skilling midwives in the documentation and brief intervention around alcohol use in pregnancy, to reinforce the community-wide interventions;

#### **and Mass Media:**

A mass media strategy targeting regional and remote communities throughout the Kimberley and Pilbara, with a further aim of ensuring state-wide impact for the program and its messages.

### **Funders of the project**

WA Department of Health, WA  
Department of Aboriginal Affairs

### **External collaborators**

Mike Daube, McCusker Centre for Action on Alcohol and Youth, Curtin University, Australia  
Maureen Carter, Nindilingarri Cultural Health Services, Fitzroy Crossing, Australia  
June Oscar, Marninwarntikura Fitzroy Women's Resource Centre, Fitzroy

Crossing, Australia

Gary Kirby, Michelle Gray, WA Mental Health Commission, Australia

### **MIDWIVES AND WOMEN AUDIT C INTERVENTION PROJECT (PART OF 3M)**

*Tracy Reibel*

#### **Project background and aims of the project: What happened in 2015**

This project is in direct response to previous research conducted by the Alcohol, Pregnancy and FASD program which identified that health professionals in general, but midwives specifically are not always confident when discussing alcohol use with pregnant women. Since 2009, the relevant NHMRC guideline of "no alcohol in pregnancy is the safest option" has been in place. However, while it is generally understood that this prevention message has penetrated the broader community, there is evidence that midwives do not always address the issue of alcohol use by pregnant women and the potential of negative outcomes on the developing baby. Further, there is a need for education which promotes the use of a screening tool to establish the risk exposure for individual women and the application a brief intervention where this may be required. Workforce development is an integral component of improving prevention measures. The project will develop a readily accessible resource guide for midwives to use in the antenatal setting when taking histories during pregnancy. It will provide guidance on where to access professional education and resources to use with women.

#### **Plain Language summary: What happened in 2015**

It is important that pregnant women are consistently informed by midwives that 'no alcohol in pregnancy is the safest option' as a public health message. This project will develop a guide for midwives to assist them in providing guidance to women during pregnancy care visits.

### **Funders of the project**

WA Department of Health

### **External collaborators**

The external collaborator for this project is the Armadale Health Service, as the trial site.

### **HEDLAND FASD PROJECT**

*Glenn Pearson<sup>1</sup>, James Fitzpatrick<sup>1</sup>, June Councillor<sup>2</sup>, Roz Walker<sup>1</sup>*

<sup>1</sup>*Telethon Kids Institute, The University of Western Australia, Perth, Australia*

<sup>2</sup>*Wirraka Maya Health Service Aboriginal Corporation, South Hedland, Australia*

### **Project staff:**

*Kaashifah Bruce<sup>1</sup>, David Tucker<sup>1</sup>, Sylvia Lockyer<sup>1</sup>, Kristen White<sup>1</sup>*

### **Project background and aims of the project**

The goals of this project are to lay the foundations and to begin to measurably and sustainably improve the health of Aboriginal children in the Pilbara by supporting the development and implementation of a Hedland Fetal Alcohol Spectrum Disorders (FASD) strategy and establish a long-term partnership around child health with BHP Billiton in the Pilbara.

The specific objectives of the project are to:

- Begin reducing the prevalence of FASD in targeted communities in the Hedland area
- Improve the outcomes of children with FASD across the life course

This research will assist efforts in each of prevention, diagnosis, treatment, family support, capacity building and policy advocacy as well as measuring the impact of the interventions on such indicators as school readiness, school attendance and learning. Critical focus will be on building the knowledge and agency of families with children with FASD, and increasing their confidence in engaging with services.

### **Plain Language summary**

Following on from Telethon Kids Institute's previous work and recognising ongoing local action, the Hedland FASD Project will work with Wirraka Maya and the Hedland FASD Network and others to support local efforts in prevention, diagnosis, treatment, family support, capacity building and policy advocacy through identifying needs, evidence-based practices, and evaluating specific strategies, programs and activities. Critical focus will also be on supporting and measuring the effectiveness of programs that build the knowledge and agency of families with children with FASD, and increasing their confidence in engaging with services and establishing/determining their own initiatives.

The current project has been funded through community investment from BHP Billiton, and as a requirement of this funding is focused specifically on the Town of Port Hedland and



surrounding communities (Warralong and Yandeyarra).

### **Funders of the project**

BHP Billiton

### **External collaborators**

Wirraka Maya Health Service Aboriginal Corporation, South Hedland, Australia  
Hedland FASD Network, South Hedland, Australia

## **AUSTRALIAN FETAL ALCOHOL SPECTRUM DISORDER (FASD) DIAGNOSTIC INSTRUMENT: FEASIBILITY TRIAL AND IMPLEMENTATION**

*Professor Carol Bower, Dr Rochelle Watkins*

### **Project staff:**

Juanita Doorey

### **Project background and aims of the project**

The Australian FASD Diagnostic Instrument and a draft Guide for its use were completed in 2012. In 2014-2015 the Telethon Kids Institute, in collaboration with the University of Sydney, was contracted by the Commonwealth Department of Health to conduct a feasibility trial of the Instrument and Guide prior to national implementation.

The associated aims of the project are that implementation of the Diagnostic Instrument and Guide will promote timeliness and consistency in diagnosis and will help estimate the prevalence of FASD in Australia. This in turn will improve the evidence base for prevention,

diagnosis, management and advocacy for improved services and supports.

### **Plain Language Summary: What happened in 2015.**

Sixteen paediatricians from across Australia took part in the feasibility trial. They worked in metropolitan, regional and remote locations and clinical settings that included specialised FASD clinics, child development services and general and developmental paediatric practices. Based on clinicians' evaluation from the trial, changes were made to the Instrument and Guide. Parents/guardians of children being assessed during the feasibility trial were invited to provide feedback on the diagnostic assessment process, with a small number electing to do so.

A Guide and five on-line training modules were developed to assist doctors in using the Instrument. The Instrument, Guide and training modules will be freely accessible on the Telethon Kids Institute website. Information and an electronic link to the website will be sent to professional colleges and a wide range of other organisations in Australia.

A draft final report, with the Guide, Instrument and on-line training modules, was submitted to the Commonwealth Department of Health in December 2015. After consideration of the new Canadian FASD Guidelines, and changes if needed, the Australian resources will be widely disseminated in mid 2016.

### **Funders of the project**

Commonwealth Department of Health

### **External collaborators**

Professor Elizabeth Elliott, The University of Sydney; Sydney Children's Hospital Network (Westmead)

## **BANKSIA HILL FASD PROJECT**

*Carol Bower, Raewyn Mutch, Rhonda Marriot, Rochelle Watkins, Steve Zubrick, Carmella Pestell, James Fitzpatrick, Peter Collins, Jonathan Carapetis*

### **Project staff:**

*Jacinta Freeman, Natalie Kippin, Bernadette Safe, Hayley Passmore, Sharynne Hamilton, Carmen Condon, Noni Walker (also Roslyn Giglia, Candice Rainsford, Candy Cheung, Vicole Bothma, Helen Shield)*

### **Project background and aims of the project**

The Alcohol and Pregnancy and FASD Research Group is working on a project that aims to determine how common Fetal Alcohol Spectrum Disorders are in young people in detention, develop appropriate management strategies for all young people assessed in the project and develop a FASD screening tool appropriate for young people entering the juvenile justice system. Partnerships are vitally important as the project connects with the Department of Corrective Services, the Department of Child Protection and Family Services, young people in detention, their families and communities.

### **Plain Language summary: What happened in 2015**

The project, based at the Banksia Hill Detention Centre in Canning Vale (the only centre in WA for detainees aged

between 10 and 17 years), began recruitment in May 2015 among young people who have been sentenced. Young people are interviewed by the project research assistant and are assessed by a paediatrician, psychologist, occupational therapist and speech pathologist to provide information that may identify FASD or other conditions or impairments.

A report for each young person includes the findings from the assessment, a provisional diagnosis if one has been identified, their individual strengths and difficulties, recommendations for managing any difficulties the young person has, and referrals for further investigation or treatment if needed. The findings are discussed with the young person and their parent / guardian / carers. Staff at Banksia Hill assist with support during detention for the young people who have been identified with FASD and other impairments and in the community following their release. We are also finding out from staff at Banksia Hill how the recommendations match with how staff currently communicate and manage young people, so that we can develop useful, appropriate and effective training and support for staff.

### **Funders of the project**

National Health and Medical Research Council (NHMRC) Targeted Call for FASD Funding



## **EVALUATING THE EVIDENCE-PRACTICE GAP BETWEEN THE NHMRC ALCOHOL AND BREASTFEEDING GUIDELINE (2009), CLINICIAN APPLICATION AND MATERNAL UPTAKE**

*Dr Roslyn Giglia*

### **Project background and aims of the project**

In 2009 the National Health and Medical Research Council (NHMRC) released the revised 'Australian Guidelines to Reduce Health Risks from Drinking Alcohol'. A national first was the inclusion of an alcohol guideline exclusively for breastfeeding women (4B), and not merely as an add-on to the pregnancy guideline. The guideline recommended 'not drinking as the safest option' however practical advice for safe drinking was included in an effort to acknowledge that lactating women may cease breastfeeding in order to start drinking alcohol. Previous public health campaigns aimed at pregnant women have shown a marked effect on the reduction of alcohol consumption during pregnancy however there has been no associated campaign for the period of breastfeeding despite continued alcohol consumption during this time.

With limited promotion of this guideline it is not known whether practitioners use this guideline in their daily practice and if a resulting decrease in maternal drinking and extended duration of breastfeeding has occurred in Australian women. This project will use both qualitative and quantitative methods to investigate the awareness and utilisation of the alcohol guideline for breastfeeding women amongst maternal health practitioners

and maternal consumers. Obstetricians, general practitioners, midwives, child health nurses and paediatricians will be the primary target group of maternal health practitioners as they most often answer questions relating to breastfeeding in the early days following the birth of a child. An educational campaign for the maternal health practitioners will be evaluated to see if any changes in their knowledge and behaviour (i.e. utilisation) of guideline 4B resulted from the education campaign. A secondary target group is breastfeeding women. Their knowledge and awareness of guideline 4B and use of educational resources relating to this guideline will be assessed following an education campaign tailored to their level of knowledge, awareness and behaviour regarding alcohol consumption during lactation.

### **Plain Language summary**

Despite wanting to breastfeed many Australian women also want to return to drinking alcohol after the birth of their baby. Drinking alcohol is the cultural norm in Australia but alcohol in breastmilk can disrupt the hormones needed to successfully breastfeed. This results in the baby receiving less breastmilk and being hungry and cranky and can often lead the mother to introduce infant formula to help settle her baby. This project will look at what doctors and nurses tell new mothers about drinking alcohol while they are breastfeeding so that they can provide supportive messages which allow a mother to drink and still safely breastfeed.

### **Funders of the project**

NHMRC Translating Research into Practice Fellowship

## FEASIBILITY OF THE EASY DIET DIARY SMARTPHONE APP FOR ESTIMATING DIETARY INTAKE

*Dr Roslyn Giglia*

*Associate Professor Gina Ambrosini (Gina is the primary investigator)*

### **Project background and aims of the project**

Assessing usual dietary intake in research settings is a major challenge due to the complexity of the human diet and limited availability of evaluated tools, each having varying degrees of accuracy and acceptability. Furthermore, respondent burden often results in poor response rates (especially paper based tools), dietary under-reporting and potentially biased observed diet-disease associations. Recently however, technological advances in smart phones, smart phone apps, and mobile internet access has

opened up new opportunities to improve dietary assessment methods.

The advantages of using a mobile phone application to record dietary intake are manifold. Firstly, the portability of a mobile phone enables real time dietary recording, avoiding the need for respondents to recall their food intake using a questionnaire, which can reduce data quality. Collecting real time data at each eating occasion provides an unparalleled opportunity to measure eating contexts e.g. where food is eaten, who the consumer is with, and what the consumer is doing; factors increasingly recognised as having the potential to influence diet quality. Finally, respondents can be automatically reminded to record their dietary intake via text message,

which also maintains data quality.

Many smartphone apps are freely available to consumers to monitor their calorie intake and assist with weight loss, yet very few have been designed or tested as a dietary assessment tool suitable for application in research (none in Australia to our knowledge). Obesity researchers in the UK have shown that use of an app (My Meal Mate) developed to record and monitor dietary intake is acceptable to users and compared to a written (paper) diet diary, results in greater participant retention (93% vs 53%) and greater adherence.<sup>2</sup> Development of an Australian app for assessing dietary intake in research is essential to record local brands of foods and to utilise Australian food composition data.

This pilot study aims to test the feasibility of a smartphone application to assess usual dietary intake in a population health research setting, specifically:

1. the acceptability of the app using qualitative data from respondents
2. a comparison of levels of dietary under-reporting in the app vs a traditional diet diary

### **Plain Language summary**

Traditional methods of recording what people eat for research is time consuming and labour intensive for the person recording what they eat. Often they will need to weigh and write down all the foods eaten over a three day period. This information then needs to be returned to the researcher for review and dietary analysis. This research will explore the possibility of research participants recording their food intake using a mobile



phone app which contains an electronic diary and a complete list of Australian foods which can be searched to match what the participant is eating. Foods can then easily be entered and dietary records can be emailed back to the researcher for analysis and feedback to participants.

### **Funders of the project**

WA Department of Health Merit Award (NHMRC near-miss funding RA/1/85/265): \$75,000; 2016 (Ambrosini GL, Scott J, Trapp G, Bull F, Oddy WH. Determining modifiable lifecourse influences that lead to poor diets in young adults: a prospective analysis in the Raine Study).

### **External collaborators**

Associate Professor Gina Ambrosini, School of Population Health, UWA. Honorary Research Fellow, Telethon Kids Institute

## **PARENTAL INFANT FEEDING INTERVENTION (PIFI)**

*Dr Roslyn Giglia (AI), Bruce Maycock, Jane A Scott, Yvonne L Hauck, Sharyn K Burns, Suzanne Robinson, Satvinder Dhaliwal, Peter A Howat, Colin W Binns*

### **Project background and aims of the project**

Very few Australian infants are exclusively breastfed to 6 months as recommended by the World Health Organization. There is strong empirical evidence that fathers have a major impact on their partner's decision to breastfeed and continuation of breastfeeding. Fathers want to participate in the breastfeeding decision making process and to know how they

can support their partner to achieve their breastfeeding goals. The aim of the Parent Infant Feeding Initiative (PIFI) is to evaluate the effect on duration of any and exclusive breastfeeding of three breastfeeding promotion interventions of differing intensity and duration, targeted at couples but channelled through the male partner. The study will also undertake a cost-effectiveness evaluation of the interventions.

The PIFI study is a factorial randomised controlled trial. Participants will be mothers and their male partners attending antenatal classes at selected public and private hospitals with maternity departments in Perth, Western Australia. Fathers will be randomly allocated to either the usual care control group (CG), one of two medium intensity (MI1 and MI2) interventions, or a high intensity (HI) intervention. MI1 will include a specialised antenatal breastfeeding education session for fathers with supporting print materials. MI2 will involve the delivery of an antenatal and postnatal social support intervention delivered via a smartphone application and HI will include both the specialised antenatal class and the social support intervention. Outcome data will be collected from couples at baseline and at six and 26 weeks postnatally. A total of 1600 couples will be recruited.

The PIFI study will be the first Australian study to provide Level II evidence of the impact on breastfeeding duration of a comprehensive, multi-level, male-partner-focused breastfeeding intervention. Unique features of the intervention include its large sample size, delivery of two of the interventions by mobile device technology, a rigorous assessment of intervention fidelity and a cost-

effectiveness evaluation.

### **Plain Language summary**

The choice to breastfeed and how long a woman breastfeeds her baby most often depends on the father's attitude and preference for breastfeeding. This study will investigate if supporting fathers during the period of breastfeeding can prolong breastfeeding in the mother. Three different ways of supporting the fathers will be trialled in three different groups of fathers including the use of a mobile phone app specific to fathers.

### **Funders of the project**

Healthway Health Promotion Research Grant (No: 24023)

### **External collaborators**

Bruce Maycock<sup>1</sup>, Jane A Scott<sup>1</sup>, Yvonne L Hauck<sup>1</sup>, Sharyn K Burns<sup>1</sup>, Suzanne Robinson<sup>1</sup>, Satvinder Dhaliwal<sup>1</sup>, Peter A Howat<sup>1</sup>, Colin W Binns<sup>1</sup>  
Curtin University<sup>1</sup>

## **UNDERSTANDING FASD: A GUIDE FOR JUSTICE PROFESSIONALS**

*Heather Jones, Associate Professor  
Raewyn Mutch, Professor Carol Bower, Dr Rochelle Watkins*

### **Project staff:**

Heather Jones

### **Project background and aims of the project**

Our previous research identified what justice professionals knew about FASD, how this impacted on their work, what information they required and how this

information should be delivered. The next phase of our work was to translate this research, together with health and legal concepts and knowledge into practical educational resources for justice professionals so they can:

- recognise cognitive impairments and possible FASD in young people engaging with the criminal justice system whether as an offender, witness or victim, and children and young people in protection and care matters
- identify legal implications
- consider referral for assessment if cognitive impairments and/or disability is suspected
- consider decision making with respect to orders, sentencing and management to accommodate cognitive impairments and disability

### **Plain Language Summary: What happened in 2015.**

We developed and implemented educational resources to build the capacity of justice professionals to use best practice interventions for young people suspected of having FASD. We developed:

- FASD and justice website
- 6 videos
- on-line continuing professional development module for lawyers

We also presented at many seminars, workshops and conferences

### **Funders of the project**

WA Government Department of the Attorney General  
Telethon Kids Institute

### **External collaborators**

Magistrate Catherine Crawford: Perth



Children's Court

Trish Heath: Office of the Commissioner for Children & Young People

Julie Waud: Aboriginal Legal Service WA

Claire Rossi and Anna O'Connor: Legal Aid WA

Robyn Williams: Community representative and PhD candidate

## 2015 Success

### THESES PASSED

*James Fitzpatrick PhD University of Sydney*  
The Liliwan Project: Prevalence of FASD among school aged children in the Fitzroy Valley

*Ester Elisaria. PhD. Curtin University. A Cohort Study of Feeding Patterns and Health Outcomes of Infants in the Rufiji District of Tanzania (Supervisor Roslyn Giglia)*

### AWARDS AND PRIZES

*Heather Jones Consumer and Community Participation Award*

*Dr James Fitzpatrick RACP Wiley New Investigator Award*

*Dr James Fitzpatrick Asia Pacific Society Alcohol and Addiction Research best oral presentation*

*Professor Carol Bower Distinguished Service Award, International Clearinghouse for Birth Defects Surveillance and Research*

### EXTERNAL COMMITTEES

#### International

1. James Fitzpatrick International FASD Conference Scientific Committee 2015
2. Carol Bower International

Clearinghouse for Birth Defects Surveillance and Research Nominating Committee

#### National

1. Carol Bower and Raewyn Mutch National FASD Technical Network 2014-2015
2. Carol Bower National Perinatal Epidemiology Statistics Unit Steering Committee for Congenital Anomalies. 2012 - 2015
3. Carol Bower Australian Paediatric Surveillance Unit Scientific Review Panel. 2012 - 2015
4. Carol Bower. Reference Group, Australian Indigenous Alcohol and Other Drugs Knowledge Centre 2014 – 2015
5. James Fitzpatrick. Australian National Advisory Council on Alcohol and Drugs (expert member) 2014-2015
6. Roslyn Giglia. Dietitians Association of Australia. Scientific and Social Planning Committee, Perth National Conference 2014 - 2015
7. Roslyn Giglia NHMRC Postgraduate Scholarships Review Panel 2015
8. Roslyn Giglia Department of Health Western Australia – Breastfeeding Key Stakeholders Group 2014 - 2015

#### Local

1. Carol Bower. Alcohol Advertising Review Board. Panel member for the Review Board. 2012 - 2015
2. Jan Payne. Alcohol Advertising Review Board. Panel member for the Review Board. 2012 – 2015
3. Kaashifah Bruce. Public Health Association of Australia WA Branch 2015 Committee member

## INVITED PRESENTATIONS

### International (abstracts submitted and subject to review)

1. Jones H, Mutch R. Developing FASD educational interventions for justice professionals. FASD & The law: Continuing the conversation about current research, best practices & ethical considerations. Vancouver March 2015.
2. Jones H, Mutch R, Watkins R, Bower C. What did the community and justice professionals want in FASD educational resources. 6th International Conference on FASD Research: Results and Relevance 2015, Vancouver March 2015
3. Payne J, Jones H, Watkins R, Reibel T, Mutch R, Wilkins A, Whitlock J, Bower C. Alcohol and Pregnancy and FASD: Midwives' knowledge, attitudes and practice. 6th International Conference on FASD Research: Results and Relevance 2015, Vancouver March 2015
4. Fitzpatrick J, Carmichael Olsen. The Lirilwan project: Neurodevelopmental outcomes and FASD in remote Australia. 6th International Conference on FASD Research: Results and Relevance 2015, Vancouver March 2015
5. Fitzpatrick J, Carter M. "It's like herding cats" Patches Paediatrics – establishing FASD diagnostic and management capacity in remote Australian communities. 6th International Conference on FASD Research: Results and Relevance 2015, Vancouver March 2015
6. Fitzpatrick J, Carter M, Oscar J, Bruce K, Wagner B, Hartness C, Elliott E. The Marulu Strategy: 'Making FAD History'

in Remote Aboriginal Communities. 6th International Conference on FASD Research: Results and Relevance 2015, Vancouver March 2015

### National (invited)

1. Bower C. Primary prevention of birth defects. Maternal, Child and Family Health Nurses Conference. Perth, Australia, 2015.
2. Mutch R. Correctional Services Healthcare Summit. Melbourne, Australia, September 2015

### National (abstracts submitted and subject to review)

3. Bower C. Addressing Fetal Alcohol Spectrum Disorders in Western Australia. 4th APSAAR/5th IDARS Conference. Sydney, Australia, August 2015
4. Fitzpatrick J. The Lirilwan Project: neurodevelopmental outcomes and FASD in remote Aboriginal Australian children. 4th APSAAR/5th IDARS Conference. Sydney, Australia, August 2015
5. Jones H. Developing FASD resources for justice professionals. 4th APSAAR/5th IDARS Conference. Sydney, Australia, August 2015
6. Fitzpatrick J. The Lirilwan Project: neurodevelopmental outcomes and FASD in remote Aboriginal Australian children. APSAD Annual Scientific Alcohol and Drug Conference, Perth, Australia, November 2015
7. Fitzpatrick J. The Marulu Strategy: Making FASD History in Remote Fitzroy Valley Communities. APSAD Annual Scientific Alcohol and Drug Conference, Perth, Australia, November 2015



8. Jones H. Developing FASD resources for justice professionals. APSAD Annual Scientific Alcohol and Drug Conference, Perth, Australia, November 2015
9. Bower C. Research in a Corrective Setting: A lesson in protocol development and procedures to conduct a prevalence study of FASD in a juvenile detention centre. APSAD Annual Scientific Alcohol and Drug Conference, Perth, Australia, November 2015
10. Freeman J. Have you talked to ... about your FASD project. APSAD Annual Scientific Alcohol and Drug Conference, Perth, Australia, November 2015

#### Local (invited)

1. Fitzpatrick JP. Keynote Address. Making FASD History in the Fitzroy Valley. The Marulu Strategy 2013-2018. Western Australian Aboriginal Maternal and Child Health Conference, Perth, Western Australia. 13 May 2015
2. Bower C. Alcohol & Pregnancy & FASD Research at the Telethon Kids Institute. Western Australian Aboriginal Maternal and Child Health Conference, Perth, Western Australia. 13-14 May, 2015
3. Mutch R. M.E.R.C.Y@Justice Fetal Alcohol Spectrum Disorder: Sharing Solutions. Institute of Advanced Studies, UWA. Perth, Australia. August, 2015
4. Kippin Natalie. Curtin University Speech Pathology Ideas Night 19 August 2015
5. Giglia R. Telethon Kids Institute. Public lecture series. Growing healthy kids through good food. 22 April 2015
6. Mutch R, Jones H. Juvenile & Family Fire Awareness (JAFFA) Program. Fire and Emergency Services. Perth. June 2015
7. Mutch R, Jones H. WA Branch Australian Psychological Society Seminar on FASD. Perth. June 2015
8. Jones H, Mutch R, Freeman J. Boronia Pre-Release Centre. Women's Education Program. Perth. June 2015.
9. Bower C. Maternal and early childhood health. Healthy Futures Forum. Great Southern Science Council. Albany, Western Australia, July, 2015.
10. Bower C, Silva D. Supportive environment for a health start to life. Wheat Belt Early Years Conference. Kellerberrin, Western Australia, August, 2015.
11. Jones H, Passmore H. FASD Presentation. Women's Council Training Day. Perth. September 2015
12. Reibel T, Jones H. Outcomes midwives survey and AUDIT-C project and FASD. WACHS Esperance. September 2015.
13. Jones H, Passmore H. Understanding FASD. Ability Centre. Perth, Western Australia. October 2015.

#### WORKSHOPS AND TRAINING

1. Jones H. 3rd year nurses Notre Dame University. 16 March 2015
2. Jones H. UWA Law Students FASD and implications for law - part of the Birth Life & Death & the Law lectures. 26 March

Assisted  
reproductive  
technology and  
child health  
outcomes

## Overview

We obtained the required ethics approvals for our major NHMRC project grant in 2015 and are currently awaiting linked data to begin analyses. Michele Hansen took on an Associate Editor role for the journal *Human Reproduction* and attended the large European Society for Human Reproduction and Embryology Conference in Lisbon in June. She also began a new collaboration with researchers at the Cerebral Palsy Alliance in NSW, co-supervising Ms Shona Goldsmith's PhD exploring the role of ART and birth defects in the aetiology of cerebral palsy. Dr Hansen also began a collaboration with other researchers at TKI (Dr Helen Leonard, Dr Jenny Downs) who are working with Claire Galea (Masters student, University of Qld) to establish an international Beckwith-Wiedemann Syndrome (BWS) Registry. Dr Hansen

provided assistance with questions around fertility and use of ART for the BWS survey (use of ART and/or subfertility have been associated with an increased risk of BWS).

We responded to an Editorial and Invited Commentary in *Human Reproduction* that heavily criticized the use of administrative databases for public health research. These commentaries were published alongside a large data linkage study from Norway examining cancer risk in parous women who had used ART. Our response, also published in *Human Reproduction*, was titled "Linked data research: a valuable tool in the ART field." These publications were discussed at an internal Telethon Kids Data Linkage Forum.

## Research Projects

### **RECENT CHANGES IN IVF CLINICAL PRACTICE: DATA LINKAGE TO INVESTIGATE THEIR IMPACT ON FETAL GROWTH AND BIRTH DEFECTS.**

*Dr Michele Hansen, Prof Roger Hart, Prof Liz Milne, Dr Lyn Colvin, Prof Adrian Charles, Prof Carol Bower*

One in every 25 births or one child in every Australian classroom is conceived using in vitro fertilisation (IVF), rising to 1 in 7 for women over 37 years of age, and this is likely to increase with the continuing trend toward later childbearing. There have been substantial changes to IVF clinical practice in the last 10 years but little is known about child health outcomes following these shifts in treatment. Specifically, there are limited birth defects data available internationally following the use of recent techniques such as extended embryo culture and rapid embryo freezing (vitrification).

Western Australia (WA) is the only State with a statutory Register of all IVF treatment that exists alongside an extensive system of population-based health datasets. This data linkage study will combine information from the Reproductive Technology Register, the Midwives' Notification System, the WA Register of Developmental Anomalies, the WA Registries of Births and Deaths, the WA Hospital Morbidity Data Collection and the Commonwealth Pharmaceutical Benefits Scheme (PBS). This will allow us to identify a retrospective cohort of all births (live and still born) and terminations of pregnancy for fetal anomaly in WA over a 13 year period (2002-2014) according



to method of conception: natural conception, those conceived using IVF, and those conceived outside the fertility clinic setting using ovulation induction medications. We will compare these births with regard to intrauterine growth, birth defects and cerebral palsy. We will also examine trends in these outcomes over the time period of the study. This information is essential for appropriate pre-treatment counselling and to inform best practice in Australian IVF clinics. This study obtained all required ethics approvals in 2015 and is currently waiting on data linkage and extraction.

### **Plain Language summary**

One in every 25 births or one child in every Australian classroom is conceived using Assisted Reproductive Technologies like in vitro fertilisation (IVF). We are comparing the health of these children to the health of other children conceived without these technologies (naturally conceived). For example, we are looking at whether children conceived following ART treatment are more likely than other children to have birth defects or cerebral palsy.

### **Funders of the project**

NHMRC Project Grant #1086530; NHMRC Early Career Fellowship #1090648 (MH)

### **External collaborators**

Prof Roger Hart - School of Women's and Infants' Health UWA; and Director, Fertility Specialists of Western Australia.  
Prof Adrian Charles - Division Chief of Anatomical Pathology, Sidra Medical and Research Centre, Qatar  
Dr Louise Stewart - Centre for Population

Health Research, Curtin University, Perth, Western Australia.

Dr Michael David, School of Public Health, University of Queensland.

Dr Ben Kamien, University of Newcastle.

Ms Claire Galea, Masters student, University of Queensland.

## **AN EXPLORATION OF CEREBRAL PALSY AETIOLOGY: ASSISTED REPRODUCTIVE TECHNOLOGY AND CONGENITAL ANOMALIES**

*Ms Shona Goldsmith (PhD student University of Sydney), Dr Sarah McIntyre (CP Alliance), Dr Michele Hansen, Prof Nadia Badawi (CP Alliance)*

Cerebral palsy (CP) is the most common physical disability of childhood, and describes a group of permanent disorders of movement caused by damage to the developing brain. The causes of CP are poorly understood for most people. Risk factors for CP span the period from preconception, to early pregnancy, to pregnancy, and to the birth/neonatal period. This research program will explore the impact of two known risk factors on

## **CP: ASSISTED REPRODUCTIVE TECHNOLOGY AND CONGENITAL ANOMALIES**

Assisted reproductive technology (ART) is used by approximately 4.0% of women who give birth in Australia. Research has suggested that ART is associated with increased risk of CP, however the pathway from ART to CP is poorly understood and evidence conflicting. This study will investigate the relationship between ART and CP in a West Australian-

born population, analysing linked data to describe the risk of CP following ART, and explore the clinical outcomes and causal pathways to CP in this group. A systematic review with meta-analysis of data will then be conducted to quantify the effect of ART on the rate of CP, using literature from around the world.

Congenital anomalies (CAs) are known to occur more often in those with CP than the general population, with Australian CA rates reported as 15 - 40%. This variation highlights the need for a detailed evaluation. Firstly, a systematic review of the literature with pooling of data and meta-analysis will be completed to determine the rate of anomalies and types of anomalies most common in children with CP. Secondly, the relationship between CAs and CP in a national, Australian-born population will be explored with data linkages and subsequent analyses.

Once the aetiology of such pathways to CP is better understood, the investigation of primary preventive strategies becomes possible. This research program is the first step toward the goal of preventing some cases of CP.

### **Plain Language summary**

The causes of cerebral palsy are not well understood. This project will explore in detail the role of two known risk factors for cerebral palsy: assisted reproductive technology and congenital anomalies. We will analyse data from large groups of people with CP in Australia, looking at their history and their outcomes. This exploration is an essential early step toward finding ways to prevent cases of cerebral palsy.

### **Funders of the project**

NHMRC Postgraduate Scholarship #1113806 (Shona Goldsmith)  
Research Foundation of Cerebral Palsy Alliance, Project Grant #1215 (SG, SM, MH)

### **External collaborators**

Ms Shona Goldsmith – PhD student  
University of Sydney, NSW  
Dr Sarah McIntyre – CP Alliance, NSW  
Prof Nadia Badawi – CP Alliance, NSW

## **2015 Success**

### **EXTERNAL COMMITTEES**

#### **Local**

Michele Hansen, WA Reproductive Technology Council, Dec 2012-present  
Michele Hansen, Scientific Advisory Committee, WA RTC, Dec 2012-present

### **INVITED PRESENTATIONS**

Michele Hansen, Health outcomes for children born following ART, Scientists in Reproductive Technology, Perth (Rottnest Island), 2 May 2015.

## Autism Research Team

### Overview

The Autism and Related Disorders research team at the Telethon Kids Institute, led by Professor Andrew Whitehouse, investigates the genetic and neurobiological causes of autism and related disorders, and conducts clinical intervention trials into these conditions. In 2015, we continued data collection for our ongoing large biological investigations (e.g. the PRISM and Australian Autism Biobank projects) and clinical trials (e.g. fish oil supplementation). We also concluded testing of an iPad intervention for young children (the TOBY trial) and commenced development and testing of a new game to improve social attention in school-aged children. This year, our research further expanded to investigations of chronic conditions, diabetes, and transgender individuals on mental health and wellbeing.

Together with our national and international collaborators, we secured a number of large and small grants to continue our research (e.g. National Health and Medical Research Council, Australian Research Council, Rebecca L. Cooper Medical Research Foundation, Perpetual Philanthropic, Telethon-Perth Children's Hospital Research Fund, WA Health Promotion Foundation Healthway).

As a group, we published or had accepted >35 articles in 2015, with Andrew's articles in *The Conversation* achieving record numbers of views online.

### Research Projects

#### **THE AUSTRALIAN AUTISM BIOBANK**

*Andrew Whitehouse*

The Australian Autism Biobank began in 2014 and is Australia's largest store of information about autism, an initiative of the Autism Cooperative Research Centre. A 'biobank' is simply a storehouse of biological information, such as blood and DNA.. This project is being conducted across four sites in Australia, including Melbourne, Sydney, and Brisbane, with all biological samples stored in long-term biobanks in Brisbane.

#### **Plain Language summary**

It is now widely thought that autism is not one condition with one cause, but many different conditions with many different causes. This means that to identify all of the different causes of autism (and there are likely dozens of these, if not hundreds), and to find early markers to assist in diagnosis, we need to study the genetics of as many individuals with ASD and their families as possible. The Australian Autism Biobank is aiming to collate a large repository of biological and phenotypic information about autism to assist in these goals. This resource will be a major asset

to the autism community and to future generations of scientists.

### **Funders of the project**

The Cooperative Research Centre for Living with Autism (Autism CRC)

### **External collaborators**

Cheryl Dissanayake (La Trobe University), Helen Heussler (Mater Research Queensland), Valsa Eappen (University of NSW); Queensland Brain Institute and Wesley Medical Research.

## **THERAPY OUTCOMES BY YOU (TOBY) PLAYPAD APP**

*Andrew Whitehouse*

This multi-site single blinded clinical trial tested the effectiveness of an early intervention program (TOBY; Therapy Outcomes By You Playpad App) for children 4 years or younger with a recent diagnosis of autism. The TOBY is delivered as an educational App on the iPad. The aims of the TOBY Trial were to determine the effectiveness of TOBY Playpad as a complement to any community therapy a child is receiving, and to examine parental empowerment. Children were recruited from the Telethon Kids Institute and La Trobe University. Recruitment for this project finished in 2015 with preliminary results available in 2016.

### **Plain Language summary**

Early and intensive intervention is expensive and requires a significant amount of time and resources to implement. This trial aims to test the effectiveness of an early intervention

iPad app for newly diagnosed children with autism. Outcomes from this project will help provide evidence whether educational apps may help to supplement intervention.

### **Funders of the project**

Australian Children's Trust

### **External collaborators**

Monash University

## **FLUOXETINE: FLUOXETINE FOR THE TREATMENT OF AUTISTIC REPETITIVE BEHAVIOURS (FAB TRIAL)**

*Andrew Whitehouse*

**Project blurb** This was a multi-site randomised double-blind controlled trial of Fluoxetine (Selective Serotonin Reuptake Inhibitor, SSRI) versus placebo. It aimed to investigate the efficacy of low dose Fluoxetine on the frequency and severity of restricted, repetitive and stereotyped behaviours among children aged 7.5-17 years with autism. Recruitment was completed in 2015.

### **Plain Language summary**

This clinical trial tested the efficacy of fluoxetine to reduce repetitive behaviours in children with autism.

### **Funders of the project**

NHMRC

### **External collaborators**

Murdoch Children's Research Institute, Royal Children's Hospital in Melbourne, Children's Hospital at Westmead



## **PRISM: THE PREGNANCY INVESTIGATION OF SIBLINGS AND MOTHERS OF CHILDREN WITH AUTISM**

*Andrew Whitehouse*

Studies investigating the potential biological origins of autism have traditionally used an 'infant-sibs' design – that is, studying the early childhood development of children who have older siblings already diagnosed with autism. This is because such children have a much higher risk of developing autism themselves compared to children who do not have an older sibling with autism. This pregnancy study recruited women in their second trimester who did or did not have a child with autism to follow their baby's development from in utero to early childhood. Potential measures of interest included testosterone exposure during pregnancy and fetal head growth. The cohort of children recruited through this study are now between 18 months and 3 years of age. The last set of 2 year assessments is scheduled in mid-2016.

### **Plain Language summary**

This pregnancy study recruited women in their second trimester who did or did not have a child with autism to follow their baby's development from in utero to early childhood. Infants who have an older sibling with autism have a higher risk of also obtaining an autism diagnosis as well. This study aims to determine pregnancy and developmental markers that may be used to help earlier diagnosis of autism.

### **Funders of the project**

NHMRC

## **FISH OIL TRIAL**

*Suzanne Meldrum, Andrew Whitehouse*

Omega -3 long chain polyunsaturated fatty acids are essential for normal brain development, but some evidence suggest that children with an Autism Spectrum Disorder (ASD) have lesser amounts compared with non-affected children. The use of fish oil supplementation among families who have a child with an Autism Spectrum Disorder is common despite little evidence for its benefits and associated costs. This double blind randomised controlled trial of fish oil supplementation aims to determine whether the high-dose of fish oil for six months improves behavioural, cognitive or language outcomes in children aged 2-6 years with a diagnosed ASD. Recruitment completed in late 2015 with 6 month follow-ups to be completed in mid-2016.

### **Plain Language summary**

Fish oil supplementation may benefit normal brain and language development. This trial aims to determine whether fish oil supplementation improves behavioural and language outcomes in young children with autism.

### **Funders of the project**

UWA Near-Miss Grant

### **External collaborators**

UWA

## **TRANS\* PATHWAYS**

*Ashleigh Lin, Dr Sam Winter, Prof. Angus Cook, Penelope Strauss*

Trans\* Pathways is an anonymous online survey of the mental health and care pathways of trans young people in Australia. The findings will help to identify and break down barriers that exist for trans young people in accessing mental health and other services in Australia.

### **Plain Language summary**

Trans\* Pathways is an anonymous online survey of the mental health and care pathways of trans young people in Australia. The findings will help to identify and break down barriers that exist for trans young people in accessing mental health and other services in Australia.

### **External collaborators**

University of Western Australia, Curtin University, YouthLink and the Freedom Centre

## **WELLBEING IN CHRONIC CONDITIONS**

*Ashleigh Lin, Kevin Runions*

This project investigates the effects of four conditions (diabetes, cystic fibrosis, hearing impairment and rare diseases) on mental health and wellbeing. Parents with a child aged 6-18 with one of the listed conditions, who attends a mainstream school, are invited to participate in this online survey. It is hoped that this research will lead to the development of programs designed to better equip young people and schools to improve the experiences, mental wellbeing, and quality of life of children and adolescents with chronic conditions.

### **Plain Language summary**

School is a place that young people spend a large majority of their time. Yet there is little research examining the school experience and psychological wellbeing of young people with chronic conditions. This study represents the first project in a program of research being conducted by the Telethon Kids Institute and our collaborators to understand mental wellbeing and the school environment for young people with chronic conditions.

### **Funders of the project**

Telethon Kids Institute RFA seed funding

## **RESILIENCE AND DIABETES (THE RAD STUDY) - A NOVEL APPROACH TO TACKLE ANXIETY, EMOTIONAL VULNERABILITY AND TREATMENT ADHERENCE IN ADOLESCENTS WITH TYPE 1 DIABETES**

*Prof. Timothy Jones and Ashleigh Lin, Daniel Rudaizky, Colin MacLeod, Assoc. Prof. Elizabeth Davis*

We investigated whether cognitive attentional biases may be related to anxiety in youth with type 1 diabetes. Young people completed cognitive tasks and questionnaires about the mental health and wellbeing. This study began in 2015 and completed recruitment in early 2016.

### **Plain Language summary**

Stress and anxiety are significant problems in children and adolescence with type 1 diabetes. Not only do they impact quality of life and wellbeing, they are also associated with poor glycaemic control in



the present and future, which is a risk for long-term diabetes-related complications. Thus identifying risk for anxiety and intervening early is paramount. However, our understanding of the link between stress, anxiety and blood glucose levels in young people with type 1 diabetes is limited. We are interested in whether specific patterns of cognitive biases may be related to anxiety and/or metabolic control in these adolescents. If so, these may be modifiable to reduce anxiety.

### **Funders of the project**

Princess Margaret Hospital Foundation Project Grant  
Children's Diabetes Research and Education Centre Seeding Grant

### **External collaborators**

Daniel Rudaizky, Colin MacLeod; University of Western Australia

## **2015 Success**

### **AWARDS AND PRIZES**

Highlights from this year:

- Andrew Whitehouse, Vice-Chancellors Mid-Career Research Award, University of Western Australia
- Andrew Whitehouse, Curtin University Alumni Achievement Award, Professional Achievement in Health Sciences
- Andrew Whitehouse, Paul Harris Award, Rotary Foundation
- Ashleigh Lin, University of Western Australia Early Career Researcher Best Publication Award: Special commendation award for 'Outcomes of Non transitioned Cases in a Sample

at Ultra-High Risk for Psychosis'

- Ashleigh Lin, Rebecca L. Cooper Medical Research Foundation: Understanding neurobiological markers for schizophrenia and autism to support diagnosis and treatment of these disorders
- Ashleigh Lin: Children's Diabetes Research and Education Centre Seeding Grant: Lin et al. Characterising moment-to-moment fluctuation in stress, anxiety and blood glucose levels in adolescents with type 1 diabetes
- Andrew Whitehouse, Gail Alvares: Perpetual Philanthropic grant
- Andrew Whitehouse (CIA): ARC grant: The role of early testosterone and brain laterality in language development
- Andrew Whitehouse (CIA): Telethon-Perth Children's Hospital Research Fund: A randomised-controlled trial of a parent-mediated therapy for infants at increased risk for autism or developmental delay

### **EXTERNAL COMMITTEES**

*Andrew Whitehouse:*

- Committee Member, Early Intervention for ASD Stakeholder Group, National Disability Insurance Agency, Commonwealth Government of Australia
- Committee member, Speech Pathology Australia committee for generating clinical guidelines for the assessment and intervention of ASD.
- Committee member, Australasian Society for Autism Research
- Voluntary board member of two community autism organisation
- Program Direction, Autism Cooperative Research Centre

*Ashleigh Lin:*

- Youth Mental Health Clinical Evaluation and Research Committee (WA Department of Health)
- Youth Mental Health Subcommittee (WA Department of Health)
- Trans Research Interest Group (led by Curtin University), the Mental Wellbeing and School Experience in Chronic Illness Working Group (hosted by Telethon Kids Institute)
- Youth Health and Wellbeing Alliance (hosted by Telethon Kids Institute)
- Child & Adolescent Psychiatry, Psychosomatics and Psychotherapy Working Group (Telethon Kids Institute).

impact in areas of social interaction, communication and behaviour. The WA Autism Register is ongoing and since 1999 it has collected data on more than 5,000 individuals.

#### **Names of investigators**

*Dr Emma Glasson*

*Keely Bebbington*

#### **INVITED PRESENTATIONS**

- Andrew Whitehouse, Invited presenter of Elizabeth Usher Memorial Lecture, Speech Pathology Australia
- Gail Alvares, fully funded invited speaker: Oxytocin in the treatment of autism spectrum disorders, European College of Neuropsychopharmacology, Amsterdam 26 August 2015.

## WA Register for Autism Spectrum Disorders

### Overview

The aim of the WA Register for Autism Spectrum Disorders is to monitor diagnostic trends of Autism Spectrum Disorders. These disorders develop in young children and have long-term



## Cancer Centre

### Overview

Most children who are diagnosed with cancer have either leukaemia or a brain tumour. In contrast, the most common types of cancer in adults are carcinomas. Over the past decades the cure rates for paediatric cancers have markedly improved, however, leukaemia and brain tumours still account for half of the deaths. In order to find better therapies for children with cancer, the Cancer Centre and the Oncology Total Care Unit at Princess Margaret Hospital (PMH) are members of the US-based Children's Oncology Group (COG). COG is the largest study group of this kind, and 240 hospitals around the globe participate in evaluating better treatments for children with cancer. Approximately 80 therapeutic and biology COG studies are open at all times, covering common diseases like acute lymphoblastic leukaemia with many subgroups as well as very rare tumours. At PMH we enrol about 1% of the total number of patients on COG trials, however, based on the number of patients diagnosed at PMH every year, our enrolments are always in the top 20% of COG centres. For a rare tumour study we may not have a single eligible patient at PMH over the life of a study, generally five or more years. Importantly, the clinical details and biological samples become the precious data to inform our understanding of the disease and to develop curative therapy. Being a member of an international co-operative group such as COG means

basic biologic discoveries are translated simultaneously into clinical care. This year the COG has launched "Project Every Child" which aims to collect tumour DNA and matching normal DNA on all patients in a unified repository, automatically linked to all the clinical data. At PMH and the Cancer Centre we have run a similar model for over 20 years, and numerous discoveries in the Cancer Centre have come using specimens from this tumour bank and linked clinical data - we were ahead of our time!

At the Telethon Kids Cancer Centre we focus on translational research into childhood cancer, drug discovery and immunotherapy. Our studies are conducted under five Programs: Brain Tumours, Rare Carcinomas, Leukaemias, Cancer Immunology, and Drug Discovery. The Cancer Centre Leadership Team directs the research and coordinates collaborations among members of individual Programs and with national and international researchers. The Leadership Team recently obtained funding for a cancer radiotherapy research platform. The X-RAD is a newly developed instrument for targeted preclinical radiation research and is the first one in Australia. It creates new and unique opportunities for radiation oncology research to understand the effects of radiation on normal and cancer cells. We will use it to explore innovative treatment options and develop new cross-disciplinary collaborations in Australia. We ensure that our studies are grounded in clinical practice, which is achieved by forging robust partnerships between laboratory-based researchers



and paediatric oncologists, pathologists, surgeons, imaging specials and radiation oncologists.

## Brain Tumour Research Program

### Overview

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

Brain tumours are the most common paediatric solid cancer, affecting 200 children in Australia each year. The BTRP, also known as Team BT, is a collaborative group of researchers dedicated to improving our understanding of paediatric brain tumour biology and finding more effective treatments to improve survival rates and quality of life for patients. Team BT leaders Nick Gottardo and Raelene Endersby both began their independent research careers at the Telethon Kids Institute following mentored training programs at St Jude Children's

Research Hospital in the USA. In recent years, we have established a strong national and international reputation and are recognised as being the largest research team in Australia primarily focussed on paediatric brain tumours. The major goals of our group are intensely focussed on improving the well-being of children with cancer. With strong ties between Princess Margaret Hospital (PMH) and Telethon Kids, leaders Nick & Raelene are acutely aware of what it takes to get a new treatment into the clinic and our research goals are sharply focussed on providing the preclinical evidence required to form the basis of new clinical trials.

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

### Research Projects

#### **HIGH-THROUGHPUT DRUG SCREENING FOR MEDULLOBLASTOMA: TRANSLATING HITS TO THE CLINIC**

*Endersby, R. Whitehouse JP, Hii H,*

*Kuchibhotla M, Strowger B, Patterson B, Schoep TD, Gottardo NG.*

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

To identify new treatments for medulloblastoma, our laboratory performed a drug screen to identify compounds active against patient-derived medulloblastoma cells. Using high-throughput, cell-based assays human medulloblastoma cells (n=6) were screened against a library of approximately 3200 compounds. Fifty effective compounds were identified and further *in vitro* assessment identified several drugs that enhanced the cytotoxic activity of the clinically-used therapeutic: cyclophosphamide (CPA). Cell cycle checkpoint kinase (CHK1/2) inhibitors (CHKi), were further assessed *in vivo* using mice bearing intracranial implants of human medulloblastoma cells. When combined with DNA-damaging chemotherapeutics, CHKi treatment reduced tumour burden and significantly increased survival of tumour-bearing animals. Immunohistochemical assessment of tumours showed the combination treatment significantly decreased tumour proliferation and significantly induced apoptosis compared with controls. These data demonstrate

our experimental approach has robustly identified effective new therapies for paediatric medulloblastoma, and our findings strongly suggest CHK inhibitors have promising potential to improve treatments for this disease.

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

## **DEVELOPING PERSONALISED THERAPEUTIC APPROACHES FOR CHILDHOOD BRAIN TUMOURS**

*Endersby, R. Whitehouse JP, Hii H, Kuchibhotla M, Strowger B, Patterson B, Schoep TD, Gottardo NG.*

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

Pineoblastoma is an invasive paediatric PNET that arises in the pineal gland. Only 50% of patients will survive with current treatments which include surgery, radiotherapy and intensive chemotherapy. In previous work from, new and unique patient derived pineoblastoma cell lines have been developed. Importantly, these are rare resources not available elsewhere in the world. To date no other pineoblastoma



cell lines have been reported in the literature. Derived from primary tumour tissue from patients at Princess Margaret Hospital (PMH) the team has carefully characterised all of these cells by comprehensive genomic profiling, including exome sequencing, SNP array and gene expression profiling and have the full clinical history for each patient and tumour. Our laboratory performed a high-throughput drug screen on paediatric pineoblastoma cell lines to identify potential new treatments. A library of 3162 rapidly translatable drugs, including drugs approved for the treatment of other cancers (n=101), a combined library of FDA approved drugs and pharmacologically active compounds used in other diseases and a kinase inhibitor library (molecular targeted drugs, developed to block specific biological pathways that are active in certain tumours) (n=208). Drugs were tested at a concentration of 10 micromolar on three pineoblastoma cell lines. This screen was undertaken at the ACRF Drug Discovery Centre for Childhood Cancer. Following more focused screening on a subset of the most active drugs, 35 drugs (1.1% of the total number screened) have been identified that were effective at doses achievable in patients. The effective drugs have diverse mechanisms of action to each other and the current drugs used in the clinic; moreover, ten of them are already approved cancer treatments and 16 are predicted or known to be able to enter the brain. The very low percentage of drugs able to kill pineoblastoma cells in vitro at low concentrations reveals that the vast majority of drugs against this disease are ineffective due to the resistant nature of this tumour type to chemotherapy. This highlights the power

of this strategy to filter out ineffective drugs early on, a strategy clearly not feasible in clinical trials or even in mouse models.

*This work is supported by a Cure Brain Cancer Australia, the Cancer Council of WA (BP and BS), Raine Clinician Research Fellowship (NGG) and the Telethon Adventurers.*

## **DEVELOPMENT OF LABORATORY TOOLS TO IMPROVE OUTCOMES FOR CHILDREN WITH EPENDYMOMA**

*R Endersby, M Ancliffe, H Hii, S Lee and NG Gottardo.*

Ependymoma is the third most common brain tumour affecting children. Contemporary standard-of-care therapy for EPN patients is surgery followed by focal radiation. Despite this, 40–60% of these tumours will recur at the primary site of disease or with metastatic spread, at which point the disease is incurable. 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. A major impediment to preclinical studies in EPN has been the limited availability of patient tissue, and more importantly, a lack of in vitro and in vivo models. To address this, we have focused efforts on developing improved preclinical models of childhood brain tumours, which appropriately recapitulate these diseases in children. One approach we have taken is to mimic that same genetic alterations that occur in the human disease in the mouse brain using a range of genetic techniques. The second approach involves implantation of human tumour

cells into mouse brains using precision stereotactic equipment within 30 minutes of surgical removal from the patient. This technique of direct injection of fresh surgical specimens into anatomically matched locations in mouse brain mice better recapitulates the human disease. Known as patient-derived xenograft (PDX) models they are now regarded as the gold standard in the field for human cancer modelling. To ensure these models robustly replicate the human disease large scale genomic and transcriptomic comparisons are being performed. These models are essential to improve our understanding of paediatric ependymomas and will facilitate the identification of improved treatments for patients.

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

## **ONCOGENIC TRANSFORMATION OF HUMAN NEURAL STEM CELLS.**

*C George, JP Whitehouse, R Endersby, PB Dallas and NG Gottardo.*

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

neural stem cells are a good candidate for investigating the cellular origin of this disease. The aim of this study is to transform normal human neural stem cells into cancer-causing cells by altering the expression of five specific genes implicated in medulloblastoma. These cancerous cells will then be implanted into the brains of mice and we will examine their potential to form medulloblastoma tumours. This methodology has been successfully achieved in another brain tumour model (glioblastoma). This study will provide for the first time a direct test of whether previously identified candidate genes are involved in causing the development of medulloblastoma. In addition, this study will generate unique mouse models and identify potential new targets for therapy.

*This work is supported by the Brain Foundation, Australian Postgraduate Award (CG), the Telethon Adventurers and Raine Clinician Research Fellowship (NGG).*

## **MOLECULAR GENETICS OF NOVEL PAEDIATRIC BRAIN TUMOUR MODELS**

*R Endersby, M Kuchibhotla, H Hii, S Lee, N Gottardo*

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



therapeutic resistance.

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

To address this, we have generated a panel of unique cell lines representative of various primary and relapsed paediatric brain tumours. Furthermore, to more closely resemble their natural microenvironment, we have established mouse models for these diseases by orthotopic transplant providing a unique resource in the preclinical analysis of novel therapies. However, the preclinical utility of these new models requires full characterization of their underlying genetic alterations such that molecularly targeted therapies are assessed in the most appropriate systems.

Our study aim is to identify mutations across the coding regions of several new models of paediatric brain tumours using whole-exome capture and deep sequencing. With our models and the results of this study we will be poised to study critical questions about malignant

brain tumour biology and be better able to test novel therapies in the most appropriate context.

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

## **UNDERSTANDING THE IMMUNE RESPONSE TO CANCER IN THE BRAIN**

*T George, R Endersby, G Brizard, M Kuchibhotla, J Waithman*

Up to 75% of patients suffering from metastatic malignant melanoma develop brain metastases. Treatment options are currently limited for these patients. While immunotherapy has shown success in treating melanoma, patients with brain involvement have traditionally not been considered for immunotherapies. This is due to the long-standing concept that the brain is immune privileged. Recently, however, it was reported that the brain is not immune privileged, and possesses lymphatic-like vessels that provide a connection between the immune system and the central nervous system (CNS).

To understand the coordination of brain tumour immunity, B16 melanoma cells expressing ovalbumin (OVA) were intracranially implanted into C57BL/6 mice. OVA-specific T cells were transferred into tumour-bearing mice to assess antigen presentation. CD69 upregulation, used as a marker of T cell activation, was observed in both the deep and superficial cervical lymph nodes (LNs). To further understand whether migratory antigen presenting cells (APCs) are involved in coordinating this CD8 T cell response, we repeated these experiments in CCR7-

/- mice, in which migration of APCs is compromised. CD8 T cell activation was impaired in CCR7-/- mice compared to wild-type mice. These findings suggests that CD8 T cell activation occurs in the tumour draining LNs, and is coordinated by APCs that migrate from the brain to the LNs, similar to peripheral sites. Future studies will aim to elucidate which APCs drive this immune response to brain tumours, which may provide insight for the design of better treatment strategies against this disease and potentially other cancers involving the CNS.

*This work is supported by the Telethon Kids institutional small grants scheme and The Telethon Adventures. TG is the recipient of an Australian Postgraduate Award and Curtin University Excellence top-up scholarship. JW is recipient of an NHMRC Career Development Award.*

## TEAM MEMBERS

Co-heads

Raelene Endersby, PhD

Nick Gottardo, MB ChB FRACP PhD

## RESEARCH STAFF

Jacqueline Whitehouse, PhD

Hilary Hii, BSc Hons

Mani Kuchibhotla, BSc MSc

Patrick Dyer, BSc Hons

## POSTGRADUATE STUDENTS

Mathew Ancliffe, BSc(Hons), PhD  
candidate

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

Tenielle George, BSc(Hons), PhD  
candidate

Courtney George, BSc(Hons), PhD

candidate

Brooke Strowger, BSc, Honours student

## CLINICAL PARTNERS

Sharon Lee, neurosurgeon

Reimar Junckerstorff, neuropathologist

## OTHER STUDENTS

Kristin Conway, Notre Dame University

Amelia Davies-Waddell, Penrhos College

Namisha Thomas, Perth Modern School

Sanchita Gera, Perth Modern School

## 2015 Success

### Theses passed

Brooke Strowger, (BSc), Honours thesis, Murdoch University. Investigating cell cycle checkpoint inhibition for the treatment of medulloblastoma. Supervisor: Dr Raelene Endersby

### AWARDS AND PRIZES

Nicholas Gottardo, Cancer Australia (2016-2018), \$193,688

Tenielle George, Australian Postgraduate Award

Tenielle George, Curtin Research Scholarship

Courtney George, Australian Postgraduate Award

### EXTERNAL COMMITTEES

#### International

Gottardo N. Member, Children's Oncology Group (COG), CNS Tumour Committee

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



### National

Gottardo N. Deputy Chair of the Australian and New Zealand Children's Haematology and Oncology Group (ANZCHOG) Executive (2014-present). The ANZCHOG is the peak professional body representing paediatric oncologists and other healthcare professionals who care for children with cancer in Australia and New Zealand.

Gottardo N. Board member of the Australian Children's Cancer Trials (ACCT) group. Established to develop and run early phase paediatric cancer clinical trials.

Gottardo N. Chair, ANZCHOG CNS Tumours Subgroup – a group of paediatric oncologists and radiation oncologists from around Australia focused on the development of clinical trials for children with brain tumours.

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

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

Gottardo N. Member: Reference group, Cancer Australia, Children's Cancer Website development

Gottardo N. Co-chair on a phase I/II neuroblastoma clinical trial conducted through the ACCT

Endersby R. State representative, Australian/New Zealand Society of Cell and Developmental Biology

Endersby R. CNS committee member,

Australian/New Zealand Children's Haematology and Oncology Group (ANZCHOG)

Endersby R. Member, national conference organising committee, Science Pathways: Effective science communication for EMCRs. April 2015. Adelaide, Australia.

Endersby R. Member, Organising committee for EMBL Australia PhD course 2015

### Local

Gottardo N. Member, PMH Ethics Scientific Advisory Committee

Gottardo N. Member, PMH Morbidity and Mortality Review Committee.

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

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

Endersby R. Category B Member, Telethon Kids Institute Animal Ethics Committee (2013-present)

Endersby R. Member, Organising committee for Combined Biological Sciences meeting 2015

## INVITED PRESENTATIONS

Gottardo, N. Speeding up drug development for childhood brain cancer. Invited lecture, Northern Institute of Cancer Research, Newcastle upon Tyne, United Kingdom, March 2015

Gottardo, N. A Phase 2 Study of Reduced Therapy for Newly Diagnosed Average-Risk WNT-Driven Medulloblastoma Patients. Children's Oncology Group meeting, Atlanta, USA, March 2015

Gottardo, N. Results of a preliminary high-throughput drug screen. Medulloblastoma in the Mountains – meeting of the

International Medulloblastoma Working Group, Lake Tahoe, USA, Feb 2015  
 Endersby R. Manipulating neural stem cells to model brain cancer. Science on the Swan. Perth, Apr 2015  
 Endersby R. Inhibiting cell cycle checkpoint kinases in combination with cyclophosphamide to treat medulloblastoma. Australian & New Zealand Children's Haematology/ Oncology Group Annual Scientific Meeting. Fremantle, Jun 2015  
 Endersby R. Inhibiting cell cycle checkpoint kinases in combination with cyclophosphamide to treat medulloblastoma. Brain Cancer Discovery Collaborative Annual Conference. Brisbane, Oct 2015

## Cancer Epidemiology

### Research Projects

#### **AUSTRALIAN STUDY OF CAUSES OF ACUTE LYMPHOBLASTIC LEUKAEMIA IN CHILDREN**

*Elizabeth Milne, Carol Bower, Nick de Klerk, Ursula Kees,*

##### **External collaborators:**

*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 continued analysing data collected between 2003 and 2007 in this national case-control study of the risk factors for childhood acute lymphoblastic leukaemia (ALL). The study recruited children with ALL and their parents from the nine paediatric oncology units nationwide, together with control children from around Australia. DNA samples were collected and parents were surveyed about a wide range of exposures.

#### **FUNDERS OF THE PROJECT: NHMRC GRANT #254539, AND CANCER COUNCIL WA.**

The following papers using data from this study were published in 2015:

- Bailey HD, Metayer C, Milne E, et al. Home paint exposures and risk of childhood acute lymphoblastic leukemia: Findings from the Childhood Leukemia International Consortium. *Cancer Causes and Control*, 2015: 26(9);1257-1270
- Bailey HD, Infante-Rivard C, Metayer C, Clavel J, Lightfoot T, Kaatsch P, Roman E, Magnani C, Spector LG, Petridou E, Milne E et al. Home pesticide exposures and risk of childhood leukemia: Findings from the Childhood Leukemia International Consortium. *International Journal of Cancer*, 2015:137(11); 2644-2663
- Paltiel O, Tikellis G, Linet L, Golding J, Lemeshow S, Phillips G, Lamb K, Stoltenberg C, Håberg SE, Stróm M, Granstróm C, Northstone K, Klebanoff M, Ponsonby A-L, Milne E et al. Birthweight and childhood cancer: preliminary findings from the International Childhood Cancer



Cohort Consortium (I4C). *Paediatric and Perinatal Epidemiology* 2015;29(4): 335-345.

- Greenop KR, Bailey HD, Miller M, Scott RJ, Attia J, Ashton LJ, Downie P, Armstrong BK, Milne E. Breastfeeding and nutrition to 2 years of age and risk of childhood acute lymphoblastic leukemia and brain tumors. *Nutrition & Cancer*. 2015;67:3, 431-441, DOI: 10.1080/01635581.2015.998839
- Rudant, J, Lightfoot T, Urayama K, Petridou E, Dockerty JD, Magnani C, Milne E, et al. Childhood acute lymphoblastic leukemia and indicators of early immune stimulation: a Childhood Leukemia International Consortium Study. *American Journal of Epidemiology* 2015. 181(8):549-62. doi: 10.1093/aje/kwu298. Epub 2015 Mar 1.
- Dawson S, Charles AK, Bower C, de Klerk NH, Milne E. Risk of cancer among children with birth defects: a novel approach. *Birth Defects Research Part A*. 2015;103:283–290. Doi: 10.1002/bdra.23364
- Milne E, Greenop KR, Scott RJ, Haber M, Norris MD, Attia J, Jamieson SE, Miller M, Bower C, Bailey HD, Dawson S, McGowage GB, de Klerk NH, van Bockxmeer FM, Armstrong BK Folate pathway gene polymorphisms, maternal folic acid use and risk of childhood acute lymphoblastic leukemia. *Cancer Epidemiology, Biomarkers and Prevention* 2015;24(1): 48-56

## **NATIONAL CASE-CONTROL STUDY OF CHILDHOOD BRAIN TUMOURS**

ELIZABETH MILNE, CAROL BOWER, NICK DE KLERK, PETER DALLAS

### **Collaborators**

*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 was a national case-control study into the risk factors for childhood brain tumours (CBT). It aimed to investigate genetic, dietary and environmental risk factors for CBT. 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.

### **Funders of the project:**

NHMRC Grant #404089.

### **The following papers were published in 2015:**

- Greenop KR, Miller M, Bailey HD, Scott RJ, Attia J, Bower C, van Bockxmeer FM, Ashton LJ, Armstrong BK, Milne E. Paternal dietary folate, B6 and B12 intake and the risk of childhood brain tumors. *Nutrition & Cancer*. 2015;67(2) 224-230.
- Greenop KR, Scott RJ, Attia J, Bower

C, de Klerk NH, Norris MD, Haber M, Jamieson SJ, van Bockxmeer FM, Gottardo NG, Ashton LJ, Armstrong BK, Milne E. Folate pathway gene polymorphisms and risk of childhood brain tumors: results from an Australian case-control study. *Cancer Epidemiology, Biomarkers and Prevention*. 2015; 24(6): 1–7.

- Greenop KR, Miller M, Bailey HD, de Klerk NH, Attia J, Kellie SJ, Bower C, Armstrong BK, Milne E. Childhood folate, B6, B12 and food group intake and the risk of childhood brain tumors: results from an Australian case-control study. *Cancer Causes and Control*. 2015; 26:871–879. doi:10.1007/s10552-015-0562-z
- Greenop KR, Hinwood A, Fritschi L, Scott RJ, Attia J, Ashton LJ, Heath J, Armstrong BK, Milne E. Vehicle refuelling, use of domestic wood heaters and the risk of childhood brain tumors: results from an Australian case-control study. *Pediatric Blood & Cancer* 2015;62:229–234 DOI: 10.1002/pbc.25268.

## **NUTRITION AND GENOME HEALTH IN CHILDREN**

*Elizabeth Milne, Nick de Klerk*

*Collaborators: Michael Fenech, Bruce Armstrong, Margaret Miller, Nathan O'Callaghan*

The Nutrition and Genome Health in Children Study aimed to identify key nutritional and genetic factors associated with DNA damage in children. It aimed to describe the nature of the interaction between nutritional and genetic factors in determining level of DNA damage in children, and also the associations

between body mass index, DNA damage and micronutrient levels in children.

This study was a cross-sectional study of 450 Western Australian children, conducted between 2009 and 2011. Participants were children aged 3, 6 or 9 years at recruitment who had never been diagnosed with asthma, diabetes, cancer, arthritis or epilepsy. Participants and their parents were recruited via primary schools, posters displays and flyers, advertisements in local newspapers and information letters distributed to a wide range of organizations. These include crèches, day care centres, playgroups, sports centres and libraries. The child's diet and macro- and micro-nutrient intake was assessed using parent-completed Food Frequency Questionnaires (FFQs). A sample of the child's blood was taken and used to assess micronutrient levels and specific biomarkers of DNA damage. The blood sample was also used to identify genetic polymorphisms related to nutrient metabolism and DNA repair. Saliva samples collected from the child were used to measure cortisol and cotinine levels, as indicators of psychological stress and exposure to environmental tobacco smoke, respectively. Parents were given feedback on their child's diet, and dietary advice was provided by a dietitian where needed. In all, 464 participants provided data.

### **Funders of the project:**

NHMRC Grant#572623.

### **The following papers were published in 2015**

- Milne E, Greenop KR, Ramankutty P, Miller M, de Klerk NH, Armstrong BK,



Almond T, O'Callaghan N, Fenech M. Blood micronutrients and DNA damage in children. *Molecular Nutrition and Food Research*, 2015;59(10); 2057-2065.

- Milne E, O'Callaghan N, Ramankutty P, de Klerk NH, Greenop KR, Armstrong BK, Miller M, Fenech M. Plasma micronutrient levels and telomere length in children. *Nutrition* 2015; 31(2):331-6

## **PRENATAL ORIGINS AND HEALTH OUTCOMES OF MALE REPRODUCTIVE CONGENITAL ANOMALIES DIAGNOSED AT BIRTH AND TESTICULAR CANCER IN ADULTHOOD**

*Elizabeth Milne*

### **Collaborators:**

*Natasha Nassar, Gavin Pereira*

This study involves record linkage of birth, birth defects, hospital, deaths and cancer data; with links to genealogy data to identify links between families. It will include the analysis of NSW and Western Australia (WA) population health data. The AIMS of the study are to:

- Identify antecedents of male reproductive congenital anomalies (hypospadias and cryptorchidism) and testicular cancer; including maternal and prenatal factors, familial aggregation and their combined role
- Identify antecedents of testicular cancer; including maternal, prenatal and familial factors and taking into account intermediary effects of hypospadias and cryptorchidism
- Describe the health outcomes and subsequent fertility (births) among males previously diagnosed with

reproductive congenital anomalies or testicular cancer

The data have not yet been received from the WA Data Linkage Branch.

### **Funders of the project:**

NHMRC Grant# ID: APP1047263

## **2015 Success**

### **AWARDS AND PRIZES**

Elizabeth Milne, awarded US\$6000 for the Nestle Nutrition Institute Award for Best Manuscript in Pediatric Nutrition 2015

### **EXTERNAL COMMITTEES**

Elizabeth Milne, Deputy Chair of Childhood Leukemia International Consortium, since 2006.

# **Cancer Immunology Program**

## **Research Projects**

### **CROSS-PRESENTATION OF CUTANEOUS MELANOMA ANTIGEN BY MIGRATORY XCR1+CD103- AND XCR1+CD103+ DENDRITIC CELLS**

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

The question of which dendritic cells (DCs) cross-present peripheral tumor antigens remains unanswered. We assessed the ability of multiple skin-derived and lymphoid resident DCs to perform this function in a novel orthotopic murine melanoma model where tumor establishment and expansion is within the skin. Two migratory populations defined as CD103-XCR1<sup>+</sup> and CD103<sup>+</sup>XCR1<sup>+</sup> efficiently cross-presented melanoma-derived antigen, with the CD103-XCR1<sup>+</sup> DCs surprisingly dominating this process. These results are critical for understanding how anti-tumor CD8<sup>+</sup> T cell immunity is coordinated to tumor antigens present within the skin.

### **Plain language summary**

Depending on if a cell is infected or healthy determines whether killer T cells, a white blood cell, will destroy it. Unfortunately, tumor cells are mistaken as normal healthy cells, stopping the killer T cells from eliminating them. Dendritic cells, another white blood cell, are the key controllers of T cell immunity. This study aims to address how dendritic cells distinguish tumors from infectious agents and identify how they disperse this information to killer T cells.

### **Funded by**

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

### **External collaborators**

Richard A. Kroczeck - Robert Koch Institute, Berlin, Germany

Sandro Prato - CSL Limited, Bio21 Institute, Victoria, Australia

Damien Zanker - La Trobe University, Victoria, Australia

Weisan Chen - La Trobe University, Victoria, Australia

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

*Ben Wylie, Jason Waithman*

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



individual subtypes are promoting distinct CD4+ T cell responses. We hope to find that certain dendritic cells drive a more productive response and that this knowledge provides the foundations for translational studies targeting maximal antitumour CD4+ T cell responses.

### **Plain language summary**

T cells, a white blood cell, can provide a coordinated attack to eliminate infectious agents and transformed cells. However, situations arise where the latter nullifies such a response and the disease known as cancer eventuates. Communication between dendritic cells, another white blood cell, and T cells is essential for manufacturing productive responses that result in a positive disease-free outcome. This study aims to address how dendritic cells survey tumors and disperse the information they acquire to T cells.

### **Funded by**

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

## **ENHANCING NATURAL KILLER CELL MEDIATED ANTI-TUMOUR RESPONSES**

*Geraldine Brizzard, Ursula Kees, Andreas Behren, Jason Waithman, Bree Foley*

Manipulating the immune system to treat cancer is currently becoming a viable option for many patients that fail to respond to conventional therapies. Due to their ability to target a wide range of different cancers, natural killer (NK) cells are ideal candidates for immunotherapy. Clinically, both increased NK cell activity

and NK cell infiltration of tumour sites has been associated with reduced risk of cancer and better prognosis. In recipients of allogeneic haematopoietic cell transplantation, NK cell alloreactivity has been associated with reduced leukaemic relapse, enhanced engraftment and reduced graft versus host disease. It's becoming increasingly clear that subsets of NK cells exist that differ in their capacity to lyse targets, produce cytokines, proliferate and survive. We, and others, have demonstrated that CMV infection has the ability to reconfigure the NK cell compartment and promote the expansion of functionally distinct subsets. So far, this phenomenon has been demonstrated to occur only with CMV infection and the mechanisms driving it remain unknown. Recently, we have characterised several subsets of NK cells that expand in the context of CMV infection. These NK cells display a mature phenotype, have increased functional capabilities, increased potential to mediate antibody dependent responses, increased survival capacity and the potential to be long lived. Clinically, CMV infection has been associated with reduced risk of leukaemic relapse and improved overall survival in transplant recipients. This project will aim to determine if these subsets of NK cells have enhanced anti-tumour properties and to evaluate their potential use as a novel immunotherapy.

### **Plain language summary**

Immunotherapy is becoming a viable option to treat patients who fail to respond to conventional therapies, however there is still much that needs to be understood in order to improve the

efficacy of this treatment. Natural Killer (NK) cells have been shown to reduce tumour burden and improve overall survival in patients with both solid and blood cancers. Recently it has been identified that a common viral infection, cytomegalovirus (CMV), can reduce the risk of leukaemic relapse. Since we have identified that CMV expands NK cells with enhanced ability to eliminate transformed cells and mediate effective antibody responses, we predict that CMV can drive NK cells to eliminate cancer in vivo. Understanding how CMV enhances NK cell responses in vivo will allow us to develop novel NK cell based therapies that may be used in the clinic to treat patients with cancer.

#### **Funded By**

NHMRC, Cancer Australia, Cure Cancer Australia Foundation, Brady Cancer Support Foundation

#### **External collaborators**

Andreas Behren – Olivia Newton-John Cancer Research Institute

### **DETERMINING WHICH INTERFERON- $\alpha$ SUBTYPE BEST INCREASES THE EFFICACY OF ADOPTIVE CELL THERAPY**

*Anthony Buzzai, Ben Wylie, Raelene Endersby, Bree Foley, Jonathan Chee, Vanessa Fear, Jason Waithman*

Immunotherapies are a promising approach to cancer treatment. Adoptive cell therapy with tumour-targeted T cells and immune checkpoint blockade inhibitors both have enhanced clinical outcomes. However, these treatments

don't help everyone and further refinement will improve patient benefit. Thus, it is rational to combine existing immunotherapy with new effective therapies to ensure more cancer patients respond long term to treatment.

We have identified that certain type I interferon alpha (IFN- $\alpha$ ) subtypes remarkably abrogate the development of melanoma in vivo. The overall aim of this project is to determine if a combination of these efficacious IFN- $\alpha$  subtypes with adoptive cell therapy will improve long term survival outcomes. Using various preclinical models, we will determine the IFN- $\alpha$  subtypes that are effective against a range of cancers at multiple anatomical sites. Those that demonstrate broad therapeutic activity will be selected as candidates for engineering T cells that express a specific anti-tumour IFN- $\alpha$  subtype. The engineered T cells will be adoptively transferred into tumour bearing hosts. We have chosen this strategy as our preliminary data shows that the effective IFN- $\alpha$  subtypes act locally, not systemically. Thus, adoptive transfer of engineered T cells will result in active infiltration of the tumour microenvironment, enabling the IFN- $\alpha$  subtypes to exert their function. Finally, we will analyse whether and how IFN subtypes induce an anti-tumour immune response during this novel therapy.

#### **Plain language summary**

Interferons are naturally occurring compounds made during infections. They inhibit the growth of invading microbes and help coordinate the body's defence against infection. We have found that certain interferons stop the growth of cancer cells. We are investigating whether



interferons help stimulate a defence against cancer cells and if combining interferons with current cancer treatment is more effective.

### **Funded by**

NHMRC and UWA Postgraduate Award to AB & BW

### **External collaborators**

Vanessa Fear - University of Western Australia, Western Australia, Australia

## **PERSONALISED THERAPEUTIC PEPTIDE VACCINATION TARGETING MUTATED CANCER ANTIGENS**

*Geraldine Brizzard, Shane Stone, Tenielle George, Justine Mintern, Raelene Endersby, Paul Watt, Jason Waithman*

The paradigm for cancer treatment is evolving from non-specific cytotoxic agents to selective, mechanism-based therapies. A successful example is immunotherapy, with this modality now proving to be an effective adjunct therapy for patients with cancer. Indeed, the journal *Science* recently named cancer immunotherapy '*The 2013 Breakthrough of the Year*'. Our understanding of immunotherapy's success and mode of action have emerged mainly from preclinical models, similar to those used in this study. The most promising and effective immune-based therapies harness the activity of helper and killer T cells. The overall aim of this project is to use a novel therapeutic peptide vaccine strategy to generate T cell immunity directed against mutated cancer antigens. Our innovative approach uses next generation

sequencing to identify cancer specific mutations, cutting-edge cellular targeting and novel intracellular delivery methods to enhance the efficiency of immune presentation. This novel vaccine delivery platform has the potential to have wide-ranging applications in the field of T-cell directed vaccination. Moreover, improving upon our ability to identify somatic mutations in a patient's tumour and using these tumour "neoantigens" in a personalised therapeutic approach has enormous potential to improve the outcomes for affected individuals.

### **Plain language summary**

Clinical interventions of paediatric and young adult cancer patients by chemo and radiation therapy come at a price not obvious by the reported survival statistics. Life-long medical problems that result from the collateral damage of healthy tissue by these treatments negatively impact patient quality of life as well as health department budgets across Australia. Immunotherapy is emerging as having the most potential to improve cancer treatment success as well as reduce off-target side effects. This project is based on the emerging concept that a personalised approach to treat an individual's cancer has significant merit. It builds on recent literature that demonstrates that many cancer mutations are capable of generating a T cell mediated immune response that is unique to each patient. The exploration of strategies to identify such neoantigens using computational biology and use immunotherapeutics to boost an immune

response is a logical next step to move this forward into the clinic.

## Funded by

NHMRC, Telethon Kids Institute Blue Sky Research Grant, Brady Cancer Support Foundation, Curtin Postgraduate Award to TG

## External collaborators

Justine Mintern – University of Melbourne, Victoria, Australia

## INDUCTION OF T CELL IMMUNITY TO BRAIN TUMOURS

*Tenielle George, Geraldine Brizzard, Raelene Endersby, Jason Waithman*

There is an urgent need for effective treatment strategies targeting tumours within the central nervous system. A promising approach is to utilise the natural and potent defenses of the immune system. T lymphocytes are particularly attractive immune cells to harness as they can actively seek out malignant cells and destroy them. One of the best demonstrations of successful immunotherapy in the clinic is against melanoma.

Melanoma metastases are found in many locations, such as the lung, liver and brain. An important question is whether immunotherapy is effective at all of these sites. This is especially important within the brain, due to the presence of multiple immune-restrictive factors. Originally the brain was defined as an immunologically privileged site, but now it is becoming increasingly evident that it is more likely an immunologically specialized site. This is due to the presence of several unique features such as the blood brain barrier and lack of conventional lymphatics, which profoundly influence immune

trafficking and function within this site. However, T cell immunity within patients with melanoma brain metastases is observed in both the circulation and at the tumour site. Little is known about how this immunity is generated and its potential to be effective with the addition of immunotherapy. The best-defined initiator of T-cell immunity is the dendritic cell. Although this has yet to be validated in brain tumour immunity, we will define in detail their role in coordinating T cell immunity at this site.

## Plain language summary

Melanoma often spreads or metastasizes from the skin to the brain, once there current treatment options are largely ineffective. However, new therapies utilizing the natural and potent defenses of the immune system have been effective against metastatic melanoma in other sites in the body. This proposal looks at how immunity is generated during melanoma brain metastases to determine if these treatments can be effective against melanoma brain metastases.

## Funded by

NHMRC, Telethon Adventurers, Brady Cancer Support Foundation and Curtin Postgraduate Award to TG

## MELANOMA SURVEILLANCE BY TISSUE-RESIDENT MEMORY CD8 T CELLS

*Jonathan Chee, Thomas Gebhardt, Jason Waithman*

Until recently, it has been widely accepted that memory T cells are a heterogeneous population, comprised



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

### **Plain language summary**

Novel cancer therapies aimed at stimulating the body's immune defense have shown remarkable clinical results, although the immune mechanisms responsible for sustained therapy success remain unclear. We will study a particular type of immune cells, termed tissue-resident memory T cells, which we hypothesize are key players in protection

from melanoma. These studies will be important for the improvement and development of emerging innovative cancer therapies.

### **Funded by**

NHMRC, Cancer Council WA

### **External collaborators**

Thomas Gebhardt – University of Melbourne, Victoria, Australia

## **2015 Success**

### **THESES PASSED**

Chelsea Wilson, Honours, UWA  
Thesis title: Enhancing adoptive T cell therapy with epigenetic modifiers

### **AWARDS AND PRIZES**

Anthony Buzzai - Curtin University Oral Presentation Award – Australian Society for Medical Research Western Australia Scientific Symposium  
Anthony Buzzai - Australian Society of Immunology Poster Award for Immunology - Combined Biological Sciences Meeting  
Anthony Buzzai - Student Poster Presentation Award (Second Place) – EMBL PhD Australia Course

### **INVITED PRESENTATIONS**

- Jason Waithman, 'Revisiting Type I Inteferon as a Cancer Therapy', Cure Cancer Australia Symposium, Sydney
- Bree Foley, 'Enhancing Natural Killer cell mediated anti-tumour responses', Cure Cancer Australia Symposium, Sydney
- Jason Waithman, 'Treating melanoma

one interferone at a time', Kirkbride Melanoma Symposium, Perth

- Bree Foley, 'Enhancing Natural Killer cell mediated anti-tumour responses', Kirkbride Melanoma Symposium, Perth
- Jason Waithman, 'Revisiting IFN $\alpha$  as a cancer therapy', Annual National Centre for Asbestos and Related Diseases Symposium, Perth
- Jason Waithman, 'XCR1+ dendritic cell presentation of cutaneous tumour antigen - targets for therapeutic peptide vaccination', The Annual DC Down Under, Sydney (Keynote Speaker)

## Leukaemia Program

### Research Projects

#### **HIGH-RISK LEUKAEMIA IN INFANTS: GENETICS AND GENOMICS**

*MN Cruickshank, A Gout, J Ford, RS Kotecha, and UR Kees, in collaboration with T Lassmann, A Bosco, K Carter and CH Cole, Haematology-Oncology, Princess Margaret Hospital*

Infant acute lymphoblastic leukaemia (iALL) patients with MLL-rearranged (MLL-r) alleles in their leukaemia cells have poor prognosis with only 30% event-free-survival. Patients are treated with a combination of up to eleven cytotoxic drugs; however, dose-escalation has caused toxic deaths and has not improved outcomes, emphasizing the need for innovative therapies. MLL-r alleles encode fusion oncoproteins with

altered gene-regulating capabilities.

While MLL-fusions are cancer drivers, they require additional cooperating mutations to establish blood cancer. However, a recent report by the *Paediatric Cancer Genome Project* revealed that MLL-r iALL has the lowest mutation burden of any cancer sequenced to date. The MLL-r iALL genome contains a mean of only 1.3 protein-altering somatic mutations.

We hypothesised that iALL may also harbour pathogenic germ-line mutations not detected by somatic mutation analyses. As a step to address this hypothesis, we investigated expressed variants in specimens from patients diagnosed at Princess Margaret Hospital (RNA-seq; n=10), matched remission bone marrow DNA samples (exome; n=7), and a panel of cell lines derived from the leukaemia samples (RNA-seq; n=4) by next-generation sequencing. Single nucleotide variants (SNVs) were called from the sequencing data and annotated with functional predictions and evolutionary conservation scores using 7 different computational tools. Candidate pathogenic variants were prioritized if: (1) called as damaged/deleterious by 4/7 functional or conservation algorithms; (2) Cancer Gene Census or predisposition genes and (3) novel or rare (minor allele frequency of < 0.5% in the Exome Aggregation Consortium [ExAC] database). The variant calling and annotation pipeline was applied to an independent cohort of MLL-r iALL patients whose samples were sequenced by the *Paediatric Cancer Genome Project* (RNA-seq; n=34, WGS n=22).

We observed expression of rare and predicted deleterious alleles at gene



loci predisposing to cancer syndromes characterised in several patients. Gene-set enrichment suggests over-representation of germ-line defects in DNA-repair pathways. These results indicate that MLL-r iALL patients are born with rare defects in cancer predisposition genes, and their leukaemia cells frequently express combinations of alleles that could promote leukaemogenesis. These mutations may represent novel therapeutic targets.

### **Plain Language summary**

Cancer genome sequencing studies typically identify mutations in cancer cells that are not present in patients' normal cells. However, a large-scale sequencing project of infants with acute lymphoblastic leukaemia has shown that their leukaemia cells carry a very small number of mutations. We have re-analysed this sequencing data and extended it to include additional patient samples, focusing on genes that are recognised as causal for inherited cancer predisposition syndromes. Accordingly, our novel data analysis methods unveiled mutations in genes linked to syndromes converging on molecular pathways that control DNA-repair and growth-signalling. These gene mutations may represent novel therapeutic targets or predictive biomarkers for responses to treatment.

### **Funders of the project**

Children's Leukaemia and Cancer Research Foundation, WA.

## **NOVEL THERAPEUTIC APPROACHES FOR PATIENTS WITH HIGH-RISK INFANT LEUKAEMIA**

*MN Cruickshank, J Ford, J Wells, A Gout, J Ford, RS Kotecha, and UR Kees, in collaboration with T Lassmann, KW Carter and D Anderson, CH Cole (Haematology-Oncology, Princess Margaret Hospital), TW Failes and GM Arndt (ACRF Drug Discovery Centre for Childhood Cancer, Children's Cancer Institute Australia for Medical Research, Lowy Cancer Research Centre), N Smithers and RK Prinjha (GlaxoSmithKline), J O'Reilly (Department of Haematology, PathWest Laboratory Medicine WA)*

To address the poor prognosis of MLL-rearranged (MLL-r) infant acute lymphoblastic leukaemia (iALL), we generated a panel of cell lines from primary patient samples and investigated cytotoxic responses to contemporary and novel FDA-approved chemotherapeutics. To characterize representation of primary disease within cell lines, molecular features were compared using RNA-sequencing and cytogenetics. High-throughput screening revealed variable efficacy of currently used drugs, however identified consistent efficacy of three novel drug classes: proteasome-inhibitors, histone deacetylase-inhibitors and cyclin-dependent kinase-inhibitors. Gene expression of drug targets was highly reproducible comparing iALL cell lines to matched primary specimens. Histone deacetylase-inhibitors, including Romidepsin, enhanced the activity of a key component of iALL therapy, Cytarabine in vitro, and combined administration to iALL-xenografted mice further reduced leukaemia burden. In conclusion, we present a valuable

resource for drug discovery, including the first systematic analysis of transcriptome reproducibility in vitro, and have identified Romidepsin as a promising therapeutic for MLL-r iALL.

### **Plain Language summary**

Infants diagnosed with leukaemia less than three months of age with a particular chromosomal rearrangement have a poor prognosis with a 5-year event free survival of less than 30%. Therapeutic approaches have reached maximum potential with the chemotherapeutic agents that are available. Current therapy protocols for infants with acute lymphoblastic leukaemia contain up to twelve different chemotherapeutics, given in an intricate drug delivery scheme over 24 months. Evidence is required as to where in the standard chemotherapy backbone, novel drugs can be safely administered with maximal effect. We have identified a number of novel cancer drugs shown to be effective in high-throughput drug screens using a novel collection of infant leukaemia patient-derived cell lines. Testing of drug combinations has identified a particular drug, Romidepsin that enhances the efficacy of a key back-bone drug, Cytarabine, and shows activity in animal models of disease. These results identify novel therapies with the potential to improve outcomes for this high-risk group of patients.

### **Funders of the project**

Children's Leukaemia and Cancer Research Foundation, WA; The Kids Cancer Project

### **External collaborators**

GlaxoSmithKline, Lowy Cancer Research Centre, Department of Haematology, PathWest Laboratory Medicine WA

### **High levels of connective tissue growth factor can accelerate disease in a model of acute lymphoblastic leukaemia**

*JE Wells, M Howlett, HM Halse, J Heng, AL Samuels, J Ford, LC Cheung, and UR Kees, in collaboration with CH Cole, M Crook and AK Charles, Princess Margaret Hospital.*

Acute lymphoblastic leukaemia (ALL) is the most common form of cancer in children, a malignancy of lymphoid progenitors that affects children and adults. Steady progress has pushed the cure rate in some paediatric patients to nearly 90%, yet close to 40% of deaths occur among patients who are expected to respond favourably to multi-drug therapy. The burden of disease for childhood cancer is 67 person years life lost, compared to 16 for breast cancer.

To tailor new therapies for ALL a better understanding of disease development is needed. Connective tissue growth factor (CTGF/CCN2) is highly expressed in leukaemia cells from the majority of paediatric patients with B-lineage acute lymphoblastic leukaemia (pre-B ALL). CTGF is a matricellular protein and plays a role in aggressive cancers. We have genetically engineered leukaemia cells to modulate CTGF expression levels. Elevated CTGF levels accelerated disease dissemination and reduced survival in NOD/SCID mice. In vitro studies showed that CTGF protein induces stromal cell proliferation, promotes adhesion



of leukaemia cells to stromal cells, and leads to overexpression of genes associated with cell cycle and synthesis of extracellular matrix (ECM). Corresponding data from our leukaemia xenograft models demonstrated that CTGF leads to increased proliferation of non-leukaemia cells and deposition of ECM in the bone marrow. We document for the first time a functional role of CTGF in altering disease progression in a lymphoid malignancy. The findings provide support for targeting the bone marrow microenvironment in aggressive forms of leukaemia.

The current studies focus on dissecting the mechanisms of growth of leukaemia cells in the bone marrow and the enhancing effect of CTGF at two critical junctures, in established leukaemia and in leukaemogenesis. We are using our well-characterised in vivo models to identify the molecular mechanisms leading to pre-B ALL relapse and the networks of molecular and cellular interactions triggered by CTGF. We have established a novel oncogene-driven disease model to investigate the role of CTGF and are investigating which cells promote the disease by expressing CTGF.

### **Plain Language summary**

Extensive evidence has demonstrated a critical role for the microenvironment in promoting leukaemia growth. We have previously reported that elevated expression of a particular gene, CTGF, is evident in 75% of patients with childhood pre-B ALL. In this study we found that the microenvironment-associated CTGF protein is capable of altering disease progression and survival in a mouse model of leukaemia. This study provides support for the rationale of targeting the bone

marrow microenvironment in aggressive forms of pre-B ALL.

### **Funders of the project**

Children's Leukaemia and Cancer Research Foundation, WA.

### **PRE-CLINICAL MODELLING OF RELAPSE AND DRUG RESISTANCE IN T-LINEAGE PAEDIATRIC ACUTE LYMPHOBLASTIC LEUKAEMIA**

*D Anderson, JE Wells, J Ford, AL Samuels, MN Cruickshank, AH Beesley and UR Kees, in collaboration with R Lock, Leukaemia Biology, Children's Cancer Institute Australia for Medical Research, New South Wales*

Children with acute lymphoblastic leukaemia (ALL) are treated with complex chemotherapy regimens of up to twelve different drugs according to risk stratification at diagnosis. Around 80% of patients achieve continuous complete remission, with early response to drug therapy being one of the strongest predictors of outcome. However, patients relapsing with T-cell ALL (T-ALL) face a dismal outcome and drug resistance continues to be a significant problem. To identify genes and pathways deregulated in T-ALL drug resistance, as well as small molecule inhibitors that could synergise with current therapies, we have used two complementary experimental systems. Firstly, we have performed gene-expression profiling, drug-testing and next-generation exome sequencing in a unique panel of 15 paediatric T-ALL cell lines to find biological signatures predictive of resistance to drugs used in therapy. These have been used to

generate models for outcome prediction in patient cohorts using microarray data from diagnosis specimens. In independent T-ALL cohorts our model was able to accurately identify patient outcome, indicating that the in vitro derived drug-gene profiles are clinically relevant. These studies have also identified genes and pathways that underpin resistances to particular drugs. Importantly, predictions of outcome within each cohort were linked to distinct chemotherapies, suggesting that different mechanisms contribute to relapse in each case.

The observation that there is considerable heterogeneity in patient responses to therapy has been mirrored in our second T-ALL model system - a powerful preclinical in vivo model of ALL induction therapy. Using a clinically relevant four-drug treatment regimen, we have demonstrated that this model accurately recapitulates the in vivo development of drug resistance. This approach has identified biological signatures associated with the development of resistance in vivo and determined that patterns of resistance are different amongst tumours derived from individual patients. We have now extended this study to larger numbers of ALL xenografts to capture a greater diversity of relapsing profiles. The results reinforce the finding that biological mechanisms of relapse in T-ALL are highly diverse and support the need for personalised approaches to patient therapy, wherein an individual's unique tumour profile is assessed as part of the decision matrix for therapy.

Taken together, these studies provide important clues for the development of new therapeutic strategies for the

treatment of T-ALL as well as potential new markers for patient stratification.

#### Plain Language summary

Patients relapsing with T-cell leukaemia face a dismal outcome and drug resistance continues to be a significant problem. Our results from model systems suggest that different mechanisms contribute to relapse in each case. The biological mechanisms of relapse are highly diverse and support the need for personalised approaches to patient therapy. In summary, these studies provide important clues for the development of new therapeutic strategies for the treatment of patients with T-cell

leukaemia, as well as potential new markers for patient stratification.

#### Funders of the project

NHMRC, Australia and Children's Leukaemia and Cancer Research Foundation, WA.

## 2015 Success

#### THESES PASSED

Julia E Wells, PhD University of Western Australia: "The bone marrow microenvironment is essential for the function of connective tissue growth factor (CTGF/CCN2) in childhood acute lymphoblastic leukaemia".

Chelsea Wilson, BSc (Hons), University of Western Australia: "Enhancing adoptive T cell therapy with epigenetic modifiers".



## AWARDS AND PRIZES

Mark N Cruickshank, Jette Ford, Ursula R Kees, Rishi S Kotecha, Sarra Jamieson, Jenefer Blackwell, Jason Waithman, Bree Foley, Timo Lassmann, Alistair Forrest, Anthony Bosco, Greg Arndt  
Blue Sky Research Grant Scheme: "Precision genome editing for precision drug discovery". \$100,000

Ursula R Kees, Mark N Cruickshank, Rishi S Kotecha  
The Kids Cancer Project: "Improving the treatment for infants with leukaemia". \$115,000

Rishi S Kotecha, Ursula R Kees, Mark N Cruickshank, Timo Lassmann  
Telethon New Children's Hospital Fund Round Three: "Identifying novel, effective and translatable drugs for high-risk infant acute lymphoblastic leukaemia". \$237,180

Ursula R Kees, Mark N Cruickshank, Rishi S Kotecha  
CLCRF Triennial Grant 2015-2018: "Testing new drugs for infants with high-risk leukaemia". \$1,396,313

Rishi S Kotecha  
Department of Health WA Merit Awards 2015-2016: "Evaluation of demethylating agents against infant acute lymphoblastic leukaemia models in vitro". \$25,000

Rishi S Kotecha  
Raine Medical Research Foundation Clinician Research Fellowship 2015 Round Four.

Rishi S Kotecha  
Raine Medical Research Foundation Strachan Memorial Prize 2015. \$1,000

## EXTERNAL COMMITTEES

### International

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

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

Rishi S Kotecha, Chief Investigator for Australia and New Zealand, International INTERFANT Group

### National

Rishi S Kotecha, Australia and New Zealand Children's Haematology/Oncology Group Leukaemia and Lymphoma Committee

### Local

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

## INVITED PRESENTATIONS

Ursula R Kees "High expression of connective tissue growth factor (CTGF/CCN2) modifies the bone marrow microenvironment and accelerates dissemination of leukaemia". Seventh International Conference on Tumour Microenvironment, Tel Aviv, Israel, October 2015

Ursula R Kees "Infant acute lymphoblastic leukaemia: Genetic insight and new therapy approaches". Australian and New Zealand Children's Haematology/Oncology Group (ANZCHOG) Annual Scientific Meeting 2015, Perth, June 2015

Mark N Cruickshank "MLL-rearranged

infant acute lymphoblastic leukaemia",  
WA Health Translation Network, Perth,  
September 2015

Mark N Cruickshank "Precision Medicine in  
Cancer", Telethon Kids Institute Precision  
Medicine Working Group Meeting, Perth,  
September 2015

Rishi S Kotecha. Conference Chair for the  
Australian and New Zealand Children's

Haematology/ Oncology Group Annual  
Scientific Meeting, Perth, June 2015

## NUT-Midline Carcinoma (NMC) Program Research Projects

### **NUT-MIDLINE CARCINOMA (NMC) RESEARCH PROGRAM**

*A/Prof Alex H Beesley*

*Dr Anja Stirnweiss*

*Ms Joyce Oommen*

*Prof. Cathy Cole*

*Prof. Ursula Kees*

NUT midline carcinoma (NMC) is a rare but extremely aggressive cancer that arises in various tissues along the midline of the body (e.g. thymus, thorax or abdomen) and can affect people of any age, including infants. Currently there is no effective therapy for NMC and median survival is less than seven months. The hallmark of the disease is

a rearrangement of DNA that joins two genes (called BRD4 and NUT) to create a new hybrid gene that initiates and drives the cancer. Resolving how this BRD4-NUT fusion causes cells to grow out of control is a major aim of our research. Importantly, the BRD4 gene is now implicated in a wide range of cancers and this work thus also contributes to our understanding of other diseases.

To study this disease, we have a rare panel of NMC cell lines grown from patients diagnosed at Princess Margaret Hospital and at other centres around the world. This now stands a total of 12 such cell lines – the most comprehensive collection of NMC cell lines in the world. To increase our understanding of the oncogenic mechanism in these NMC cells we have performed next-generation transcriptome and whole-exome sequencing; through these studies we now know that there are at least six different molecular subtypes of NMC and this is likely to have important implications for patient stratification and clinical outcomes. We have also identified other, previously unknown, genetic features in these cells and we are investigating their clinical significance in follow-up laboratory studies.

To identify agents likely to be effective in NMC, we have performed high-throughput drug screening against our unique NMC cell line panel. Our data show that anthracyclines, topoisomerase inhibitors and microtubule poisons are among the most cytotoxic drug classes for these cells in vitro, but the efficacy of aurora kinase and bromodomain inhibitors varies considerably. Such pre-clinical drug



screening is an essential step towards finding effective treatment strategies for an orphaned disease that is refractory to current therapy approaches.

### **Plain Language summary**

NUT midline carcinoma (NMC) is a rare but extremely aggressive cancer for which there is no effective therapy and patient survival is typically less than one year from diagnosis. However, from five decades of research into childhood leukaemia we know that it is possible to convert a fatal cancer into one that is curable and we wish to achieve the same for children with Midline Carcinoma. By studying the biology and genetics of the disease our research aims to identify the best ways to successfully treat such patients.

### **Funders of the project**

- The Children's Leukaemia and Cancer Research Foundation (CLCRF)
- The Raine Foundation

### **External collaborators**

- Dr Greg Arndt, ACRF Drug Discovery Centre for Childhood Cancer, Children's Cancer Institute Australia for Medical Research, Sydney
- Prof. K Iyer, School of Chemistry and Biochemistry, UWA.
- Dr Antoinette Anazado & Dr Kristy McCarthy, Kids Cancer Centre, Sydney Children's Hospital, Randwick, New South Wales, Australia
- Dr Christopher French, Women and Brigham's Hospital, Boston
- Professor Steve Wilton, Foundation Chair in Molecular Therapies, Centre for Comparative Genomics, Murdoch University.
- Dr Karim Malik, School of Cellular and

Molecular Medicine, Bristol University, UK.

## **2015 Success**

### **External Committees**

National Anja Stirnweiss, Australian Society for Medical Research Committee, 2014 - present

### **INVITED PRESENTATIONS**

Beesley AH (2015). NUT Midline Carcinoma: a Deadly Orphaned Disease. Australia & New Zealand Children's Oncology Group (ANZCHOG) Conference, Perth WA.







# CELL BIOLOGY & IMMUNOLOGY

## Research Projects

### **ACUTE VIRAL BRONCHIOLITIS IN INFANTS AND YOUNG CHILDREN**

*Jones A<sup>a</sup>, Bosco A<sup>a</sup>, Strickland DH<sup>a</sup>, Holt PG<sup>a</sup> in collaboration with Sly PD<sup>b</sup>*

Division of Cell Biology<sup>a</sup>, Telethon Kids Institute, University of Western Australia, Perth, Australia

<sup>b</sup>Queensland Children's Medical Research Institute, Brisbane, Australia.

Severe lower respiratory viral infections (sLRI) cause acute viral bronchiolitis (AVB) in infancy and are a major risk factor for the development of asthma. Current treatments for this age group are suboptimal and new advances in effective treatment options are necessary. To enable the development of new therapies we need to identify and characterise the molecular mechanisms that underpin the pathogenesis of AVB during infancy, which are currently unknown. We will employ cutting-edge systems biology approach to dissect the inflammatory gene networks in local and systemic responses underlying AVB. Further, we aim to investigate the contribution of different cell populations to the inflammatory response in AVB and will identify age-related changes in AVB-associated inflammatory responses. Molecular profiling (RNA-Seq) is being carried out on airway epithelial cells (AECs) and PBMC derived inflammatory cells acquired from hospitalised infants

(<18 months of age) and pre-schoolers (>18 months – 5 years of age) with moderate to severe AVB, and at 6-8 weeks convalescence, at Royal Children's Hospital Brisbane. The gene expression profiling data will be analysed with network analysis and bioinformatics to elucidate the underlying disease mechanisms. Drug compounds will then be screened *in silico*, to identify drugs that perturb AVB-associated gene networks. Finally, the identified drug candidates will be validated with *in vitro* cell culture. The project will be the first study to look at AECs from the upper airway mucosa and their likely contribution to the local inflammation in the airways. It will allow for a direct comparison between local versus systemic signals in AVB.

#### **Plain language summary**

The drugs currently available for treatment of severe AVB in infants have all been developed based on studies on older children and adults. However it is known that immune and inflammatory functions are immature in infants and it is unclear whether the currently available anti-inflammatory drugs are therefore appropriate for this age group. This project aims to plug this knowledge gap, and to open up new opportunities for development of better treatments targeted specifically at infants.

#### **Funders of the project**

National Health and Medical Research Council of Australia.



## CHARACTERIZATION OF “BYSTANDER” EFFECTS OF THE DIPHTHERIA-PERTUSSIS-TETANUS (DTP) VACCINE ON THE IGE SYSTEM

Holt PG<sup>a</sup>, Snelling T<sup>b</sup>, White OJ<sup>a</sup>, Sly PD<sup>c</sup>, deKlerk N<sup>a</sup>, Carapetis J<sup>a,b</sup>, Van Den Biggelaar A<sup>b</sup>, Wood N<sup>d</sup>, McIntyre P<sup>d</sup>, Gold M<sup>e</sup>

<sup>a</sup> Telethon Kids Institute, The University of Western Australia, Perth, Australia

<sup>b</sup> Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, The University of Western Australia, Perth, Australia

<sup>c</sup> Queensland Children's Medical Research Institute, University of Queensland, Brisbane, Queensland

<sup>d</sup> National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, The Children's Hospital at Westmead, Sydney, Australia

<sup>e</sup> Discipline of Paediatrics, School of Medicine, University of Adelaide, Australia

In the late 1990s the original version of the DTP vaccine which contained bacterial cell walls (DTwP) was replaced by a better chemically defined (“cleaner”) formulation which lacked the cell wall components (acellular DTaP). Despite the effectiveness of DTaP in preventing severe Pertussis infection (“whooping cough”) which requires hospitalization, overall rates of Pertussis infections in the community are now rising, suggesting that there is a need to improve the vaccine. This project tested the degree to which the vaccine promotes “bystander” IgE responses to vaccine antigens which theoretically may interfere with vaccine performance, and whether these bystander responses also affect responses to food allergens. To do this we have re-evaluated the impact of DTaP-only versus mixed DTwP/

DTaP vaccination on Th2-dependent “bystander” IgE responses in three cohorts of children, using stored serum samples collected during immunization. We confirmed the generalised IgE-stimulatory activity of the DTaP vaccine on responses to vaccine-specific antigens in pre-schoolers, and demonstrated similar effects in infants on food allergen-specific IgE which were mild/transient and unlikely to be clinically significant. We additionally showed that use of an alternative mixed infant priming schedule encompassing an initial dose of DTwP significantly attenuates this IgE-stimulatory property. We conclude that followup studies may be warranted to ascertain whether IgE responses against Pertussis antigens have any effects on the effectiveness of DTaP-mediated protection against Pertussis infection.

### Plain language summary

Community rates of whooping cough are increasing world wide, suggesting that the current vaccine is not 100% effective. We are seeking more detailed information on how the immune system of infants responds to the vaccine, with the aim of identifying which aspects of the immune response need to be improved to optimize protection. This information will be made available to vaccine developers and health regulatory authorities, to inform debate surrounding future development of an improved vaccine.

### Funders of the project

Internal funding from the Telethon Kids Institute.

## **EPIGENETIC CHANGES UNDERPINNING ALLERGEN SENSITIZATION: A TWIN-BASED STUDY.**

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The most common chronic inflammatory disorders afflicting humans are allergic diseases. Genetically susceptible individuals have dysfunctional immune responses that cumulatively result in the adaptive generation of IgE to specific environmental antigen(s). Defining the molecular pathways that are disrupted in IgE mediated antigen sensitization has proven to be one of the most elusive aspects in our understanding of how to better direct approaches towards preventive or improved treatment strategies targeting allergic disease. The development of allergic disease appears to involve a complex interplay between genetic susceptibility and environmental exposure. Recent findings suggest a role for epigenetic change, in particular DNA methylation, in the causal pathway. The central aim of this study is to identify differences in epigenetic profiles of specific immune cell populations specifically associated with environmentally induced allergen sensitization in humans, using allergic asthma as an archetypal allergic disease. Recent unequivocal data in inducible mouse models of asthma have demonstrated specific disruption of DNA methylation profile in the peripheral T cell compartment. The

equivalent data is lacking in humans due to the difficulties associated with teasing out the relative roles of genes and environment in the modulation of epigenetic state. To overcome such issues associated with population diversity, we have chosen the elegant approach of studying human twins in childhood. This study aims to definitively test the link between altered DNA methylation in isolated subpopulations of immune cells and allergy in genetically identical twins discordant for allergic sensitization to house dust mite. The first aim is to identify methylation sensitive genes (MSG) associated with gene expression differences in monozygotic twins discordant for house dust mite (HDM) sensitization (SPT+ and SPT-) through a within-pair comparison of the epigenetic and gene expression profiles of cells of the adaptive immune system (CD4+ T and APC cells). We have used flow cytometry to sort purify subsets of immune cells from PBMC of twin pairs and are currently in the process of examining genome wide methylation profiles. Additionally we have characterized PBMC samples to determine frequency, activation state and function of the immune cell subpopulations and are currently in the process of data analysis.

### **Plain language summary**

Many humans suffer from allergic disease, which often develops in early life years, can be severe and impose a significant burden over the course of their lives. Why some people develop disease and others do not is still not well understood. We are studying immune cells from identical twins of which one suffers and one does not suffer from allergic disease to identify



specific mechanisms that may play important roles in disease development.

### **Funders of the project**

National Health and Medical Research Council of Australia.

### **STUDIES ON THE IMMUNOLOGICAL MECHANISMS UNDERLYING PROGRESSION VERSUS RESOLUTION OF ASTHMA BETWEEN ADOLESCENCE AND ADULTHOOD.**

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It is now recognized that late onset and persistent (early onset) asthma in young adults represent different forms of the disease that are likely to be driven by different mechanisms, and are therefore likely to need different treatment. However details of the underlying mechanisms driving progression of asthma in this age range, or the spontaneous remission which frequently occurs, are sparse. We are studying these in the Western Australian Pregnancy (Raine) Cohort, using clinical material collected in the 22 year respiratory follow-up of ~1000 participants, complementing a similar follow-up that took place at age 14 years. In addition to collecting clinical data relating to asthma, both follow-ups created an archive of cryobanked

viable immune cell samples (peripheral blood mononuclear cells) that were collected from subjects at the time of clinical assessment, at both 14 and 23 years. During 2015 we initiated studies at both ages to identify immunological markers associated with remitting asthma, persistent asthma, and late-onset asthma. Data collection will continue until late 2016, including systems level transcriptomic analyses on aeroallergen specific Th-memory responses to aeroallergens associated with atopic asthma risk.

Plain language summary:

During the teen years asthma spontaneously resolves in approx. 50% of affected subjects, who are replaced by another group of "late onset" asthmatics that often show immune response profiles that are subtly different to typical teenage asthmatics. The current level of understanding of what inflammatory mechanisms drive asthma in the persistent versus late onset young adult asthmatics is frustrating the development of newer and more effective asthma therapies for this age group. This project seeks new information on these disease mechanisms, to help propel development of new and better anti-asthma drugs.

### **Funders of the project**

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### **TARGETING THE MUCOSAL IMMUNE SYSTEM IN A MOUSE MODEL TO PREVENT PREGNANCY COMPLICATIONS FOLLOWING MATERNAL BACTERIAL INFECTION**

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Maternal exposure to microbial pathogens during pregnancy is frequently associated with exaggerated inflammatory responses and accompanying high intensity acute symptoms, and in some cases more profound follow-on effects ranging from the extreme of premature termination of pregnancy, to growth restriction in the offspring. Preterm birth is the single most important health care issue in fetal-maternal medicine, with a high prevalence in Australia and other developed countries. Children born with low for gestational age weight have an increased susceptibility to subsequent development of a range of persistent diseases, exemplified by atopic asthma. Safe effective treatments that can be used to protect against infection-induced complications would provide exciting new opportunities for improving maternal, fetal and neonatal health. We have developed preclinical mouse models to study mechanisms underlying infection induced pregnancy complications. Recent studies in our lab have demonstrated for the first time that **premature pregnancy termination and/or fetal weight loss in response to maternal microbial infection is potentially preventable**. We investigated if OM85, a bacterial-derived immunomodulator already in clinical use to control the intensity and duration of infection-associated inflammatory symptoms in susceptible infants and adults, could be repurposed to protect

against the effects of infection-associated inflammation in preclinical pregnancy models. Our initial studies with this agent in pregnant mice have involved exposure to bacterial LPS or live influenza virus, and these have demonstrated that OM85 treatment reduces both maternal and fetal susceptibility to the effects of infection-associated inflammatory stress by subtle attenuation of proinflammatory effector pathways exemplified by those driven by TNF $\alpha$ /IL-1, without blunting the capacity of the maternal innate immune system for pathogen eradication. We have demonstrated that a central component of OM-mediated effects in pregnant animals involves fine-tuning of the functions of both innate and adaptive immune cell populations present in maternal gestational tissues. The maintenance of immunological homeostasis at the fetomaternal interface is recognized to be of crucial importance in relation to preservation of normal fetal growth and development, and these proof-of-concept findings with OM85 point towards new therapeutic approaches to protection-of-pregnancy. While our findings to date are unique and conceptually exciting, we will follow up with a more detailed understanding of the precise mechanism-of-action of OM85 in maternal and fetal tissues in experimental infection models as the next step in progression towards human studies in pregnancy with OM85 itself, or a better defined derivative therapeutic.

### Plain language summary

During pregnancy, bacterial and viral infection of the mother can cause significant problems to the health of the growing fetus, including loss of life,



early delivery and low birth weight. This study has identified how cells within the reproductive tissues respond to maternal bacterial infection during pregnancy to induce these complications, and how this is potentially preventable. This work is the first step to develop safe treatments for use in pregnant mothers to protect against preterm delivery and low birth weight caused by maternal infections.

### **Funders of the project**

National Health and Medical Research Council of Australia.

## **THE ROLE OF BACTERIAL INFECTIONS DURING INFANCY IN ASTHMA DEVELOPMENT**

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Respiratory viral infections during infancy, particularly against a background of early allergic sensitization, have been implicated as risk factors for asthma development. Furthermore, bacterial pathogens may also contribute to pathogenesis although definitive

longitudinal data are lacking. We are testing this hypothesis in our Childhood Asthma (CAS) birth cohort study, where we had initially characterized the nasopharyngeal microbiome (NPM) in the children across the first year of life, employing 16S rRNA gene deep sequencing. The resultant data base of >193 million sequence reads was utilized in describing dynamic changes in the NPM associated with viral infections, and linking these with asthma risk at 5 and 10yrs. Analyses are in progress examining the impact of both viral and bacterial infections out to the 5th birthday, including additional viral typing (focusing on rhinovirus subtypes) carried out by our collaborators from the lab of Dr James Gern at University of Wisconsin. Initial findings suggest that the NPM becomes increasingly complex with age, and some organisms (exemplified by Staphylococcus), which were apparent commensals during infancy, appear to take on a more pathogenic role in regards to airways inflammation, at later ages. We are additionally focusing on the role of IgG antibodies to bacterial pathogens, including those of maternal origin, on susceptibility to invasive infections in infancy and beyond. We conclude that dynamic changes in the constituents of the infant NPM contribute independently to driving asthma development, and also play key modulatory role(s) in the parallel asthma causal pathway driven by interactions between virus-driven and allergen-driven inflammatory mechanisms.

### **Plain language summary**

Recent studies have established that both genetic susceptibility and viral infections during early childhood are important

drivers of asthma development. It has also been noted that asthmatics' airways contain different populations of bacteria to non-asthmatics. In this project we are studying how interactions between bacteria and viruses in children's airways promote the development of allergy and asthma.

### **Funders of the project**

National Health and Medical Research Council of Australia.

## **DEVELOPMENTAL-ASSOCIATED DYSREGULATION OF INNATE ANTI-MICROBIAL IMMUNITY IN EARLY LIFE AS A DETERMINANT OF SUSCEPTIBILITY TO ATOPIC ASTHMA**

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We have established that children most likely to develop persistent asthma are those who experienced repeated/intense lower respiratory tract infections (LRIs) during infancy, especially if they showed early signs of atopy. This suggests that their antimicrobial responses are dysregulated such that they contribute directly to airway tissue damage. Findings in the Childhood Asthma Study (CAS) birth cohort indicate that the most asthmatic infant LRIs are those accompanied with fever, a classical marker of acute inflammation and associated with the underlying activation of the inflammasome complex, which mediates production of the fever-inducing cytokine, IL-1 $\beta$ . Using cryobanked peripheral blood mononuclear cells (PBMCs) from the CAS, we examined

age-associated changes in regulation of inflammasome-associated functions. We performed microcultures from cord blood samples and PBMCs obtained at 4 and 10 years of age, in the presence of innate stimuli. Regulatory and inflammatory cytokine responses, including IL-1 $\beta$  were examined and cultured cells were cryobanked for transcriptomic studies. A subset of cord blood samples, comprising those who did not exhibit fever against those who had multiple fevers during an LRI, was assessed by flow cytometry for caspase-1 activity, a critical component of the inflammasome complex. These data are being utilized in integrative analyses, which aim to identify risk factors for asthma development by ages 5 and 10yrs. During 2016 we will undertake further analyses involving transcriptomic profiling of innate immune responses from groups of children who displayed high versus low susceptibility to severe symptomatic lower respiratory tract infections during infancy, focusing on the function of the inflammasome. These will directly test the hypothesis that dysregulated inflammasome function during infancy is responsible for heightened susceptibility to airways disease in this age group.

### **Plain language summary**

Previous findings from our research group has demonstrated that one of the strongest risk factors for subsequent development of asthma is having chest infections during infancy that are so severe that they trigger symptoms of fever and wheeze. It is not known what predisposes susceptible infants to these severe infections, and this project will attempt to define the mechanisms of susceptibility.



## Funders of the project

National Health and Medical Research Council of Australia.

## FINDING THE CELLULAR EXPLANATION FOR RECURRENT ASTHMA EXACERBATIONS

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Allergic asthma is a chronic inflammatory disease affecting the airways of mainly young children. The disease unfortunately has a particularly high prevalence in WA. Asthma is a very heterogeneous disease with a range of severities and some children suffer from very severe and recurrent exacerbations leading to frequent hospitalisations. Although much is known about asthma pathogenesis, we only have a limited understanding of recurrent exacerbations. To address this, we will investigate the systemic immunological and genetic profiles of children in WA with frequent exacerbations using a combination of flow cytometry and RNA sequencing. The outcome will inform us of the molecular and immunological processes associated with frequent exacerbations, which in the short term may be used to guide clinicians in better treating these patients and in the long term to identify novel therapeutic targets for this hard-to-treat patient group.

We are employing state of the art

technology to characterize the cellular and molecular signatures of peripheral blood mononuclear cells (PBMC) collected from healthy individuals, and from young patients presenting at hospital during acute asthma exacerbations. The patients are then followed through the open patient administration system in WA to identify the frequency of respiratory events in each patient. We are performing multi-parameter flow cytometry and transcriptome profiling (RNA-Sequencing) of PBMC samples to determine proportions of cellular subsets, activation status and corresponding gene expression. These studies will improve our current understanding of the inflammatory responses in this hard-to-treat patient group and may unveil novel therapeutic targets leading to improved treatment options for these children.

### Plain language summary

Allergic asthma is a chronic disease affecting many young children. Some children suffer from more frequent severe asthma attacks that require hospitalization and do not respond well to treatment that is currently available. We do not know the reason for this. This study is designed to identify the specific unique immune cell response that occurs in these children with recurrent disease. This will enhance our understanding of potential alternate treatments for this subset of patients.

## MECHANISMS OF IGE SENSITIZATION

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Increasing prevalence of immunological sensitization has been identified as a key risk factor for allergic asthma. The nature of the immunological mechanisms that underlie generation of mucosal IgE sensitization, as opposed to the normal response of protective tolerance to aeroallergens, remains unclear. To identify mechanisms promoting sensitization versus tolerance we use a two-strain experimental rat model where one strain is susceptible to sensitization after repeated allergen exposure whereas the other is non-susceptible and develops tolerance. We have observed that the non-susceptible strain has a larger proportion of regulatory T cells in their airways and that this prevents activation and tissue destruction by Th2 effector cells. We have previously demonstrated that the ability of airway mucosal dendritic cells to sample and transport allergens from the airways to the draining lymph nodes where T cells are induced is crucial to ensure a regulatory response. In line with this, we have shown that exposure to a high dose of allergen can be protective and prevent airway hyper responsiveness. We hypothesize that effective allergen uptake is essential to induce tolerance upon primary exposure and have observed that this ability differ between the two strains during repeated exposures. We have also observed differences in the dendritic cell subset composition in the airways and this is something we are currently analysing.

## **PLAIN LANGUAGE SUMMARY**

Some people are more likely than others to develop allergies to substances contained within the air we breathe. Children of parents with allergies have a higher risk of having allergies and of

developing allergic asthma. How and why allergies develop is still not fully understood. This project investigates how cells of the immune system respond to substances to cause allergies. This information will potentially help us to develop new treatments aimed at preventing the development of allergic disease.

## **Funders of the project**

National Health and Medical Research Council of Australia.

## **THE CELLULAR EFFECTS OF ESTROGEN ON ALLERGIC ASTHMA**

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After puberty allergic asthma converts from a disease that mainly affects boys to a disease with a higher prevalence in females who also suffer from more severe symptoms. This transition suggests a crucial role for the female sex hormones in disease pathology. Interestingly, we have previously observed a similar relation in our experimental asthma rat model consisting of two-rat strains with different susceptibility to chronic respiratory disease. To identify if estrogen is the causative agent for the high-susceptibility phenotype, we used slow releasing estrogen pellets inserted into male rats and managed to induce a disease phenotype analogous to the females with more severe asthma exacerbations. Interestingly this was only observed in one of the two rat strains,



used in the model, that is characterized by chronic respiratory disease compared to the other strain characterized by resistance to chronic disease. In 2016 we will investigate the immunological mechanisms relating to the observations. We will also map the immunological differences in between male and females in our model and how estrogen exposure alters the immunological balance. The model is clinically relevant given that the same phenotype is observed in humans. In addition, the effect of estrogen appears dependent on genetic background since the influence is only evident in the strain that is also susceptible to chronic disease.

### Plain language summary

Based on human population studies on allergies and asthma, it is apparent that after puberty females suffer more often and more severely from these diseases compared to males. To identify the immunological reason for this we have designed a study to investigate how the female sex hormone, estrogen, affects asthma exacerbations. The study aims to identify the mechanism for this so that this knowledge can be used to better treat asthma and allergies in both males and females.

### Funders of the project

National Health and Medical Research Council of Australia.

## EXAMINING RELATIONSHIPS BETWEEN VITAMIN D OVER THE FIRST DECADE OF LIFE AND DEVELOPMENT OF ASTHMA AND ALLERGY

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To investigate the postulated but controversial link between vitamin D and childhood asthma, we tracked vitamin D levels from birth to age 10y in 233 members of the Perth Childhood Asthma Study (CAS). Using a highly specific, internationally-standardised method developed by Metabolomics Australia at the University of Western Australia, we measured the storage form of vitamin D (25(OH)D) from cryobanked CAS plasma samples collected at birth (cord blood), 6 months and 1, 2, 3, 4, 5, & 10 years. We have demonstrated that low 25(OH)D in infancy is linked with increased risk for concurrent allergy in early life, and that repeated periods of vitamin D deficiency in the first decade are associated with higher likelihood of experiencing asthma, allergy or eczema at age 10. To our knowledge this is the first study to extensively track 25(OH)D trajectories over childhood, and our findings highlight the limited utility of investigating just one or two ages in childhood for unraveling the relationship between vitamin D

inadequacy and pediatric asthma.

Children in the CAS cohort were visited by the study doctor for every episode of respiratory infection up to age 5 years; nasopharyngeal aspirates were collected from participants at these visits as well as at the “healthy” visits during which blood was collected. While 25(OH)D levels of CAS children were not related to either the number or severity of respiratory infections experienced, they were related to timing of infection. Children with vitamin D deficiency at age 6 months tended to experience lower respiratory infections with fever earlier in life than children with higher vitamin D at 6 months, and this early incidence has been associated with an increased risk for developing asthma. In addition, as part of an ongoing collaboration with Dr. Kathryn Holt and Assoc. Prof. Michael Inouye in Melbourne, the microbial flora (microbiome) of the upper airways has been profiled for CAS children during the first year of life. When we examined whether vitamin D levels were related to differential colonisation of the upper airways, we found that children deficient in vitamin D at age 6 months showed higher levels of colonisation by *Streptococcus* species, which is in turn associated with higher risk for asthma development.

### **Plain language summary**

Vitamin D is a strong regulator of the immune system that may offer protection against asthma development, but this field remains controversial due to the conflicting findings of human studies. We have addressed the current lack of knowledge about how vitamin D levels fluctuate over childhood in individuals,

and how this relates to asthma risk, by examining 233 Perth children at high risk for asthma and allergy. We took vitamin D measurements from participants in the Childhood Asthma Study (CAS) at eight ages from birth to age 10. We found that allergic immune responses were more common in children with low current vitamin D in the first few years. Furthermore, repeated periods of vitamin D deficiency in the first decade were linked to higher rates of current asthma, allergy or eczema at age 10. Children with vitamin D deficiency at 6 months of age were more likely to experience two conditions previously associated with heightened asthma risk: increased colonisation of the upper airways by harmful bacteria and increased susceptibility to severe lower respiratory infections involving fever. This study shows for the first time the importance of considering vitamin D levels over a prolonged period during childhood, rather than at just one or two ages, when studying the interaction between vitamin D and asthma development.

### **Funders of the project**

Asthma Australia, Health Department of Western Australia, National Health and Medical Research Council of Australia.

### **PREDICTION OF ASTHMA IN CHILDHOOD FROM WHEEZING PHENOTYPES UP TO AGE 3 YEARS: FINDINGS FROM COMMUNITY COHORTS IN WESTERN AUSTRALIAN AND THE UNITED KINGDOM.**

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In this project we are examining how well different wheezing phenotypes in the first 3 years of life predict current asthma in adolescents and young adults. From birth to age 3 years, parents of Western Australian Pregnancy (Raine Study) Cohort participants documented each instance of wheeze, including whether this occurred in the presence or absence of a cold. We performed multivariate logistic regression, adjusting for relevant potential confounders, to identify associations between wheezing phenotypes and asthma; analyses included 1216 participants at age 14y, 1034 participants at age 22y and 459 participants who were followed up at both ages. Any wheezing during the first 3 years of life was associated with around a tripling of asthma risk at age 14, and with a doubling of asthma risk at age 22. Wheezing without a cold in the 3rd year of life was the strongest predictor of asthma at 14 or 22, and was also significantly associated with increased risk of asthma that persisted from age 14 to age 22.

Measures of lung function and airway calibre were reduced in 14-year-olds who had ever wheezed by age 3 (with or without a cold) compared to those who had not. Furthermore, a higher number of episodes of wheezing with a cold by age 3 predicted poorer lung function at age 14; there was no such association for wheezing without a cold, suggesting that it is increased respiratory infections rather than wheezing alone that is likely to have

a persistent detrimental effect on lung function. We are currently extending these analyses to examine lung function at age 22y. In addition, we are collaborating with Prof. Adnan Custovic (Imperial College, London), an expert in asthma and allergy epidemiology and custodian of several large British birth cohorts. His laboratory is currently conducting analyses to determine whether the UK cohorts show associations between early wheeze phenotypes and risk for asthma which are similar to those demonstrated in the Raine Study.

### **Plain language summary**

In the first few years of life many children wheeze when they have a cold, due to their small airway size, and this often subsides with increasing age and the associated increase in lung size. However, in some children such wheezing, or wheezing in the absence of a respiratory infection, can be a precursor of asthma development. We are attempting to better understand the relationships between wheeze in early life and risk for asthma development in childhood by examining members of the Western Australian Pregnancy (Raine Study) Cohort, who have taken part in respiratory health follow-ups at age 14, age 22 or at both ages. In addition, we are collaborating with experts in the United Kingdom to determine whether the associations we see in the Raine Study, which is representative of the Western Australian population, resemble those demonstrated in British community cohorts.

### **Funders of the project**

National Health and Medical Research

Council of Australia.

## **RELATIONSHIP BETWEEN CYTOKINE EXPRESSION PATTERNS AND CLINICAL OUTCOMES: TWO POPULATION-BASED BIRTH COHORTS**

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As part of the age 14y follow-up of the Western Australian Pregnancy (Raine Study) Cohort, we have previously profiled the immune responses of peripheral blood mononuclear cells (PBMC) collected from 1380 adolescents. This experimental work (led by Dr Elysia Hollams) gave rise to the largest dataset of in vitro cytokine responses published to date, and we have related these individual cytokine responses to asthma and allergy phenotypes in multiple publications. The collaborative study described here arose from the idea that models incorporating patterns of multiple cytokine responses to

allergens, rather than individual cytokine production, may better predict allergic sensitisation and asthma.

Our UK collaborators in the laboratory of Prof. Adnan Custovic collected PBMC from 268 8-year-olds from the Manchester Asthma and Allergy Study (MAAS); these cells were then cultured in our laboratory following the protocols used for the Raine Study. They then used machine-learning techniques to characterise cytokine response patterns in children from both cohorts to the allergen house dust mite, sensitisation to which is a strong risk factor for asthma. After demonstrating the consistency of cytokine responses between the two cohorts, they used model-based clustering to identify six classes of cytokine responders within the merged cohorts. The majority of children were non-responders (55%), and responders could be split into the following categories: IL-10 responders (3%); IFN- $\gamma$  & IL-13 medium responders (3.4%); IL-13 medium responders (21.4%); 'IL-5 & IL-13 medium responders (n = 77, 4.7%); IL-13 & IL-5 high responders (12.4%). IL-13 & IL-5 high responders were at much higher risk of house dust mite sensitisation and asthma compared to all other classes, with 88% of children assigned to this class being sensitised and 28.5% having asthma. These findings suggest that positive house dust mite 'allergy tests' and asthma are associated with a broad range of immunophenotypes, which may have important implications for the use of cytokine-targeted treatment approaches.

### **Plain language summary**

Allergy results from the inappropriate production of a family of immunological signals, known as cytokines, following



exposure to an otherwise harmless substance. Allergy to house dust mite is a strong risk factor for asthma, and this collaborative project arose from the idea that getting a detailed picture of how cytokine responses to house dust mite differ between children may allow us to more accurately predict which children will go on to develop asthma. We have previously measured the cytokine responses to house dust mite of white blood cells collected from over 1000 14-year-olds in the Western Australian Pregnancy (Raine Study) Cohort. Our collaborators in the UK did the same for a smaller group of 8-year-olds from the Manchester Asthma and Allergy cohort. After showing that cytokine response patterns were similar in the two groups of children, advanced computational modeling was used to identify six distinct categories of house dust mite cytokine response amongst the children; children in one of these categories had an asthma rate five times that of the other categories. The diversity of cytokine patterns shown in this study may have important implications for the usefulness of asthma and allergy treatment approaches that block action of single cytokines.

### **Funders of the project**

National Health and Medical Research Council of Australia, UK Medical Research Council (MRC); JP Moulton Charitable Foundation and National Institute for Health Research; Clinical Research Facility at University Hospital of South Manchester NHS Foundation Trust.

## **TARGETING THE MUCOSAL IMMUNE SYSTEM IN A PREGNANT MOUSE MODEL TO PREVENT EXPERIMENTAL ALLERGIC AIRWAYS DISEASE IN THE OFFSPRING**

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Seminal studies of traditional farming families across Europe indicate that maternal exposure to benign environmental microbial stimuli whilst pregnant can potentially play a key role in mitigation of asthma risk in their offspring. The potential to harness this environmental phenomenon by therapeutically mimicking farm microbial exposure in pregnant women therefore represents a novel strategy for protection against the onset of allergic disease in children. In this pre-clinical study, we aim to investigate the therapeutic potential of a novel microbial derived immune stimulating agent (OM85) in protecting against the development of allergic asthma in offspring via treatment of the pregnant mother during gestation. We have so far shown that at baseline, ovalbumin sensitised and challenged female offspring have a significantly increased airways eosinophil population than their male counterparts. This finding is further reflected in an increased concentration of pro-inflammatory cytokines within the lungs of females. Importantly, we have also shown that sensitised female offspring from OM85 treated mothers have significantly attenuated airways eosinophilia after aerosol challenge. Multi-colour flow cytometry has enabled us to identify alterations within both regulatory T cell (Treg) and dendritic

cell (DC) populations of the airways draining lymph nodes, parenchymal lung and trachea of 6-week old offspring. This preliminary data suggests maternal OM85 treatment has the capacity to modulate immunological mechanisms within the offspring that have previously been implicated in the pathogenesis of allergic airways disease. Furthermore, maternal OM85 treatment may have a differential impact on gender-associated disease outcomes. Future studies will investigate the underlying mechanisms promoting protection in the offspring. Fetal samples (fetal bone marrow, fetal liver, fetal thymus, fetal lung and placenta) collected at gestation day 18.5 will enable the identification of molecular signatures associated with maternal OM85 treatment. Fetal DNA will be used to determine fetal gender via PCR. After sex determination, female only tissue samples will undergo RNA-seq to identify molecular signatures within fetal tissue associated with maternal OM85 treatment during gestation. Maternal bone marrow will also undergo RNA-seq to assess the molecular impact of OM85 from a maternal perspective.

### **Plain language summary**

Studies in Europe have shown that exposure of pregnant women to high levels of microbial products such as dust from farm barns, somehow stimulates the maturation of immune function maturation in their offspring, making them strongly resistant to development of asthma and allergies. We are trying to reproduce this finding experimentally in mice using a microbial derived product (OM85) which is used in Europe to boost resistance to infection. If this is successful,

we will investigate the underlying protective mechanisms, with the long term aim of developing a new protective treatment for trialling in humans.

### **Funders of the project**

National Health and Medical Research Council of Australia.

### **ASTHMA: THE ROLE OF INTRINSIC AND AEROALLERGEN-SPECIFIC IMMUNE RESPONSES IN THE HEIGHTENED SUSCEPTIBILITY OF ATOPICS TO RESPIRATORY VIRAL INFECTIONS: RAT MODEL STUDIES**

Jones A<sup>a</sup>, Lauzon-Josef J-F<sup>a</sup>, Mincham K<sup>a</sup>, Thomas J<sup>a</sup>, Szakaly R<sup>b</sup>, Rosenthal L<sup>b</sup>, Bosco, A<sup>a</sup> Holt, PG<sup>a</sup>, Strickland DH<sup>a</sup>

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<sup>b</sup>University of Wisconsin School of Medicine and Public Health, Department of Medicine, Madison, United States

Common (usually benign) respiratory infections exemplified by rhinovirus (HRV) can trigger asthma exacerbations requiring hospitalization in atopics. It is unclear whether sensitization plays a direct role in this context, or whether generic features of the underlying Th2high atopic immunophenotype are responsible for this effect. The aim of this project is to elucidate the cellular and molecular mechanisms underlying susceptibility to respiratory infection-induced asthma exacerbations in atopics, employing an animal model. Our model comprised Th2high (atopic equivalent) BN rats and immunologically normal (non-atopic) PVG rats, unsensitized



and OVA-sensitized. We inoculated the animals with an HRV-mimic, with or without aerosol exposure to OVA, and cellular and transcriptomic profiling was performed on bronchoalveolar lavage (BAL) of unsensitized animals. Gene expression profiling of sensitized animals will be completed in 2016. Transcriptomic analysis will enable the characterisation of underlying disease mechanisms. We found that intrinsic, and particularly acquired defects in anti-viral defence mechanisms triggered by co-exposure to aeroallergen, contribute to hypersusceptibility to infection-associated airways inflammation characteristic of the Th2high immunophenotype. These findings provide a plausible rationale for therapeutic targeting of aeroallergen-specific immunity in human atopics for prevention of virus-associated severe asthma exacerbations.

### **Plain language summary**

In children, appropriate treatment for severe episodes of allergic asthma exacerbation often require admission to hospital. A common finding in these children is that the most severe asthma symptoms occur in association with a respiratory viral infection. This study investigates how respiratory viral infection may cause allergic asthmatic disease symptoms to be worse, which will help us to identify possible directions for improved treatment.

### **Funders of the project**

National Health and Medical Research Council of Australia.

## **ASTHMA: ACUTE ASTHMA FLARE-UP IN SCHOOL-AGE CHILDREN**

Jones A<sup>a</sup>, Mok D<sup>a</sup>, Read J<sup>a</sup>, Serralha M<sup>a</sup>, Holt BJ<sup>a</sup>, Bizzintino J<sup>a,b</sup>, Khoo S-K<sup>a,b</sup>, Rueter K<sup>b</sup>, Laing I<sup>a,b</sup>, Goldblatt J<sup>b</sup>, LeSouef PN<sup>b</sup>, Kusel M<sup>a</sup>, Sly PD<sup>c</sup>, Holt PG<sup>a</sup>, Bosco A<sup>a</sup>, Strickland DH<sup>a</sup>.

<sup>a</sup>Division of Cell Biology, Telethon Kids Institute, The University of Western Australia, Subiaco, Australia,

<sup>b</sup>School of Paediatrics and Child Health, The University of Western Australia, Princess Margaret Hospital, Subiaco, WA, Australia

<sup>c</sup>Queensland Children's Medical Research Institute, The University of Queensland, Brisbane, QLD, Australia

Severe lower respiratory viral infections cause acute viral bronchiolitis in infancy and are a major risk factor for the pathogenesis of asthma later in life. The immune system of infants is in a transient state of functional immaturity relative to adults. Thus, findings in adults cannot be extrapolated to young children. Given that maturation of immunological function in early life can have a major impact on risk for infection and development of asthma related traits, detailed studies based on defined age groups will be essential. At present, our understanding of how antiviral responses change from infancy to older children is limited. Hence, a systematic study is required of the cellular and molecular mechanisms underlying acute viral respiratory illnesses from infants with bronchiolitis through to school age children with asthma. The aim of this study is to investigate the cellular and molecular immune responses in peripheral blood samples collected from children during an acute asthma

flare-up. Peripheral blood mononuclear cells (PBMC) were collected during an acute asthma flare-up and following recovery. PBMC were phenotyped employing multiparametric flow cytometry (14-colours) and a subset was utilised for transcriptomic profiling. We have found that an asthma flare-up is associated with significant modulation of immune cell populations in peripheral blood.

### Plain language summary

Asthma is a chronic disease of the airways affecting 2 million Australians. Viruses that infect the lungs can trigger asthma flare-ups severe enough to require hospitalisation in asthmatic children. Current treatments improve the symptoms of asthma but are unable to prevent the disease. The aim of this study is to identify differences in immune cells that are involved in the disease. This research will employ a combination of innovative technologies to compare cells in the blood from asthmatic children with healthy children. Ultimately, we hope to identify new treatment targets to prevent the development of asthma.

### Funders of the project

National Health and Medical Research Council of Australia.

## 2015 Success

### INVITED PRESENTATIONS

PG Holt

- NIAID Symposium Speaker: Immunologic basis for primary prevention of allergic diseases. American Academy of Allergy, Asthma

and Immunology Congress, Houston, 2015.

- Symposium Speaker: Translating the allergen to the adaptive immune system. American Academy of Allergy, Asthma and Immunology Congress, Houston, 2015.
- Symposium Speaker: Viral-bacterial-host interactions driving early asthma pathogenesis. EAACI Congress, Barcelona, 2015.
- Plenary Speaker: Viral infection and atopy in asthma pathogenesis – new rationales for asthma prevention. Konsul Bergh Scientific Symposium, Stockholm, 2015.
- Plenary Speaker: The allergic march in childhood – progression to respiratory disease. 10th SOSA Symposium on Specific Allergy, Rome, 2015.
- Guest Speaker: ThermoFisher Immunodiagnostics, Uppsala, Sweden, 2015: Specific IgE:IgG ratios as predictive indices of allergy susceptibility.

Anthony Bosco

- Invited Speaker. EMBL PhD course, Perth, Australia
- Invited Speaker. American Thoracic Society (ATS), Denver, Colorado
- Invited Speaker. Science on the Swan, Perth, Australia

Deborah Strickland

- Symposium speaker -World Allergy Conference, South Korea
- Guest speaker, Curtin University, Perth
- Guest Speaker, SPICE teacher education program, UWA, Perth

Elysia Hollams gave the following invited talk: *“Insights into asthma phenotypes and risk factors from the Raine Study”*



**Combined TSANZ** (Thoracic Society of Australia and New Zealand) **and ANZSRS** (Australian and New Zealand Society of Respiratory Science) **Annual Scientific Meeting**, Perth, Western Australia 24-25 July 2015





# COLLABORATION FOR APPLIED RESEARCH AND EVALUATION

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

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

The following provides a summary of research projects completed in the calendar year 2015; as well as ongoing research projects.

## Services for Healthy Children

### **ANAEMIA IN WESTERN AUSTRALIA: INCIDENCE IN ABORIGINAL AND NON-ABORIGINAL POPULATIONS ACROSS THE STATE**

*Grant Smith (Telethon Kids Institute)*  
*Professor Karen Edmund (Princess Margaret Hospital (PMH))*

The major aim of this study is to use existing full blood count data to identify diagnoses of moderate to severe anaemia in children across Western Australia. Differences across subpopulations of the state will be examined to identify risk factors for anaemia and identify significant differences across Western Australian communities (particularly remote/rural Aboriginal communities). Where possible, incidence rates of various subtypes of anaemia will be also be examined. There has been issues

with ethics and engagement with key stakeholders that have delayed this project. This project is expected to be completed by the middle of 2016.

### **Funders of the project**

Department of Health (WA)

## Services for Healthy Early Years

### **EVALUATION OF THE INTEGRATED SERVICE INITIATIVES TARGETING THE EARLY YEARS IN WESTERN AUSTRALIA**

*Dr Kim Clark and Rhonda Breen (Telethon Kids Institute)*  
*Sue Kiely (Child Adolescent Community Health, Child Adolescent Health Service)*

This project explores the provision of children's services in communities, assess how these services work together and evaluate their resulting impact on children's social, emotional and academic functioning across the early years through to early primary (0-8 years). The study will provide insights into how integrated networks can be evaluated and the impact of an integrated approach to service on families' and children's functioning. The study hypothesis is that higher levels of local education, health, and community service integration lead to higher levels of parent and teacher and other service

provider role satisfaction and lower levels of developmental vulnerability among children in their first year of full-time schooling living in the lowest SES quintile of school areas in WA. The final report of this project is currently in draft form and is anticipated to be completed early in 2016.

#### **Funders of the project**

Department of Health (WA)

## Services for Healthy Adolescents

### **EVALUATION OF THE CHOICE AND PARTNERSHIP APPROACH (CAPA) WITHIN CHILD AND ADOLESCENT MENTAL HEALTH SERVICES (CAMHS)**

*Tess Fletcher, Tanyana Jackiewicz and Dr Kim Clark (Telethon Kids Institute)*

This project is designed to aid CAMHS with both implementation and assessment of the effects of CAPA on these services. CAPA offers an important opportunity for WA CAMHS services to address enduring service delivery challenges and critiques of service policy made in a number of mental health reviews. The aim of this project is to conduct a comprehensive evaluation of the Choice and Partnership Approach (CAPA) across a number of trial sites in the Perth Metropolitan Area. The evaluation aims to document the effect of CAPA on:

- [1] CAMHS service,
- [2] CAMHS staff,
- [3] external referrers (to CAMHS), and

[4] external referral services (from CAMHS). This study commenced as an evaluation of implementation of CAPA at a single CAMHS site (Rockingham) as a means of assessing the impact of this model ahead of a decision about broader roll-out of the model. Subsequently, the decision was taken by CAMHS management to roll out CAPA across all metropolitan services (i.e. prior to completion of the evaluation). Consequently, it was subsequently agreed the evaluation plan would be modified to identify how the CAPA model was translated into practice at six metropolitan CAMHS sites. This study, to date, has involved reviewing activity and financial data for the six CAMHS teams and collecting referrer and staff data on perceptions of the need for change and on the impact of the CAPA model on services. To date, reports relating to Warwick and Rockingham CAMHS has been prepared and activity, financial and demographic data for 2013 have been analysed for all sites. Further, a case study report on Clarkson has been prepared as well as a Referrers report and a Staff Survey Report. The evaluation will be complete by October 2016.

#### **Funders of the project**

Department of Health (WA)

### **WESTERN AUSTRALIAN CORONIAL SUICIDE INFORMATION SYSTEM**

*Jenn Hafekost (Telethon Kids Institute)*

*Tanyana Jackiewicz (Telethon Kids Institute)*

*Kirsten James and Michael Moltoni (Mental Health Commission)*

*Gary Cooper (State Coroners Office)*



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

The Western Australian Coronial Suicide Information System is anticipated to:

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

This project is funded by the Mental Health Commission until 2017. In October 2015 carriage of this project was transferred to the Human Capabilities Team due to a lack of capacity within the Collaboration for Applied Research and Evaluation.

## Services for Healthy Pregnancy and Birth

### **A STUDY EXAMINING POST NATAL FOLLOW-UP OF WOMEN RECEIVING PREGNANCY CARE WITH THE WOMEN AND NEWBORN DRUG AND ALCOHOL SERVICE (WANDAS)**

*Anna Fletcher (Telethon Kids Institute)*

*Angela O'Connor (WANDAS)*

*Renate McLaurin (WANDAS)*

This study aims to inform further development of WANDAS to better facilitate the transition of patient care from the tertiary environment into the community post-birth. To inform this development the study endeavours to describe the experiences of those who attended WANDAS during their pregnancy, and to identify possible barriers and enablers to accessing care during the postnatal period. Consultation with health and support services will provide information on the barriers and enablers to engaging with WANDAS patients which, together with the patient perspective, will help to inform the recommendations for service improvement. This project is currently underway with more than half of the case note review completed; brief interviews are in the field and in-depth interviews are being conducted where appropriate. A GP survey has been conducted. An interim report has been prepared. Due to delays in data collections this project will not be complete until 2016.

## Funders of the project

Department of Health (WA)

## WESTERN AUSTRALIAN HEALTH AND PREGNANCY SURVEILLANCE SYSTEM: DEVELOPMENT OF A STATEWIDE SURVEILLANCE SYSTEM

*Dr Paula Wyndow (Telethon Kids Institute)*

*Tanyana Jackiewicz (Telethon Kids Institute)*

*Professor Carol Bower (KEMH)*

This project attempts to establish a state-wide capacity for the monitoring and surveillance of behavioural and other risk factors in pregnancy that lead to adverse outcomes such as birth defects. It requires the design and establishment of a database to store the data; as well as provide a data collection interface for participants to use when filling in their online questionnaires. This survey is now complete, with a total of 1,218 new mums providing information on their pregnancy behaviors and risk factors. These results are currently being analyzed and the final report will be prepared by July 2016.

## Funders of the project

Department of Health (WA)

## TRIAL OF A NOVEL PREGNANCY CARE MODEL FOR WOMEN WITH OBESITY

*Anna Fletcher (Telethon Kids Institute)*

*Lisa Gibson (Telethon Kids Institute)*

*Tanyana Jackiewicz (Telethon Kids Institute)*

*Professor Yvonne Hauck (KEMH)*

This project builds on a previous research project that was conducted by Telethon

Kids Institute. The outcome of that research project was an evidence-based, acceptable model of care designed to support women with obesity to achieve a healthy gestational weight gain and reduce obstetric and neonatal complications called 'Blooming Together'. Blooming Together provides, among other things, early intervention (at 12-14 weeks gestation); comprehensive, clear, consistent and supportive lifestyle education and antenatal care; continuity of carer (and peers) providing accountability for patients; as well as social support. This new research looks at piloting the Blooming Together Program in its entirety to determine whether the Program can be delivered effectively in both a community and tertiary setting and to quantify the Program costs in the context of operational efficiency and Activity-based Funding. The first pilot at the Woodbridge Women's Clinic, Rockingham is now complete, and the second pilot will be at Fiona Stanley Hospital and will commence in 2016.

## Funders of the project

Department of Health (WA)

## External Committees

Tanyana Jackiewicz, Member, Commissioner for Children and Young People's Wellbeing Framework Committee since 2012

Tanyana Jackiewicz, Member, Commissioner of Children and Young People's Management Committee for Building Blocks tender since 2014

Tanyana Jackiewicz, Committee Member, Child and Youth Health Network Executive



Advisory Council since 2007 (resigned July 2015)

Dr Tracy Reibel, Consumer Engagement Committee, WA Primary Health Alliance

Dr Tracy Reibel, Consumer Advisory Panel, PSANZ

Dr Tracy Reibel, Consumer Advisory Panel, Australian College of Midwives

Tanyana Jackiewicz, Committee Member, National Child and Community Health Council since 2008

Dr Rachel Skoss, Chair, Ministerial Advisory Council on Disability since 2013

Dr Rachel Skoss, Disability Health Network, EAG

Dr Rachel Skoss, Chair, Consumer Reference for WA Register for Developmental Anomalies since 2011

Dr Rachel Skoss, Committee Member, Early Childhood Intervention Council since 2013

Dr Rachel Skoss, Member, Disability Services Commission Board since 2014

Dr Rachel Skoss, WA NDIS "My Way" Reference Group





# COMPUTATIONAL BIOLOGY

## Overview

Our computational biology team focusses on developing innovative approaches to utilize genomes, transcriptomes and epigenomes in translational studies. We aim to understand how individual bases in our genome predispose, alter and interact in normal and disease contexts. The computational frameworks developed in the group help drive the application of large public datasets in medical and translational research.

Advances in next generation sequencing (NGS) has lead to the routine generation of thousands of genome wide datasets for individual studies. Research groups focussing on particular diseases rarely possess the analytical or computational capabilities to utilize these datasets in their work. Therefore, vast amounts of publicly available data relevant to medical research are not being utilized to drive research and translation. To meet this challenge we are developing innovative data modeling techniques to facilitate data repurposing in translational studies.

Research Projects

## Research Projects

### **TRANSCRIBED ENHANCERS LEAD WAVES OF COORDINATED TRANSCRIPTION IN TRANSITIONING MAMMALIAN CELLS.**

*Erik Arner, Carsten O Daub, Kristoffer Vitting-Seerup, Robin Andersson, Berit Lilje, Finn Drabløs, Andreas Lennartsson, Michelle Rönnerblad, Olga Hrydziusko, Morana Vitezic, Tom C Freeman, Ahmad MN Alhendy, Peter Arner, Richard Axton, J Kenneth Baillie, Anthony Beckhouse, Beatrice Bodega, James Briggs, Frank Brombacher, Margaret Davis, Michael Detmar, Anna Ehrlund, Mitsuhiro Endoh, Afsaneh Eslami, Michela Fagiolini, Lynsey Fairbairn, Geoffrey J Faulkner, Carmelo Ferrai, Malcolm E Fisher, Lesley Forrester, Daniel Goldowitz, Reto Guler, Thomas Ha, Mitsuko Hara, Meenhard Herlyn, Tomokatsu Ikawa, Chieko Kai, Hiroshi Kawamoto, Levon M Khachigian, S Peter Klinken, Soichi Kojima, Haruhiko Koseki, Sarah Klein, Niklas Mejhert, Ken Miyaguchi, Yosuke Mizuno, Mitsuru Morimoto, Kelly J Morris, Christine Mummery, Yutaka Nakachi, Soichi Ogishima, Mariko Okada-Hatakeyama, Yasushi Okazaki, Valerio Orlando, Dmitry Ovchinnikov, Robert Passier, Margaret Patrikakis, Ana Pombo, Xian-Yang Qin, Sugata Roy, Hiroki Sato, Suzana Savvi, Alka Saxena, Anita Schwegmann, Daisuke Sugiyama, Rolf Swoboda, Hiroshi Tanaka, Andru Tomoiu, Louise N Winteringham, Ernst Wolvetang, Chiyo Yanagi-Mizuochi, Misako Yoneda, Susan Zabierowski, Peter Zhang, Imad Abugessaisa, Nicolas Bertin, Alexander*

D Diehl, Shiro Fukuda, Masaaki Furuno, Jayson Harshbarger, Akira Hasegawa, Fumi Hori, Sachi Ishikawa-Kato, Yuri Ishizu, Masayoshi Itoh, Tsugumi Kawashima, Miki Kojima, Naoto Kondo, Marina Lizio, Terrence F Meehan, Christopher J Mungall, Mitsuyoshi Murata, Hiromi Nishiyori-Sueki, Serkan Sahin, Sayaka Nagao-Sato, Jessica Severin, Michiel JL de Hoon, Jun Kawai, Takeya Kasukawa, Timo Lassmann, Harukazu Suzuki, Hideya Kawaji, Kim M Summers, Christine Wells, David A Hume, Alistair RR Forrest, Albin Sandelin, Piero Carninci, Yoshihide Hayashizaki

Although it is generally accepted that cellular differentiation requires changes to transcriptional networks, dynamic regulation of promoters and enhancers at specific sets of genes has not been previously studied en masse. Exploiting the fact that active promoters and enhancers are transcribed, we simultaneously measured their activity in 19 human and 14 mouse time courses covering a wide range of cell types and biological stimuli. Enhancer RNAs, then messenger RNAs encoding transcription factors, dominated the earliest responses. Binding sites for key lineage transcription factors were simultaneously overrepresented in enhancers and promoters active in each cellular system. Our data support a highly generalizable model in which enhancer transcription is the earliest event in successive waves of transcriptional change during cellular differentiation or activation. (*PUBLISHED IN **SCIENCE***)

### **Plain Language summary**

In order to understand cellular differentiation, it is important to understand the timing of the regulation

of gene expression. Arner et al. used cap analysis of gene expression (CAGE) to analyze gene enhancer and promoter activities in a number of human and mouse cell types. The RNA of enhancers was transcribed first, followed by that of transcription factors, and finally by genes that are not transcription factors.

### **REFERENCE GENOTYPE AND EXOME DATA FROM AN AUSTRALIAN ABORIGINAL POPULATION FOR HEALTH-BASED RESEARCH.**

Denise Anderson, Jenefer M. Blackwell, Richard W. Francis, Sarra E. Jamieson, Timo Lassmann, Genevieve Syn, Dave Tang

Genetic analyses, including genome-wide association studies and whole exome sequencing, provide powerful tools for the analysis of complex and rare genetic diseases. To date there are no reference data for Aboriginal Australians to underpin the translation of health-based genomic research. Using microarray and next-generation sequencing technologies, we generate a reference panel of genetic variants that will serve as a useful reference point for genomic studies in Aboriginal Australians. (*ACCEPTED IN "**Scientific Data**" (Nature Publishing Group)*).

### **Plain Language summary**

The genetic makeup of an individual, i.e. genotype, can influence an individual's observable characteristics, i.e. phenotype, which includes traits such as eye colour or clinically relevant abnormalities. We have provided a reference set for aboriginal Australians.



## 2015 Success

### INVITED PRESENTATIONS (TIMO LASSMANN)

- Machine learning techniques in NGS data processing. 11th GeneMappers Conference at the Rendezvous Hotel Perth Scarborough, Western Australia.
- Towards large scale integration of sequencing data. HGSA WA Branch, Perkins Institute Perth.
- Towards large scale integration of sequencing data. 2015 Winter School in Mathematical and Computational Biology, ARC Centre of Excellence in Bioinformatics, Brisbane.
- Accelerating NGS based research using machine learning approaches. Computational Biology Seminar Series at the Biozentrum of the University of Basel, Switzerland.
- Large Scale Transcriptomics from a computational perspective. Pawsey Petascale Bioinformatics Symposium, Perth.

## McCusker Charitable Foundation Bioinformatics Centre

### Overview

Our main focus this year from a platform perspective has been to establish a series of key data analysis pipelines to be used by the Institute and external collaborators. The pipelines (or procedures) enable the complex series of steps to analyse data (eg comparing gene expression of one type cancer to another) to be tested, repeated, and reused for similar tasks – to dramatically reduce errors and increase efficiency. We've also made improvements to our hardware platform, with the purchase of a large server from SGI, which provides a powerful platform for analysing big data.

From a research perspective, one of our areas of key interest is the area of data sharing. During 2015 we published and released our ViPAR (Virtual Pooling and Analysis of Research data) software to enable researchers to securely share and analyse data with their colleagues around the world (using a method that is sensitive to ethical, privacy and confidentiality constraints across borders).

## Research Projects

### **GAMA project**

*Melinda Judge, Erica Parker, Denise Naniche, Lucia Pastor, Kim W Carter, Denise Anderson, Peter LeSouëf.*

This is the largest acute HIV cohort recruited in sub-Saharan Africa, the first study to use the RNA-seq platform to investigate gene expression during early HIV infection and, importantly, the first to consider HIV-1 subtype C which is responsible for more than half of infections globally.

### **Plain Language summary**

The ability to accurately identify acute HIV infection (AHI) in a resource-limited setting would enable earlier and optimised treatments for individual patients, and also contribute to reducing onward transmission. Identification of reliable biomarkers for use in novel incidence assays is required. This study investigated host gene expression in response to new HIV infection.

### **Funders of the project**

Bill and Melinda Gates Foundation

### **External collaborators**

Denise Naniche, ISGlobal, Barcelona, Spain

Lucia Pastor, IrsiCaixa Institute for AIDS Research, Institut Germans Trias i Pujol (IGTP), Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona, UAB, Badalona, Spain

### **MULTIGENERATIONAL FAMILIAL AND ENVIRONMENTAL RISK FOR AUTISM (MINERVA) NETWORK**

*Avi Reichenberg, Joseph Buxbaum, Alexander Kolevzon, Michaeline Bresnahan, Ezra Susser, Mady Hornig, Erik Parner, Christina Hultman, Yudi Pawitan, Sven Sandin, Camilla Stoltenberg, Andre Sourander, Mika Gissler, Helen Leonard, Nan Hu, Kim Carter, Richard Francis, Emma Glasson, Andrew Whitehouse*

Better understanding of the etiologic roles of family history, prenatal environmental factors, and potential biologic mechanisms, such as epigenetic changes, in autism spectrum disorders (ASD) are research priorities identified in the Autism Coordinating Committee 2011 Strategic Plan for Autism Spectrum Disorder Research, but rapid progress is hampered by the challenges of acquiring relevant data in large epidemiologic samples. The goals of the current proposal are to examine: (1) fundamental controversies concerning familial and environmental contributions to risk for ASD; (2) transmission of risk across generations; (3) investigate pregnancy-related environmental factors in ASD, and (4) the potential role of epigenetic changes in those factors.

### **Plain Language summary**

The resource established by the MINERVA Network will allow more accurate and precise determination of the contributions of familial and environmental factors to the etiology of autism, in particular if medications for maternal chronic and acute conditions prescribed in pregnancy contribute to



ASD risk, and whether epigenetic processes underlie a biological abnormality linked to autism. From a public health perspective the study will accelerate the characterization of high risk groups, modifiable risk factors and the elucidation of mechanisms in autism etiology that could ultimately contribute to preventive measures or interventions and treatments.

### **Funders of the project**

NIH (ACE program)

### **External collaborators**

Avi Reichenberg, Mount Sinai School of Medicine, US

Joseph Buxbaum, Mount Sinai School of Medicine, US

Alexander Kolevzon, Mount Sinai School of Medicine, US

Michaeline Bresnahan, Columbia University Medical Center, US

Ezra Susser, Columbia University Medical Center, US

Mady Hornig, Columbia University Medical Center, US

Erik Parner, University of Aarhus, Denmark

Christina Hultman, Karolinska Institute, Sweden

Yudi Pawitan, Karolinska Institute, Sweden

Sven Sandin, Karolinska Institute, Sweden

Camilla Stoltenberg, Norwegian Institute of Public Health, Norway

Andre Sourander, Turku University, Finland

Mika Gissler, Turku University, Finland

## **HERITABLE AND ENVIRONMENTAL DETERMINANTS OF HOSPITALISATION FOR COMMON CHILDHOOD ILLNESSES**

*David Burgner, Nick de Klerk, Kim Carter*

Infection is the leading cause of global child mortality and morbidity, and in Australia the commonest reason for childhood hospitalisation. Infection-related conditions are the commonest surgical procedures in children. Although all children are repeatedly exposed to life-threatening pathogens, only a minority develop severe infection. Understanding the basis for this differential susceptibility is critical to reduce the huge infectious disease burden. Host factors contribute to infection-related mortality, and to susceptibility to specific, largely tropical diseases, but the genetic and environmental determinants of hospitalisation with common infections are unexplored. We will leverage the unique Western Australian data linkage resources, which include the largest population-based twin registry and sophisticated genealogical linkages, to undertake the definitive twin and sibling study of infection-related hospitalisation. We will determine the relative contributions of genetic, and shared and non-shared environment on risk of hospitalisation for common childhood infection and related procedures.

### **Plain Language summary**

This study combines the unique and powerful resources of the Western Australian (WA) Data Linkage System and the WA Twin Register to disentangle the effects of genetics and the environment on the most common infectious causes

of hospital admissions in children. It will highlight appropriate pathways to prevent such admissions in the future.

### **Funders of the project**

NHMRC

### **External collaborators**

David Burgner, Murdoch Children's Research Institute, Melbourne

## **2015 Success**

### **EXTERNAL COMMITTEES**

#### **National**

- Australian Bioinformatics and Computational Biology Society

#### **Local**

- WA Committee Member, Australian Society for Medical Research (ASMR)





# DEVELOPMENTAL PATHWAYS IN WA CHILDREN PROJECT

## Overview

In 2005, the Developmental Pathways in Western Australian Children Project (DPP) was established at the Telethon Kids Institute, in collaboration with the Department of Health and three other state government departments.

The DPP is a landmark project taking a multidisciplinary and holistic approach to investigate pathways to health and wellbeing, as well as developmental and social outcomes. The project encompasses a number of important areas of research including mental and physical health, child abuse and neglect, alcohol and drug use, juvenile delinquency, disability, education and housing.

The DPP was created to establish the linkage of non-health datasets to the Western Australian Data Linkage System (WADLS), to allow for the investigation, reporting, monitoring and evaluation of outcomes across all health and social service sectors to answer complex cross-agency questions.

The DPP is internationally innovative in its use of linked statutory and government agency data sets to measure and monitor these development and health and wellbeing outcomes at the population level.

The DPP pioneered the process of linking together de-identified longitudinal,

population based data collected and stored by a large number of Western Australian (WA) government departments and the Telethon Kids Institute, to create a powerful and unique research and policy planning/evaluation resource for use by researchers and decision makers.

Researchers from the Telethon Kids Institute and the University of Western Australia (UWA) partner with community and consumer groups, and a number of state government departments, including the Departments of Health, Education, Training and Workforce Development, Child Protection and Family Support, Corrective Services, Local Government and Communities, Aboriginal Affairs, Treasury, Housing, Attorney General (Courts), the Disability Services Commission, the Mental Health Commission, the School Curriculum and Standards Authority, and WA Police.

The primary aims of this collaboration are to:

1. Extend and expand the pioneering population level data linkage across multiple disciplines and government sectors in WA;
2. Ascertain whether changes in factors at the child, family and community level increase or reduce vulnerability to adverse outcomes in mental and physical health, education, child maltreatment and juvenile offending in all WA children;
3. Identify areas of prevention and intervention across multiple government sectors, particularly in



regard to mental health, disabilities, child protection, juvenile justice, educational achievement and school attendance;

4. Use these data to evaluate existing government initiatives and determine, at a population level, how initiatives have impacted on educational, social and health outcomes;
5. Improve the collection, utilisation and reliability of government department data in program evaluation and policy development; and
6. Respond to the government departments' agendas and policy frameworks, while enhancing whole of government initiatives.

During 2015, the Data Linkage Branch (DLB) completed updates to the following linkages for use by projects under the DPP:

- Department of Corrective Services data (Adults): To December 2014
- Department of Corrective Services data (Juveniles): To December 2014
- Department of Education data (Attendance): To December 2014

The DLB also received and evaluated the following datasets, to be linked during 2016 for use by projects under the DPP:

- Department for Child Protection and Family Support: Update
- Department of the Attorney General (Courts): New linkage
- WA Police (Domestic violence cohort): New linkage

In 2015, the DPP and DLB were successful in gaining approval to add data from the Department of Housing into the WADLS. This was formalised in a memorandum of understanding (MoU) between the

Department of Health and the Housing Authority in January 2015.

Three PhD theses were submitted in 2015. These projects investigated early risk factors, and education and justice outcomes for children with Attention Deficit Hyperactivity Disorder (ADHD); the relationship between mental health and educational achievement; and educational outcomes for children in contact with the child protection system.

A new PhD student was recruited to the DPP in 2015 to investigate the impact of intimate partner violence (IPV) on children's outcomes. This will be the first project to use linked data from WAPOL.

In 2015, DPP researchers developed a National Health and Medical Research Council (NHMRC) grant to further research in the area of alcohol-related injuries and violence in young people. The grant resulted from a paper comparing rates of harm in England and Australia, which found that rates of alcohol related harm were decreasing in England and increasing in WA. The project will utilise demographic details and predictors of harm based on data from the Departments of Education, Child Protection and Family Support and WA Police. There will also be a spatial analysis component, in which the density of liquor outlets will be linked with call out data from WA Police.

In 2015, Dr Melissa O'Donnell and her team completed the data analysis and finalised a paper examining the risk of child protection involvement for children with disabilities. Dr O'Donnell and PhD candidate, Miriam Maclean,

also completed a systematic review on outcomes for children taken into out-of-home care compared to those who remain at home with their family, and submitted revisions following review by the journal *Child Abuse Review*.

Miriam Maclean completed her PhD in 2015, and submitted her thesis in December 2015. Miriam received re-extracted education data from the DLB in October 2014, and consequently was able to finalise data cleaning and preparation, analyse the data, and complete four studies using the linked data in 2015.

In 2015, Jocelyn Jones completed the final draft for the paper 'Violence in lives of incarcerated Aboriginal mothers in WA', and worked on another paper titled 'Aboriginal women's experiences of mothering in and out of prison'. Jocelyn also worked on an application for an NHMRC Early Career Fellowship, which will be submitted in early 2016. Jocelyn's PhD is expected to be submitted in April 2016.

In 2015, Professor Desiree Silva worked on an original paper titled 'Education and justice outcomes for Australian Aboriginal children and youth with Attention Deficit Hyperactivity Disorder'. Professor Silva also worked on a study looking at early anesthetic risk in childhood associated with a later diagnosis of ADHD.

In 2015, Janice Wong finalised three papers, which will be submitted for publication in 2016. Janice finalised her PhD thesis in 2015, which comprised a literature review, a methodology chapter regarding data linkage, and a general discussion chapter summarising the results

of all six studies completed using linked data.

Nan Hu finalised four papers in 2015. Nan also worked on another paper titled 'Experience in care of maltreated children and their risk of deliberate self-harm in adolescence'. Nan's PhD is expected to be submitted in April 2016.

In 2015, Ifrah Abdullahi worked extensively on the research design for the project investigating the health and developmental outcomes of children from immigrant and refugee backgrounds in WA. Ifrah's research proposal was approved by the UWA Graduate Research School in 2015, and the Department of Health Human Research Ethics Committee also granted access to existing linked data through an amendment to an existing project. In 2015, Ifrah finished cleaning and preparing the data and began to analyse existing data. Ifrah also worked on ethics applications for Phase II and Phase III of the project, as well as a systematic review paper.

In 2015, Carol Orr submitted a research proposal to UWA for the project investigating the impact of IPV on children's outcomes, as well as an expression of interest to the Department of Health for data to be linked by the Data Linkage Branch.

In 2015, a paper by PhD candidate Megan Bell titled 'Child and mother chronic illness is associated with developmental vulnerability at school entry', was accepted for publication by the journal *Pediatrics*, and will be published in 2016. Megan also worked on



a paper titled 'Parental mental illness is associated with lower school readiness in offspring'.

In 2015, Professor Gwynnyth Llewellyn obtained the final component of data required for the prevalence study looking at parents with intellectual disability and their children. Professor Llewellyn was also able to finish analysing existing data, and produce a preliminary report.

In 2015, Dr Anett Nyaradi received Western Australian Certificate of Education (WACE) data required for the project investigating the relationship between diet and academic achievement amongst children in the Western Australian Pregnancy Cohort (Raine) Study. Dr Nyaradi also finished analysing Western Australian Literacy and Numeracy Assessment (WALNA) data for this project.

In 2015, Jane Bell completed the analyses for studies comparing long term survival, hospitalisations and school performance between children born with orofacial clefts and children without clefts. Jane also commenced analyses examining whether school absence influences school performance for children with and without orofacial clefts.

In 2015, Caitlin Dowell cleaned the project data and completed a first analysis measuring the prevalence of maternal incarceration in WA. Caitlin also commenced data analysis for a second study describing the nature of children's exposure to maternal incarceration.

## Research projects

### **DEVELOPMENTAL PATHWAYS PROJECT**

Research from the DPP provides new knowledge to inform whole of government intervention and prevention strategies designed to improve health and wellbeing, and developmental and social outcomes. The DPP produces research that can be used to influence policy frameworks, and evaluate and monitor existing initiatives and policies that aim to improve outcomes.

The DPP has a large number of research projects incorporating several different research focus areas (as listed above).

A list of all DPP projects, including those that have been completed, is provided in Appendix 1.

Researchers and government agencies apply for project approvals through the DPP Research Management Group (RMG) throughout the year. To date, a total of 35 DPP projects have been approved through this mechanism and are now in various stage of completion.

### **Names of investigators and collaborators**

Professor Fiona Stanley  
Professor Stephen Zubrick  
Professor Nicholas de Klerk  
Dr Jianghong Li  
A/Professor Natasha Nassar  
Dr Helen Leonard  
Dr Cate Taylor  
Dr Rebecca Glauert  
Dr Melissa O'Donnell  
A/Professor Anna Ferrante

Professor Desiree Silva  
Janice Wong  
Miriam Maclean  
Nan Hu  
Jocelyn Jones  
Scott Sims  
Megan Bell  
Michael Moltoni  
Professor Rhonda Marriott  
Ifrah Abdullahi  
Professor Gwynnyth Llewellyn  
Dr Anett Nyaradi  
Caitlin Dowell  
Jane Bell  
Carol Orr  
Dr Lina Gubhaju  
The Directors' General/Commissioners of  
11 WA government departments

The DPP takes a multidisciplinary and holistic approach to research into the health, development and wellbeing of children and youth, by initiating and utilising linked, longitudinal population level data from a number of government agencies.

The DPP has a large number of research questions which overlap areas of focus. This reflects the complex nature of many of the problems facing Australian children and youth, and highlights the strengths of the project to address these multi-sectoral issues.

Research questions can be grouped into two broad areas:

1. Improving the understanding of the child, family and community factors involved in the pathways to juvenile offending, child abuse and neglect, poor physical and mental health outcomes, educational achievement and school attendance/suspension,

and identification of required interventions to optimally influence pathways; and

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

### **Plain language summary**

The DPP links de-identified population level data from WA government departments and agencies to investigate risk and protective factors leading to differences in developmental outcomes for children and youth.

The DPP represents an innovative collaboration between researchers, primarily based at the Telethon Kids Institute, and a number of government jurisdictions in WA.

The data are used to determine risk and protective factors leading to poor and good outcomes in WA children.

The DPP encompasses a number of important areas of research; mental and physical health, child abuse and neglect, alcohol and drug use, juvenile delinquency, disability, education, and housing. We have a large number of research questions which overlap these areas of focus.

With the Department of Health WA, the DPP has pioneered population level data linkage across multiple government service sectors in WA, creating a unique data resource for use by researchers and policy makers.

### **Funders of the project**

The DPP has been funded by two



consecutive Australian Research Council (ARC) Linkage Project Grants, with generous additional cash and in-kind contributions provided from the partnering government agencies.

### **External collaborators**

There is significant engagement amongst the partner agencies involved in the DPP. This has led to a large number of researcher applications for projects using linked data, as well as interest amongst agencies for the use of linked data to evaluate programs and services.

The DPP facilitates the provision of de-identified, non-health linked population level data to a number of research projects conducted within other research institutions and government departments, including the following:

Professor Gwynnyth Llewellyn  
Centre for Disability Research and Policy,  
University of Sydney  
New South Wales, Australia

Professor Leonie Segal  
University of South Australia  
South Australia, Australia

Dr Natasha Nassar  
Kolling Institute for Medical Research,  
University of Sydney  
New South Wales, Australia

Dr Jianghong Li  
WZB Berlin Social Science Center  
Germany

Dr Cate Taylor  
Child and Family Centres, Tasmanian  
Government

Tasmania, Australia

Professor Rhonda Marriott  
Murdoch University  
Western Australia, Australia

Dr Sophie Davison  
Clinical Research Centre, Graylands  
Health Campus  
Western Australia, Australia

A/Professor Anna Ferrante  
Population Health Research Network  
Centre for Data Linkage, Curtin University  
Western Australia, Australia

Dr Lina Gubhaju  
Baker IDI Heart & Diabetes Institute  
Victoria, Australia

Investigators from the DPP also have ongoing collaborations with Professor Ruth Gilbert and her team at the Institute of Child Health, University College London, United Kingdom, and Rosemary Cant who is currently completing her PhD through the School of Population Health at UWA in Perth, Western Australia, in the area of child sexual abuse.

In 2015, DPP researchers were involved in a cross-country comparison on neonatal withdrawal syndrome using hospital administrative data from England, the United States, WA and Ontario, Canada.

## **2015 success**

### **PHD THESES SUBMITTED**

Professor Desiree Silva  
MBBS, FRACP, MPH

UWA

Early risk factors of children diagnosed with Attention Deficit Hyperactivity Disorder and their education and justice outcomes

Janice Wong (under examination)  
BSc (Psych) (Hons), MPsych (Clinical)  
UWA

Using population level linked data to examine the relationship between mental health and educational achievement: A longitudinal study

Miriam Maclean (under examination)  
BA (Psych) (Hons), MSc  
UWA

Educational outcomes of children in contact with the child protection system: A longitudinal population study

## AWARDS AND PRIZES

Dr Melissa O'Donnell  
Consumer and Community Involvement Award

## EXTERNAL COMMITTEES

Researchers from the DPP were involved in a number of international, national and local committees, representing the DPP and their research interests:

### International

Professor Desiree Silva  
Organising Committee for the 5th World Congress on ADHD  
2015

### National

Janice Wong  
Australian Association of Cognitive Behavioural Therapy  
2010 – Present

Professor Fiona Stanley  
Australian Broadcasting Corporation Board  
2011 – Present

Professor Fiona Stanley  
McCusker Alcohol Advertising Review Board (Chair)  
2012 – Present

Professor Fiona Stanley  
Australian Research Council Centre of Excellence for the History of Emotions Advisory Board  
2013 – Present

Professor Fiona Stanley  
Gurrumul Yunupingu Foundation Board  
2014 – Present

Professor Fiona Stanley  
RAND Australia Advisory Council  
2015 – Present

Jocelyn Jones  
Ombudsman's Advisory Panel  
2014 – Present

### Local

Dr Melissa O'Donnell  
Youth Health Working Group  
2014 – 2015

Dr Melissa O'Donnell  
Mental Health and Suicide Working Group  
2015

Dr Rebecca Glauert  
Ngala Professional Advisory Committee  
2011 – Present

Miriam Maclean  
Telethon Kids Institute Student Circle



Committee  
2014 – 2015

## INVITED PRESENTATIONS

The DPP had its work presented at a number of international, national and state conferences, meetings and forums in 2015.

Megan Bell  
Chronic illness in early childhood impacts school readiness  
Australian Early Development Census Conference  
Adelaide, Australia  
February, 2015

Megan Bell  
Physical and mental health in the early years: Impacts on school readiness  
Society for Research in Child Development Biennial Meeting  
Philadelphia, United States  
March, 2015

Janice Wong  
Patterns of participation in Year 9 academic testing and environmental characteristics predicting absence on the day of test  
Developmental Pathways Project  
Consumer & Community Reference Group meeting  
Perth, Australia  
March 26, 2015

Jane Bell  
Presentation of early results for studies comparing hospital admissions and school test results for children born with and without clefts  
WA CleftPALS Annual General Meeting,  
Princess Margaret Hospital

Perth, Australia  
May 17, 2015

Miriam Maclean & Dr Melissa O'Donnell  
Early educational outcomes for children in out-of-home care  
Department for Child Protection and Family Support Education Services Workshops  
Perth, Australia  
May 26-27, 2015

Professor Desiree Silva  
Life course for Aboriginal and non-Aboriginal children with ADHD  
5th World Congress on ADHD  
Glasgow, Scotland  
May 28-31, 2015

Dr Rebecca Glauert  
Deliberate self-harm and suicide rates and risk factors in WA adolescents  
Drug and Alcohol Office  
Perth, Australia  
July 1, 2015

Ifrah Abdullahi  
Investigating the health and developmental outcomes for children of immigrant and refugee backgrounds in Western Australia  
Student Advisory Panel meeting  
Perth, Australia  
August 27, 2015

Dr Anett Nyaradi  
The relationship between diet and educational outcomes in a cohort of Western Australian children  
School of Population Health UWA  
Perth, Australia  
September 8, 2015

Carol Orr

Using linked population data to investigate the impact of intimate partner violence on children's outcomes  
Developmental Pathways Project  
Consumer & Community Reference  
Group meeting  
Perth, Australia  
September 17, 2015

Dr Anett Nyaradi  
The relationship between diet and educational outcomes in a cohort of Western Australian children  
Raine study meeting  
Perth, Australia  
September 18, 2015

Jane Bell, Dr Camille Raynes-Greenow, Dr Robin M. Turner, Professor Carol Bower, Alan Dodson & Dr Natasha Nassar  
Does being born with a cleft lip or palate affect children's school test results?  
School of Public Health Research Day, University of Sydney  
Sydney, Australia  
September 28, 2015

Caitlin Dowell, Professor David Preen & Professor Leonie Segal  
Quantifying children affected by maternal incarceration: to count you need to be counted.  
South Australia Population Health Conference  
Adelaide, Australia  
October 31, 2015

Jocelyn Jones  
'I've got to live my life, I can't live mad all day, all my life': Lived experiences of Aboriginal youth  
Public Health Association Australia, Second National Complex Needs

Conference  
Canberra, Australia  
November, 2015.

Jocelyn Jones  
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  
Public Health Association Australia, Second National Complex Needs Conference  
Canberra, Australia  
November, 2015.

Dr Melissa O'Donnell & Scott Sims  
Trends in injury admissions associated with alcohol in adolescents in Western Australia and England: Intentional and unintentional causes  
APSAD Annual Scientific Alcohol and Drug Conference  
Perth, Australia  
November 8, 2015

Professor Desiree Silva  
Is early inflammation associated with Attention Deficit/Hyperactivity Disorder?  
World Congress on Developmental Origins of Health and Disease  
Cape Town, South Africa  
November 8-11, 2015.

Dr Melissa O'Donnell & Scott Sims  
Trends in injury admissions associated with alcohol in adolescents in Western Australia and England: Intentional and unintentional causes  
Telethon Kids Institute Scientific Retreat  
Perth, Australia  
November 16-17, 2015

Dr Melissa O'Donnell attended the



meeting, Big Data and the 2030 Agenda for Sustainable Development: Achieving the development goals in the Asia and Pacific Region, as part of the United Nations Economic and Social Commission for Asia and the Pacific  
Bangkok, Thailand  
December 14-15, 2015

Dr Melissa O'Donnell also attended the meeting, Potential Research on Linked National Child Protection Data, facilitated by the Australian Institute of Health and Welfare  
Canberra, Australia  
August 21, 2015

Dr Melissa O'Donnell was also invited to attend the Western Australian Senate Enquiry into the Review of the Role of the Commissioner for Children and Young People coordinated by the Western Australian Parliament Senate Committee  
West Perth, Australia  
2015





# FRASER MUSTARD CENTRE

## TELETHON KIDS INSTITUTE (ADELAIDE TEAM) AND THE FRASER MUSTARD CENTRE

### Overview

A key component of the Adelaide Team's continues to include the Australian Early Development Census (AEDC) programme, an Australian Government backed commitment that measures children's development across the nation. The AEDC is a population measure of how our children develop through to their early school years. Teachers collect data across core areas of learning, health and wellbeing and this data is used to develop a snapshot of child development in communities across Australia. AEDC data was collected nationally for the third time in 2015; with this comes the opportunity for communities to begin to look at emerging trends in child development, and to identify what is working well and what needs to be improved to best support children and their families.

Another primary aspect of the Adelaide Team is the Fraser Mustard Centre, established in September 2012 and named in recognition of Dr Fraser Mustard's contribution to South Australia. The Telethon Kids Institute has joined forces with the South Australian Department for Education and Child Development to create a research partnership aimed at improving developmental, health and educational outcomes for children and young people. The Fraser Mustard Centre has been created to bring together

leading Australian child researchers and innovative government policy makers and planners with a focus on enhancing programs and services for young people.

In just three years since its commencement, the Centre has established itself as a practical and unique example of how research and policy can and should interact to achieve real results. Some of the key achievements and highlights exemplifying the uniqueness of the collaboration include:

- Hosting of the Fraser Mustard Centre Lunchbox Lectures. These Lectures are an effective way to share local, national and international research, experience and knowledge and ensure direct translation of research into policy. The Fraser Mustard Centre has so far hosted researchers from both Australia and Canada, and covered a broad range of child development related topics. Lectures are free and open to all interested staff of South Australian Government Agencies.
- The award of an Australian Research Council grant for the implementation of the Middle Years Development Instrument, and its adaptation for use with Aboriginal and Torres Strait Islander communities. Without the unique collaboration that is the Fraser Mustard Centre, the Department would not have been eligible for leveraging academic research funding and the Institute gains the backing of the South Australian Government to deliver the research.

- The design and technical support for the expansion of the Early Years System, to capture the activities of the SA Children's Centres for both operational and reporting purposes as well as for monitoring and evaluation. The Centre has provided unconstrained access to experts in database development and program evaluation throughout this process.
- Providing capacity building, training and ongoing support to data analysts within the Department.
- Undertaking professional development for Children's Centres staff in the use of evidence and data to help support local level planning.
- Undertaking sessional teaching to upskill Early Childhood Teachers.
- Hosting Peer Review sessions where the Institute staff and the Department staff take turns to present their work and raise any problems they are encountering to the group. The aims of the sessions include enhancing healthy critical debate within a supportive environment and the sharing of skills and capacities amongst the team.
- Providing continued and ongoing capacity building and support to South Australia around the Australian Early Development Census, with a particular focus on policy implications, population wide planning and local level community support.

Many of these achievements would not have been possible without being embedded within the Department of

Education and Child Development. Additionally many of the achievements are outside the normal scope of traditional academic research groups or even contract research organisations. Co-location of the Institute staff within the Department has enabled ready access from DECD staff to strategic advice, support for policy briefs, and ad hoc information requests. As the Institute staff are apprised of the research at an international level we are able to provide a quick synthesis of the latest evidence and practice trends. The Institute's network of academic colleagues locally, nationally and internationally has helped to facilitate and support broader collaboration between government and academia.

The Fraser Mustard Centre provides a simple, extremely cost effective way for the South Australian Government to develop evidence based policies and services, evaluate and monitor these policies, and support their pragmatic implementation into mainstream practice. The Centre has developed a Knowledge Translation Model, to provide a framework for the development of evidence based policy and programs, and to inform future research priorities for the Fraser Mustard Centre.

## Research Projects

### **AUSTRALIAN EARLY DEVELOPMENT CENSUS (AEDC) RESEARCH PROJECTS**

*Sally Brinkman, Yasmin Harman-Smith, Tess Gregory, Alanna Sincovich*



The AEDC is a population measure of young children's development. Like a census, it involves collecting information to help create a snapshot of children's development in communities across Australia. Teachers complete the checklist for children in their first year of full-time schooling. The AEDC measures five developmental domains: physical health and wellbeing, social competence, emotional maturity, language and cognitive skills (school-based), and communication skills and general knowledge.

The AEDC has now been completed nationwide three times: in 2009, 2012, and most recently in 2015. Throughout 2015, researchers at the Telethon Kids Institute finalised works based on the 2009 and 2012 AEDC data, with research focusing on a range of questions pertinent to early childhood development such as:

- Are there jurisdictional differences in the level of developmental vulnerability across Australia?
- Is there a differential impact of living in mining towns vs. non-mining towns for Aboriginal child development?
- How does the AEDC predict later academic outcomes during the primary school years?
- What is the best methodology to use to determine whether communities, LGAs etc have experienced significant change in the childhood development from 2009 to 2012, and what is the best way to communicate this information to various stakeholders?
- How well do perinatal factors (e.g. low birth weight) predict childhood development at 5 years old?

### **Funder of the Project**

Department of Education and Training  
(Australian Government)

### **PROVISION OF ENGAGEMENT SERVICES FOR THE AEDC**

*Sally Brinkman, Yasmin Harman-Smith, Tess Gregory, Alanna Sincovich*

Throughout 2015 the Telethon Kids Institute continued to provide support services in relation to the Australian Early Development Census (AEDC). Within this scope of works, support services are provided to both the Department of Education and Training (Canberra) and the eight AEDC State and Territory Coordinators and their support staff across Australia.

The Institute's AEDC support team provides professional development opportunities, strategic advice and support, and develops AEDC engagement resources to support the implementation and utilisation of the AEDC by community, schools, governments and researchers. The team also manages an online learning portal and forum for AEDC coordinators, delivered a National Conference focused on the AEDC in 2015, and coordinates monthly national teleconference and quarterly national meetings.

### **Funder of the Project**

Department of Education and Training  
(Australian Government)

### **External Collaborator**

Social Research Centre, Fenton

## **AUSTRALIAN EARLY DEVELOPMENT CENSUS (AEDC) PILOT COMMUNITIES – EXPLORING RESULTS OVER TIME**

*Sally Brinkman, Tess Gregory, Lydia Braunack-Mayer*

The AEDC provides a snapshot of child development at school entry for all of the children living in Australia once every three years. In 2015, the third census will be completed providing the first opportunity to explore trends in child development for Australia.

Prior to the first national census in 2009, about 60 communities across Australia were involved in early pilot research using the same instrument. This project aimed to provide these communities with comparable data from the pilot (2004-2008) and the first two census collections (2009 and 2012), so that they can compare the child development outcomes in their communities over time. This project has a strong research translation component by exploring a range of different ways to present trend data on the AEDC over time, which will inform the development of community reports using 2009, 2012 and 2015 AEDC national census data. This project has now been complete, and over 93 Australian communities received a community report, detailing child development outcomes in their communities across multiple data points.

### **Funder of the Project**

Department of Education and Training  
(Australian Government)

## **EVALUATION OF SOUTH AUSTRALIAN CHILDREN'S CENTRES**

*Sally Brinkman, Yasmin Harman-Smith*

To reduce the impact of social inequality on children's outcomes, the South Australian Government has established a number of Children's Centres across South Australia. There are presently 42 Children's Centres across South Australia. Children's Centres are generally located in areas of high need to enable the provision of high quality services to children and families who may not otherwise have access to these supports. Children's Centres are based on a model of integrated practice, bringing together education, health, care, community development activities, and family support services in order to best meet the needs of vulnerable children and families.

Specifically, Children's Centres are tasked to provide universal services with targeted support in order to effect population outcomes in four areas: 1) Children have optimal health, development and learning; 2) Parents provide strong foundations for their children's healthy development and wellbeing; 3) Communities are child and family friendly; 4) Aboriginal children are safe, healthy, culturally strong and confident (Department for Education and Child Development, 2011).

The Telethon Kids Institute through the Fraser Mustard Centre has been engaged to undertake a process and impact evaluation of South Australian Children's Centres. The mixed methods evaluation commenced in 2012 and the first stage of qualitative works were completed in 2014. An interim report



on the qualitative findings has been produced and is available on the Fraser Mustard Centre website. A survey of staff working in Children's Centres, Service Providers working with Children's Centres, and families using Children's Centres was undertaken during 2014. The survey results will be reported in 2016 alongside service usage data, which was collected systematically in Centres for the first time in 2015.

### **Funders of the Project**

Government of South Australia,  
Department for Education and Child  
Development

### **CONCEPTUAL PAPER ON SCREENING AND ASSESSMENT IN EARLY CHILDHOOD AND AT SCHOOL ENTRY**

*Sally Brinkman, Yasmin Harman-Smith, Tess Gregory, Alanna Sincovich*

South Australia, through the Department for Education and Child Development, has been tasked with leading a national project that will provide a comprehensive picture of the range of data collections and specific screening and assessment tools used across health, early childhood and education sectors to consider ways in which these tools can support practice, policy development and national research priorities. The Department has engaged the Telethon Kids Institute to undertake an initial state specific review that will provide a foundation for this project.

The overall objectives of the evaluation are to: 1) consider what developmental domains (and family factors that influence) should be screened and

assessed to best respond to learning and development needs, 2) when these measures would be best implemented taking into consideration sensitive periods in development, 3) current contact points for screening and assessment in South Australia. Using the findings from these reviews, a range of recommendations will be formulated for consideration by the Department.

### **Funders of the Project**

South Australian Department for  
Education and Child Development

### **STRONG START PROGRAM EVALUATION**

*Sally Brinkman, Yasmin Harman-Smith*

Researchers from the Fraser Mustard Centre have been engaged to support the Strong Start program – a pilot program targeted at first time mothers who are experiencing numerous complex issues. The program seeks to engage pregnant women to help them prepare emotionally and practically for the arrival of their infant. By working with mothers to develop their skills to cope with challenges, connect them to resources, and increase their parenting capacity, Strong Start seeks to support the development of children who may otherwise be at risk of adverse outcomes.

The evaluators have worked with the program providers to establish a database to collect administrative and outcomes data for clients of the service. The Strong Start program has been established for the first time, thus the evaluators have worked closely with the program providers

to design an evaluation that enables them to respond to implementation challenges as the program becomes imbedded as well as to measure what difference the program is making for clients and their infants. The evaluation uses a mixed-methods design to measure both process (how well the program was being delivered) and impact (improved outcomes for mothers and their infants).

### **Funders of the Project**

Government of South Australia,  
Department for Education and Child  
Development

## **ASSESSING THE DEVELOPMENT, WELL-BEING AND COMMUNITY CONNECTEDNESS OF CHILDREN IN THE MIDDLE YEARS: THE MIDDLE DEVELOPMENT INSTRUMENT FOR AUSTRALIA**

The Middle Years Development Instrument (MDI) is a validated population-level measure of well-being and contextual assets in middle childhood. The MDI was designed in Canada, to provide schools and communities with pragmatic data to inform policies and practice. The Middle Development Instrument gives children a voice, an opportunity to communicate to adults about what their experiences are inside and outside of school. The MDI has great potential to provide educators, parents, researchers, and policy makers with much needed information about the psychological and social worlds of children.

Researchers completed a pilot project in 2013, measuring the wellbeing of approximately 6,000 children across South

Australia and Victoria in the middle years of school in order to provide summary information back to policy makers, schools and communities about the health and wellbeing of their children. In 2014, DECD completed a second round of data collection involving almost 18,000 children, including schools and students which participated in the 2013 research trial, allowing the accuracy of data to be explored further and to provide these schools with two data points.

Participating schools have now received their school report containing data on student's self-reported wellbeing. In 2013 the MDI received additional financial support through an ARC Linkage Grant. The grant provides further funding to establish the validity of the MDI in Australia, explore the international comparability of the instrument between Australian and Canada, and culturally adapt the MDI for Australian Aboriginal children, by leveraging off the MDI data collected.

### **Funders of the Project**

Australian Research Council Linkage Grant, Government of South Australia, Department for Education and Child Development.

### **External Collaborators**

Prof Sven Silburn (Menzies School of Health Research, NT), Dr Kimberly Schonert-Reichl, A/Prof Martin Guhn and Dr Anne Gadermann (University of British Columbia), Rosemary Cahill (Department for Education, WA), and David Engelhardt (Department for Education and Child Development, SA).



## EVALUATION OF THE COMMUNITY PLAYGROUP PROGRAM

*Sally Brinkman, Yasmin Harman-Smith, Tess Gregory, Alanna Sincovich*

At the request of Playgroup Australia, in 2015 researchers at the Telethon Kids Institute completed works on the evaluation of the Community Playgroup Program across Australia. Community playgroups provide an opportunity for children to learn through unstructured play and for parents to develop social networks and improve parenting skills. Playgroup attendance is likely to impact child development through several pathways, there is, however, limited national and international research quantifying the specific impact of playgroups on childhood development and wellbeing.

The overall objectives of the evaluation are to explore the facilitators and barriers that influence Community Playgroup attendance, and examine the impact of attending playgroups on children's early development. There is a lot of research on the positive impact of playgroups on parents, though less is known about the direct impact of playgroups on children's development. Researchers explored the impact of playgroups on physical, social, emotional, and language development was explored, as well as the impact of playgroups for children with different background characteristics. Findings from the evaluation will be used to advocate for the importance of playgroups for children's development.

### **Funder of the Project**

Playgroup Australia

## THE EARLY HUMAN CAPABILITY INDEX (EHCI)

*Sally Brinkman, Alanna Sincovich*

Despite the fact that billions of dollars are being spent on early childhood initiatives around the globe, the current tools available to measure the effectiveness and impact of such interventions are not adequate, particularly in marginalised and poor communities. There is crucial need for an instrument that can truly detect the impact of interventions seeking to enhance early human capability through health, nutrition and early stimulation programs.

The Early Human Capability Index is a holistic measure intended to capture early child development across diverse cultures and contexts. The eHcI has been developed with a view to capture the key aspects of child development in 3-5 year olds that predict future capabilities. The eHcI is an easy-to-use survey tool that can be completed by parents/caregivers, child care workers, teachers, allied health and other health or early childhood practitioners. It is not a developmental milestone test, but is a measure of where a child can be placed on a developmental spectrum. As such the eHcI can determine if a child is thriving or doing poorly on different aspects of development, and can detect developmental change over time. The eHcI covers the following aspects of child development including: general verbal communication, approaches to learning, numeracy and concepts, formal literacy – reading and writing, cultural knowledge, social and emotional skills, perseverance, and physical health. The eHcI can be used for: population

monitoring and surveillance; impact evaluations of interventions aimed at improving child health, early education and development; and for longitudinal cohort studies looking to predict the future capabilities and capacities of children.

A/Prof Brinkman has received an NHMRC Early Career Fellowship which is currently enabling the rigorous field testing of the EHCI across China, Lao PDR, Tonga, Samoa, and Tuvalu.

### **Funder of the Project**

National Health and Medical Research Council

### **External Collaborators**

World Bank, China Development Research Fund

## **KIDS IN COMMUNITIES STUDY (KICS)**

*Sally Brinkman, Ashleigh Wilson*

Researchers at the Telethon Kids Institute are collaborators on an ARC linkage grant working to understand how different factors in our communities (physical environment, social environment, socio-economic factors, access to services, and governance) influence the way that children develop.

KICS uses a variety of research methods conducted in three phases. In Phase 1, different types of data about child development and socio-economic status were used to find communities in VIC, NSW, QLD, SA, and the ACT where children are developing unexpectedly well or poorly when compared with the socio-economic status of their suburb.

These communities were then compared to other communities where children's outcomes match the predicted outcomes based on their socio-economic status. In Phase 2, we will collect data using community surveys, service surveys, and focus groups, interviews with local stakeholders and experts, and mapping of neighbourhoods. In Phase 3, we will analyse the data and develop a manual for communities and local governments to use in measuring and improving child development outcomes.

Findings from KICS will have the potential to help governments at all levels improve policies relating to child development, by providing more information on what factors are consistently related to better outcomes for children. This information will also help researchers and community stakeholders to properly measure outcomes in their communities, and respond with new evidence-based ways of improving children's wellbeing.

### **Funder of the Project**

Australian Research Council Linkage Grant

### **External Collaborators**

The Smith Family, Murdoch Childrens Research Institute, Wesley Mission Brisbane, Uniting Care, The Benevolent Society, Australian Government Dept of Education and Training, Australian Bureau of Statistics, VIC Dept of Education and Training, ACT Community Services Directorate, Children's Health Queensland Hospital and Health Service, QLD Dept of Education, Training and Employment, SA Dept for Education and Child Development, NSW Dept of Education



and Communities, The University of Melbourne, The University of Canberra, The University of Western Australia, The University of New South Wales, University of British Columbia, Mount Saint Vincent University

## **INTERDISCIPLINARY EDUCATION FOR THE EARLY YEARS PROJECT**

*Sally Brinkman, Alanna Sincovich*

Researchers at the Telethon Kids Institute are collaborators on the Interdisciplinary Education for the Early Years Project. This project aims to develop a national interdisciplinary learning and teaching framework to inform curriculum for the education of professionals across diverse disciplines who will work with children from birth to five years of age (the early years) and their families through:

- A statement of common outcomes that recognises various disciplinary foci.
- An interdisciplinary map of evidence informed theories and national regulatory requirements.
- A statement of universal essential elements (knowledge, skills and attributes).

### **Funder of the Project**

Australian Government Office for Learning and Teaching

### **External Collaborator**

Flinders University, Charles Sturt University, Queensland University of Technology, Gowrie SA, Australian Centre for Child Protection.

## **FRASER MUSTARD CENTRE PHD TOP-UP SCHOLARSHIPS**

### **Supervisors**

Sally Brinkman and Tess Gregory

In honour of Dr Fraser Mustard, the Fraser Mustard PhD Scholarship was established to fund one PhD student, based in the Fraser Mustard Centre, Adelaide. The scholarship provides additional funding support to a PhD candidate who has been awarded an Australian Postgraduate Award (APA) to undertake a PhD. The intent of this is to attract outstanding students who are passionate about improving developmental, health and educational outcomes for children and young people. It is envisaged that with the appropriate support, these researchers will later contribute to the advancement of policy and practice in the area of child development.

The first Fraser Mustard Centre Top-Up Scholarship was awarded in 2013 to Shiao Chong. Shiao is completing a PhD in the School of Population Health at the University of Adelaide. Her project is titled: The influence of early childhood temperament and parenting on cognitive, social and health outcomes. The second Fraser Mustard Centre Top-Up Scholarship was awarded in 2014 to Catherine Johnson. Catherine is completing a PhD in the School of Psychology at Flinders University. Her project is titled: Mindfulness in Schools: A transdiagnostic prevention programme. In 2015, the third Fraser Mustard Centre Top-Up Scholarship was awarded to Veronica Smyth. Veronica is completing her PhD in the School of Population Health

at the University of Adelaide. Her project examines inequalities in communication between children and their caregivers, and will make use of innovative speech recognition technology and linked data to investigate influences on children's capability formation, particularly in relation to language development.

Funder of the Project: Government of South Australia, Department for Education and Child Development

External Collaborators: A/Prof Lisa Smithers, Prof John Lynch (Adelaide University, SA), Prof Tracey Wade (Flinders University, SA).

## 2015 Success

### EXTERNAL COMMITTEES

#### International

Sally Brinkman

- Measuring Early Learning Quality and Outcomes (MELQO) Technical Advisory Group, United Nations. (2014 – current).

#### National

Sally Brinkman and Tess Gregory

- Australian Royal Commission into Institutional Child Abuse. Prevalence Study Advisory Group. (2015 – current).

#### Local

Sally Brinkman

- Vice President of the Board, Playgroups Association of South Australia, (2013-current)
- Subject Specialty Member (Data Linkage), South Australian Human Research Ethics Committee (2013-current)

Yasmin Harman-Smith

- Board Member, Gowrie SA

(2011-current)

- Council Member, National Community Child Health Council (2014-current)

Veronica Smyth

- Deputy Member, South Australian Human Research Ethics Committee (2014 – current)

### INVITED PRESENTATIONS

Sally Brinkman

- Invited Keynote. Population Based Outcome Measures in Multiple Countries. ARNEC Conference, Beijing, China. October 2015.
- Invited Speaker. Sustainable Development Goals, United Nations Post 2015 Development Agenda. West Australian Council of Social Services, Perth, Western Australia. August 2015.
- Invited Keynote. Partnership in Practice. Single day Professional Development offered to all social workers, and family carers (foster families) in South Australia. Child Development – what does healthy child development look like and how to enhance supportive environments to promote healthy child development. South Australian Govt Dept Families SA and the Child and Family Welfare Association. August 2015.
- Invited Keynote. The Australian Early Development Census in Practice. Building Capacity Conference, Albany, Western Australia. July 2015.
- Invited Keynote. The measurement of linguistic and cognitive outcomes. Early Child Development Measurement for Preschool Children. Worldbank, Washington D.C., USA. May 2015.
- Invited Keynote. The Australian Early Development Census: reflections over 13 years. Australian Early Development



Census 2015 National Conference, Adelaide. February 2015.

- Invited Speaker. The Fraser Mustard Centre: Trials and Tribulations. Australian Early Development Census 2015 National Conference, Adelaide. February 2015.
- AEDC Pilot Communities, exploring change in results from 2003 to 2012. Australian Early Development Census 2015 National Conference, Adelaide. February 2015.
- Invited Speaker. Predictive validity of the AEDC. Australian Early Development Census 2015 National Conference, Adelaide. February 2015.
- Invited Keynote. What the recent science in brain development tells us about the importance of early childhood. Launch of the Early Childhood Education Program, Vientiane, Lao PDR. January 2015.
- Invited Keynote. What do we mean by early childhood health and developmental stimulation. Launch of the Early Childhood Education Program, Vientiane, Lao PDR. January 2015.

#### Tess Gregory

- Invited speaker. Exploring change in the EDI over time – calculation of a critical difference. Australian Early Development Census 2015 National Conference. Adelaide, Australia. February 2015.
- Invited speaker. Inequality in child development between Australia's Aboriginal and Torres Strait Islander children and non-Indigenous children: Are we closing the gap? Australian Early Development Census 2015 National Conference. Adelaide, Australia. February 2015.

- Invited speaker. Exploring a new strength based indicator from the EDI: The Multiple Strength Index. Australian Early Development Census 2015 National Conference. Adelaide, Australia. February 2015.

#### Yasmin Harman-Smith

- Invited Keynote. Our children, our families and our communities: How are we doing? Early Years Conference, Cairns. September 2015.
- Invited Keynote. Social and emotional development in children. Families SA training day, Adelaide. August 2015.
- Invited Keynote. Partnership in Practice. Single day Professional Development offered to all social workers, and family carers (foster families) in South Australia. Services and supports for children and families in South Australia. South Australian Govt Dept Families SA and the Child and Family Welfare Association. August 2015.







# GENETICS AND HEALTH

## Overview

Our group uses 'omics-based technologies, including genomics (studies of human genetic variation), transcriptomics (global analysis of gene expression), epigenetic profiling (how environment determines gene expression), studies of the microbiome, and metabolomics, to understand both rare and complex diseases. The overall objectives of our research are to understand pathogenesis of disease to help us to find better diagnostics, therapeutics and vaccines. These modern 'omics-based research tools allow us to look at all of our genes and metabolic products to identify biomarkers of complex diseases like infections and diabetes, as well as using Next Generation sequencing to identify rare genetic variants causing single gene disorders and to study the microbiome.

In Australia, our current focus is on investigating the genetic basis to extreme outcomes like severe otitis media in children, and end-stage renal disease in adults, in a Western Australian Aboriginal population. Ear infections are the most common reason for young children to visit a doctor, and are a major cause of burst eardrums and hearing loss in Aboriginal children. Otitis media is a continuing focus of our research both in relation to human genetic risk factors, and in relation to the composition of the microbiome, associated with pathogenesis of disease. We are also interested in congenitally acquired diseases, including the outcomes

of infections such as toxoplasmosis transmitted to babies in utero, as well as developmental anomalies such as hypospadias. Toxoplasmosis is caused by a ubiquitous parasitic infection with the most severe clinical signs observed in babies infected early in pregnancy, but also influences neurodegenerative and psychiatric disorders in later life. We have exciting new data demonstrating how the parasite dysregulates dopamine and amyloid processing pathways by altering the host cell epigenome. Hypospadias is the second most common birth defect in boys in WA. Our research is looking at why some boys are born with hypospadias with a focus on how the genome interacts with environmental factors resulting in changes to gene expression by mechanisms other than changes in the underlying DNA code, i.e. through epigenetic ("above genetics") mechanisms. Our group is also leading the SeqNextGen project which aims at improving the genetic diagnosis of all rare diseases in Western Australian children using Next Generation sequencing, in particular to develop better computational pipelines to pinpoint the disease-causing variants.

Our group also leads international consortia that are using genetics and metabolomics to understand infections of resource-poor nations, especially for a disease called leishmaniasis, in India, Brazil and Sudan, and fevers caused by bacterial infections and malaria in Africa. In 2013 we initiated a major new study using metabolomics to address the diagnostic conundrum of severe febrile illness in African Children. A particular



need in Africa is to be able to rapidly diagnose the cause of fever in children, and metabolomics is being used to identify rapid diagnostic biomarkers especially for bacterial infections. In 2015 we were successful in identifying such biomarkers. In the case of life-threatening visceral leishmaniasis, the major effort is focused on research that could aid in vaccine development. There are no vaccines in routine use against this disease, and there is a particular need to ensure that next generation defined vaccines will be effective even in genetically susceptible individuals. In 2013 we published our major findings in *Nature Genetics* on the role of HLA Class II molecules in determining susceptibility to visceral leishmaniasis. The significance of this finding is that we have determined that the most important genetic risk factor for visceral leishmaniasis lies at the heart of eliciting T cell immunity. Our more recent focus has been to identify the specific antigens presented to the immune system by protective versus risk-associated HLA Class II molecules, so that we can design a vaccine(s) that will subvert the inappropriate immune response normally made by a susceptible individual encountering infection for the first time, and transform this into a protective outcome.

## Research Projects

### **FAMILY STUDY OF EAR HEALTH AND METABOLIC DISEASES IN A WESTERN AUSTRALIAN ABORIGINAL COMMUNITY**

*Jenefer M Blackwell, Sarra E Jamieson, Heather J Cordell, Denise Anderson, Dave*

*Tang, Timo Lassmann, Michaela Fakiola, Elizabeth S H Scaman, Elizabeth Davis, Harvey L Coates*

In 2015 our attention turned to the use of whole exome sequencing (WES) (i.e. protein coding and adjacent regulatory sequences) to identify novel variants that may be associated with severe ear and renal disease phenotypes in Aboriginal Australians. The data from this whole exome sequencing will also provide the first reference panel of genetic variation in an Australian Aboriginal population that can be used to support other health-based research projects, as well as the diagnosis of rare diseases in Aboriginal children. We provided a catalogue of variants called after sequencing the exomes of 72 Aboriginal individuals to a depth of 20X coverage in ~80% of the sequenced nucleotides. We determined 320,976 single nucleotide variants (SNVs) and 47,313 insertions/deletions using the Genome Analysis Toolkit. We had previously genotyped a subset of the Aboriginal individuals (70/72) using the Illumina Omni2.5 BeadChip platform and found ~99% concordance at overlapping sites, which suggests high quality variant detection. Finally, we compared our SNVs to six publicly available variant databases, such as dbSNP and the Exome Sequencing Project, and 70,115 of our SNVs did not overlap any of the single nucleotide polymorphic sites in all the databases. That is, these variants are novel in this Australian Aboriginal population. Our data set, which is deposited in the European Genome Phenome Archive and available for health-based studies through application to a Data Access Committee, provides

a useful reference point for genomic studies on Aboriginal Australians. In our laboratory the data are currently being used to identify variants associated with both severe otitis media in Aboriginal children, and with end stage renal disease in Aboriginal adults.

### **Plain language summary**

Extreme susceptibility to runny ears in children and end stage renal disease in adults are major health issues for Australian Aboriginal communities. Our research is designed to determine whether these extreme manifestations of disease are associated with rare or novel genetic variants in a Western Australian Aboriginal population, in the hope that this might provide leads for improved therapeutic interventions.

### **Funders of the project**

NHMRC

### **External collaborators**

Prof Heather Cordell, Newcastle University, UK

Clinical Prof Harvey L Coates, SPACH, PMH and UWA

Dr Michaela Fakiola, Institute of Molecular Genetics, Milan, Italy

## **SEQNEXTGEN: TRANSLATING NEXTGEN SEQUENCING FOR THE DIAGNOSIS OF DEVELOPMENTAL ANOMALIES AND RARE DISEASES**

*Jenefer M. Blackwell, Dave Tang, Timo Lassmann, Karen Simmer, Nigel Laing, Jan Dickinson, Jack Goldblatt, Carol Bower, Sarra E. Jamieson, Richard Allcock, Gareth*

*Baynam, Gina Ravenscroft, John Beilby, Mark Davies, Kym Mina, Caroline Graham, Helen Leonard, Rachel Skoss, Hugh Dawkins, Stephanie Broley, Michelle*

Rare diseases collectively affect >1 person in every 17. This equates to ~1.3 million Australians, including 400,000 children, living with a rare disease. Approximately 80% of all rare diseases have a genetic basis. Next generation sequencing allows partial or complete genomes to be sequenced at high speed and low cost. Whole exome sequencing (WES) (i.e. protein coding and adjacent regulatory sequences) has recently been implemented in WA as the diagnostic method of choice for rare diseases. As part of the TPHCRF collaborative project SeqNextGen (for "Sequence the Next Generation"), we have implemented new pipelines to improve the rate of genetic diagnosis from the current ~30% to ~50% based on deeper interrogation of the genome. Original aims of the project also included: (i) determining the clinical and social outcomes for patients and families receiving a diagnosis by WES using follow-up interviews and/or questionnaires as appropriately designed by epidemiologists, sociologists and consumer representatives on the project team; and (ii) undertaking economic analysis to estimate the costs of WES (relative to current clinical genetic practice), the cost of potential investigations and repeat consultations saved and also quality-adjusted life year (QALY) impacts from this technology. This work is ongoing, with our ultimate goal being development and implementation of a person-centric Model of Care for people living with developmental anomalies and rare diseases in Western



Australia.

### **Plain language summary**

Rare diseases collectively affect >1 in 17 people. This equates to ~1.4 million Australians, including 500,000 children, living with a rare disease. ~80% of all rare diseases are genetic, characterized by increased rates of mortality, suffering, pain, frequently associated with intellectual impairment, a high burden for the child, family and the health system and often the uncertainty of a diagnostic odyssey. Just the 10 most prevalent single gene and chromosomal conditions in children account for 2.8% of all admissions to WA hospitals for children aged 0-19. These children have a higher number of admissions per patient, longer mean length of stay and an increased cost per admission compared to other children. This cohort accounted for 5.1% of the cost of hospital admissions of 0-19 year olds in this limited cohort in WA in 2006.<sup>2</sup> Therefore, the early unambiguous diagnosis, enabled by Next Generation sequencing and functional validation of the genetic diagnosis, has the potential to enhance best practice and medical management, including genetic counselling, and also to provide efficiencies and savings to the health system.

### **Funders of the project**

TPCHRF

Téa Lake and the Rare Disease Association Inc.

Office of Public Health Genomics, WA Health

### **External collaborators**

Prof Karen Simmer (Director, Neonatal Intensive Care Unit, KEMH/PMH)

Prof Nigel Laing (Developmental Neurobiologist, Harry Perkins Institute for Medical Research)

Prof Jan Dickinson (Director, Fetal Medicine Services, KEMH)

Prof Jack Goldblatt (Director, Genetic Services WA, KEMH)

Assoc Prof Richard Allcock (Head LotteryWest Sequencing Facility, UWA School Pathology & Laboratory Medicine)

Clin Assoc Prof Gareth Baynam (Clinical Geneticist, UWA and Murdoch University)

Dr Gina Ravenscroft (NHMRC Early Career Fellow, UWA Harry Perkins Institute for Medical Research)

Adjunct Professor John Beilby (Head of Diagnostic Genomics, Pathwest Laboratories)

Dr Mark Davies (Senior Medical Scientist, Diagnostic Genomics, Pathwest Laboratories)

Dr Kym Mina (Diagnostic Genomics, Pathwest Laboratories)

Dr Caroline Graham (Manager, Office of Public Health Genomics, WA Health)

Dr Rachel Skoss (WA Register for Developmental Anomalies (WARDA) Consumer Group)

Ms Monique Garcia (WA Representative, Rare Voices Australia (RVA))

Ms Amanda Samanek (Executive Director, Genetic and Rare Diseases Network (GARDN))

Professor Hugh Dawkins (Head, Office of Public Health Genomics, WA Health)

Ms Stephanie Broley (Genetic Counsellor, Genetic Services of WA)

Ms Michelle Ward (Genetic Counsellor, Genetic Services of WA)

## **INFLUENCE OF TOXOPLASMA GONDII ON HOST CELL FUNCTION**

*Genevieve Syn, Sarra E. Jamieson, Jenefer M. Blackwell*

*Toxoplasma gondii* is a ubiquitous pathogen capable of infecting most animals, including humans and is a significant health burden in developed and developing countries. Infection in healthy individuals is usually asymptomatic, although chronic infection with *T. gondii* has been reported to be a risk factor for neurodegenerative and psychiatric disorders, including Parkinson's Disease, Alzheimer's Disease, and schizophrenia. Vertical transmission of *T. gondii* in mothers infected for the first time during pregnancy can lead to congenital toxoplasmosis, with affected babies born with characteristic brain and eye lesions including retinochoroiditis, hydrocephalus and intracranial calcifications.

Pathogenic pathways that may link congenital and latent toxoplasmosis have been largely unexplored. In this study, we used the Illumina 450K Human Methylation Beadchip and the Illumina HT-12 v4 Expression Beadchip to identify global changes in the host methylome and transcriptome over a time-course of 2, 6 and 24 hours following *T. gondii* infection in the clinically relevant WERI retinal cell line. Only genes in concordance (132, 186 and 128 genes at 2, 6 and 24 hours post-infection), i.e. hypermethylated and decreased expression or hypomethylated and increased expression, were selected for downstream pathway analyses. Seven pathways were significantly enriched at 6 hours post-infection, including two neurologically-associated pathways: dopamine-DARPP32 feedback in cAMP signalling (p-value =  $8.3 \times 10^{-5}$ ; adjusted

p-value = 0.02); and amyloid processing (p-value =  $1.0 \times 10^{-3}$ ; adjusted p-value = 0.043). These pathways are of interest for their roles in utero in eye and brain development (i.e. synapse formation, neuronal migration) and in adulthood where the dopamine pathway is involved in Parkinson's disease and schizophrenia and amyloid processing contributes to Alzheimer's disease. Thus, epigenetic dysregulation of these pathways by *T. gondii* may contribute to the known pathologies of *T. gondii* at the congenital level and its later life effect on the brain.

### **Plain language summary**

The toxoplasma parasite is very common throughout the world. In Australia between 30-40% of people will be infected with this parasite, usually through eating contaminated, undercooked meat. Most infected people will be unaware they have the parasite as it causes no symptoms. However, the parasite can cause serious problems if mothers catch the parasite for the first time whilst they are pregnant as the parasite can pass across the placenta to the developing baby. If the baby becomes infected they can be born with eye and brain disorders. Latent acquired infection has also been associated with neurodegenerative and psychiatric disorders in adults. To understand how acute fetal and acquired latent infection with the parasite results in the eye and brain disorders we are looking at how the parasite influences host cell function. We believe that changes we reported previously in host cell mitochondrial function might relate directly to clinical signs being focused to the eye and the brain of babies infected in utero. If this



is the case, we might be able to provide evidence to support the repurposing of drugs currently used to treat genetic eye and brain diseases that are associated with mitochondrial dysfunction for the treatment of babies born with congenital toxoplasmosis. We also have some exciting new data on how the parasite affects dopamine and amyloid processing pathways which might provide the link to its association with neurodegenerative and psychiatric disorders.

### Funders of the project

PhD studentship support

## UNDERSTANDING LEISHMANIASIS THROUGH HLA

*Jenefer M Blackwell, Michaela Fakiola, Joyce Oommen, Toolika Singh, Noel H. Smith, Shyam Sundar*

In a previous (Nature Genetics, 2013, 45:208-213) genome-wide association study (GWAS) we identified HLA DRB1 allele groups tagged by ancestral haplotypes that confer disease risk (DRB1\*11/\*13/\*14 allele groups), or protect (DRB1\*15/\*16/\*01 allele groups) from, human visceral leishmaniasis in India and Brazil (Combined  $P=2.76 \times 10^{-17}$ , OR=1.41, 95%CI 1.30-1.52). One mechanism to account for this association is that the top single nucleotide polymorphisms (SNPs) associated with visceral leishmaniasis tag variants that determine functional differences at the amino acid level which directly influence epitope selection and antigen presentation. To understand how amino acid sequence differences in these genetic risk factors could influence binding of leishmanial epitopes for

presentation to the immune system, we successfully captured leishmanial epitopes from antigen presenting cells. We eluted peptides from HLA class II molecules purified from  $4-5 \times 10^6$  dendritic cells and characterized the amino acid sequences of peptides eluted from risk versus protective DRB1 molecules. Based on 9-mer cores for the 20-mers with strongest DRB1 allele-specific binding affinity there was, as we had also demonstrated in a purely in silico analysis of epitopes from 43 candidate vaccine antigens, a greater number and complexity of amino acid residues making up the 9-mer cores of peptides eluted from the DRB1\*1301 or \*1404 risk alleles than for the DRB1\*1501 protective allele, suggesting greater promiscuity in binding of Leishmania epitopes to risk compared to protective DRB1 alleles. In addition, there was a bias towards hydrophobic and polar AAs in DRB1\*1501-specific peptides at 4 and 6, pointing to the potential importance of these anchor residues interacting with the DRB1 residues at position 11 and 13, that are the core positions determining the association with visceral leishmaniasis. Overall this epitope capture experiment demonstrated greater promiscuity of amino acid usage across the 9-mer core epitopes for risk DRB1 alleles (DRB1\*1404 and DRB1\*1301) compared to more restricted amino acid usage in the protective allele group (DRB1\*1501). This appears to be different to viral infections where HLA-DRB1 variants linked with low HIV viremia promiscuously present a larger breadth of peptides with lower functional avidity when compared to DRB1 variants linked with high HIV viremia, or Hepatitis C where dominant and highly promiscuous epitopes characterize the CD4+ T helper cell response of spontaneously controlled

infection. For VL it could be an indication that an over-enthusiastic pro-inflammatory CD4+ T cell response associated with DRB1 risk alleles early in infection could be counter-protective, a hypothesis consistent with high TNF in clinical VL that will be testable in humanized HLA\_DRB1\*1404 and HLA\_DRB1\*1501 transgenic mice which we are now using to pursue this research.

### **Plain language summary**

Visceral leishmaniasis is a parasitic disease found in resource poor regions of tropical countries and is life-threatening in susceptible individuals. Drugs are toxic and expensive, with drug resistance a growing problem. No vaccines are available to protect against this disease, and there is a particular need to ensure that next generation defined vaccines will be effective even in genetically susceptible individuals. We have therefore employed modern genomics to identify the major genetic risk factor for visceral leishmaniasis, knowledge of which is helping us to engineer vaccines that will specifically aid in protecting susceptible individuals.

### **Funders of the project**

NIH Tropical Medicine Research Centre (Leader S Sundar, India; Project leaders J M Blackwell and M Fakiola)

### **External collaborators**

Professor Shyam Sundar, Institute for Medical Science, Banaras Hindu University, Varanasi, India  
Ms Toolika Singh, Institute for Medical Science, Banaras Hindu University, Varanasi, India

Dr Michaela Fakiola, Institute of Molecular Genetics, Milan, Italy

Professor Mary Wilson, University of Iowa, Iowa, USA

Dr Noel Smith, Lonza Biologics plc, Cambridge, UK

## **TOWARDS IMPROVING POINT-OF-CARE DIAGNOSIS OF NON-MALARIA FEBRILE ILLNESS: A METABOLOMICS APPROACH**

*Decuypere S, Maltha J, Deborggraeve S, Rattray NJ, Issa G, Bérenger K, Lompo P, Tahita MC, Ruspasinghe T, McConville M, Goodacre R, Tinto H, Jacobs J, Carapetis JR.*

Non-malaria febrile illnesses such as bacterial bloodstream infections (BSI) are a leading cause of disease and mortality in the tropics. However, there are no reliable, simple diagnostic tests for identifying BSI or other severe non-malaria febrile illnesses. We hypothesized that different infectious agents responsible for severe febrile illness would impact on the host metabolome in different ways, and investigated the potential of plasma metabolites for diagnosis of non-malaria febrile illness. We conducted a comprehensive mass-spectrometry based metabolomics analysis of the plasma of 61 children with severe febrile illness from a malaria-endemic rural African setting. Metabolite features characteristic for non-malaria febrile illness, BSI, severe anemia and poor clinical outcome were identified by receiver operating curve analysis. The plasma metabolome profile of malaria and non-malaria patients revealed fundamental differences in host response, including a differential activation of the hypothalamic-pituitary-adrenal axis. A simple corticosteroid signature was a



good classifier of severe malaria and non-malaria febrile patients (AUC 0.82, 95% CI: 0.70-0.93). Patients with BSI were characterized by upregulated plasma bile metabolites; a signature of two bile metabolites was estimated to have a sensitivity of 98.1% (95% CI: 80.2-100) and a specificity of 82.9% (95% CI: 54.7-99.9) to detect BSI in children younger than 5 years. This BSI signature demonstrates that host metabolites can have a superior diagnostic sensitivity compared to pathogen-detecting tests to identify infections characterized by low pathogen load such as BSI. This study demonstrates the potential use of plasma metabolites to identify causality in children with severe febrile illness in malaria-endemic settings.

#### Plain language summary

In the tropics, malaria is commonly attributed to be the cause of most childhood fevers, while in fact this condition is more commonly caused by other pathogens that are clinically indistinguishable from malaria. These so-called non-malaria febrile illnesses include bacterial bloodstream infections, which are associated with a higher mortality than malaria. Most health care facilities in the tropics have malaria diagnostic tests available, but tests for non-malarial febrile illnesses are extremely limited. There is the critical need for new tests that can address the question 'if a febrile patient is not suffering from malaria, then what is it and what treatment will be effective?' Using metabolomics, we have comprehensively screened the biochemical profile of patients with severe febrile illness for biological markers of non-malaria febrile illness. The results show that severe malaria and non-malaria febrile illness trigger a distinct metabolic

response in the host. We demonstrate that this pathophysiological difference can be exploited for differential diagnosis of severe febrile illness and identification of patients with bacterial bloodstream infections.

#### Funders of the project

Telethon Kids Institute Small Grant Merit Award, WA Department of Health Institute of Tropical Medicine, Belgium Flemish Ministry of Science

#### External collaborators

Maltha J2,3, Deborggraeve S4, Rattray NJ5, Issa G6, Bérenger K6, Lompo P6, Tahita MC6, Ruspasinghe T7, McConville M7, Goodacre R5, Tinto H6, Jacobs J2,8  
2Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium.  
3Center for Molecular and Vascular Biology, KU Leuven, Leuven, Belgium.  
4Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium.  
5School of Chemistry, Manchester Institute of Biotechnology, University of Manchester, Manchester, United Kingdom.  
6Clinical Research Unit Nanoro-IRSS-CRUN, Nanoro, Burkina Faso.  
7Metabolomics Australia and Bio21 Institute of Molecular Sciences and Biotechnology, University of Melbourne, Melbourne, Australia.  
8Department of Immunology and Microbiology, KU Leuven, Leuven, Belgium.

## **DEFINING THE MICROBES IN THE MIDDLE EAR AND UPPER RESPIRATORY TRACT THAT LEAD TO RECURRENT EAR INFECTIONS – A METAGENOMIC STUDY**

*Christopher S Peacock, Sarra E Jamieson, Rachael Lappan, Timo Lassmann, Elyce Iagallo, Kara Imbrogno, Christopher Blyth, Harvey L Coates, Paul Bumbak, Lea-Ann Kirkham, Ruth Thornton, Deborah Lehmann, Tim Perkins, Michael Wise, Richard Francis, Paul Rigby, Richard Lipscombe.*

Otitis media (OM, or ear infection) is a very common illness of childhood. Some children will have multiple ear infections in their early years and are diagnosed with recurrent acute OM. There is a high level of complexity within the microbial community of the middle ear during an episode of OM. This project is using the latest sequencing technology to examine the microbial composition of the middle ear and the nasopharyngeal region, the site of initial colonization prior to OM. This is being compared to the same environment in children who appear resistant to recurrent ear infections but who attend daycare, a known risk factor for OM. To date we have recruited >80 cases (i.e. children having grommets inserted for recurrent acute otitis media) along with an age and season matched control for each case. From case children we gained parental consent to collect any middle ear fluid present at the time of grommet insertion, a nasopharyngeal swab and a swab of the ear canal. From control children we gained parental consent to collect a nasopharyngeal swab. From these samples we have extracted all of the microbial DNA and these samples are

currently undergoing sequencing of the 16s rRNA gene, a bacterial specific gene found in all bacterial species that can be used to identify the bacteria present in the sample. Once this data has been analysed we will then select a subset of cases and controls and undertake whole genome shotgun sequencing to microbial genes and variants that may be involved in disease severity or disease resistance.

In addition, we are currently undertaking a pilot project to look at the use of Dual RNA-Seq in furthering our understanding of host-pathogen interactions in otitis media. Dual RNA-Seq is a methodology that sequences RNA from a sample, both host and bacterial, and then looks at what genes are being expressed in these samples. This will be done in middle ear fluid collected from children undergoing grommet insertion for recurrent acute otitis media and chronic otitis media with effusion. Recruitment to this study will start within the next few weeks. In this pilot study we will recruit 12 children. The use of Dual RNA-Seq has not been applied to otitis media previously so this pilot project will help us determine if this is likely to be an informative approach and potentially provide preliminary data to aid in designing a larger study.

### Plain language summary

Recurrent middle ear infections (or otitis media) are one of the most common reasons for children to visit their GP, to be prescribed antibiotics and to undergo surgery. Currently we know of several specific microbes that cause ear infections, however it is thought that are probably many more microbes that also cause ear infections. It is also likely that there are microbes normally present in the



middle ear and at the back of the nose that are not responsible for causing any illness but could be considered as useful microbes that help the body to maintain its healthy state and fight off the microbes that do cause illness. To try and identify all of the microbes in the middle ear and at the back of the nose (the ones that cause illness and the ones that are useful) this project will use a new type of technology that allows us to look at the DNA (also called “the building block of life”). We hope this information will help to develop novel treatments that will reduce the number of ear infections that children in the future have.

### **Funders of the project**

Telethon-New Children's Hospital  
Research Fund

Wesfarmers Seed Grant

External collaborators:

Harvey L Coates, SPACH, PMH & UWA

Paul Bumbak, Princess Margaret Hospital  
for Children & UWA

Lea-Ann Kirkham, SPACH

Ruth Thornton, SPACH

Michael Wise, UWA

Paul Rigby, CMCA@Perkins, UWA

Richard Lipscombe, Proteomics

International Pty Ltd, Nedlands, WA.

## **UNDERSTANDING THE MOLECULAR MECHANISMS THAT LEAD TO HYPOSPADIAS**

*Sarra E Jamieson, Natasha Nassar,  
Andrew Barker, Naeem Samnakay,  
Andrew Holland*

Hypospadias is a clinically significant birth defect that affects boys and that

is characterised by abnormal urethral fusion during the masculinisation period, between 8-14 weeks gestation. Hypospadias is accompanied by the incomplete fusion of the prepuce (or foreskin), varying degrees of penile curvature and is associated with a long-term risk of male sub-fertility, reduced semen quality, testicular cancer and psychosocial consequences. Our research has shown that hypospadias is the second most common birth defect among boys in Western Australia affecting 1 in 130 boys with rates doubling over the last 25 years. The majority of hypospadias cases require major surgical repair after 6 months of age to enable normal urinary function and fertility in the long term. To further understand the etiology of hypospadias we have used genome-wide array based methodologies to identify genes/ pathways that are disrupted at the level of DNA methylation and/or gene expression in human hypospadias compared to normal tissue. For the analysis of DNA methylation we analysed a total of 24 tissue samples (11 cases and 11 controls total; replicated across two arrays) using the Illumina HumanMethylation 450K array. For gene expression we analysed a total of 24 tissue samples (12 cases and 12 controls; replicated across 2 arrays) using the Illumina HT-12 microarray.

Analysis of DNA methylation reveals 201 CpG sites, mapping to 189 unique genes, that are significantly differentially methylated in hypospadias compared to control tissue; these replicated sites show the same directional change in methylation. The top hit at probe cg17053251 at MIR5100 (combined  $p=1.34 \times 10^{-6}$ ) shows a 7% decrease in methylation in cases compared to

controls. 14 genes contain multiple replicated probes. IPA analysis of genes harbouring replicated probes identifies the top networks as Cardiovascular System Development & Function, Embryonic Development, Organ Development. Analysis of gene expression array data shows a total of 400 probes with significant (nominal  $p < 0.05$ ) differential expression (fold change  $\leq 1.5$ ) on at least one array with 13 probes showing replicated significant differential expression in hypospadias cases vs. controls. The top hit was at the keratin 13 gene (KRT13), this shows a 6-fold increase in expression in hypospadias tissue (combined  $p = 0.009$ ). Embryonic development is one of the top networks via IPA analysis, specifically Embryonic Development, Endocrine System Development and Function, Organ Development. Comparison of the DNA methylation and gene expression results also identified one gene of particular interest, PITX2. This gene shows replicated differential methylation and expression in hypospadias tissue. PITX2 encodes a homeodomain transcription factor that is essential for normal development. Previously reported data from the murine model shows Pitx2 is expressed in murine male urethra during and in the testis postnatally. PITX2 mutations are also associated with Axenfeld-Rieger syndrome, in which hypospadias is sometimes observed. As such, this gene is of interest for ongoing investigations, particular in relation to its potential role in postnatal gonadal development.

### **Plain language summary**

Hypospadias is a birth defect in boys that affects the penis. Specifically, the urethral opening (where the urine comes from) is

not located at the tip of the penis, as it would normally be, but is instead located somewhere else along the penis. Boys with hypospadias need surgery in the first few years of life to correct this problem and to ensure they have full urinary function and fertility in later life. The factors that lead to hypospadias are not currently known in full but one theory is that a mother's exposure during pregnancy to environmental chemicals that mimic our natural hormones could be important. It is thought that exposure of a developing baby to these chemicals results in alterations to chemical markers (called epigenetic marks) that are normally found on our DNA which turn leads to changes in how our genes are turned on and off. This project has compared the epigenetic marks seen in the DNA of boys with hypospadias compared to boys who do not have hypospadias. By doing this we have found several genes that have different epigenetic marks, these genes may play an important role in the development of hypospadias.

### **Funding**

None current

### **External collaborators**

Assoc/Prof Natasha Nassar, University of Sydney

Andrew Barker, Princess Margaret Hospital for Children

Naeem Samnakay, Princess Margaret Hospital for Children

Andrew Holland, University of Sydney



## **THE USE OF NATURALLY OCCURRING SMALL PEPTIDES (PHYLOMERS) AS PENETRATING PEPTIDES TARGETING LEISHMANIA.**

*Christopher S Peacock, Shib Sankar Sen, Kara Imbrogno, Katrin Hoffman, Susanna Juraja, Richard Hopkins.*

The current treatments for cutaneous leishmaniasis use drugs developed decades ago, which are based on heavy metals and are toxic to the patients. Phylomers represent a new class of peptide, derived from genomes of biodiverse archaeal and bacterial species, which encode basic structural motifs within proteins. Phylomer peptides can exhibit superior functional hit-rates, when compared to randomly derived peptides, due to evolutionary selection for structure and stability. This project screened a number of phage-displayed Phylomer libraries to identify novel cell penetrating peptides that specifically target Leishmania parasites. The use of a novel direct capture technique allows for the rapid identification of Phylomer peptides from a library of many millions that can enter both macrophages and the phagosomal compartments where the parasites reside. Analysis of the sequences from several rounds of library screening have generated a small number of candidate peptides which be tested in an in vitro system for their activity on a clinical isolate of Leishmania tropica, both of which cause cutaneous disease.

### **Plain language summary**

Cutaneous leishmaniasis is a severe skin disease afflicting millions of people in more than 60 countries. It is caused by infection with a parasite that invades

the immune cells that are responsible for fighting infection leading to a chronic condition that can last for years. Current drug treatments are based on toxic heavy metals and often cause significant side effects in patients. Phylomers are small peptides derived from bacteria that can be used for a range of therapeutic purposes. This project utilized a process where millions of these naturally occurring peptides were tested to examine their ability to target and enter the parasite that causes this disease. Once specific peptides have been identified in this screening process they can be used to deliver very low doses of anti-leishmania molecules directly to the parasite avoiding the problems associated with current treatments of drug toxicity.

### **Funding**

Endeavor Scholarship

## **COMPARATIVE ANALYSIS OF HUMAN AND KANGAROO LEISHMANIA: DEFINING HUMAN PATHOGENICITY GENES**

*Christopher S Peacock, Calila Santos, Kara Imbrogno.*

The lack of safe drugs, prophylaxis or effective vaccines for Leishmaniasis is a serious issue for a disease that afflicts millions of people in more than 90 countries. The use of attenuated vaccines that have been genetically engineered to reduce or remove their ability to cause overt diseases have shown to be the most effective at providing a protective immune response. However there have been issues related to the parasites ability to regain virulence. This project has used

the recently discovered Australian species of leishmaniasis that does not appear to have the capacity to cause disease in humans. Our extensive characterization of this novel species has shown that while it can infect human cells in vitro and the mouse model in vivo it only survives for a few weeks without causing any symptoms. It therefore has the potential for use as a safe attenuated vaccine. Sequencing has revealed that it is highly related to the human pathogenic species with only a small number of genetic differences. In order to stimulate a specific response protective response, known immunogenic genes from the human pathogenic species have been transfected into this parasite and it is currently being tested in the susceptible animal model for human disease. Two of these transfected parasites that express immunogenic proteins from the human pathogenic species have been used as a vaccine model to induce protection against *Leishmania major* infection in mice.

### **Plain language summary**

Leishmaniasis is a major global disease that affects millions and kills many thousands of people. There are no vaccines; prophylaxis and the few drugs that are available are toxic and difficult to deliver. This project has utilised a non-human pathogenic strain of leishmania recently discovered in Australia for use as a possible novel vaccine against human forms of the disease. During this project we have sequenced this novel *Leishmania* species that is non-pathogenic to humans to help identify what genes are involved in the human disease. The parasite has also been extensively tested in both cell culture to help characterise and examine

it's it's potential for use in future vaccine studies.

### **Funding**

NHMRC

## **2015 Success**

### **AWARDS AND PRIZES**

Jenefer Blackwell, Fellow of the Australian Academy of Science (FAA)  
Jenefer Blackwell, Vice Chancellor's Senior Research Award

### **EXTERNAL COMMITTEES**

#### **International**

Jenefer Blackwell, Member of the Scientific Advisory Board for the Faculty of Associated Medical Sciences, Khon Kaen University, Thailand, 2009+  
Jenefer Blackwell, Editorial Board Genomic Medicine: 2005+  
Jenefer Blackwell, Editorial Board Genes and Immunity: 2006+

### **INVITED PRESENTATIONS**

Jenefer Blackwell, Seventh meeting of the NIH Tropical Medicine Research Centre for studies on Visceral Leishmaniasis in Bihar, India, Co-convener, Chair and Speaker, 28 January to 1 February 2015, Varanasi, India.

Jenefer Blackwell, 51st Annual Conference of the Malaysian Society of Parasitology and Tropical Medicine, Plenary Speaker, 3 to 5 March 2015, Kuala Lumpur, Malaysia.



Jenefer Blackwell, Science at the Shine  
Dome, Invited Speaker (New Fellow), 25 to  
28 May 2015, Canberra, Australia.





# HEALTH PROMOTION AND EDUCATION RESEARCH AND TRANSLATION GROUP

## Overview

Health Promotion and Education Research and Translation Group's research focuses on the development and evaluation of innovative school and community-based interventions to enhance the emotional and social wellbeing of children and adolescents.

## Research Projects

### **ENHANCING ADOLESCENT MENTAL HEALTH THROUGH POSITIVE EDUCATION 2013-2016**

*Dianne Vella-Brodrick (University of Melbourne), Nikki Rickard (Monash University), Donna Cross (Telethon Kids Institute), John Hattie (University of Melbourne), Justin Robinson (Institute of Positive Psychology), Christine King (University of Queensland)*

Mental disorders are the single greatest burden of disease for adolescents with reports of around 1 in 4 people aged 16-24 years experiencing mental illness in Australia. Positive Education in schools may offer feasible solutions for reducing the escalating incidence of mental illness and promoting engaged learners, flourishing and pro-social behaviours among young people.

This project involves evaluation and identification of key features of the

Positive Education Program at Geelong Grammar, and the adaptation of the program to suit public schools. Program evaluation will utilize momentary sampling and physiological indicators, to complement focus groups and self-report measures.

Positive education is a preventative, strengths-based approach to address the mental health needs of young people in schools. This project uses innovative methods to examine the contribution of positive education to adolescent mental health, and to social and learning outcomes.

Mental disorders are the single greatest burden of disease for adolescents with reports of around 1 in 4 people aged 16-24 years experiencing mental illness in Australia. This project involves evaluation and identification of key features of the Positive Education Program at Geelong Grammar, and the adaptation of the program to suit public schools. This project uses innovative methods to examine the contribution of positive education to adolescent mental health, and to social and learning outcomes.

### **Funders of the project**

Australian Research Council

### **External collaborators**

Geelong Grammar School

## **TESTING A COMPREHENSIVE TARGETED INTERVENTION TO REDUCE STUDENT BULLYING**

### **(BEYOND BULLYING: POSITIVE CHANGE FOR ALL) 2013-2016**

*Donna Cross (Telethon Kids Institute), Marilyn Campbell (Queensland University of Technology), Phillip Slee (Flinders University), Ken Resnicow (University of Michigan), Christina Salmivalli (University of Turku)*

Peer bullying is a stubborn social problem. Despite attention to the problem by schools, communities and researchers, bullying continues to be highly prevalent in Australian schools. Researchers have found that working with the whole school to address cultures that support bullying has some effect, but further work is needed to develop strategies to prevent these behaviours. To date, one of the chief challenges has been stopping bullying at the source: the young people who engage in repeated or severe bullying behaviours.

The Beyond Bullying project is trialing an innovative approach known as Motivational Interviewing (MI). Motivational Interviewing is particularly powerful when changing the problem behaviour elicits resistance from the person engaging in this behaviour. MI has previously been successfully used in counselling and guidance settings to help young people change and resolve problems with alcohol and substance use, eating disorders, gambling problems, and, most importantly, to reduce violent

behaviour.

The Beyond Bullying project involves counselling young people who are identified as bullying others with Motivational Interviewing. In addition, the 'Friendly Schools Plus' program is used to provide schools with resources and strategies to prevent and address bullying behaviours and attitudes among all students.

This project will test the effectiveness of a whole-school bullying prevention program plus a Motivational Interviewing (MI) counselling intervention to reduce the mental health problems experienced by Year 8 and 9 students who bully others, and those who are the targets of bullying. This project will provide policy makers and school staff with a framework to reduce bullying among young people.

#### **Funders of the project**

National Health and Medical Research Council, "Mental Health Targeted Call for Research"

#### **External collaborators**

Government of Western Australia,  
Department of Education  
Independent School's Association of  
Western Australia

Catholic Education Office of Western  
Australia  
Government of Western Australia, Child &  
Adolescent Community Health  
The Western Australian Association of  
Teacher Assistants Inc (WAATA)  
Middle Years of Schooling Association  
(MYSA)  
Mindmatters  
The School Psychologists' Association of



Western Australia Inc (SPAWA)  
The Independent School Counsellors' Association of WA (ISCA WA)  
The Association of Independent Schools of WA (AISWA)  
APS College of Educational and Developmental Psychologists (CEDP)  
APS College of Counselling Psychologists  
School Chaplaincy Program (WA)  
Independent School Nurses Association of Western Australia  
Child and Adolescent Community Health (CACH) Department of Health  
Child and Adolescent Mental Health Service (CAMHS)  
Headspace  
Youth Focus

## **REDUCING PEER VICTIMISATION IN AUSTRALIAN SCHOOLS THROUGH TARGETED AND UNIVERSAL APPROACHES (PREVENTING ANXIETY AND VICTIMISATION THROUGH EDUCATION: PAVE) 2013-2018**

*Ron Rapee (Macquarie University), Donna Cross (Telethon Kids Institute), Kay Bussey (Macquarie University), Caroline Hunt (University of Sydney), Jennifer Hudson (Macquarie University), Cathy Mihalopoulos (Deakin University), Clare Roberts (Curtin University of Technology), Nick Titov (Macquarie University)*

The project is being conducted by the Centre for Emotional Health at Macquarie University and the Telethon Kids Institute, The University of Western Australia. This project will evaluate the effectiveness of two evidence-based approaches to support students who have been frequently targeted by bullying in primary schools:

- Friendly Schools Plus: a strengths-

based, whole-of-school program designed to enhance students' social and emotional learning and foster the prevention of bullying behaviours;

- Cool Kids: Taking Control: a strengths-based, targeted program designed to build resilience in those children who have been targeted by bullying behaviours

These programs will help schools reduce all forms of bullying by developing students' social and emotional learning, building positive peer relationships, and empowering students to cope successfully with difficult situations.

PAVe is an exciting new research intervention project being conducted in over 100 NSW and Western Australian primary schools, which aims to support students who have been frequently bullied. The project will help schools reduce all forms of bullying by developing students' social and emotional learning, building positive peer relationships, and empowering students to cope successfully with difficult situations.

This project will evaluate the effectiveness of two evidence-based programs to support students who have been frequently targeted by bullying in primary schools. The cost effectiveness, acceptability and feasibility of conducting programs to reduce anxiety and victimisation in children in Australian schools will be evaluated.

### **Funders of the project**

National Health and Medical Research Council, "Mental Health Targeted Call for Research"

## External collaborators

Australian Government Department of Education  
Catholic Education Diocese of Parramatta  
Australian Government, Department of Education  
Australian Human Rights Commission  
Government of Western Australia, Department of Education  
NSW Department of Education and Communities  
Association for Independent Schools in Western Australia  
Catholic Education Office in WA

## **ASSESSING THE PUBLIC HEALTH IMPLICATIONS OF HIGHER RISK ONLINE BEHAVIOURS IN YOUNG PEOPLE & STUDENTS LEADING CHANGE TO REDUCE SEXTING-RELATED HARM TO YOUNG PEOPLE (THE CYBER SAVVY PROJECT) 2012-2016**

This body of research into sexting and electronic-image sharing is funded through two research projects

- Assessing the public health implications of higher risk online behaviours in young people: Donna Cross (Telethon Kids Institute), Thérèse Shaw (Telethon Kids Institute), Rebecca Guy (University of New South Wales); Meagan Roberts (Department of Health, Western Australia); Shirlee-Ann Knight (Curtin University)
- Students leading change to reduce sexting-related harm to young people: Donna Cross (Telethon Kids Institute), Thérèse Shaw (Telethon Kids Institute), Rebecca Guy (University of New South Wales), Shirlee-Ann Knight (Curtin University)

Recent research suggests approximately a quarter of teenagers have sent nude or semi-nude images or videos of themselves via an electronic medium. The consequences of sexting include leaving an online digital trail that might affect future employment and relationships; provide opportunities for blackmailing; humiliation if the image is shared further; and the resulting emotional trauma. This study aims to improve what we know about this behaviour and help young people make safe and healthy decisions about the images they share. Young people's perspectives are being actively used to develop and test an online resource that will enable families, schools and other adults working with young people to respond more effectively to reduce sexting-related harms.

During a two-day student Cyber Leader Summit in 2014, qualitative data exploring young people's understanding of online behaviour, including sexting, was collected from approximately 80 students through group activities.

Findings from these qualitative data were used to help to develop surveys measuring how and why young people interact with and respond to images in a cyber environment. Cyber Leaders and staff with experience in online educational materials development used the qualitative and quantitative data to inform the development of the online resource. This resource is being implemented via schools in 2015 and 2016.

Advisory stakeholder committees engaging young people, parents, school staff and policy makers have been



recruited to facilitate and maximize translation validity of the resources developed, while also guiding the progress of this research.

Very limited research is currently available to support legislators, policy makers, schools, families and other young people to help prevent or deal effectively with sexting behaviour. Accordingly this project is focussed on improving what we know about helping young people deal more safely and effectively with this behaviour. This research will be conducted with young people as co-researchers, rather than on young people, as they know better than any adult what is occurring in cyber space among others who are their age, and are also more able to recognise and propose what recommendations will be acceptable, feasible for and 'doable' by young people.

### Funders of the project

- Assessing the public health implications of higher risk online behaviours in young people: Telethon-New Children's Hospital Research Fund
- Students leading change to reduce sexting-related harm to young people: Healthway
- Department of Education, Western Australia

### External collaborators

Stakeholder committee comprising representatives from:  
 Government of Western Australia,  
 Department of Education  
 Boarding Schools Association  
 Association for Independent Schools in Western Australia

Catholic Education Office in WA  
 Institute for Professional Learning (Department of Education)  
 School Psychologists' Association of WA  
 School Curriculum and Standards Authority  
 Department for Child Protection  
 Commissioner for Children and Young People WA  
 Department of Local Government and Communities  
 Australian Research Alliance for Children and Youth (ARACY)  
 Youth Affairs Council of WA (YACWA)  
 Youth Futures  
 Communicare  
 Healthway  
 Australian Psychological Society (APS) College of Educational and Developmental Psychologists  
 APS College of Clinical Psychologists  
 APS College of Counselling Psychologists  
 APS College of Clinical Neuropsychologists  
 Australian Council on Children and the Media  
 ReachOut.com (Inspire Foundation)

### SCHOOL SOCIAL EXPERIENCES OF CHILDREN WITH ASTHMA: CONTRIBUTIONS TO MENTAL HEALTH PROBLEMS CO-MORBIDITY 2016-2017

*Kevin Runions (Telethon Kids Institute),  
 Donna Cross (Telethon Kids Institute),  
 Mark Everard (The University of Western Australia),  
 Graham Hall (Telethon Kids Institute)*

Children with asthma are at risk of mental health problems, including hyperactivity and anxiety, which can impact on their asthma control, overall wellbeing and

academic success. These children are also at risk of being targets of bullying at school, which poses further risk for mental health problems. A very small body of research indicated, however, that children with asthma are also more likely to bully other students. To date, no research has examined the complex relationships between asthma control, problems with hyperactivity and anxiety, and the risk of children with asthma being bullied or bullying others. Moreover, no research has examined how asthmatic children's relationships with teachers might affect peer relationships and the course of behaviour problems, despite evidence that conflict with teachers is linked to increased behaviour problems and victimisation risk.

This research will provide a crucial first step forward examining how peer, parent and teacher relationships at school affect behavioural and emotional problems for children with asthma. Data will be collected from a sample of 64 children presenting to the Asthma Clinic and the Respiratory Medicine Clinic at Princess Margaret Hospital for asthma-related problems and a comparison groups of 64 children presenting for non-chronic condition related clinics (Plastics and Orthopaedics). We will collect data from children, their parents (Phase I), and teachers (Phase II). These preliminary data will shed light on how these risks work together in the lives of children with asthma and will provide a strong base for larger studies of how these things work together over time. With better understanding of these school social experiences, evidence-based holistic school interventions can be developed to promote mental health and improve

asthma control, with positive implications for overall health for children with asthma

Children with asthma more often have mental health problems, or problems with bullying, compared to healthy children, but little research has studied the problem in detail. Our study will work with children, their parents and their teachers to better understanding how the things that go on at school may matter for children with asthma.

### **Funders of the project**

Asthma WA

### **External collaborators**

Princess Margaret Hospital

## **CYBER-AGGRESSION AND CYBER-VICTIMIZATION (CAV): A MIXED-METHODS STUDY OF STRUCTURAL FEATURES AND INDIVIDUAL DIFFERENCES IN ONLINE SOCIAL INFORMATION PROCESSING 2013-2016**

*Danielle Law (Wilfred Laurier University), Kevin Runions (Telethon Kids Institute), Jennifer Shapka (University of British Columbia), Debra Pepler (York University)*

Some experiences that may be interpreted as cyber-aggression and victimisation (CAV) may not, in fact, have been acts intended to harm, but are nevertheless interpreted as harmful and result in psychological harm. Interpreting the intent and emotional tone behind cyber-communications is a key digital skill, and one that can be challenging.



Our conceptual framework (Runions et al., 2012) systematically considers how the new technologies enabling online social networks might present distinct influences (i.e., opportunities and constraints) for aggression and victimization that are different from those afforded by traditional modes of communication. In this study, we seek to analyze how interpretation of semantic content is influenced by the opportunities and constraints that arise via communicating over that medium.

The present study aims to better understand how ambiguity operates in young people's interpretation and response to cyber-communication. A second phase addresses, via an experimental design, whether participants discern between intentionally harmful (exemplar) messages and intended jokes, and whether emoticon usage, the status of the sender (a popular acquaintance vs. an unpopular acquaintance), and the perceived audience for the communication (private or public) influence youth's interpretation and response to cyber-aggressive communications.

Thus there is a skill in both crafting and interpreting digital communications, but it is a skill about which we know very little. The present research aims to increase our understanding of how youth navigate this ambiguity and their experiences in interpreting ambiguous but potentially hostile/bullying communications, and to provide preliminary tests of a new conceptual model (Runions et al., 2012). The outcomes of this research would provide important directions for how best to prepare youth and their teachers and

parents for the complexities of their digital lives, so that misinterpretation does not fuel psychological problems.

It is not uncommon to hear stories about misunderstandings that arise from emails or text messages. At times, those misunderstandings can turn into grievances or even fights. Such misunderstandings may also fuel cyberbullying – or at least what young people see as cyberbullying. Our study involves listening to young people about the role of misunderstandings in cyberbullying, and then testing what drives certain misunderstandings being seen as cyberbullying.

#### **Funders of the project**

Social Sciences and Humanities Research Council (Canada)

#### **External collaborators**

Wilfred Laurier University, Kitchener-Waterloo, Ontario, Canada  
University of Victoria, British Columbia, Canada

### **DEVELOPING AN INNOVATIVE ONLINE INTERVENTION TO SUPPORT SCHOOLING FOR CHILDREN AND ADOLESCENTS WITH CYSTIC FIBROSIS 2015-2016**

*Donna Cross (Telethon Kids Institute), Steven Stick (Telethon Kids Institute), Kevin Runions (Telethon Kids Institute), Cindy Branch-Smith (Telethon Kids Institute), Linda Shields (Charles Sturt University), Thérèse Shaw (Telethon Kids Institute), Lidjia Turkovic (Telethon Kids Institute), Ashleigh Lin (Telethon Kids Institute), Heather Hugo (Princess Margaret*

*Hospital), Donald Payne (Telethon Kids Institute; Princess Margaret Hospital)*

Mental health problems such as depression can not only impact upon psychological wellbeing of children with CF, but they can also affect their physical health, including lung functioning, nutritional status and treatment adherence. As such, the prevention of mental health problems in this population is critical for their overall health and wellbeing. The project aims to develop and pilot an intervention that specifically targets the prevention of school-based problems that contribute to mental and physical health problems.

The project also aims for innovation in how schools work with children and youth with CF, utilising innovative methodologies to achieve that aim. Using current technology as a way to connect children/adolescents with CF is a secondary aim. Involving students with CF and their parents explicitly engaged as co-researchers, we are able to develop innovative plans that are ecologically valid for this population.

The project is motivated by a spirit of partnership with the participants. The engagement of the students with CF recognises that young people should not be recipients of change, but rather 'change partners'. Collaborative stakeholder partnerships will form a basis for intervention implementation across schools nationally with assistance from state and federal CF organisations.

Negative school experiences of students with cystic fibrosis (CF) can increase feelings of social isolation, reduce academic achievement and increase risk of mental health problems. Efforts to

support these students have been limited. This proposal uses online methods to engage students with CF and their families as co-researchers to develop and pilot an intervention's effectiveness. This approach to intervention development ensures the social, mental and emotional health needs of young people and their families with CF are met.

### **Funders of the project**

The Ian Potter Foundation

### **External collaborators**

Princess Margaret Hospital  
Cystic Fibrosis Western Australia  
School of Special Educational Needs,  
Department of Education, Western  
Australia  
Ronald McDonald Learning Program,  
Western Australia

## **ENHANCING THE MENTAL HEALTH AND WELLBEING OF CHILDREN WITH IMPAIRED HEARING 2016-2018**

*Donna Cross (Telethon Kids Institute), Marcus Atlas (Ear Science Institute Australia), Thérèse Shaw (Telethon Kids Institute), Rob Eikelboom (Ear Science Institute Australia), Cheryl Kickett-Tucker (Pindi Pindi, Centre for Research Excellence in Aboriginal Wellbeing), Kevin Runions (Telethon Kids Institute), Ian Li (The University of Western Australia), Juli Coffin (The University of Notre Dame Australia)*

For one of the most common conditions experienced by children, surprisingly little research has investigated the social, emotional and academic experiences of vulnerable children with hearing loss and the ways these experiences



can be enhanced. Children and adolescents with hearing loss are nearly four times more likely to experience psychosocial difficulties and mental health symptoms than those without hearing impairment. Moreover, adverse school experiences can impact even more negatively on their mental health and academic achievement, for example by exacerbating social isolation, with long-term health and education costs. Importantly, Aboriginal children and adolescents are even more likely to experience hearing loss than their non-Aboriginal peers, at an earlier age, with more severe episodes over an extended period of time and have more complications.

This three-year mixed methods research project aims to support children with hearing loss by engaging them, their families and their teachers (as well as other major stakeholders and decision-makers) as co-researchers to develop and test innovative school- and family-based intervention strategies to enhance their developmental health i.e., mental health, emotional and social wellbeing, and education outcomes. This highly participatory approach to intervention development and its evaluation will ensure it is viable and authentic, as the recommendations from children with hearing loss and those of others who are associated personally and/or professionally with their condition, will form the core components of the intervention. This collaborative development process will ensure the advice from students with hearing loss and those who care for them is purposefully addressed in the intervention, while simultaneously building the capacity of those in their immediate

social environments (schools, teachers and families).

This targeted intervention will be evaluated in 152 metropolitan and regional schools with 144 students (aged 10-12 years) with hearing loss using a group-randomised control design. Schools/students will be randomised to one of two conditions, either receiving the developed intervention immediately, or one year after its evaluation. Intervention impact will be determined based on data measuring the students' mental health, social and educational outcomes, using online surveys of the students, their parents/carers, teachers and existing school records. An economic analysis will also be conducted to determine the cost effectiveness and economic implications of the intervention recommendations. Hence, this study and targeted intervention will be developed, disseminated and evaluated actively engaging the target audience and key stakeholders to maximise the likelihood of it being relevant for translation into health and education policy and practice.

Children with hearing loss are at a greater risk of being socially isolated, perform less well at school and are up to four times more likely to experience mental health problems than children without hearing loss. However, specific, evidence-based resources to support the mental health and wellbeing of this vulnerable group of students are not currently available to families and primary and secondary WA schools. This research will, together with Aboriginal and non-Aboriginal children with hearing loss, their parents/carers and teachers, examine why they may not do as well as their peers and how their

school environment can positively impact on their wellbeing. Efforts to generate meaningful change in the lives of young people are known to be most effective when young people are partners in determining the change needed and therefore able to help adults to help them. Children with hearing loss will therefore be involved as co-researchers in this innovative three-year study, including as 'Ambassadors' at the Participant Forum to recommend and design actions schools and families can take to support their mental, emotional, social and physical wellbeing in the school environment.

As part of the study these recommended actions will be developed, disseminated in an online format and evaluated with a sample of approximately 144 Years 4-6 students in WA schools. Recommendations for policy and practice will be developed in conjunction with an advisory group comprising children with hearing loss and their parents and teachers, local Aboriginal cultural translators, Aboriginal Islander Education Officers as well as stakeholders and policy-makers from relevant government and non-government organisations. Involvement of these groups, together with the input from the young people themselves, will ensure the proposed strategies are relevant, sustainable and able to be translated into policy and practice for schools and other institutions working with hearing impaired children.

### **Funders of the project**

Healthway

### **External collaborators**

Telethon Speech and Hearing

Australian Hearing  
WA Deaf Society  
Deafness Council of WA  
WA Foundation for Deaf Children  
Department of Education School of Special Education Needs: Sensory (SSEN: Sensory)  
Catholic Education Western Australia  
Association of Independent Schools Western Australia  
Australian Primary Principals' Association  
Edith Cowan University School of Education  
WA School Psychologists' Association  
Child and Adolescent Community Health (CACH)

## **STATE OF WA YOUTH HEALTH AND WELLBEING FORMATIVE STUDY 2015-2016**

*Donald Payne (Telethon Kids Institute; Princess Margaret Hospital); Donna Cross (Telethon Kids Institute); Kevin Runions (Telethon Kids Institute); Matt Byrne (Edith Cowan University); Trish Heath (Commissioner for Children and Young People); Lewis Marshall (Fiona Stanley Hospital); Myra Robinson (Youth Affairs Council of Western Australia); Jenny Allen (Youth Focus)*

There is increasing recognition of the global importance of youth health – the growing burden of health problems within this group, the poor health outcomes relative to other age groups and the need for health services to adapt accordingly. The collection and use of data to drive the development of policies and services is fundamental to understanding ways to improve youth health and wellbeing. This project will focus on identifying opportunities to improve the youth health



and wellbeing evidence base in WA. It will support research to bring together all sources of existing data, including previous reports and research and active data linkage, to obtain a picture of the state of young people's health in WA. This information coupled with a preliminary review of the literature would form the baseline for future work, help identify gaps in data collection and support the development of longer-term priority areas of research.

This project will bring together all sources of existing data, including previous reports and research and active data linkage, to obtain a picture of the state of young people's health in WA. This information will help identify gaps in data collection and support the development of longer-term priority areas of research.

### **Funders of the project**

Telethon Kids Institute, Working Group  
Project Funding

### **External collaborators**

Princess Margaret Hospital  
Youth Affairs Council of WA  
School of Special Educational Needs,  
Department of Education, Western  
Australia  
Eating Disorders Program, Child and  
Adolescent Mental Health Service  
(CAMHS)  
Youth Focus  
Youth Cancer Service, Sir Charles Gairdner  
Hospital  
Sexual Health and Blood-borne Virus  
Program, Department of Health  
Fiona Stanley Hospital  
Fremantle Hospital  
The University of Notre Dame Australia

Office of the Commissioner for Children  
and Young People (CCYP)  
WA Child and Youth Health Network  
WA Child and Youth Health Network  
Youth Mental Health Service  
Injury Control Council of WA  
VisAbility

## **MAPPING AND REVIEW OF HEALTH SERVICES AVAILABLE TO YOUNG PEOPLE 2015-2016**

*Roz Walker (Telethon Kids Institute);  
Donna Cross (Telethon Kids Institute);  
Donald Payne (Telethon Kids Institute;  
Princess Margaret Hospital); Kevin Runions  
(Telethon Kids Institute)*

Improvements in young people's health in Australia are not commensurate with the progress made in other age groups. The Australian Research Alliance for Children and Youth ranked Australia 17 out of 30 countries in the OECD on the physical health of children and young people. Young people's access to quality services is one of the major factors contributing to these poorer outcomes. According to the CCYP Young People's Experiences with Health Services report, young people state that their health services need to be youth friendly (by incorporating youth workers and staff who are respectful and listen to their concerns), have a greater presence in schools, be easy to access by public transport, ensure confidentiality, provide support on issues around sexual health and drugs and alcohol, and facilitate mental health consultations.

This project will use a comprehensive web search strategy combined with purposeful snowball sampling with peak youth organisations, agencies and stakeholders,

to identify the service providers and the services / interventions offered to young people throughout Western Australia. As these agencies are identified, an online survey will be used to determine the nature of these services for young people. The agencies that do not respond to the survey will be invited to be interviewed by phone or in person according to their needs. We will use the 2014 CCYP report findings and the above mentioned youth friendly criteria to understand, for example, the types of interventions offered, the overall use of this service by young people (via aggregated records), reach (target groups) and focus of these health services.

This project will identify the health services available to young people throughout Western Australia in terms of the nature of the services offered, the overall use of this service by young people and focus of these health services.

### **Funders of the project**

Telethon Kids Institute, Working Group  
Project Funding

### **External collaborators**

Princess Margaret Hospital  
Youth Affairs Council of WA  
School of Special Educational Needs,  
Department of Education, Western  
Australia  
Eating Disorders Program, Child and  
Adolescent Mental Health Service  
(CAMHS)  
Youth Focus  
Youth Cancer Service, Sir Charles Gairdner  
Hospital  
Sexual Health and Blood-borne Virus  
Program, Department of Health

Fiona Stanley Hospital  
Fremantle Hospital  
The University of Notre Dame Australia  
Office of the Commissioner for Children  
and Young People (CCYP)  
WA Child and Youth Health Network  
WA Child and Youth Health Network  
Youth Mental Health Service  
Injury Control Council of WA  
VisAbility

### **IMPACT OF CHRONIC DISEASES ON MENTAL HEALTH AND SCHOOL SUCCESS 2015-2016**

*Kevin Runions (Telethon Kids Institute);  
Donna Cross (Telethon Kids Institute);  
Steven Stick (Telethon Kids Institute);  
Donald Payne (Telethon Kids Institute;  
Princess Margaret Hospital); Elizabeth  
Davis (Telethon Kids Institute); Ashleigh  
Lin (Telethon Kids Institute); Thérèse Shaw  
(Telethon Kids Institute); Grant Wheatley  
(School of Special Educational Needs:  
Medical & Mental Health); Matt Byrne  
(Edith Cowan University); Gareth Baynam  
(Telethon Kids Institute)*

A recent series of meta-analyses indicates that children with chronic physical illnesses are at increased risk for internalizing problems, including anxiety and depression, as well as increased risk for externalizing and total behaviour problems. School as a developmental setting might serve to protect against this risk, or to amplify it, but little empirical research has examined this role for schools. A systematic examination of the potential for school-based processes (including peer relationships (e.g., bullying victimisation); stigmatisation due to symptoms of the condition, etc.) across a range of conditions is warranted. The working group is constituted by



researchers working across conditions including cystic fibrosis, diabetes, hearing loss, and rare diseases of childhood, amongst others, and researchers on the school experiences of children.

Children and young people who have chronic health conditions such as diabetes, cystic fibrosis, and hearing loss, face challenges beyond the obvious physical health-related ones. Research has shown they are also more likely to have mental health problems. There have been a few studies indicating that what happens to these young people at school might either help protect them from mental health problems, or make them worse. This study will gather together all the published research and critically review it.

### **Funders of the project**

Telethon Kids Institute, Working Group Project Funding

### **External collaborators**

Adolescent Medicine and Eating Disorders, Princess Margaret Hospital  
School of Special Educational Needs, Department of Education, Western Australia  
Medical & Mental Health, Department of Education, Western Australia

## **IMPACT OF CHRONIC DISEASE ON MENTAL HEALTH AND EDUCATION 2015-2016**

*Ashleigh Lin (Telethon Kids Institute), Kirsten Hancock (Telethon Kids Institute); Kevin Runions (Telethon Kids Institute); Donald Payne (Telethon Kids Institute; Princess Margaret Hospital); Graham Hall (Telethon*

*Kids Institute); Cindy Branch-Smith (Telethon Kids Institute), Gareth Baynam (Genetic Services of Western Australia, Department of Health), Rob Eikelboom (Ear Sciences Institute Australia), Donna Cross (Telethon Kids Institute); Mark Everard (Princess Margaret Hospital), Caron Molster (Office of Population Health Genomics, Public Health and Clinical Services Division, WA)*

The primary aim of this study is to characterise the mental health, wellbeing and school and other social experiences of large numbers of Western Australian children and young people living with chronic illnesses. Secondary aims are to investigate condition-specific vs. generalizable experiences, and to understand the impact of age- and illness-related factors on mental health, wellbeing and school experiences. Methodology: We will achieve these aims via a secure online survey to be completed by for children age 6-11 years (via parent-report) and by adolescents aged 12-18 with chronic diseases in WA. We will also survey parents. For comparisons to the general population, survey content will be developed to align with the content of the Young Minds Matter Survey, a nationally representative survey of 4-17 year olds conducted in 2014 that captured prevalence of mental health, wellbeing, and educational experiences. The link to the survey will be distributed through the Telethon Kids Institute, Princess Margaret Hospital, Genetic Services of Western Australia, Ear Science Institute Australia, School of Special Educational Needs: Sensory, and our other established education and health networks. To recruit participants with well-defined conditions, we will

approach community organisations to advertise our link (e.g. the Cystic Fibrosis Association of WA; Genetic and Rare Disease Network; Deafness Council of Western Australia). We have chosen to focus primarily on the diseases in which our group has expertise: type 1 diabetes, cystic fibrosis, moderate to severe asthma, ear disease and hearing impairment, and rare diseases.

The survey will be designed to facilitate 1) the necessary parental consent and child/young person assent procedures 2) parent vs. young person completion and age-appropriate questions; and 3) distinct pathways to illness-specific questions.

We have chosen to exclude children and young people with developmental disorders or primary mental health conditions without co-morbid physical illness. Outcomes of interest: mental health indexed by symptoms severity; social and school functioning; academic achievement; experiences of bullying; peer and teacher relationships; stigma; indices of disease severity and management. Community participation: We will consult with young people with chronic conditions and their families in the development of the survey to better understand appropriateness and barriers to completion. We will pilot the survey with a small group of children and young people and their parents.

Children and young people who have chronic health conditions such as diabetes, cystic fibrosis, and hearing loss, face challenges beyond the obvious physical health-related ones. Research has shown they are also more likely to have mental health problems. There have been a few studies indicating that what happens to these young people at school

might either help protect them from mental health problems, or make them worse. This study will use an online survey of parents of children (4-17) with type 1 diabetes, cystic fibrosis, hearing loss, or a 'rare condition' to help us understand the mental health of these young people and the role of school in helping them.

### **Funders of the project**

Brain & Behaviour Research Focus Area and Chronic Diseases of Childhood Research Focus Area, Telethon Kids Institute.

### **External collaborators**

Cystic Fibrosis Association of WA  
Genetic Services of Western Australia,  
Department of Health  
Ear Sciences Institute  
Australia Genetic and Rare Disease Network  
Deafness Council of Western Australia

## **USING NEUROFEEDBACK (NF) AS A NON-PHARMACOLOGICAL INTERVENTION STRATEGY IN YOUNG PATIENTS WITH PSYCHIATRIC DISORDERS: TARGETING TIC SYMPTOMS AND TOURETTE'S SYNDROME. 2016-2017**

*Florian Zepf (The University of Western Australia; Child and Adolescent Mental Health Service), Ashleigh Lin (Telethon Kids Institute), Kevin Runions (Telethon Kids Institute), Andrew Whitehouse (Telethon Kids Institute), Desiree da Silva (School of Paediatrics and Child Health, The University of Western Australia), Wai Chen (The University of Western Australia; Child and Adolescent Mental Health Service), Richard Stewart (Bentley Mental Health*



Services), John Wray (The University of Western Australia; Child and Adolescent Mental Health Service).

Current evidence suggests that the treatment of attention deficit hyperactivity disorder (ADHD) in minors should comprise a multimodal treatment approach, including stimulant medications. However, many children with ADHD also experience co-morbid tics, which can create significant impairments. Moreover, stimulants (which are frequently prescribed to children with ADHD) can make tic symptoms even worse. In this project we will use EEG-based neurofeedback as a non-pharmacological approach to treat ADHD and tic symptoms in children within a pilot approach.

Aims and Methodology: a.) To implement EEG-based neurofeedback for the treatment of ADHD and co-morbid tic symptoms in young patients in a community setting within a short open-label pilot approach. EEG-based neurofeedback will be administered to patients over two weeks within daily 1-hour sessions on weekdays (5 sessions per week). Relevant symptomatology (ADHD symptoms, tics) will be assessed before and after the intervention. b.) To evaluate the effectiveness of this pilot intervention on a preliminary basis in terms of a pre vs. post comparison, and to calculate the effect and sample sizes for future large-scale research on the basis of the pilot data obtained in the present approach.

Treatment for attention deficit hyperactivity disorder (ADHD) often relies on stimulant medications. Such stimulants, however, can make tic symptoms – which

are relatively common in children with ADHD – worse. This study will pilot a system called EEG-based neurofeedback (NF). This approach measures your brain activity in real time, then sends the signal to a monitor in front of you, so you can see it change. NF research has shown that children with ADHD can learn to control their attention better using this kind of feedback. Our study will see if this works for children who have both ADHD and tic symptoms.

### **Funders of the project**

Brain & Behaviour Research Focus Area;  
Telethon Kids Institute

### **External collaborators**

Princess Margaret Hospital Foundation (PMHF)  
The University of Western Australia, Child and Adolescent Psychiatry  
Child & Adolescent Mental Health Services  
Bentley Mental Health Services  
Child Development Services

### **SUPPORTING PARENTS TO SUPPORT YOUTH 2015-2016**

*Robyn Johnston (Edith Cowan University); Thérèse Shaw (Telethon Kids Institute; The University of Western Australia); Conor Gilligan (University of Newcastle); Shelley Beatty (Edith Cowan University); Laura Thomas (Edith Cowan University)*

Effective strategies parents can use to delay and reduce alcohol use by young people have been identified, e.g. alcohol-related communication; rule setting and consequences; monitoring; and non-supply of alcohol.

However, not enough is known about WA parents' use of such strategies with their adolescent children, nor their attitudes, norm perceptions, or self-efficacy around delaying and reducing alcohol use by their children. To develop effective parent interventions, it is vital to understand parents' current practices and enablers and barriers to their use of the recommended strategies. This research aims to explore these issues as well as the support needs of parents and their perceptions of appropriate mechanisms for the delivery of a parent intervention.

The study is using a sequential mixed methods approach. Data were collected in cross-sectional online surveys from 823 Year 7, 10 and 12 students (June 2015) and 298 parents (July-Aug 2015) from 5 non-government schools in WA (124 child-parent pairs). The student survey contained questions on adolescents' alcohol use, and their parents' use of the recommended alcohol-related parenting practices. The parent survey asked parents about their attitudes, alcohol-related parenting behaviours, alcohol use and views on alcohol programs. The surveys were followed by focus groups/ interviews with 40 parents (Oct-Dec 2015). The focus groups and interviews explored parents' awareness and use of the recommended strategies to reduce and delay adolescent alcohol use, their self-efficacy and beliefs about the appropriateness and effectiveness of the recommended strategies, their support needs and their views on different delivery mechanisms and modes for parent programs. Data analyses are ongoing.

Underage binge drinking by Western Australian teens has become increasingly

common, placing them at risk of alcohol-related harms to their mental and physical health. Parents have a key role in addressing this issue, but not enough is known about WA parents' use of recommended strategies with their children, nor their attitudes, perceptions of what other parents allow, or self-confidence around taking steps to delay and reduce alcohol use by their children. The findings will be used to guide the development of programs that are acceptable and useful to parents.

### **Funders of the project**

Healthway

### **External collaborators**

Shelley Hill, Parent & Friends Federation of Western Australia (PFFWA)

Janette Gee, Western Australian Secondary Schools Executives Association (WASSEA)

Anne Miller, School Drug Education and Road Aware (SDERA)

Megan Milligan, South Metropolitan Population Health Unit

## **2015 Success**

### **THESES PASSED**

Kate Hadwen PhD Edith Cowan University - Leaving home: Investigating transitioning challenges faced by boarding students and their families. Supervisor Donna Cross

### **AWARDS AND PRIZES**

Kevin Runions – Cockell Research



Collaboration Award, Raine Medical Research Foundation  
Donna Cross – Fellow of the Australian Academy of Health and Medical Sciences

## EXTERNAL COMMITTEES

### International

Donna Cross, Editorial Committee, Australian and New Zealand Journal of Public Health

Donna Cross, Editorial Committee, Advances in School Mental Health Promotion Journal

Donna Cross, Editorial Committee, School Psychology Quarterly

### National

Donna Cross, Editorial Committee, Health Promotion Journal of Australia

## INVITED PRESENTATIONS

### Conferences

- Donna Cross, Cyberbullying risks for the mental health and wellbeing of young people, Annual Rotary District 9465 Conference. Albany, 20 March 2015. Keynote.
- Donna Cross, Evidence-based practice to enhance the quality of pastoral care and reduce bullying and student wellbeing in Australian schools. Positive Schools 2015 Mental Health and Wellbeing Conference. Perth, 28 May 2015. Keynote.
- Donna Cross, School staff wellbeing: current research, Cockburn Schools District Conference, Perth, 29 May 2015. Keynote.
- Donna Cross, Optimal student wellbeing is about empowerment and social learning, not just pastoral support. Teaching and Supporting

Students with Special Needs 5th National Conference. Melbourne, 30 July 2015. Keynote.

- Donna Cross, Closing the Chasm between Bullying Prevention Intervention Research Evidence and Policy and Practice. 17th European Conference on Developmental Psychology. Portugal, 10-11 September 2015.
- Donna Cross, Next Practice: Positioning pastoral care as learning not just support. School Psychologists' Association of WA Conference 2015. Perth, 25 September 2015. Keynote.
- Donna Cross, The Wellbeing of Young Men - How do we move from strength to strength? National Boys' Education Conference. Sydney, 5 October 2015. Keynote.
- Donna Cross, Evidence-based research addressing how principals can strategically improve school culture and reduce bullying and its harms among students. Principals in Schools Conference, 2015. Keynote.
- Donna Cross, Evidence from the Strong Schools Safe Kids 5-year longitudinal research project. Youth Health Conference. Melbourne, 13 November 2015. Plenary.

## COMMUNITY PRESENTATIONS AND WORKSHOPS

- Donna Cross, Bullying and student wellbeing research. Several seminars for senior school staff, parents and students at Trinity College. Melbourne, January-December 2015
- Donna Cross, Enhance pastoral care to support students' social and emotional skills. Workshops for students, staff and

parents at Wenona College. Sydney, March 2015.

- Donna Cross, Current research on adolescents' use of drugs and alcohol. Workshops for parents and teachers, on behalf of SDERA. Perth, March-June 2015.
- Donna Cross. Research and opportunities for partnership. Presentation to Wesfarmers for TKI. 2015.
- Donna Cross, iPhone kids losing social skills. Presentation to Rotary Club Perth, Perth, 4 June 2015.
- Donna Cross, Resiliency and supporting student wellbeing. Whole-school presentation at St Stephen's College, Perth, July 2015.
- Donna Cross, Social-emotional learning and cybersafety. 2-day staff workshop for the Association of Independent Schools of Victoria. Melbourne, 26-27 August 2015.
- Donna Cross. Research and opportunities for partnership. Presentation to BHP Billiton for TKI. 20 October 2015.
- Donna Cross. Children's social and emotional wellbeing. Presentation to Margaret River Montessori School. 26 October 2015.
- Donna Cross. Supporting student wellbeing. Presentation to parents at Christchurch Grammar School. 13 November 2015.



# HUMAN CAPABILITY

## Overview

The Human Capability Team focuses on population mechanisms that underpin child health, social and emotional wellbeing, and child development more generally. This allows us to contextualise the impact of mental health problems within the wider framework of population health. In this theme, we address fundamental mechanisms that contribute to social inequalities and social gradients in child and youth health.

The concept of human capability extends the notion of human capital beyond the focus on human economic productivity to include the contributions that individuals make to community and society through their social, civic and economic participation. Thus, where good health status makes a person more efficient for productivity in the workplace, then this is seen to also enhance human capital. However, a person's good health status also increases their capacity for social activity and child rearing and parenting, being able to physically engage, make healthy food choices and so on. That is, the benefits of good health exceed its role as human capital in work productivity. A person highly trained and proficient in a particular job skill has the potential to make a productive contribution to the economy when their particular skill is in demand. If a person also has broader capabilities and potential beyond their specialist job skill area they may also make meaningful contributions to society outside their job, including contributions to their family, community and the

pursuit of new ideas and innovations. In this way, human capability describes the capacity of individuals to improve their health, wealth, knowledge and the opportunities available to facilitate these improvements, as well as manage the risks that pose barriers to these opportunities. The human capability approach includes the broader concept of having capacity to develop a wider range of skills and talents that allow people to have greater choice over the direction of their lives, and to participate in all aspects of society.

## Research Projects

### **YOUNG MINDS MATTER: THE SECOND AUSTRALIAN CHILD AND ADOLESCENT SURVEY OF MENTAL HEALTH AND WELLBEING**

*David Lawrence, Jennifer Hafekost, Sarah Johnson, Wavne Ridders, Stephen Zubrick with Michael Sawyer (The University of Adelaide) and John Ainley (Australian Council for Educational Research)*

*Young Minds Matter: The Second Australian Child and Adolescent Survey of Mental Health and Wellbeing* is part of the National Survey of Mental Health and Wellbeing initiative. This is an Australian Government Department of Health funded initiative comprising national surveys of adults in the general population in 1997 and 2007, those with psychotic illnesses in 1997-98 and 2010, and the first national child and adolescent survey in 1998. *Young Minds Matter* was conducted in partnership with Roy Morgan Research.

The main aims of the survey were to determine the prevalence of mental disorders in children and adolescents in Australia, the impact that these disorders have on children and their families, and the use of services and unmet need for services in the health and education sectors.

*Young Minds Matter* was the largest and most comprehensive survey of child and adolescent mental health ever conducted in Australia. Over 6,000 families with children aged 4-17 years from across Australia participated in the survey, which included a face-to-face interview with the primary carer, as well as a self-report questionnaire on a tablet computer for young people aged 11-17 years.

The survey findings were released by the Hon Sussan Ley, Minister for Health, in August 2015. The survey found that mental disorders remain common and disabling in children and young people. An estimated 560,000 4-17 year-olds, or approximately 14%, were assessed as having mental disorders in the previous 12 months. Since the first survey was conducted in 1998, the prevalence of Attention-Deficit/Hyperactivity Disorder (ADHD) and conduct disorder has decreased, while there has been an increase in the prevalence of major depressive disorder. Mental disorders were more common in families facing other challenges, including unemployment and family breakup. Mental disorders impact on children in various ways and to differing extents. They are often persistent and disabling. They can have major impacts on schooling. Major depressive disorder had the largest impact on absence from school with children missing an average of 20 days of

school in the past year due to symptoms of their disorder.

The survey found very high rates of distress, depression and self-harming and suicidal behaviours in teenagers, particular older teenage girls, which highlight the challenges faced in the transition to adulthood. Over 7% of young people aged 11-17 years had major depressive disorder, based on information they reported themselves. This prevalence was highest among older teenage girls, with almost one in five 16-17 year old females having major depressive disorder. One in twelve 12-17 year-olds reported having self-harmed in the past 12 months. Around one in thirteen 12-17 year-olds had seriously contemplated ending their own life, and 2.4% reported having attempted suicide in the previous 12 months.

Since the first survey in 1998 there has been a large increase in the number of children with mental disorders receiving help, and a substantial reduction in the number of families dealing with problems on their own. Specialist mental health services provide vital services for children dealing with severe and challenging problems, but most mental health problems are dealt with in primary care and the education system. In 1998 only one in four children with a mental disorder received any form of help. *Young Minds Matter* found that 56% of children and adolescents with a mental disorder received help, with 53% receiving help in the health sector, and 40% receiving help in the education sector. However, there are still substantial numbers of families whose needs for help go unmet and many others who receive less help than they feel that they need.



Young Minds Matter is the largest survey of child and adolescent mental health and wellbeing ever conducted in Australia. The parents and carers of over 6,000 children aged 4-17 years around Australia were interviewed, and almost 3,000 young people aged 11-17 years completed a separate questionnaire in private. The survey found one in seven Australian children and adolescents had a mental disorder in the past 12 months. This prevalence has remained relatively stable since the first survey was conducted in 1998. Fewer 4-17 year-olds now have ADHD or conduct disorder, but there has been an increase in the number of children and adolescents with major depressive disorder. Mental disorders were more common in families facing other challenges, including unemployment and family breakup. The survey found very high rates of distress, depression and self-harming and suicidal behaviours in teenagers, particular older teenage girls, which highlight the challenges faced in the transition to adulthood. Since the first survey in 1998 there has been a large increase in the number of children with mental disorders receiving help, and a substantial reduction in the number of families dealing with problems on their own. However, there are still substantial numbers of families whose needs for help go unmet and many others who receive less help than they feel that they need.

### **Funders of the project**

Australian Government Department of Health

### **External collaborators**

Michael Sawyer, The University of Adelaide  
John Ainley, Australian Council for

Educational Research  
Roy Morgan Research

## **ESTIMATING THE POPULATION EFFECT OF MATERNAL ALCOHOL-USE DISORDERS ON THE EDUCATIONAL ACHIEVEMENT OF CHILDREN**

*Carol Bower, Sarah Johnson, Nadia Cunningham, Kirsten Hancock*

The use of alcohol by Australian women has been increasing over the past four decades. Over half of Western Australian women report drinking alcohol at some stage during pregnancy, and 4% report drinking more than four drinks on a single occasion at some point during their pregnancy. Heavy prenatal alcohol exposure places the fetus at risk of Fetal Alcohol Syndrome (FAS) and a range of disorders classified as Fetal Alcohol Spectrum Disorders. The consequences of these can include a range of effects, such as impacts on speech and learning, and cognitive development which can lead to poorer educational outcomes.

This study uses Western Australia's data linkage environment to conduct a population wide study of the effects of alcohol exposure during pregnancy on educational outcomes. The project uses data from the WA Midwives Notification System to identify children born in Western Australia between 1983 and 2007. These data are combined using data linkage with information from the WA Hospital Morbidity Data System, the Mental Health Information System and the Drug and Alcohol Service to identify maternal use of alcohol during pregnancy. Educational data including attendance at school and achievement as measured in the NAPLAN

(National Assessment Program — Literacy and Numeracy) and its predecessor the Western Australian Literacy and Numeracy Assessment (WALNA) are also linked to study the association between alcohol exposure and educational outcomes.

This project aims to examine the association between in-utero and childhood exposure to maternal alcohol-use disorder and child education outcomes, and to identify modifiable risk factors associated with maternal alcohol-use disorder that increase the risk of poorer educational outcomes such as maternal and child health and mental health, regional and social factors. All analyses will be stratified by Indigenous status.

Many Western Australian women drink alcohol during pregnancy, with some drinking at quite high levels. Alcohol exposure during pregnancy is associated with Fetal Alcohol Spectrum Disorders (FASD) which can, among other things, impact speech and language development, cognitive development and their learning at school. This project uses information from Western Australia's Data Linkage System to study the educational outcomes of Western Australian children born between 1983 and 2007 who were exposed to alcohol during pregnancy, compared with a matched sample of children born during the same period who were not exposed to alcohol during pregnancy by Indigenous status.

### **Funders of the project**

Australian Research Council Discovery Project Grant DP140101573

### **External collaborators**

James Semmens, Curtin University  
Colleen O'Leary, Government of Western Australia Department of Health

### **ENGAGING, SUPPORTING AND WORKING WITH CHILDREN AND FAMILIES IN TASMANIA'S CHILD AND FAMILY CENTRES**

*Cate Taylor, Kim Jose, Daniel Christensen, Weitse van de Lageweg.*

The aim of the study was to understand the impact of Child and Family Centres on parents' use and experiences of early childhood services. In Tasmania, Australia's island state, Centres have been established as a whole-of-government response to the profound spatial patterning of socioeconomic disadvantage and vulnerable child development (AEDC, 2015; Marmot 2010). A holistic view of the child and the multiple ecologies of child development guided the study (Bronfenbrenner, 2005; National Scientific Council on the Developing Child, 2004). A mixed methods approach was used. The methods included a survey, focus groups and interviews and the results were integrated according to topic not method. The study was approved by the Tasmanian Social Science Human Research Ethics Committee. Parents who used Centres made more use of universal early childhood services and Vocational Education and Training than parents who were eligible but did not use Centres. The results showed that parents experienced Centres as welcoming, respectful and inclusive places that were helping them develop positive child, family, school



and community connections. Parents said that these qualities made the critical difference to their engagement and positive experiences of services and supports in Centres, in contrast to some of their experiences in the past. Child and Family Centres are showing promising early signs that they are having a positive impact on parents' use and experiences of early childhood services and Vocational Education and Training.

In twelve communities across the state, Tasmania's Child and Family Centres are a one-stop-shop for services and supports to help give children the best possible start in life. Well before the first brick was laid, the Centres have been steered by members of the local community, ensuring services and supports provided are tailor-made to meet local needs. This study found that Centres are having a positive impact on parents' use and experiences of early childhood services and Vocational Education and Training.

### **Funders of the project**

Tasmanian Early Years Foundation in partnership with the Tasmanian Department of Education.

## **EVALUATION OF THE HEADSPACE PROGRAM**

*Francis Mitrou, Daniel Christensen, Katherine Hafekost, Hanh Ngo, Stephen Zubrick (Telethon Kids Institute) with Fiona Hilferty, Kristy Muir, Ilan Katz (The University of New South Wales) and Rebecca Cassells, Alan Duncan, Grace Gao, Astghik Mavisakalyan, Ha Nguyen, Yashar Tarverdi, Chelsi Wingrove (Curtin University).*

In January 2013 the Australian Government Department of Health funded a consortium of researchers to conduct the second evaluation of the headspace program, following a competitive tender process in 2012. The consortium was led by a team from the Social Policy Research Centre at the University of New South Wales, and included researchers from the Telethon Kids Institute at the University of Western Australia as well as researchers from the Bankwest Curtin Economics Centre at Curtin University.

headspace (the National Youth Mental Health Foundation) was established by the Australian Government in 2006 with a primary focus on the mental health and wellbeing of young Australians aged 12–25 years. The vision of headspace is to improve young people's mental, social and emotional wellbeing through the provision of high quality, integrated services when and where they are needed. headspace was previously evaluated in 2009, when there were only 30 centres nationally, but the second evaluation provided assessment of the program using data from 67 fully operational centres.

While headspace receives a small amount of funding from other sources, and some in-kind contribution from lead service agencies that it partners with, over 90% of reportable funding comes via Department of Health grants. In 2015 Department of Health grants to headspace totalled approximately \$126m. As a publically funded service it is important that headspace achieves its aims in a manner considered efficient by the standards of the broader mental health sector and that

its activities represent a value-for-money investment for the Australian Government and the general public.

The evaluation assesses the extent to which the centre-based headspace program is achieving its objectives, with a specific focus on:

- The clinical outcomes of young people who have received services;
- Young people's access and engagement with headspace;
- The centre-based service delivery model; and
- The cost effectiveness of headspace centre services.

The evaluation began in January 2013 and a draft final report was provided to the Department of Health in October 2015 for review. The report is currently under embargo and is expected to be released by mid-2016.

headspace (the National Youth Mental Health Foundation) was established by the Australian Government in 2006 to help service the mental health and wellbeing of young Australians aged 12–25 years. The vision of headspace is to improve young people's mental, social and emotional wellbeing by providing a range of youth friendly services under one roof. The headspace service is funded mostly by the Australian Government Department of Health. It is important that headspace achieves its aims helping young people with mental health issues in a way that also delivers value-for-money for taxpayers. This evaluation will describe how well headspace is achieving these goals. The report is expected to be released by mid-2016.

## Funders of the project

Australian Government Department of Health

## External collaborators

Fiona Hilferty, Kristy Muir, Ilan Katz (Social Policy Research Centre at The University of New South Wales)

Rebecca Cassells, Alan Duncan, Grace Gao, Astghik Mavisakalyan, Ha Nguyen, Yashar Tarverdi, Chelsi Wingrove (Bankwest Curtin Economics Centre at Curtin University)  
Roy Morgan Research

## ARC CENTRE OF EXCELLENCE FOR CHILDREN AND FAMILIES OVER THE LIFE COURSE

The ARC Centre of Excellence for Children and Families over the Life Course (Life Course Centre or LCC) is investigating the critical factors underlying disadvantage to provide life-changing solutions for policy and service delivery. We aim to identify the drivers of disadvantage, characterised by the spread of social and economic poverty within families and across generations, and to develop innovative solutions to reduce disadvantage. The Life Course Centre is a national centre funded by the Australian Research Council Centre of Excellence Scheme. Hosted through the University of Queensland, the University of Western Australia is one of the collaborating Universities that comprise the centre. Staff at the Telethon Kids Institute and UWA participate in a range of funded projects with the **Life Course Centre**. [These include:](#)



## CAUSES AND CONSEQUENCES OF STUDENT MOBILITY IN AUSTRALIA

*Kirsten Hancock, Stephen Zubrick*

Research shows that students who change schools are at greater risk of lower educational attainment and early dropout than non-mobile students. While it is understood that there are many reasons – both positive and negative – that underpin unscheduled school transfers, all types of school moves are typically considered equal. This approach has led to inconsistent findings related to student mobility and how it relates to other student outcomes. In addition, our knowledge regarding the extent and nature of student mobility for Australian students is limited. The aim of this study is to provide an overview of student mobility in Australia using a nationally representative longitudinal cohort of Australian children, and to determine whether the different reasons underlying mobility are related to differences in progress over time. In particular, we will address the following questions:

- 1) What is the nature of student mobility in Australia?
- 2) Besides the transition from primary school to secondary school, how often do students change schools, and what are the main reasons behind these changes?
- 3) What are the family and socio-demographic characteristics associated with each of the reasons for students changing schools?
- 4) How are the different reasons underlying school changes related to differences in achievement progress over time at different developmental points?

Addressing these questions will help

to further understand the nature of student mobility. The results of the study will help schools to understand some of the issues facing their new students, and the likelihood of which students may need more attention than others after transitioning school. This paper will also complement other work underway examining differences in progress outcomes for students who move to similar, higher or lower-SES schools.

Research shows that students who change schools are at greater risk of lower educational attainment and early dropout than non-mobile students. Yet the reasons, both positive and negative, that underpin school moves are typically considered equal, which leads to inconsistent findings on student mobility and outcomes. The aim of this study is to provide an overview of student mobility in Australia, and to determine whether the different reasons underlying mobility are related to differences in educational attainment over time.

### Funders of the project

Australian Research Council

### FAMILY DYNAMICS AND CHILD MENTAL HEALTH

*David Lawrence, Janeen Baxter, Stephen Zubrick, Sarah Johnson, Jennifer Hafekost, Paco Perales*

While little is known about the true cause of most mental illnesses, it is believed that a combination of genetic and environmental risk factors underpin common mental health conditions. The

majority of adults with mental disorders report that their symptoms begin in childhood or adolescence. The family environment is a critical component of life experiences of children and adolescents during the period of development that is most critical for the first emergence of symptoms of mental disorders. This can include the experience of stressful life events, such as family break-up or re-formation as well as the day to day experience of a more or less supportive and well-functioning family environment.

Mental illnesses are the most common and disabling health conditions in young people. About 14% of children and adolescents experience a mental disorder in any 12 month period. Mental disorders are associated with significant impacts on functioning and development, and only a fraction of children and young people experiencing mental disorders receive professional help. Of those children and families who do receive help, there are often lengthy delays in getting to appropriate help. The consequences of mental illness can be very significant in that experiencing challenges during critical stages of development may negatively impact the entire life course. Because of the prevalence and burden associated with mental disorders, they are a major factor in constraining human capability development.

This project aims to examine the association between family structure, family breakup, family functioning and child and adolescent mental disorders.

The family environment is a critical component of the life experiences of children and adolescents during the period of development that is most critical

for the first emergence of symptoms of mental disorders. This project will examine the relationship between family dynamics and child mental health, with a focus on the experience of stressful life events, such as family break-up or reformation, and family functioning.

### **Funders of the project**

Australian Research Council

### **External collaborators**

Janeen Baxter, University of Queensland  
Paco Perales, University of Queensland

## **MULTIGENERATIONAL DISADVANTAGE IN AUSTRALIA**

*Kirsten Hancock, Stephen Zubrick,  
Francis Mitrou*

The majority of research examining social mobility and intergenerational disadvantage has done so at an individual level or family level of parent-child associations (e.g. the role of parent education on outcomes in childhood and beyond). These associations can be extrapolated to describe the cyclical nature of intergenerational disadvantage, where parents directly affect their offspring in the same way that they themselves were affected by their own parents. In this way, grandparents have no influence on their grandchildren except via the parent generation. This approach, however, ignores the direct relationship grandparents may have with their grandchildren, for example, via bequests or paying for their grandchild's education where they might not have been able to do the same for their own children. As Mare (2011) notes "the



impact of one generation on the next is not as straightforward as the simply estimated “effect” of parents on offspring.

Even in a Markovian world in which individuals affect their children but not their grandchildren, we should not just multiply intergenerational correlations or elasticities together to estimate the multigenerational impact”

The ability of multigenerational studies to contribute to the understanding of intergenerational mobility is well recognized. While the research base has been building rapidly in the last decade, particularly in Europe, previous research has been criticised for dealing too extensively with mid-twentieth century US and therefore may not be appropriate for other contexts. The limited availability of appropriate Australian data to date represents a significant gap in understanding intergenerational disadvantage in the Australian context. While some multigenerational studies have been published with respect to socio-economic status, family separation and joblessness and mental health, our current understanding of intergenerational transfers of disadvantage in Australia remains limited.

Beyond this limitation, current multigenerational research tends to focus on only one area of advantage or disadvantage at a time, for example, correlations in income, neighbourhood effects, occupational prestige, joblessness or mental health. Yet studies have shown that disadvantages are often multiple, and may combine together in different ways. Additionally, notions of disadvantage measures are increasingly including other aspects or correlates such as health, education, social support,

community participation and personal safety.

The aim of this project is to enhance our understanding of intergenerational disadvantage in Australia by adopting advances in both multigenerational patterns of disadvantage and experiences of multiple markers of disadvantage. Which combinations of disadvantage are particularly salient in Australia and to what extent are these combinations maintained from one generation to the next?

Families are a critical pathway in the transmission of disadvantage. While the literature broadly focusses on parent-child transfers in understanding intergenerational disadvantage, further insight can be achieved by examining markers of disadvantage across multiple generations of the same family. Studies examining multigenerational patterns of disadvantage are therefore valuable, but the availability of Australian data to investigate these patterns has been limited. With new data now available, this study aims to examine the experience of multiple disadvantages in two generations of Australian families, and how these experiences relate to the trajectories of children, the third generation.

### **Funders of the project**

Australian Research Council

### **LANGUAGE STABILITY AND CHANGE**

*Stephen Zubrick, Cate Taylor, Daniel Christensen, Francis Mitrou*

Our uniquely human capacity for

language is one of the most important developmental accomplishments of childhood. Language enables literacy, education, and employment and is one of the major pathways that supports human capability formation.

It is well known that language acquisition is not robust for all children and that disparities in language acquisition emerge early and may foretell persistent low levels of language abilities.

Past work has shown a range of substantive risks for poor language development. Typically these risks are considered in isolation, controlling for other risks. However, some children are exposed to overlapping risks, and there is scant evidence of how multiple risks affect these children.

The Longitudinal Study of Australian Children takes a broad 'ecological' look at children's development, allowing us to consider a number of risks simultaneously.

Aims:

- 1) Summarise key risks for poor language development in the extant literature
- 2) Summarise the distribution of concurrent risks for poor language development in a nationally representative study of Australian children
- 3) Examine the impact of multiple risks on patterns of stability and change in language development (logistic regression, growth models, latent class analyses and/ or other techniques as appropriate).
- 4) Examine whether these risks can be grouped into conceptually distinct domains.
- 5) Examine the extent to which we can

identify children who are persistently low in language from those who are transitory lows.

- 6) Extend this analysis to other cognitive domains, such as NAPLAN

Disparities in language acquisition emerge early and may foretell persistent low levels of ability. Past work has shown a range of substantive risks for poor language development, typically considered in isolation, but there is scant evidence of how multiple risks affect these children. This project will examine the impact of multiple risks on patterns of onward stability and change in language development. It will identify key risks for poor language development and the distribution of concurrent risks for poor language development. It will also explore the impact of multiple risks on patterns of stability and change in language development, and whether it is possible to identify children who are persistently low in language from those who are transitorily low in language.

### **Funders of the project**

Australian Research Council

### **DATA FOR POLICY**

*Francis Mitrou, Michele Haynes, Stephen Zubrick, Mark Western, Janeen Baxter, David Lawrence*

Over the course of our lives, Government departments and other agencies routinely collect administrative information about us, relating to where we live, if or where we work, our education, our health and our family. Collected for myriad reasons, these administrative datasets are increasingly being recognised as a source



of rich insight about our society, and how different paths and inputs lead to different outcomes for individuals, families and population groups. They can therefore be an invaluable resource to help answer questions relating to intergenerational transmission of deep and persistent disadvantage, and to develop new policies and interventions aimed at ameliorating social disadvantage. Centrelink and Medicare records are among the government data that can allow us to follow a family's journey across generation, and provide the evidence needed to inform effective solutions for the seemingly intractable problems of deep and persistent disadvantage. LCC is leading important advances in integrating longitudinal administrative and survey data collected by the Australian Government. The aim is to harness the power of newly established data linkage processes pertaining to Australian Government administrative information to build a picture of the longer term development of deep and persistent disadvantage and potential divergence between individuals and families over time.

Given the breadth of information, population coverage and long timespan of administrative datasets, LCC collaborators are looking to help build a lens through which we are better able to understand the social determinants of disadvantage over time, using datasets which provide population-wide information. Not only can data linkage shed more light on the effects that ill-health or poor education (as just two examples) may have on disadvantage, but it can help us to further drill down to uncover the impact that multiple

factors may have on individual, group and societal outcomes, importantly linking administrative datasets gives us the potential to further explore how intergenerational disadvantage arises. To date, Australian researchers have had only limited access to Commonwealth administrative datasets, and access requests have typically taken many years to be approved, often well beyond typical research project timeframes. LCC is collaborating with government agencies to unlock the potential of these rich datasets to tackle social problems, and is uniquely positioned to bring together academic, policy, data, government and community experts to address the administrative, technical, methodological and substantive research challenges associated with this opportunity. Recognition of the power of governments' administrative datasets has driven much of the LCC's work to date, and inspired its founding projects, including the Data for Policy engagement project.

LCC researchers will work with relevant government agencies to address policy gaps using rich tracts of administrative data.

This engagement strategy will facilitate partnerships between the LCC team and government agencies to utilise administrative service data to inform policy and practice in the Australian human services sector. The ultimate goal of this project is to enable policy-makers and researchers to work together to influence positive changes in the life trajectories of disadvantaged Australians via research driven policy initiatives.

## Funders of the project

Australian Research Council

## External collaborators

Michele Haynes, University of Queensland  
Mark Western, University of Queensland  
Janeen Baxter, University of Queensland  
A range of Australian Government human services and data agencies

## RISK AND PROTECTIVE PATHWAYS IN ABORIGINAL JUSTICE: A LONGITUDINAL PATHWAY STUDY

*Stephen Zubrick, Francis Mitrou, David Lawrence, Katrina Hopkins, Glenn Pearson*

The well-documented over-representation of Aboriginal children and youth in the child protection and justice systems results in an unremitting and increasing social and financial cost to Aboriginal families and wider Australian society. Incarceration represents a source of ongoing socioeconomic and health inequity between Aboriginal and non-Aboriginal populations limiting life chances and opportunities. Effective prevention and intervention policies and strategies must be built on an accurate understanding of the causes of offending. The root causes of contact with justice systems may begin early in the early life course e.g., with poor physical health, and reflect cumulative disadvantage impacting on the WA Aboriginal population, e.g., lower educational status of parents, poor quality housing and overcrowding. Furthermore, recent research on juvenile offending highlighted greater heterogeneity in the pathways to offending by Aboriginal compared to non-Aboriginal

offenders. This indicates a need to better understand these pathways and the most potent environmental influences leading to Aboriginal juvenile offending, early in the life course. Understanding this would underpin advocacy and targeted planning. A focus on early life environments is further supported by this same study finding that early onset offending (between the ages of 7-12) was predictive of further offending, and that 35% of all Aboriginal offenders were early onset offenders compared to 9% of non-Aboriginal offenders. Further, this preliminary evidence found that diversion early in a criminal career acted to increase the likelihood of a higher rate of subsequent offending.

This prior research raises the following questions:

- Does diversion actually increase the chance of higher rates of offending? If so, why and for whom?
- Are children in the care of child protection agencies at higher or lower risk of early offending than children living with their own families?
- Why, and through what mechanisms, is living in some regions, but not others, protective against higher rate offending?

There is a large body of research undertaken with individuals already in contact with the justice system, i.e., offender populations. Linking WAACHS records to child protection and justice system data provides a unique opportunity to examine developmental pathways of children and youth who have not had contact with the justice system, as well as understanding early risk factors impacting on likelihood of offending, in



a population representative sample of one in six Western Australian Aboriginal children and their families.

Updating the original Western Australian Aboriginal Child Health Survey (WAACHS) data links and extending data links to administrative datasets now available (e.g., justice, child protection and potentially police) would provide an internationally unique and powerful evidence base of factors that have shaped the maturation of the WAACHS children over the past 14 years. This data linkage proposal would enable identification of the critical factors and transition points shaping child and family pathways towards or away from contact with the criminal justice system and would not involve another survey.

Incarceration represents a source of ongoing socioeconomic and health inequity between Aboriginal and non-Aboriginal populations, limiting life changes and opportunities. This project seeks to identify the social determinants of physical and mental health and academic attendance and achievement associated with contact with child protection agencies and justice systems across the life course, with a focus on Aboriginal populations. Findings from this research will help inform effective prevention and intervention policies and strategies by improving our understanding of the causes of offending.

### **Funders of the project**

Australian Research Council

## **2015 Success**

### **EXTERNAL COMMITTEES**

#### **International**

Stephen Zubrick, Member, Scientific Advisory Board, Swedish Research Council for Health, Working Life and Welfare, Karlstad University, Sweden

#### **National**

Stephen Zubrick, Chair, Consortium Advisory Group, Longitudinal Study of Australian Children, 2002-present.

Stephen Zubrick, Board Member, Australian Research Alliance for Children and Youth, 2015-present.

Stephen Zubrick, Member, Steering Committee, Families and Children Activity Expert Panel, Department of Social Services

Daniel Christensen, Member, Australian Institute of Health and Welfare Burden of Disease Indigenous Reference Group

#### **Local**

Stephen Zubrick, Ambassador, Western Australian Commission for Children and Young People, 2012-present.

### **INVITED PRESENTATIONS**

Sarah Johnson. Service use by Australian children and adolescents with mental disorders: Findings from the 2013-13 national survey - Young Minds Matter. The Mental Health Services (TheMHS) Conference, Canberra, August 2015.

Sarah Johnson. A snapshot of mental disorders, distress and help-seeking among

Australian children and adolescents from a recent national survey. International Life Course Conference, Brisbane, October, 2015.

David Lawrence. Young Minds Matter: The second Australian Child and Adolescent Survey of Mental Health and Wellbeing. Mental Health Week, October, 2015.

David Lawrence. The mental health of Australian children and adolescents: Findings from Young Minds Matter. Mental Health Super Summit (webinar), October 2015.

David Lawrence. Young Minds Matter. The second Australian Child and Adolescent Survey of Mental Health and Wellbeing: Results. Presentation to the Mental Health Information Strategy Sub-Committee, Canberra. October 2015.

David Lawrence. Young Minds Matter. The second Australian Child and Adolescent Survey of Mental Health and Wellbeing. Presentation to the National Community Child Care Council, November, 2015.

Kirsten Hancock. The ups and downs of school mobility: How changing schools relates to student progress over time, Brisbane, Australia. In The International Life Course Conference, October 2015.

Francis Mitrou and David Lawrence. Mental Health and Smoking; Implications for Tobacco Control, Perth, Australia. In Oceania Tobacco Control Conference, October 2015.

Francis Mitrou. Using longitudinal administrative data linked with cross-sectional survey data to describe human

capability trajectories for Indigenous families, Brisbane, Australia. In The International Life Course Conference, October 2015.

Francis Mitrou. Using longitudinal administrative data linked with cross-sectional survey data to describe human capability trajectories for WA Aboriginal children and families, Perth, Australia. In Telethon Kids Scientific Retreat, November 2015.

Kirsten Hancock. Education research programs at Telethon Kids Institute and the ARC Life Course Centre, Perth, Australia. In WA Department of Education - an overview of education related research at Telethon Kids and the Life Course Centre, December 2015.

Francis Mitrou. Event outline and summary of outcomes, Brisbane, Australia. In LCC Data Workshop #2, March 2015.

Francis Mitrou. Methodological Opportunities and Challenges for Life Course Research Using Administrative and Linked Data: Data to describe deep persistent disadvantage, Canberra, Australia, September 2015.



# Looking at Language

## Overview

Looking at Language places the institute at the forefront of research in language and literacy worldwide. Our approach and our research crosses a multitude of disciplines and sits within a number of the institute's Research Focus Areas. The study, combines epidemiological, behaviour genetics and molecular genetics methods to study language development, language impairment, reading and reading impairment from infancy to adolescence.

This internationally unique study is following the language development of more than 2000 WA children from 2-14 years. It is the world's only study to conduct such detailed assessment of language and literacy development from infancy through the formative adolescent years. For the institute, the ability to continue following the study children through early adolescence is ground-breaking. It is vitally important that we understand the developmental course of language and literacy from infancy and what different trajectories mean for young people's opportunities at school and beyond. Data collection for this project is based entirely in WA and involves 5000 children and families overall. The study has received 15-years continuous funding from the USA National Institutes (National Institute on Deafness and Other Communication Disorders). The project is a joint initiative between the Telethon Institute for Child Health Research and

UWA and the USA's University of Kansas and University of Nebraska Medical Centre. All study participants and data collection is based in Western Australia.

## Research Projects

### LOOKING AT LANGUAGE

*PROFESSOR MABEL RICE FROM THE UNIVERSITY OF KANSAS, PROFESSOR CATE TAYLOR AND WINTHROP PROFESSOR STEPHEN ZUBRICK FROM THE TELETHON KIDS INSTITUTE AND PROFESSOR SHELLEY SMITH FROM THE UNIVERSITY OF NEBRASKA MEDICAL CENTER.*

Ask any mum or dad what they consider a key milestone in their child's development and more often than not they will say it is language development. Looking at Language is following the language development of more than 2000 WA children from 2 – 14 years. It is the world's only study to conduct such detailed assessment of language and literacy development from infancy through the formative adolescent years. Our findings will help improve services and supports for children with language difficulties.

### Funders of the project

National Institutes of Health (RO1DC05226, P30DC005803, P30HD002528)

## 2015 Success

### EXTERNAL COMMITTEES

*International*

Member, CATALISE: Criteria and

Terminology Applied to Language Impairments: Synthesising the Evidence. An international panel aimed at achieving consensus about identification of and terminology for language impairment in children.

### National

Member, Expert Reference Group on Screening and Assessment Practices Across Health and Education for Children aged birth - 12 Years. Australian

Education, Early Childhood Development and Youth Senior Officials Committee (AEESOC) and the Australian Health Minister's Advisory Council (AHMAC).

Member, Expert Reference Group for right@home: A randomized controlled trial of sustained nurse home visiting. Australian Research Alliance for Children and Youth, Centre for Community Child Health and Centre for Health Equity Training Research and Evaluation.

### INVITED PRESENTATIONS

Taylor, C.L. (June, 2015). Trajectories in language and literacy development in the first ten years of life. Seminar presented at the Menzies Institute for Medical Research Tasmania, Hobart, Tasmania.



# INFLAMMATION

## Inflammation Group

### Overview

The Inflammation group has continued to study the beneficial effects of sunlight exposure on our health. Most importantly, members of the group have been asking whether these effects are attributable to UV-induced vitamin D or to other molecules produced in our skin upon sunlight (i.e. UV) exposure. This question becomes more and more important as trials of vitamin D supplementation for conditions for which positive associations of vitamin D levels and disease incidence or severity have been reported, continue to fail and give less than hoped for benefits.

Members of the inflammation group have performed both mouse and human studies to determine the contributions of vitamin D-dependent and vitamin D-independent pathways to the responses studied. The group leads the first trial in the world to give UVB phototherapy to patients with an early form of multiple sclerosis. In the mouse, we are studying alternate pathways of UVR control by alterations to blood cell precursors in the bone marrow. We are studying modulation by UV radiation of pathways controlling weight gain in mice on a high fat diet. There were also studies to dissect the impact of UV radiation and vitamin D on murine models of inflammatory bowel disease.

## Research Projects

### **UVB PHOTOTHERAPY FOR PARTICIPANTS WITH AN EARLY FORM OF MULTIPLE SCLEROSIS**

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

Latitude gradients for the incidence and prevalence of multiple sclerosis (MS) are well established, with more disease at higher latitudes where there is reduced sun. Exposure to sun has been linked with the initiation and progression of MS, and there is evidence that sun exposure is important at all stages of life for MS pathogenesis, even in utero. Seasonal effects on MS disease activity have also been described. Many believe that a lack of UV-induced vitamin D is responsible, but vitamin D supplementation trials have not shown the reduced disease progression that was hoped for. We propose that UV via vitamin D-independent pathways may be responsible. We have an ongoing NHMRC-funded trial of narrow band UVB phototherapy for participants diagnosed with their first demyelinating event in the last 120 days. Participants are randomised to receive, or not receive, UVB phototherapy (24 sessions over 8 weeks). Blood is taken for phenotyping of immune cell subsets in their blood, and biobanking, over a 12 month period. We believe that this is the first trial in the world of UVB phototherapy for participants with Clinically Isolated Syndrome. The trial is called PhoCIS as it is Phototherapy for participants with Clinically Isolated



Syndrome.

### **Plain Language summary**

Patients are not diagnosed with multiple sclerosis until they have had two demyelinating (clinical) events. In the PhoCIS trial, we are recruiting individuals who have had only one event as we believe that if we can catch them very early in their disease progression, we can dampen it or halt its course. We give them phototherapy over the first 2 months and follow the cells in their blood, and images of their brain, for the next 12 months. The phototherapy is delivered in a dermatologists rooms and is similar to that given to patients with the skin condition, psoriasis.

### **Funders of the project**

NHMRC

### **External collaborators**

Prof Allan Kermode, Prof Bill Carroll, WA Neuroscience Research Institute, Perth.  
Dr David Nolan, Royal Perth Hospital, Murdoch University.  
Prof David Booth, Westmead Millenium Institute, University of Sydney.  
Dr Judy Cole, St John of God, Dermatology, Perth

## **THE EFFECT OF VITAMIN D AND UV RADIATION ON A PRECLINICAL MODEL OF CROHN'S DISEASE**

*Simon Ghaly, Prue Hart*

Low vitamin D levels have been associated with increased incidence of Crohn's disease. However supplementation trials have not generally

been successful. It is possible that low vitamin D levels merely reflect low sun exposure and that exposure to UV may be a more realistic treatment strategy. A preclinical model of Crohn's Disease has been established using dextran sulphate delivered in drinking water. Mice have been fed deficient, sufficient and excessive levels of vitamin D in their diets, superimposed with UV phototherapy (low dose twice weekly). The mice on the diet containing the highest levels of vitamin D had the worst pathology. Blood and all the tissues were removed from the mice and analysed for inflammatory markers. The microbiota has been measured. We have tried to dissect out the outcomes due to dextran sulphate, the vitamin D diets, and to UV radiation exposure. We have also analysed the effect of inflammation in the bowel (as in Crohn's disease) on vitamin D biochemistry.

### **Plain language summary**

For about a decade, patients with bowel problems have been advocated vitamin D supplementation. However, it is not known if these are appropriate recommendations and the mechanism by which vitamin D may improve inflammation in the bowel. We have found that excess, not deficiency in vitamin D levels is detrimental to development of an inflamed bowel.

### **Funders of the project**

Special grant to Simon Ghaly by Gastroenterology Society of Australia

### **External collaborators**

Prof Ian Lawrance, Harry Perkins Institute of Medical Research, School of Medicine

and Pharmacology, University of Western Australia, Murdoch, WA, Australia.

## **EFFECT OF UV IRRADIATION OF SKIN ON THE GLYCOLYTIC ACTIVITY OF DENDRITIC CELLS GENERATED FROM BONE MARROW CELLS**

*Terry McGonigle, Prue Hart*

We have previously shown that signals sent from skin irradiated with erythemal UV to the bone marrow stimulate the development of dendritic cells that are poorly immunogenic and cannot induce a strong immune response. Similar responses have been detected following multiple exposures to sub-erythemal UV radiation. The phenotype and function of cells generated by culture of the bone marrow of animals administered a single inflammatory dose of UV have been further analysed. We studied the metabolism and bioenergetics of dendritic cells generated from the bone marrow of UV-irradiated mice and UV chimeric mice (i.e. mice engrafted with bone marrow cells from UV-irradiated mice). Contrary to our hypothesis, we believe that the cells differentiated from the bone marrow of UV-irradiated mice versus those from non-irradiated control mice have increased glycolytic activity, with no difference observed in mitochondrial respiratory function. This suggests that metabolism and function of dendritic cells may be linked. Our data suggest that the greater glycolytic flux is due to greater transcription of 3-hydroxyanthranilate 3,4-dioxygenase, an enzyme that ensures sufficient NAD<sup>+</sup> is available for enhanced glycolysis.

## **Plain language summary**

We have recently learnt that the function of immune cells and flux through metabolic pathways are intertwined and targeting points of regulation in metabolic pathways can alter immune cell function. We have observed that exposure to UV radiation as in sunlight can alter bone marrow cells by changing their metabolic pathways. The immune function of these cells is also altered resulting in a reduced ability to start protective responses.

## **Funders of the project**

Scott Kirkbride Melanoma Research Foundation, Private Funds

## **External collaborators**

Professor Philip Newsholme, Curtin University

Dr Kevin Keane, Curtin University

## **REDUCED GLYCOLYTIC ACTIVITY AND REDUCED CHEMOTACTIVE ABILITY OF MACROPHAGES GENERATED FROM THE BONE MARROW OF UV-IRRADIATED MICE**

*Terry McGonigle, Prue Hart*

In contrast to increased glycolytic flux in dendritic cells, glycolytic responses were significantly reduced in macrophages differentiated with colony stimulating factor-1 from the bone marrow of UV-irradiated and UV-chimeric mice (i.e. mice reconstituted with bone marrow from UV-irradiated mice). Macrophages differentiated from the bone marrow of UV-chimeric mice also produced significantly less lactate upon activation with the bacterial product,



lipopolysaccharide. Further, they were less chemotactic towards Colony Stimulating Factor-1, highlighting a functional link with metabolism. Alterations to immune cells post UV-irradiation of skin are compatible with reprogrammed energy metabolism. For example, UVR exposure can stimulate increased numbers and activity of CD4+CD25+ Treg cells, impair the development of peripheral memory T cells and decrease the activation, expansion and cytotoxic activity of antigen-specific CD8+ T cells. All these functions are compatible with changes in cell fate decisions that are metabolically regulated.

### **Plain language summary**

The effects of UV irradiation of skin are prolonged by the ability of UV radiation to alter haematopoietic progenitors in the bone marrow. Macrophages differentiating from bone marrow progenitors have reduced energy pathways and a reduced ability to move toward attracting signals.

### **Funders of the project**

Scott Kirkbride Melanoma Research Foundation, Private Funds

### **External collaborators**

Prof Fiona Pixley, Pharmacology, University of WA

Ms Amy Dwyer, Pharmacology, University of WA

Professor Philip Newsholme, Curtin University

Dr Kevin Keane, Curtin University

## **INTERVENING WITH ULTRAVIOLET RADIATION TO REDUCE SIGNS OF OBESITY AND TYPE-2 DIABETES**

*Naomi Fleury (Honours student) and Shelley Gorman*

In 2015, Naomi Fleury, a student from Notre Dame University conducted an Honours project, which aimed to investigate whether ongoing low dose exposure to ultraviolet radiation could intervene in already overweight mice fed a high fat diet, to reduce signs of obesity and type-2 diabetes. The major findings from this study were that ongoing exposure to ultraviolet radiation reduced weights and weight gain, fasting insulin levels in serum, circulating LDL-cholesterol levels and hepatic steatosis (fat accumulation in liver) in mice fed a high fat diet. With the exception of hepatic steatosis, these effects were independent of skin release of nitric oxide post-irradiation.

### **Plain Language summary**

In this project we found that ongoing exposure to low dose ultraviolet radiation (like that in sunlight) intervened to reduce signs of obesity and type-2 diabetes in already overweight mice.

### **Funders of the project**

Telethon Kids Institute, University of Western Australia

### **External collaborators**

Martin Feelisch (Southampton University, UK), Richard B Weller (University of Edinburgh, UK), Vance Matthews (Harry Perkins Medical Institute)

## **INVESTIGATING THE EFFECTS OF MATERNAL INTAKE OF A HIGH FAT DIET ON OFFSPRING LUNG FUNCTION.**

*Jordan Smoothy (Honours student), Alex Larcombe and Shelley Gorman*

In 2015, Jordan Smoothy, a student from Murdoch University conducted an Honours project, which aimed to investigate the effects of maternal intake of a high fat diet on the lung function of her offspring. Female mice were fed a high fat diet for 12 weeks, before they were mated and the lung function of their offspring assessed at 2 weeks of age. The major finding from this study was that the lung function of both dams and offspring was compromised by maternal intake of the high fat diet, with increased signs of inflammation observed in the lung lavage fluid of dams (but not offspring) fed a high fat diet.

### **Plain Language summary**

In this project we found that feeding female mice a high fat diet altered the capacity of these mice to breathe in a normal way, and had similar effects on their offspring. Increased signs of inflammation were observed in the lungs of female mice but not their offspring.

### **Funders of the project**

Asthma Foundation of Western Australia

### **External collaborators**

Vance Matthews (Harry Perkins Medical Institute)

## **VITAMIN D SUPPRESSES SKIN INFLAMMATION THROUGH REGULATORY T CELLS**

*Shelley Gorman and Prue Hart*

In these studies, we investigated the capacity of topically-applied vitamin D or dietary vitamin D to suppress skin inflammation through regulatory T cells. In 2015, investigated how vitamin D is required for optimal regulatory T cell function through the cytokine interleukin-9, with potential downstream effects on mast cells.

### **Plain Language summary**

The sunlight hormone, vitamin D, is applied to skin, or can be taken as a supplement to reduce the severity of inflammatory skin disorders, like psoriasis. In this project, we investigate how vitamin D can affect the function of immune cells in the skin to dampen skin inflammation.

### **External collaborators**

Michele Grimbaldston (Centre for Cancer Biology, SA)

## **EYE AUTOFLUORESCENCE, VITAMIN D AND OBESITY IN 20 YEAR-OLDS OF THE RAINE COHORT**

*Aidan Allen-Hall (MD student, Scholarly Activity), Lucinda Black, Robyn Lucas, Shelley Gorman*

In 2015, Aidan Allen-Hall commenced his Scholarly Activity project (MD), which aims to investigate the associations between sun exposure as measured by conjunctival ultraviolet autofluorescence, and signs of obesity in 20 year-olds of the Raine cohort.



### Plain Language summary

This project aims to investigate whether there are links between the amount of sun exposure we receive and signs of obesity, and will be performed in 20 year-olds of the Raine study.

### KIDS IMAGING SUNHEALTH STUDY (KISS)

*Shelley Gorman, Lucinda Black, Anderson Jones, Robyn Lucas*

These studies were performed as part of the Telethon weekend (October 2015), where we collected information on skin type, and sensitivity to sun exposure in >120 attendees of the Telethon Weekend activities at the Perth Convention Centre. The aim of these studies is to determine whether we can develop a new method of measuring skin type using mobile phone technology.

#### Funders of the project

Telethon Kids Institute

### ALLERGIC SENSITISATION HAS A GREATER EFFECT ON THE LUNG MICROBIOME THAN DIETARY VITAMIN D

*Shelley Gorman, Anthony Kicic, Alexander Larcombe, Prue Hart*

In these studies we are investigating the capacity of dietary vitamin D to modulate the microbiome of the lungs. The main findings of these studies are that dietary vitamin D may reduce the total number of operating taxonomic units of *Pseudomonas* spp., as well as neutrophil and macrophage numbers in

the lung lavage fluid of mice. However, the effects of allergic sensitization of mice with an experimental allergen (ovalbumin) and T helper-2 immune-skewing agent (Aluminium hydroxide) had a greater effect on the lung microbiome than dietary vitamin D alone.

#### Plain Language summary

Bacteria present in the lungs may determine our susceptibility for lung disease. These can be altered by environmental exposures. In this study we compared how dietary vitamin D or exposure to an experimental allergen affected the lung microbiome of mice. Exposure to the allergen had more profound effects on the lung microbiome than dietary vitamin D, and was linked with increased lung inflammation.

#### Funders of the project

BrightSpark Foundation, Raine Medical Research Foundation

#### External collaborators

Michael Roggenbuck (University of Copenhagen), Kenneth Klingenberg Barfod (National Centre for the Working Environment, Denmark)

## 2015 Success

### THESES PASSED

1. Jordan Smoothy, Honours (Molecular Biology, Murdoch University, 2015), Does maternal obesity affect the lung function of her offspring?
2. Naomi Fleury, Honours (Medicine,

Notre Dame University, 2015); Can ultraviolet radiation prevent or reverse weight gain and signs of the metabolic syndrome in mice fed a high fat diet?

## AWARDS AND PRIZES

1. Jordan Smoothy, Asthma Foundation Western Australia Honours Scholarship
2. Shelley Gorman, Young Tall Poppy Science Award

## EXTERNAL COMMITTEES

### National

Prue Hart, Invited Member, NHMRC Academy

Prue Hart, Deputy Chair, Royal Perth Hospital Research Foundation Scientific Grants Committee.

Prue Hart, Member, Organising Committee, Australasian Society for Dermatology Research Annual conference, Adelaide, May 2015.

Shelley Gorman, Secretary, Molecular Experimental Pathology Society of Australasia

### Local

Prue Hart, CoChair, D-Light Show Case project, Telethon Kids Institute.

## INVITED PRESENTATIONS

Prue Hart

1. Prue Hart, Keynote plenary speaker at the European Society for Photobiology Congress in Portugal in 2015 (honorary). Title: Sunlight-induced immunosuppression: How much is attributed to vitamin D?

2. Prue Hart; D-Light Symposium (Perth, September 2015). How UVB phototherapy may suppress immunity.
3. Prue Hart, Keynote plenary speaker at the Progress in MS Research meeting in Melbourne in Oct 2015. Title: Effect of ultraviolet radiation and vitamin D3 on the immune system.
4. Prue Hart, Invited speaker at the IMB (Institute of Molecular Bioscience) Inflammation meeting, Brisbane, Nov 2015. Title: UV irradiation of skin alters the phenotype and function of myeloid cells from the bone marrow.

Shelley Gorman

1. Shelley Gorman; Princess Margaret Hospital CLASP (Changes in Lifestyle are Successful in Partnership) Team meeting (Perth, Feb 2015). Low dose sunlight exposure: A possible add-on intervention for very obese children and adolescents in the CLASP program?
2. Shelley Gorman; School of Anatomy, Physiology and Human Biology Seminar Series (Perth, May 2015). Could sunlight be harnessed to suppress the development of obesity?
3. Shelley Gorman; D-Light Symposium (Perth, September 2015). Sunlight, nitric oxide and obesity: investigating mechanisms by which ultraviolet radiation suppresses signs of obesity and metabolic dysfunction.
4. Shelley Gorman; Asthma Foundation of Western Australia, Asthma Seminars for Health Professionals (Perth, October 2015). Sun exposure and asthma: vitamin D-dependent and -independent effects.
5. Shelley Gorman; Respiratory Department, University of Tasmania (Hobart, November 2015). Sun



exposure and asthma: beyond vitamin D.

6. Shelley Gorman; Australia and New Zealand Bone Mineral Society, Molecular Experimental Pathology Society of Australasia and Matrix Biology Society of Australia and New Zealand conjoint Annual Scientific Meeting (Hobart, November 2015). Could sun exposure be used to control obesity? Vitamin D-dependent and -independent effects.





# INTELLECTUAL DISABILITY

## Child Disability Group

### Overview

Our research involves four key areas of research relating to disability and rare diseases in childhood and the subsequent translation of research findings into practice. These include the following: the use of population-based state, national and international datasets to examine the determinants and outcomes of developmental disorders including autism and trends in their occurrence; the development and maintenance of registers to understand the epidemiology and natural history of rare childhood disorders and improve their diagnosis and management; the investigation of the impact of rare and common developmental disorders (in terms of health and quality of life) both on the affected individual and on their family over time; and the evaluation of clinical interventions for rare and common developmental disorders. During 2015 our core group members and students included Dr Helen Leonard, Dr Jenny Downs, Ms Jenny Bourke, Dr Kingsley Wong, Dr Emma Glasson, Dr Jenny Fairthorne, Dr Yuka Mori, Amy Epstein, Nada Murphy, Nan Hu, Sharolin Boban, Meghana Mangatt, Jessica Mackay, Amanda Jefferson, Anna Urbanowicz, Ifrah Abdullahi, Thomas Horne, Barbara Anderson and Tami Alhaddad.

Our group has been awarded funding from international, national and local sources. Internationally, we have received ongoing funding through to the end of 2017 for the running and developmental of our CDKL5 Disorder database from the International Foundation for CDKL5 Research. We also received funding from Rettsyndrome.org to conduct a study in China testing the effectiveness of early intervention. Nationally, we received two NHMRC project grants that each involve interstate collaborations. One of these grants will investigate quality of life in intellectual disability in collaboration with clinicians and researchers from the Royal Children's Hospital and the University of Melbourne. The other NHMRC grant will investigate comprehensive outcomes of gastrostomy for children with severe disability in collaboration with the University of New South Wales. Locally, we have received seed grants from the Telethon Kids Institute to investigate mental health outcomes in children with disability and quality of life in children with autism.

Our group has made numerous conference presentations both overseas and nationally, including 6 invited presentations to a wide range of audiences. Rett syndrome.org hosted a series of international webinars for families, clinicians, and researchers interested in Rett syndrome. Dr Jenny Downs presented at three and Dr Helen Leonard at one webinar.

## Research Projects

### **TOWARDS EVIDENCE BASED CARE FOR RETT SYNDROME: A RESEARCH MODEL TO INFORM MANAGEMENT OF RARE DISORDERS**

*Helen Leonard, Jenny Downs, Kingsley Wong, Peter Jacoby, Amy Epstein, Amanda Jefferson, Anna Urbanowicz, Thomas Horne*

Project blurb Rett syndrome is a rare neurological disorder usually affecting females and caused by a mutation in the MECP2 gene. AussieRett, as the Australian Rett Syndrome Study is known, is a population-based study which, since 1992, has followed a cohort of Australian Rett syndrome cases born since 1976. The study aims to describe the natural history of Rett syndrome and assess the impact of the condition on resource utilisation as well as to examine the economic and social burden for families and the community.

We are still undertaking analyses and publishing papers pertaining to our NHMRC study for which the final year of funding was 2014. This study aimed to:

- develop recommendations for the diagnosis process for Rett syndrome;
- identify longitudinal changes in gross motor abilities, hand function and development of scoliosis and;
- evaluate the clinical effectiveness of scoliosis and gastrostomy surgery in children and adults with Rett syndrome.

For the diagnostic study we asked clinicians to complete questionnaires relating to the characteristics of their

patients for whom they requested MECP2 testing at one of the three Australian accredited laboratories. These were completed prior to the result of genetic testing being known. During the study period there were 297 referrals where a clinician could be contacted and agreed to participate. Questionnaires were completed and available for analysis on 258/297 (86.9%). Of these, 223(86.4%) were female and pathogenic MECP2 mutations were identified in 14.8% and in no males (12.8% positive overall). When clinicians thought a Rett syndrome diagnosis was very or somewhat likely, there was a positive result in 13/23 (57%) females. In 6/111 (5%) of “unlikely” cases the result was positive and in 2/6 parental request was cited as the reason for the referral. Diagnosing an evolving clinical scenario as occurs in Rett syndrome is challenging. The core features of regression of hand function and communication and the development of hand stereotypies persisted as important predictors of a positive molecular diagnosis. Most of the supportive criteria were of less value as they tend to appear with age. However parental request should not be ignored even if the diagnosis thought unlikely by the clinician and asking about crawling ability, gross motor regression and the presence of teeth grinding could also be helpful. It remains to be seen whether in the future Next Generation Sequencing will take over from conventional mutation testing making a clinical diagnosis less necessary.

As part of the longitudinal study follow-up questionnaires were administered in September 2011 to 269 families enrolled in the study and families could return data online, on paper or during a telephone



interview. The response fraction from parents and care-workers was excellent at over 86%. Information has been collected on the affected individual's functional ability in daily living, behaviour, hand function, medical conditions, use of health and education services, and family health and functioning. Questions have also been included to assess parental satisfaction with spinal fusion and gastrostomy procedures for those children and adults who have undergone these procedures. We have also collected video data and by year end 2014, 175 families had provided video footage of their daughter's functional abilities.

Scoliosis is a common complication of Rett syndrome, however little was previously known about the natural history of curve progression and the relationship with the type of genetic mutation, age and mobility level. X-ray data on the progression of the spinal curve of children and adults with scoliosis has been collected on 196 girls and women with scoliosis. We confirmed that the median age of scoliosis onset was 11 years with earliest onset in those with a p.Arg255\* mutation or large deletion. Scoliosis was progressive for all mutation types except for those with the p.Arg306Cys mutation. Scoliosis progression was reduced when there was capacity to walk independently or with assistance. We also found that Cobb angle and walking ability at 10 years could be reliably used to identify those who would develop a very severe scoliosis by 16 years of age.

Spinal fusion (for scoliosis) is a surgery faced by many children and adults with Rett syndrome. The decision to proceed is often difficult for families, and both

clinicians and families need accurate information about the short and long term risks and benefits of these procedures. In the past, there have been gaps in our knowledge of outcomes. With respect to our investigation of the outcomes of spinal surgery and with the benefit of collection of data from hospital records we found that survival was better in those with severe scoliosis who had surgical compared to conservative management. We found this was particularly marked in those with earlier onset scoliosis where possible protective effects on respiratory health were also observed. Our methods demonstrate the value of well-managed databases for the investigation of rare disorders.

During 2015 occupational therapist Anna Urbanowicz used the AussieRett questionnaire and video data in her PhD study of communication in Rett syndrome. In combination with the use of our international InterRett data she showed that those with a p.Arg133Cys mutation were the most likely to use one or more words, prior to and after speech-language regression. She also found from parent report that eye gaze was used by the majority of girls and women as a means of communication irrespective of MECP2 mutation type. Most recently she has used the video data to assess the ability of girls and women with Rett syndrome to make choices.

PhD student Amanda Jefferson has also used the longitudinal bank of AussieRett questionnaire and bone density data to assess bone mineral content and density both cross-sectionally and longitudinally in girls and women with Rett syndrome. In her paper published in 2015 she showed

that overall bone mineral content, bone mineral density, bone area and lean tissue mass z-scores declined over time with total body bone mineral content showing the most significant decrease. These findings supported our earlier work demonstrating the increased risk of fracture for girls and women with Rett syndrome and contributed to the basis for the bone health guidelines which were developed in conjunction with an international group and submitted for publication in 2015.

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. We also have a multi-disciplinary investigative team from the fields of medicine, physiotherapy, epidemiology, biostatistics, dietetics and occupational therapy. It has national collaborations with the Children's Hospital at Westmead and the Children's Hospital Randwick, Sydney, the Royal Children's Hospital, Melbourne, the Mater Children's Hospital, Brisbane and the Royal Children's Hospital, Brisbane and the Children's Hospital, Adelaide.

We have conducted a qualitative investigation in relation to quality of life in children with Rett syndrome, a new direction for our research. We identified the domains of quality of life that are important for Rett syndrome and these data form a framework to understand quality of life. In the future, these data will be combined with similarly collected data

in relation to children with other causes of intellectual disability including Down syndrome, severe cerebral palsy and autism to develop and validate a quality of life outcome measure for children with intellectual disability.

During 2015 ten articles relating to Rett syndrome were published or accepted for publication by our group. These articles included investigations of scoliosis, bone health, sleep disturbances and communication and the development of outcome measures in Rett syndrome. During the year we also made either oral or poster presentations at the Australian Spine Society (Canberra), the Human Genetics Association of Australasia (Perth), the IASSIDD Americas Regional Conference (Hawaii), the Australian Association of Developmental Disability Medicine (Sydney), 4th European Congress on Rett syndrome (Rome), Science Lands in Parliament (Perth), World Confederation for Physical Therapy Conference (Singapore) and the the Rett Syndrome Journey: Pathways to Follow (Rett Syndrome Association of Australia, Geelong) meetings. Four presentations were also made to the international webinar series run for families, clinicians and researchers by Rettsyndrome.org.

### **Plain Language summary**

We have continued to recruit families to participate in the national-wide Australian Rett Syndrome Database. In 2015, we have investigated the characteristics clinicians have observed in children referred for genetic testing prior to any diagnosis. We have analysed how scoliosis develops and the influences of the type of mutation and walking, and found that



surgery for a severe scoliosis improves survival. We have identified the areas of life that are important to girls with Rett syndrome. Three students have worked with our data in 2015.

### **Funders of the project**

#### **Previous:**

NHMRC Project Grant (1004384), NHMRC Program Grant (572742), NHMRC Senior Research Fellowship-Helen Leonard (572568).

#### **Current:**

Near Miss Grant University of Western Australia, Department of Health Merit Award.

### **External collaborators**

John Christodoulou, Department of Paediatrics, University of Melbourne

Carolyn Ellaway, Sydney Children's Hospitals Network (Westmead)

Elizabeth Elliott, Sydney Children's Hospitals Network (Westmead)

Ian Torode, Royal Children's Hospital, Melbourne (deceased)

Mark Davis, Neurogenetics Laboratory, QEII Medical Centre

Bruce McPhee, Department of Orthopaedics, University of Queensland

Madhur Ravikumara, Princess Margaret Hospital, Perth

Sue Thompson, Westmead Children's Hospital, Sydney

Margaret Thomson, Princess Margaret Hospital, Perth

Geoff Askin, Lady Cilento Hospital, Brisbane

Maree Izatt, Lady Cilento Hospital, Brisbane

Dinah Reddihough, Murdoch Children's Research Institute, Melbourne

Katrina Williams, Murdoch Children's

Research Institute, Melbourne

Elise Davis, Melbourne University, Melbourne

### **INTERNATIONAL RETT SYNDROME STUDY: INTERRETT**

*Helen Leonard, Jenny Downs, Amy Epstein, Nada Murphy, Barbara Anderson, Nan Hu, Jessica Mackay, Sharolin Boban*

Project blurb Rett syndrome is a rare neurological disorder affecting approximately 1:9000 females and is associated with a mutation in the MECP2 gene. Given the low number of cases at a national level (~415 in Australia) international collaboration and data collection are imperative. The InterRett database project allows clinicians and families caring for an individual with Rett syndrome to directly contribute to the global research effort by completing web or paper-based questionnaires. The project, which is funded by Rettsyndrome.org (formerly the International Rett Syndrome Foundation), was established in 2002 and continues to grow and expand with online questionnaires available in Mandarin and six European languages. The database currently contains ~ 2,600 cases representing more than 50 different countries. New participants register using a form on the project website (also available in different languages). International support for the InterRett project continues to strengthen, particularly in China and we have a Chinese national, Nan Hu who is providing translational expertise and assisting families in submitting their information. The website also allows users to: generate graphs based on summary data; download clinical guidelines

for the management of scoliosis and gastrointestinal issues; and to read snapshots of the over 20 peer-reviewed publications arising from analyses of the InterRett data. Our research covers a wide range of topics such as: pain sensitivity; the characteristics that influence diagnosis; diagnostic challenges in China; the influence of mutation type or DNA variations in the BDNF gene on clinical severity; and ageing in Rett syndrome. To allow families to contribute at all levels of the research process, from study design to the dissemination of findings, a Consumer Reference Group (CRG) has been established. In 2014 we were awarded a further two years ongoing funding from Rettsyndrome.org to continue the management of the database. Our current aims are to:

- To give families a strong voice in research about Rett syndrome,
- To expand data collection to facilitate evidence-based management,
- To focus on families who live in under-represented majority world countries, and
- To further develop the InterRett infrastructure to enable linkage with other Rett syndrome and international rare disease database initiatives.

There has been little research investigating which girls and women with Rett syndrome may be particularly at risk either of specific breathing problems or of sleep disturbances. Although we hypothesise that both comorbidities are particularly burdensome both for those affected and their families, there has been no such investigation and neither do we know what treatments may be effective for these conditions. During 2015 we undertook a major project with English-

speaking InterRett families living mainly in the US, Canada and the UK. We aimed:

- To identify how commonly specific breathing and sleep abnormalities are occurring in girls and women with Rett syndrome.
- To identify what may be risk factors and what may be protective factors for sleep and breathing problems in Rett syndrome.
- To find out whether there are treatments that are working for these conditions.

Using for the first time, the web-based electronic data capture system Redcap we invited English-speaking families with whom we had recent contact, to fill out a questionnaire specifically designed to answer these questions. We have had a very gratifying 83% response from the 570 families we have invited.

We found that breathing irregularities such as hyperventilation and breath-holding affected girls and women of all ages and with most mutation types. However, the impact especially for breath-holding was worse for those with a p.Arg294\* mutation, one of the generally milder mutations. We also found that respiratory infections, often involving hospital admission were common, but less likely to occur in those who were ambulant.

Night waking was the most prevalent sleep problem affecting over 80% with nearly half (48.3%) currently waking often at night. Night laughing also occurred but was less common. Using standardized sleep disturbance scales we also found that sleep problems were much more prevalent in Rett syndrome than in a normal control population. In particular,



we found that those with Rett syndrome had particular difficulties with initiating and maintaining sleep and also excessive somnolence (falling asleep during the day). Once again we found relationships with the p.Arg294\* mutation, a mutation usually associated with a mild phenotype. Severe seizure activity was also associated with poor sleep after adjusting for age group, mutation type and mobility. Our findings highlight the complexities of aberrant MECP2 function in Rett syndrome and explain some of the variation in manifestation of sleep disturbances.

Part of the above work on breathing and sleeping difficulties is currently being prepared or has been submitted for publication and further analyses are ongoing.

One aim of InterRett is to focus on families who live in under-represented majority world countries. With materials translated into Mandarin and with collaborations dating back to 2002, a country with strong growth for InterRett is China. Dr Downs and Dr Leonard have visited families affected by Rett syndrome in Shenzhen, China on several occasions since 2013 and developed a collaboration with the Rett Syndrome Comprehensive Research Institute (RSCRI). Together with colleagues from the RSCRI, Shenzhen Children's Hospital and the Chinese Academy of Science, they were awarded a grant by Rettsyndrome.org in 2015 to conduct a randomized stepped wedge design trial investigating the effects of an intensive environmental enrichment program on primarily functional abilities in girls with Rett syndrome younger than six years. This study is being led by Dr Jenny Downs and the InterRett database has formed the

infrastructure for recruitment.

### **Plain Language summary**

We have continued to recruit families to the InterRett database. Families have participated in new questionnaires on breathing and sleep disturbances. We commenced a study in China that will assess whether an intensive therapy program will help the health and wellbeing of young girls with Rett syndrome. Two Honours students have worked on our InterRett data in 2015.

### **Funders of the project**

Rettsyndrome.org

### **External collaborators**

Andrew Wilson, Princess Margaret Hospital, Perth

Dr Chen Li, Shenzhen Children's Hospital, China

Mr Tam Cruise, Rett Syndrome Comprehensive Research Institute, Shenzhen, China

Professor Sean Huang, Shenzhen Institute of Advanced Technology, Chinese Academy of Science, China

## **THE NATURAL HISTORY OF THE CDKL5 DISORDER: DEVELOPMENT OF AN INTERNATIONAL REGISTER**

*Helen Leonard, Jenny Downs, Meghana Mangatt, Amy Epstein, Barbara Anderson, Kingsley Wong, Yuka Mori, Stephanie Fehr*

The CDKL5 disorder is caused by mutations on the cyclin-dependent kinase-like 5 (CDKL5) gene. Clinical features include early-onset seizures (generally within the first three months of life), global

developmental delay, abnormal muscle tone, hand stereotypies, gastrointestinal problems and bruxism. In the past this disorder was considered an atypical form of Rett syndrome, but from our research published in 2012 we now conclude that it is an independent disorder.

Since our 2012 publication, which included the largest cohort of individuals with the CDKL5 disorder, we have worked at establishing and further developing the International CDKL5 Disorder Database. This has been done in collaboration with the International Foundation for CDKL5 Research. Data collection commenced in September 2012 and involved families of individuals with the CDKL5 disorder completing a questionnaire either online or on paper. The questionnaire has now been translated into French, German, Spanish and Mandarin. More than 300 individuals are now registered with the database, with 41 new families registering during 2015. The largest proportions of cases come from the USA, Canada, Australia, UK, Germany, France, the Netherlands and Brazil. However we now have over 20 other countries represented.

In October 2015, Dr Leonard attended a meeting in London that brought together clinicians and researchers already working in the CDKL5 field as well as those with the potential to do so in the future. The Forum was organised and hosted by the Loulou Foundation, a private not-for-profit foundation which was established to accelerate research into CDKL5. The meeting was held in collaboration with the International Foundation for CDKL5 Research (IFCR) and CDKL5 UK, and parents from both organisations were represented. The goal of the Forum was

to create a community of knowledge sharing and collaboration through brainstorming and peer-group discussion about future avenues of research and therapeutic approaches. One of the positive outcomes of the Forum was the establishment of a collaboration between Dr Richard Chin from the Muir Maxwell Epilepsy Centre at Edinburgh University and our group here in Perth.

The infrastructure of the database has allowed us to investigate important research questions and 2015 was an extremely busy year from the perspective of data analysis and drafting of publications in relation to our findings. We submitted a manuscript examining factors affecting motor and communication abilities in the CDKL5 disorder. In general this is a very severe disorder with extremely limited functional abilities. We did identify some variability in relation to gender, with girls more likely to be able to sit on the floor independently and use words than boys. The strongest pattern related to the type of genetic mutation. Compared to those whose genetic mutation resulted in no functional protein, individuals with a mutation in the later part of the CDKL5 gene (after position aa781) were more likely to be able to stand, walk or use words.

In collaboration with Dr Richard Chin we also undertook a comprehensive investigation of epilepsy outcomes in this disorder. All but three (169/172) cases had a history of epilepsy with six weeks being the median age at seizure onset. At ascertainment fifteen percent of individuals were having more than five seizures a day, over half one to five seizures and around one fifth less than one seizure per day. Only about eight percent were seizure free demonstrating how



refractory this epilepsy is to treatment. However after adjusting for confounders we did find that the seizure rate was lower in one particular mutation group, those with truncating mutations between aa172 and aa781. We also found that those with better functional abilities had lower rates of seizures.

Meghana Mangatt, an Honours student from UWA also undertook a comprehensive investigation of other comorbidities occurring in this disorder. She found that gastro-intestinal problems, respiratory problems, and scoliosis increased in prevalence with age and that males were more vulnerable to respiratory and sleep problems than females. However no statistically significant relationships with genotype were identified for these comorbidities. When making a comparison with Rett syndrome she found that epilepsy, gastro-intestinal problems and sleep abnormalities were more common in the CDKL5 disorder whilst scoliosis and respiratory problems were less prevalent than in Rett syndrome.

A Japanese paediatrician, Dr Yuka Mori, has also been identifying the factors most likely to adversely affect mother's health and quality of life in this condition. With respect to child comorbidities it would appear that sleep disturbances stand out as particularly burdensome in this regard.

Finally we were also extremely pleased to ratify an agreement with the International Foundation for CDKL5 Research for ongoing funding of our database which will provide some funding for this important infrastructure through to 2017.

## Plain Language summary

We have continued to recruit families internationally to participate in the International CDKL5 Disorder Database. In 2015, we have investigated functional abilities, epilepsy and other health issues, and factors that influence the mother's wellbeing. Two students have worked on our CDKL5 data in 2015.

Funders of the project      International Foundation for CDKL5 Research  
External collaborators      John Christodoulou, Department of Paediatrics, University of Melbourne  
David Forbes, School of Paediatrics and Child Health, The University of Western Australia  
Simon Williams, Princess Margaret Hospital, Perth  
Richard Chin, Muir Maxwell Epilepsy Centre at Edinburgh University

## THE NATURAL HISTORY OF THE MECP2 DUPLICATION DISORDER: AUSTRALIAN SURVEILLANCE AND PLANS FOR DEVELOPMENT OF AN INTERNATIONAL REGISTER

*Helen Leonard, Jenny Downs, Zhan Lim, Kingsley Wong*

Mutations in the MECP2 gene were first identified in 1999 as the major cause of Rett syndrome. Six years later micro-duplications involving the MECP2 gene were reported to be a cause of severe intellectual disability in males. Subsequent studies have now established MECP2 Duplication as a specific syndrome that might account for approximately 1% of unexplained X-linked intellectual disability in males. To date most publications have been based on small case series with no studies describing prevalence or

epidemiology such that the natural history of MECP2 Duplication syndrome remains unclear.

We are currently using the Australian Paediatric Surveillance Unit to collect information on newly diagnosed cases of MECP2 Duplication Syndrome in Australia. Our specific study aims are to: use the information collected to generate population-based estimates of incidence and prevalence of this syndrome, and describe the core clinical features of MECP2 duplication syndrome. In the first eighteen months of surveillance we have had 13 cases (12 males and one female) reported to the study.

During 2015 we analysed data on 57 cases (49 males and 8 females) with MECP2 Duplication syndrome which had been provided to our International Rett syndrome (InterRett) database. The median age at ascertainment of our cases was 7.4 years (range 1.2-37.6 years) and at diagnosis 3.0 years (range 3 weeks-37 years). Less than a third had learned to walk. Speech deterioration was reported in over a third and only one if five used word approximations or better at ascertainment. Over half of the individuals had been hospitalised for respiratory infections in the first two years of life. Just under half had seizures, occurring daily in nearly half of this group. The majority had gastrointestinal problems and a third had a gastrostomy. A manuscript is in preparation.

Following a recent publication of phenotype reversal in a mouse model, establishing an early diagnosis and understanding the natural history of the disorder will be important to design

future therapeutic strategies and monitor outcomes. We propose the development of an international registry specific to MECP2 Duplication syndrome to facilitate future studies. It would also allow for better depiction of phenotypic variability, developmental trajectories and disease progression.

### **Plain Language summary**

We have collected and will continue to collect clinical and genetic information on children newly diagnosed with the MECP2 duplication syndrome throughout Australia. We have analysed our internationally collected data and this is the largest number of affected children and adults reported thus far. One student has worked on these data in 2015.

### **Funders of the project**

Van Wright Foundation

### **External collaborators**

Carolyn Ellaway, Sydney Children's Hospitals Network (Westmead)  
David Amor, Royal Children's Hospital, Melbourne  
Elizabeth Thompson, Women's and Children's Hospital, Adelaide  
Michael Gattas, Lady Cilento Children's Hospital, Brisbane

### **IDEA (INTELLECTUAL DISABILITY EXPLORING ANSWERS) DATABASE**

*Helen Leonard, Jenny Bourke, Jenny Fairthorne, Emma Glasson, Kingsley Wong, Carol Bower*

The IDEA Database provides an infrastructure for population-based



epidemiological research into the determinants and outcomes associated with intellectual disability. Information in the database is sourced from data from the Disability Services Commission (DSC) since 1953, as well as information from the Department of Education for children born since 1983. It is currently updated to 2012. Medical information on the cause of intellectual disability is provided through the DSC where available. The current prevalence of intellectual disability is estimated to be 17.03/1000 livebirths.

Current linked studies include the long term survival of people with Down syndrome which found that improved survival for children born with Down syndrome over the last 60 years has occurred incrementally, but disparities still exist for children who are preterm or have low birth weight. A study investigating the mental health of mothers has shown women with a previous outpatient psychiatric contact were more than twice as likely to have a child with autism spectrum disorder (ASD) or intellectual disability (ID). However in relation to investigating the burden of care, the study also showed that for those with no prior psychiatric history, mothers of children with ASD without ID, ID of unknown cause and ID of known cause (not Down syndrome) were approximately twice as likely to have a treatment episode for a psychiatric disorder after the birth compared to mothers of children with no ASD/ID. Mothers of children with ASD with ID had a higher treatment rate for psychiatric disorders than comparator mothers while mothers of children with Down syndrome had a lower rate, however these were not significant. Services might be implemented to assist in

the prevention of psychiatric disorders in these women, thereby raising their quality of life and that of their families.

### **Plain Language summary**

The IDEA database has information on all children born since 1983 who have been identified with an intellectual disability. Approximately 2% of children are estimated to have an intellectual disability and researchers can apply to link to this database in order to identify children in their cohort of interest who have an intellectual disability. Current studies that have linked to IDEA have looked at the improved survival of people with Down syndrome over the last 60 years. Another study looked at all mothers who had no previous psychiatric history before the birth of their child and found that those mothers who had a child with autism, intellectual disability of unknown cause or intellectual disability of known cause (but not Down syndrome) were more likely to have a psychiatric disorder after the child's birth compared to other mothers with no psychiatric history. This may be related to the burden of care associated with their child's disability and targeted support services could assist them to maintain their mental health.

### **Funders of the project**

Disability Service Commission

### **External collaborators**

Disability Services Commission, WA  
Department of Education

## **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, Jenny Bourke, Kitty-Rose Foley, Katherine Bathgate, Terri Pikora, Paula Dyke, Sonya Girdler, Tami Alhaddad.*

This project explored the challenges faced and outcomes achieved by young people with an intellectual disability as they moved 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. 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; (iii) the Australian Child to Adult Development (ACAD) Study at the University of Sydney and (iv) the Australia-wide Rett syndrome cohort.

A comparison of the transition experiences of the young people and their families in the WA and Queensland cohorts showed Queensland parents were more likely to have had planning meetings than WA parents. Nearly two thirds of Queensland parents, compared to half of WA parents, reported that worries and concerns about transition issues affected their daily life and wellbeing regardless of school status. The three most helpful strategies indicated by parents that assisted with transition planning related to the provision of more

information about financial assistance, the school transition program and the building of informal community-based supports.

Using the existing ACAD data previously collected in New South Wales and Victoria we compared the behavior of individuals with Down syndrome using both the WA and ACAD cohorts (n=323), with young people with intellectual disability of other cause in the ACAD cohort (n=466). We found fewer behavioural problems on all scales except communication disturbance for young people with Down syndrome compared to those without Down syndrome. We found depressive symptoms did not significantly decline for those with Down syndrome compared to those without Down syndrome. The trajectory of the social relating behaviours subscale differed between these two cohorts, where those with Down syndrome remained relatively steady and, for those with intellectual disability from another cause, the behaviours increased over time.

A further study using the WA data is investigating the quality of life of young people with Down syndrome, as measured by the Kidscreen, with a focus on aspects of their wellbeing, participation and daily activities.

### **Plain Language summary**

This project investigated the outcomes for young people with intellectual disability transitioning from school to adulthood in WA, Queensland, NSW and Victoria. We compared the transition experiences for those in WA and Queensland and found nearly two thirds of Queensland parents, compared with half of WA parents,



reported that worries and concerns about transition issues affected their daily life and wellbeing regardless of school status. The three most helpful strategies indicated by parents that assisted with transition planning related to the provision of more information about financial assistance, the school transition program and the building of informal community-based supports. The study also found that young people with Down syndrome experienced fewer behaviour problems compared with those with intellectual disability of another cause. However over the study period depressive symptoms did not decline for those with Down syndrome and social behaviours worsened for those with intellectual disability of other cause.

### **Funders of the project**

ARC Linkage Grant LP0989847

### **External collaborators**

Gwynnyth Llewellyn, Stewart Einfeld,  
Trevor Parmenter, Vivienne Riches-  
University of Sydney  
Bruce Tonge, Monash University  
Nick Lennox, University of Queensland  
Ron Chalmers, Disability Services  
Commission  
John Brigg, WA Department of Education  
Greg Lewis, Edge Employment  
Jackie Softly, Down Syndrome WA

## **DETERMINANTS AND OUTCOMES OF PRETERM BIRTH & PATHWAYS INTO DEVELOPMENTAL DISORDERS**

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

*Glasson, Jenny Fairthorne, Carrington  
Shepherd, Brad Farrant, Ami Bebbington*

Increases in preterm birth and survival over time of those born pre-term are occurring due to a range of factors. These include increasing maternal age and co-morbidity (particularly obesity and maternal diabetes), increases in multiple births, social factors such as higher fertility rates in socially disadvantaged high risk mothers and changes in obstetric practice relating to reproductive technologies, early induction of labour and use of caesarean section. Our group undertakes complex statistical analyses principally using linked deidentified Western Australian population data relating to pregnancies, births and hospitalisations to investigate the determinants and outcomes of preterm birth and the pathways leading to developmental disorders. We have already shown how the determinants of both spontaneous and medically indicated pre-term births are changing over calendar time. We have also compared neonatal outcomes for babies born pre-term in the public and private systems. Interestingly following the Australian Private Health Insurance Incentive policy reforms, which were implemented in 1997–2000, births in privately insured patients and also caesarean deliveries increased. We also showed that from 1996 to 2005, the rising caesarean delivery rate in nulliparous women could mostly be attributed to an increase in prelabour caesarean deliveries for private patients delivering in private hospitals.

Current work published in 2015 investigating the causes of hospitalisation following discharge after birth, found

gestational age was inversely associated with risk of hospitalisation with more than 90% of those born at 33 weeks gestational age being rehospitalised in the first 18 years, compared to 59% of infants born at 39 weeks. In the neonatal period growth related concerns were the main cause for hospitalisation, whilst infection was the most common reason post-neonatal to 1 year of age, and up to 5 years of age. Injury-related hospitalisations increased in prevalence from 5 years to 18 years of age.

We are also examining mortality risks and pathways in the early lifecourse, including the scale of difference in stillbirth and neonatal death rates in Western Australia (1998-2010) by maternal ethnicity. We showed that Aboriginal and/or Torres Strait Islander (Indigenous) mothers, African mothers and mothers from 'Other' ethnic backgrounds were found to have increased risk of stillbirth compared with Caucasian mothers. Babies of Indigenous mothers also had increased risk of neonatal death. We highlighted a significant downward trend in stillbirth and neonatal death rates at every gestational age, with the results indicating that changes in clinical practice related to pregnancy terminations have played a substantial role in shaping stillbirth and neonatal death rates in Western Australia. We also found that improved survival for children born with Down syndrome has occurred incrementally, but disparities still exist for children who are preterm or have low birth weight. In relation to the mortality of mothers, we found that Aboriginal mothers had a distinctly higher risk of death from external causes (accidents, suicides and homicides) than other Australian mothers—with

excess risk only partly explained by socio-demographic circumstances.

Another sequel to our examination of the causes of pre-term birth, will be to follow these vulnerable infants born at different gestational ages and determine what factors increase or decrease their likelihood of survival with or without a major developmental disability (e.g. intellectual disability, cerebral palsy and autism). This will allow us to explore the impact of changes in antenatal and perinatal care on these important pathways.

### **Publications 2015**

Fairthorne J, de Klerk N, Leonard H. Brief Report: Burden of Care in Mothers of Children with Autism Spectrum Disorder or Intellectual Disability. *J Autism Dev Disord* 2015;1-7

Fairthorne J, de Klerk N, Leonard H. The relationship between maternal psychiatric disorder, autism spectrum disorder and intellectual disability in the child: a composite picture. *Journal of Autism* 2015; 2(1):2.

Fairthorne J, Jacoby P, Bourke J, de Klerk N, Leonard H. Onset of maternal psychiatric disorders after the birth of a child with intellectual disability: a retrospective cohort study. *J Psychiatr Res* 2015;61:223-30.

Fairthorne J, Jacoby P, Bourke J, de Klerk N, Leonard H. Onset of maternal psychiatric disorders after the birth of a child with autism spectrum disorder: A retrospective cohort study. *Autism* Forthcoming 2016.



Einarsdottir K, Ball S, Pereira G, et al. Changes in Caesarean Delivery Rates in Western Australia from 1995 to 2010 by Gestational Age at Birth. *Paediatr Perinat Epidemiol* 2015;29:290-8.

Srinivasjois R, Slimings C, Einarsdóttir E, Burgner D, Leonard H. Association of gestational age at birth with reasons for subsequent hospitalisation: 18 years of follow-up in a Western Australian population study. *PLoS One* 2015;10(6):e0130535.

Glasson EJ, Jacques A, Wong K, Bourke J, Leonard H. Improved Survival in Down Syndrome over the Last 60 Years and the Impact of Perinatal Factors in Recent Decades. *The Journal of pediatrics*. 2015 Dec 2.

Farrant BM, Shepherd CCJ. Maternal Ethnicity, Stillbirth and Neonatal Death Risk in Western Australia 1998-2010. *ANZJOG* Forthcoming 2016.

### **Plain Language summary**

This study is investigating the factors associated with preterm birth and the outcomes for these children, as well as the pathways leading to developmental disorders such as intellectual disability, autism and cerebral palsy. Current work looking at the causes of hospitalisation after birth, found more than 90% of those born at 33 weeks gestational age were hospitalised in the first 18 years, compared to 59% of infants born at 39 weeks. In the first month of life, growth related concerns were the main cause for hospitalisation, whilst infection was the most common reason for those up to 5 years of age.

Injury-related hospitalisations increased from 5 years to 18 years of age. We also found that Indigenous mothers, African mothers and mothers from 'Other' ethnic backgrounds were found to have an increased risk of stillbirth compared with Caucasian mothers. Babies of Indigenous mothers also had increased risk of neonatal death.

### **Funders of the project**

Previous NHMRC Program Grant (572742), NHMRC Senior Research Fellowship-Helen Leonard (572568)

### **External collaborators**

Dr Zulfiqar Bhutta, Chair - Department of Paediatrics and Child Health, The Aga Khan University, Pakistan

### **DOWN SYNDROME CLINICAL TRIAL-BTD-001**

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

The purpose of the study was to determine if a new formulation of the drug called BTD-001, which behaves as a GABA antagonist, can improve function and cognition in people with Down syndrome. This randomized, double blind, placebo-controlled trial has assessed the safety and preliminary efficacy of the drug. The study involved taking an oral formulation of BTD-001 for 12 weeks and undergoing cognitive tests over 7 clinic visits. Participants were monitored for adverse events for the duration of the study.

The study was conducted in eight sites across Australia. For our site study participants were generally contacted through the Down Syndrome NOW database developed at the Institute through previous survey studies involving families with a child with Down syndrome. Participants had to aged 13-35 years, be able to complete the required cognitive tests and be screened for current medical conditions such as epilepsy and hypothyroidism, which may indicate exclusion from the study. Overall 88 out of a planned 90 participants were enrolled in the study Australia wide. At our site 26 potential participants completed a study screening visit and of the 26 screened, 17 were eligible to participate in the study and were randomised (minimum target 12). All participants have now completed the study and the final study report is pending.

### **Plain Language summary**

This study is a clinical trial being conducted across Australia that is looking at whether a new drug can improve function and cognition in people with Down syndrome. At our site in WA we had 26 potential participants who were screened for current medical conditions and their ability to complete the required tests. There were 17 who were found eligible to be in the study and were randomised to either the drug or a placebo. The participants were required to take their medication for 12 weeks and attend 6 visits where medical assessments and other cognitive testing was undertaken. All participants have now completed the study and the final study report is pending.

### **Funders of the project**

Balance Therapeutics Pty Ltd

### **External collaborators**

Novotech Pty Ltd

### **ICARE AND MINERVA**

*Helen Leonard, Kim Carter, Richard Francis, Emma Glasson, Nan Hu, Kingsley Wong*

Although it is well known that genetics are important in the aetiology of autism, the recent increase in the prevalence of autism as well as reports from some studies of a lower familial contribution suggest that non-genetic and environmental factors may also be important. For other diseases with complex causes, like diabetes or cancer, it has been necessary to pool data across many different study groups and populations to achieve large enough sample sizes. The International Collaboration for Autism Registry Epidemiology (iCARE) was established as a multinational consortium for sharing and pooling of data for research on autism spectrum disorders (ASDs). iCARE partners from seven different countries (Australia, Denmark, Finland, Israel, Norway, Sweden, and the USA) contribute data for analyses. The data that are used in iCARE come from data sets that already exist in each country for public health purposes. These public health data sets have information on everyone in the country or the state, such as data sets that record every birth or death. The data in iCARE from all seven partners are best used for studies that require very large sample sizes or for making comparison across the different countries. The purpose of the original



project funded by Autism Speaks was to establish the iCARE partnership and build the necessary tools and ways to carry out research on data from different countries. Another purpose was to undertake studies on risk factors and trends in autism using the pooled data.

Data from each site undergo rigorous harmonization and quality control processes prior to analyses; local datasets are fixed snapshots of registry data at a particular point of time and the harmonization process is repeated following registry data updates (new 'snapshots'), the addition of new variables, or variable modifications. Analyses are performed using database federation techniques developed and maintained by our Institute's bioinformatics group. These techniques permit transparent access to iCARE datasets located and managed at each site without the need for data export for pooling or permanent archiving at a single location. Thus iCARE has created a computational infrastructure with a secure, web-based, interface to facilitate analysis of the federated, harmonized, research datasets. Investigators give careful consideration to the consequences of site differences in case ascertainment (e.g., registry-specific variation in ascertainment of different ASD diagnostic or phenotypic subtypes), differences in registry reporting, and changes in diagnostic criteria across sites and over time, and their impact on case characteristics and associations with risk factors. Pre-analytical, descriptive steps to assess between site heterogeneity include exploration, variable by variable, of autism and risk factor differences over time, by site, and diagnostic system. Overall, the

benefits of establishing iCARE include: (1) cost efficiency through use of existing data resources; (2) flexible infrastructure accommodating current research needs and future network growth and data upgrades; (3) flexibility in study designs to suit particular analyses (e.g., cohort, case-cohort, multigenerational or sibling designs); (4) largest sample sizes achieved to date based on federated data that enhance statistical precision; (5) ability to characterize population trends in reported diagnoses over time (e.g., by age at reporting, birth cohort or time period), as well as changes over the life course of affected individuals; and (6) enhanced comparison and interpretation of between-site results based on data harmonization and application of uniform analytic methods to multi-site data.

In 2013 a paper describing the iCARE infrastructure and methodology was published with Dr Diana Schendel as lead author. The previous year the iCARE researchers under the leadership of Dr Abraham Reichenberg from the Mount Sinai School of Medicine had been successful in their application to be a NIH Autism Center of Excellence. The goals of the new program known as MINERvA are to examine: fundamental controversies concerning familial and environmental contributions to risk for ASD; transmission of risk across generations; pregnancy-related environmental factors in ASD, and the potential role of epigenetic changes in those factors. Building on the existing iCARE network study data will now be based on over 4.5 million births (1998-2007), over 20,000 cases of ASD, and family linkages over three generations and will be again analysed using database federation via a computational

infrastructure with a secure, web-based, interface.

During 2015 we published a paper under the leadership of Kim Carter and Richard Francis describing the bioinformatics infrastructure developed to support both iCARE and MINERvA. This software platform known as ViPAR (an acronym for Virtual Pooling and Analysis of Research data) employs free and open source methods to provide researchers with a web-based platform to analyse datasets housed in disparate locations. Furthermore, using the original iCARE data of over 30,000 cases of autism spectrum disorder (ASD) and their underlying populations we also published in 2015 on an investigation of the relationship between maternal and paternal age and risk of ASD with Dr Sven Sandin as lead author. Advancing paternal and maternal age were each associated with an increased risk as was younger maternal age. However there was also a joint effect of maternal and paternal age with increasing risk of ASD for couples with increasing differences in parental ages. We have also been working on a manuscript investigating the relationship between caesarean section delivery and subsequent risk of ASD.

The MINERvA work undertaken in 2015 has mainly involved the development of a manual for the harmonization processes required to occur at each site once the data has been received by the seven sites in Scandinavia (Norway, Sweden, Denmark and Finland), Israel, the US (California) and Western Australia. This manual has been developed by the data programmers in conjunction with the data analysts and those who are going to lead

the individual projects. It has involved considerable time spent on weekly teleconferences with our international partners by members of the Western Australian team.

Our large multinational research team looks forward with anticipation to the arrival of data in 2015 after which the harmonization work will commence to ensure the compatibility of all the local datasets.

### **Plain Language summary**

This project provides the ability to pool and analyse data on 20,000 cases of autism from seven different countries using a bioinformatics infrastructure developed here at our Institute. It will allow us to answer questions about the recurrence risk of autism and the role of parental and grandparental age and mother's country of birth as risk factors for autism. Finally it will allow us to investigate whether or not the use of certain medications during pregnancy such as those prescribed for mental health disorders increases the risk of autism in the offspring.

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

External collaborators Diana Schendel, Department of Public Health and Department of Economics and Business, University of Aarhus, 8000 Aarhus C, Denmark

Jakob Christensen, Therese Grønborg, Erik Parner, Department of Public Health, University of Aarhus, Aarhus, Denmark  
Marlene Lauritsen, Research Unit for Child and Adolescent Psychiatry, Aalborg Psychiatric Hospital, Aarhus University



Hospital, Aalborg, Denmark  
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 Auli Suominen, Department of Child  
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 of Psychiatry, Mount Sinai School of  
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 Raz Gross, Division of Psychiatry, Sheba  
 Medical Center, Tel Hashomer, Israel  
 Michaeline Bresnahan, Mady Hornig,  
 Ezra Susser Department of Epidemiology,  
 Mailman School of Public Health,  
 Columbia University, New York, USA  
 Sarah Stock, Queen's Medical Research  
 Institute, Little France, Edinburgh, Scotland  
 Benjamin Yip, Division of Family  
 Medicine, School of Public Health and  
 Primary Care, University of Hong Kong

## 2015 Success

### THESES PASSED

Stephanie Fehr, PhD, The University of  
 Western Australia, The natural history of  
 the CDKL5 disorder: development of an  
 international database.

Jenny Fairthorne, PhD, The University of  
 Western Australia, Mothers of children with  
 intellectual disability or autism spectrum  
 disorder: pre-existing differences, health  
 and quality of life.

### AWARDS AND PRIZES

Jenny Downs, World Congress of Physical  
 Therapy outstanding poster presentation  
 award from the Asia Western Pacific  
 Region.

Jenny Downs, Friends of the Telethon Kids  
 Institute National Travel Award.

Jessica Mackay, Jean Rogerson  
 Undergraduate Scholarship in the  
 Faculty of Medicine, Dentistry and Health  
 Sciences

### EXTERNAL COMMITTEES

#### National/International

Helen Leonard, Honorary appointment  
 for the Australian Institute of Health and  
 Welfare Global Burden of Disease 2010  
 study, start March 2015.

Helen Leonard, Member of Executive,  
 Australian Association of Developmental  
 Disability Medicine, (2002-).

Helen Leonard, Member of the Scientific  
 Program Committee, International  
 Association for the Scientific Study of  
 Intellectual and Developmental Disabilities  
 (IASSIDD) Conference 2015

#### Local

Jenny Downs, Committee Member,  
 Human Research Ethics Committee,  
 Princess Margaret Hospital for Children,  
 start June 2010.

Helen Leonard, Member of Women's and  
 Newborns' Health Network Executive  
 Advisory Group.

Helen Leonard, Executive Committee  
 Member, Perth Epidemiology Group,  
 (2008-).

Kingsley Wong, Executive Committee  
 Member, Perth Epidemiology Group,  
 (2008-).

Helen Leonard, Brain and Behaviour,

Steering Group, Telethon Kids Institute  
Helen Leonard, Member, Research  
Excellence Council, Telethon Kids Institute  
Helen Leonard, Member, Women's and  
Newborns' Health Network Executive  
Advisory Group  
Helen Leonard, Committee member, Dr  
Louisa Alessandri Memorial Fund

Journey: Pathways to Follow, Rett  
Syndrome Association of Australia,  
Geelong, Victoria, 21 November 2015.  
Jenny Downs, Child and family needs in  
a severe disability: A population-based  
study of Rett syndrome in Australia,  
Paediatric Research Driving Clinical  
Practice, School of Physiotherapy and  
Exercise Science, Curtin University, Perth,  
28 May 2015.

## INVITED PRESENTATIONS

Helen Leonard, Feeding difficulties  
and growth problems in Rett syndrome  
and their management, AADDM 2015  
Conference Its Alimentary, Sydney 13  
August 2015.

Helen Leonard, Participated as a panel  
member planned to accelerate research  
in CDKL5, The Loulou Foundation, London,  
UK 5th-6th October, 2015.

Helen Leonard, Rett syndrome: evolution  
over time and over the lifespan, 4th  
European Rett Syndrome Congress, Rome,  
31st October-2nd November.

Helen Leonard, Epidemiological Data  
on Mortality from Australian Database  
and Cause of Death using the Australian  
Death Index, 4th European Rett Syndrome  
Congress, Rome, 31st October-2nd  
November.

Jenny Downs (presented by Helen  
Leonard), Motor development: new  
frontiers for walking activity evaluation, 4th  
European Rett Syndrome Congress, Rome,  
31st October-2nd November.

Helen Leonard, The contribution made  
by families to research outcomes in Rett  
syndrome., The Rett Syndrome Journey:  
Pathways to Follow, Rett Syndrome  
Association of Australia, Geelong, Victoria,  
21 November 2015.

Jenny Downs, Understanding quality of  
life in Rett syndrome, The Rett Syndrome

## Molecular Biotechnology Group

### Overview

The focus of the Molecular Biotechnology group has been to use recombinant or synthetic molecules to define the specificity of immune responses for asthma and allergy. The overall aim is develop therapies to target respiratory disease.

The ability to differentiate the T-cell responses to the related rhinovirus A and rhinovirus C species afforded by our epitope analysis (details below) will enable the study of immunity to two viruses that have shared antigenicity, but have a different biology and produce a different spectrum of disease. For cat allergy, our group has defined the different allergen components that are produced by the cat that has led to the discovery that people differ in their relative response to these components. Responses to these components differ markedly from person to person. Indeed a companion study to the cat allergy project showed that immunological correlates with clinical disease could only be obtained when the two most important cat allergen components were used, not just one as done in previous studies. Finally the definition of allergen components that mediate major cross

reactivities between IgE antibodies to house dust mite allergens will greatly facilitate studies of allergy in developing regions where the current clinical tests are not useful due to cross-reactivities, such as with scabies. Since scabies is not only limited to developing environments, the inclusion of these components into the multi-allergen microarray tests will be able to eliminate a potential major confounder.

### Research Projects

#### **T AND B-CELL IMMUNITY TO RHINOVIRUS C AND OTHER RHINOVIRUS SPECIES**

*A/Professor Belinda J. Hales*

*Ms Cibele M. Gaido*

*Ms Caitlyn Granland*

The newly recognised rhinovirus C (RV-C) is associated with more severe respiratory tract infections than rhinovirus species A and more frequently with exacerbations of asthma. As shown by antibody responses, natural immunity to RV-C is also different with low responses suggesting an element of a stealth infection. The two species however have about 45% amino acid identity in their capsid proteins making it necessary to account for cross reactivity. To delineate the underlying T-cell responses specific to each species of virus peripheral blood cell T-cell responses were measured to a series of synthetic 15-mer peptides that would encompass the T-cell epitopes of the VP-1 capsid protein of each virus species.

Proliferative responses revealed peptides that were both frequently recognised and were species-specific, showing no cross-reactivity with the homologous of peptides of the other species.

### **Plain Language summary**

The investigation has shown it is possible to distinguish the immune responses made by T cells to the related rhinovirus A and rhinovirus C viruses. This can now be used to investigate how the more serious rhinovirus C infections appear to either evade or blunt the body's protective responses.

### **Funders of the project**

Telethon seeding grant, Telethon-Perth Children's Hospital Research Fund

### **External collaborators**

Andrew Currie (Murdoch University), Abha Chopra (Murdoch University) and Peter N. Le Souëf (SPACH, UWA)

## **ALLERGIC SYMPTOMS AND T-CELL RESPONSES TO ALLERGENS IN CHINESE IMMIGRANTS**

*A/Professor Belinda J. Hales  
Ms Aarti Saiganesh*

The effect of migration to a new environment on the prevalence of allergy and T-cell responses to allergens was studied in Chinese immigrants to Perth. There was a marked increase in hay fever with increased prevalence of positive skin tests to both house dust mites and grass pollen allergens. Stimulation of peripheral blood mononuclear cell cultures with HDM allergen and the mitogen PHA revealed

little change in the production in the Th lineage associated cytokines IL-5, IL-10, IL-13 and IFN- $\gamma$  but there were increases in the regulatory cytokine IL-10

### **Plain Language summary**

Conclusion: An increase in hay fever symptoms and levels of IL-10 was present in Chinese immigrants who have lived in Australia for a longer period of time.

### **Funders of the project**

Telethon seeding grant, Princess Margaret Hospital Foundation

### **External collaborators**

Brad Zhang (Curtin University), Andrew Currie (Murdoch University), Peter N. Le Souëf (SPACH, UWA)

## **DIVERSITY IN ALLERGIC AND IMMUNE RESPONSES TO CAT ALLERGENS**

*Professor Wayne R Thomas  
A/Professor Belinda J. Hales*

Immune responses in cat allergy are not only directed to the canonical Fel d 1 allergen but also to a number of lipocalin and lipocalin-like proteins made exclusively by salivary glands. Studies at this Institute have shown that cat allergy can be more complex than the largely homogeneous pattern of house dust mite allergy, because while Fel d 1 is the most important allergen component for about half of the cat allergic subjects, the others can have one of several proteins as the immunodominant specificity. This reveals deficiencies in the current diagnostics test and critical knowledge



for the development of new types of immunotherapy. It is however necessary to test this in other parts of the world especially sub-temperate zones where cats are kept almost exclusively indoors and constitute a much bigger allergy problems. The allergens were made with recombinant technology for collaborators in Sweden and Seattle to test. Professor Kwok and his team in Seattle showed large memory T-cell frequency to Fel d 4 with 30% of subject responding best to this allergen. IgE antibody studies with Fel d 7 in Sweden showed significant responses in 37% of subjects and that they had a high degree of cross-reactivity with the homologous dog allergen Can f 1.

### **Plain Language summary**

Investigations from this Institute show that cat components made by their salivary glands need to be included in the diagnosis of cat allergy and considered for the development of new treatments.

### **Funders of the project**

Molecular Biotechnology research funds

### **External collaborators**

Marianne van Hage (Karolinska Institute, Stockholm, Sweden), Rudolph Valenta (Medical University Vienna, Vienna, Austria), William W. Kwok (Benaroya Research Institute, Seattle, USA)

## **HIGHLY CROSS-REACTIVE SCABIES AND HOUSE DUST MITE ALLERGEN COMPONENTS**

*A/Professor Belinda J. Hales  
Professor Wayne R Thomas*

Spurious but high IgE binding responses to house dust mite extract has been found in northern Australian Aboriginal communities with no or little binding to the serodominant allergens Der p 1 and Der p 2, but with high and frequent IgE binding to the usually low IgE binding component Der p 4. Study of the IgE binding to house mite components by sera from subjects with scabies have revealed IgE binding to Der p 4 and the abundant body component Der p 20 in subjects with current scabies infections. Binding to Der p 4 but not to Der p 20 was found in subjects living in an environment with endemic scabies perhaps due to previous infections. The IgE was found in both Aboriginal and non-Aboriginal subjects. House dust mite extracts therefore have little use for allergy testing in regions of the world with endemic scabies, but the studies show that anti-scabies responses can be identified by testing with the Der p 4 and Der p 20 components, with uses for both allergy and scabies diagnosis.

### **Plain Language summary**

House dust mite extracts are not suitable for allergy diagnosis in regions of the world with endemic scabies. Der p 4 and Der p 20, in combination with serodominant allergens Der p 1 and Der p 2 can be used to discriminate in the diagnosis of allergy and scabies.

### **Funders of the project**

Molecular Biotechnology research funds

### **External collaborators**

Shelley F. Walton (University of the Sunshine Coast, Qld), Bart J. Currie (Menzies School of Health Research).

## 2015 Success

### **AWARDS AND PRIZES**

Cibele Gaido, UWA travel award  
Aarti Saiganesh, Perron top up award

### **EXTERNAL COMMITTEES**

International. Thomas, IUIS allergen nomenclature subcommittee; Thomas, World Allergy Organization ask the expert panel

### **INVITED PRESENTATIONS**

Cibele Gaido, Combined Biological Science Meeting/CBSM, Perth, Australia (Aug 2015):  
Cibele Gaido, World Society for Pediatric Infectious Diseases/WSPID, Rio de Janeiro/ Brazil (Nov 2015):  
Aarti Saiganesh, The Australia and New Zealand Society of Respiratory Science/ ANZSRS - oral presentation (abstract selected for media interview) - Gold Coast, Australia (Mar 2015)  
Aarti Saiganesh, Thoracic Society of Australia and New Zealand/TSANZ - Gold Coast, Australia (Mar 2015)



# NUTRITION AND OBESITY

## ChaMMP

### Overview

ChaMMP or “Changing the molecular mechanisms of programming of obesity” is aiming to break the cycle of obesity from one generation to the next. To do this the group is currently running two projects looking at the epigenetics of obesity and related non communicable diseases, using a large Raine study dataset funded through NHMRC as well as pilot testing an RCT during early pregnancy for maintaining gestational weight gain.

In 2015, ChaMMP began pilot work on the early pregnancy RCT through the help of the RFA working group seed funding and also recruited a dietitian to join their research team. Work on the epigenetic generational study using the Raine cohort has finished data collection and has commenced analysis and reporting of results.

There is also a major new development with the Raine cohort looking into the 3rd generation of participants.

### Research Projects

#### **THE CYCLE OF OBESITY**

*CIA Associate Professor Rae-Chi Huang  
University of Western Australia*

*CIB Associate Professor Karen Lillycrop  
University of Southampton, UK*

*CIC Associate Professor Graham Burdge*

*University of Southampton, UK*

*CID Doctor Jeffrey Craig Murdoch*

*Childrens Research Institute*

*CIE Professor Lawrie Beilin University of  
Western Australia*

*CIF Professor Trevor Mori University of  
Western Australia*

*CIG Professor Wendy Oddy Telethon  
Institute for Child Health Research*

*CIH Professor Keith Godfrey University of  
Southampton, UK*

*CII Doctor Joanna Holbrook Singapore  
Institute for Clinical Science*

We will identify epigenetic marks that are associated with higher body mass index (BMI) and obesity in a large and established pregnancy cohort. We will determine whether such marks (associated with the risk of obesity) are constant between two generations and consistently predict BMI.

Understanding how persistent obesogenic pressures affect the epigenotype in humans over two generations is a critical step towards predicting future consequences of the obesity epidemic. There is considerable evidence that epigenetic processes underlie the induction of persistent changes in gene expression and metabolism by environmental challenges in early life. This is called “fetal programming”. In animal studies, an obese parent fed a high-fat diet has offspring with epigenetic changes in key genes controlling appetite and metabolism. These offspring are prone to obesity themselves. Thus epigenetic changes in key regulatory genes are likely to play a major role in the development of

obesity in populations. Epigenetic marks passed from generation to generation, unrelated to genetic variation, are likely to indicate an obesity risk induced by environmental exposure.

Despite growing evidence from animal models that epigenetic alterations play a key role in the development of obesity, limited epigenome wide association studies (EWAS) for obesity exist in humans. The largest to date involved 74 participants.

Our first objective was to identify which epigenetic marks are associated with obesity (n=1259) and its comorbidities. We will then determine whether these epigenetic marks are stable between two generations and associated with adiposity in the parents of Generation 2 (n=997). This will be important in showing that environmentally induced epigenetic marks associated with

obesity are constant from generation to generation. This project will be a step towards understanding the overarching question- are epigenetic biomarkers associated with the obesity epidemic, and possibly the rapid escalation of obesity over a few generations?

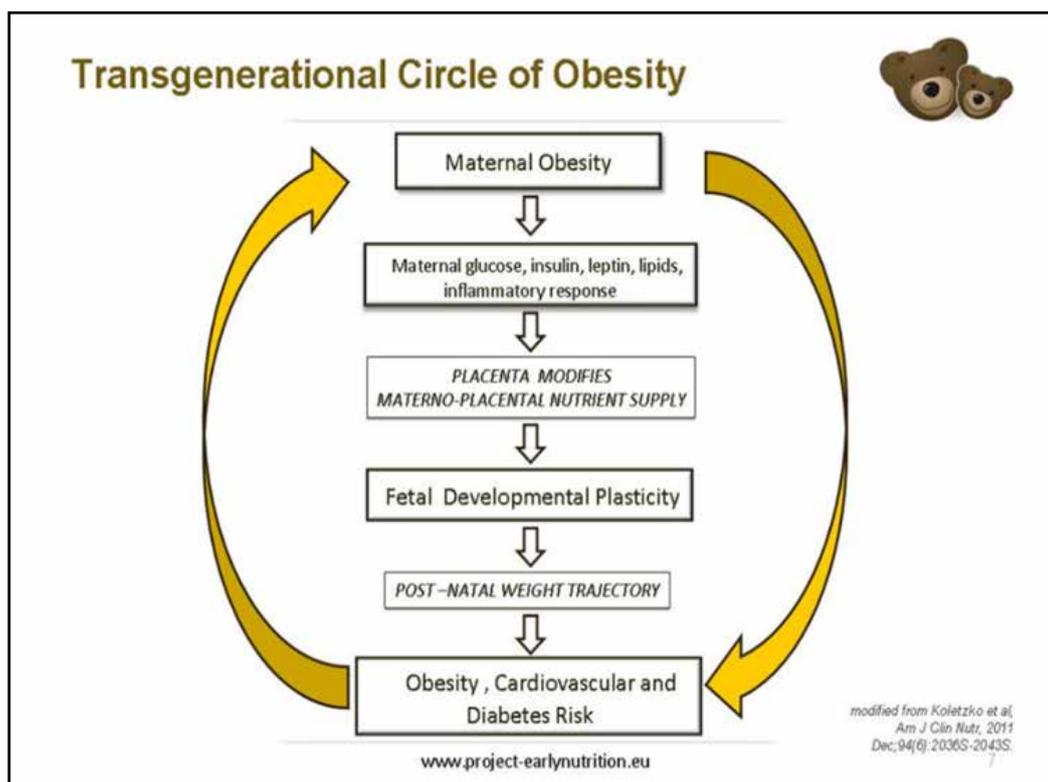
We aim to identify traits that are associated with higher body mass index (BMI) and obesity in humans and whether these traits are similar between two generations (from parent to child) and can be a predictor of obesity in the future.

### Funders of the project

NHMRC

### External collaborators

Keith Godfrey, Karen Lillycrop and Graham Burdge – University of Southampton, UK



## **THE PLAN PROJECT: PREGNANCY LIFESTYLE ACTIVITY AND NUTRITION**

*CIA Associate Professor Rae-Chi Huang  
University of Western Australia*

*CIB Professor Susan Prescott University of  
Western Australia*

*CIC Emeritus Professor Lawrie Beilin  
University of Western Australia*

*CID Professor Karen Lillycrop University of  
Southampton, UK*

*CIE Associate Professor Graham Burdge  
University of Southampton, UK*

*CIF Professor Keith Godfrey University of  
Southampton, UK*

*CIG Professor Vincent Jaddoe Erasmus  
University Medical Centre*

*CIH Associate Professor Gina Ambrosini  
University of Western Australia*

Obesity and related conditions are increasing exponentially with each generation, presently costing Australia in excess of \$58 billion pa. Such conditions are projected to affect 75% of the Australian population by 2030, unless the inter-generational cycle of obesity is broken. Excess weight gain early in pregnancy is an independent risk factor for obesity for the next generation. We hypothesize that early pregnancy provides a critical window of opportunity for a short-term intervention to break a 'vicious cycle' of obesity from one generation to the next. This RCT will test if a lifestyle intervention in early pregnancy reduces offspring adiposity. Even small changes in infant adiposity have the potential to change future obesity trajectory, leading to a lifetime of cost savings. It will also examine epigenetic biomarkers in offspring (differential DNA methylation), determining if these are modified by optimization of gestational

weight gain (GWG) or associated maternal lifestyle changes, and whether these predict subsequent infant outcomes.

Despite strong evidence that maternal-fetal interactions in early pregnancy and preconception are important for programming subsequent infant metabolic and epigenetic responses, little is known about the effects of modulating lifestyle in the first trimester in pregnancy in humans. To date, most lifestyle RCTs addressing GWG have intervened through the middle and last trimester rather than on the first trimester in pregnancy<sup>12</sup> when intervention may be more effective. The key novel aspect of this study is that it commences in early pregnancy (as soon as practically possible ≈3 to 8 weeks post-conception).

We are running a study that aims to manage gestational weight gain in early pregnancy (commencing at 6-10 weeks gestation) in line with recommended medical guidelines. There is evidence that gaining excess weight during pregnancy can lead to poor health outcomes (such as obesity, heart disease and diabetes) in the child in later life. We aim to break the cycle of obesity by maintaining weight in pregnancy within a healthy range using mobile technology.

### **Funders of the project**

Telethon Kids Institute – RFA Working Group seed funding

### **External collaborators**

Lucilla Poston – King's College London



## 2015 Success

### AWARDS AND PRIZES

Rae-Chi Huang – UWA Research Collaboration Award

### INVITED PRESENTATIONS

Rae-Chi Huang “DNA methylation is associated with body composition in young adults” – ANZOS Annual Scientific Meeting, Melbourne October 2015  
Rae-Chi Huang “Genome wide methylation analysis identifies differentially methylated CpG loci associated with severe obesity in childhood”  
DOHaD 9th World Congress Meeting November 2015  
ANZOS Annual Scientific Meeting – Workshop Presentation on Early Pregnancy Intervention. Melbourne, October 2015  
Episcopo one day Colloquium – Highlights of epigenetic research. Sydney, October 2015

## Nutrition Team Overview

Cardio-metabolic risk factors (obesity, cardiovascular disease, type 2 diabetes, liver injury) and mental health disorders (depression, anxiety, stress) are of increasing population health concern for Australia as well as globally. The primary aim of the nutrition team is to describe relationships between nutritional factors, cardio-metabolic and mental health risk from infancy to adulthood. A wide range of data have been collected in the Raine Study during pregnancy, at

birth (n=2868), and at 1, 2, 3, 6, 8, 10, 14, 17, 20 and 22 years of age. Existing and newly collected data are being used by the Nutrition team. The Raine study is ideally placed for a life-course approach in cardio-metabolic and mental health risk. By examining these trajectories of risk to 22 years of age we can identify early determinants risk and key times for intervention.

In 2015 the Nutrition Team were involved in the projects listed below:

## Research Projects

### DIET CARDIOMETABOLIC AND MENTAL HEALTH OUTCOMES

*Wendy Oddy, Gina Ambrosini, Trevor Mori, Lawrie Beilin, Rae-Chi Huang, Georgina Trapp, Lucinda Black, Karina Allen*

**Background:** Observational studies suggest that dietary patterns may impact mental health outcomes, however biologically plausible pathways are yet to be tested. We aimed to elucidate the relationship between dietary patterns, adiposity, inflammation and mental health including depression longitudinally in a population-based cohort of adolescents.

**Methods:** Data were provided from 843 adolescents participating in the Western Australian Pregnancy Cohort (Raine) Study at 14 and 17 years of age. Structural equation modelling was used to test hypothesised models relating dietary patterns, energy intake and adiposity (body mass index) at 14 years to adiposity and the inflammatory markers leptin and C-reactive protein (CRP) at 17 years, depressive symptoms (Beck

Depression Inventory) and internalising and externalising problem behaviours (Child Behaviour Check List Youth Self-Report) at 17 years. adiposity and the pro-inflammatory adipokine (leptin), inflammation (high sensitivity C-reactive protein – hs-CRP) at 17 years, depressive symptoms (Beck Depression Inventory) and internalising and externalising problem behaviours (Child Behaviour Check List Youth Self- Report) at 17 years.

**Results:** The tested models provided a good fit to the data. A 'Western' dietary pattern (high intake of red meat, takeaway, refined foods and confectionary) at 14 years was independently associated with higher energy intake and BMI at 14 years and BMI and biomarkers of inflammation at 17 years. A 'Healthy' dietary pattern (high in fruit, vegetables, fish, whole-grains) was inversely correlated with BMI and inflammation at 17 years. Higher BMI at 14 was correlated with higher BMI, higher leptin and hs-CRP, depressive symptoms and mental health problems at 17 years. This is not mentioned or discussed in the discussion section at all?

**Conclusions:** A 'Western' dietary pattern associates with an increased risk of mental health problems including depression in adolescents through biologically plausible pathways of adiposity and inflammation. A 'Healthy' dietary pattern appears protective in these pathways. Further longitudinal modelling into young adulthood is indicated to confirm these complex associations.

## DIET AND DEPRESSION OUTCOMES

*Wendy Oddy, Lucinda Black, Georgina Trapp, Therese O'Sullivan*

Poor dietary habits have been implicated in the development of mental health and depression however little is known about the role of specific dietary patterns in depression. We examined prospective associations between dietary patterns and depression in a population-based cohort of young adults at 14 and 17 years of age. A Western dietary pattern at 14 years was associated with increased risk of mental health problems in girls only at 17 years.

## EARLY NUTRITION

*Wendy Oddy, Trevor Mori, Lawrie Beilin, Rae-Chi Huang*

We investigated whether a shorter duration of breastfeeding was associated with increased risk of being in a growth trajectory associated with obesity in the long-term. Our objective was to investigate associations between early infant feeding and growth trajectories at 20 years in the West Australian Pregnancy (Raine) Cohort Study cohort. We showed that rapid growth to 20 years was linked to a shorter duration of breastfeeding prior to three months of age ( $p < 0.05$ ). We concluded that a shorter duration of breastfeeding was associated with rapid growth in childhood and into young adulthood.



## 2015 Success

### THESES PASSED

Anett Nyaradi PhD University of Western Australia 'The relationship between diet, cognitive performance and educational outcomes in a prospective cohort study of Western Australian children'

Bianca Petterson DPsych University of Western Australia 'Individual, Socio-demographic, and Mental Health Predictors of Alcohol Consumption and Binge Drinking in Adolescence: The Western Australian Pregnancy Cohort (Raine) Study'

### AWARDS AND PRIZES

Gina Trapp '2015 Young Tall Poppy Science Award', Australian Institute of Policy & Science & the Tall Poppy Campaign

Gina Trapp 'Bendat Family Foundation Children's Research Scholarship', Telethon Kids Institute (\$8,400)

### EXTERNAL COMMITTEES

#### Local

- Gina Trapp: Early Career Advisory Group Committee. The University of Western Australia (2014-current)
- Gina Trapp: Food Environment Working Group, Centre for the Built Environment and Health, UWA (Chair, 2010 – current)

### INVITED PRESENTATIONS

Gina Trapp "How neighbourhood environments around schools shape what children eat". Science Teachers' Association of Western Australia, Future

Science Conference. Young Tall Poppy Science Award Winner. Curtin University, Perth WA. December 4 2015. INVITED SPEAKER

Gina Trapp "Collecting research data: tips, tricks and troubleshooting?". Research Workshop. UWA, Perth WA. November 25th, 2015. INVITED SPEAKER





# ORIGINS

## The ORIGINS Project

### Overview

The ORIGINS Project is a new birth cohort study, designed to collect detailed information about how the early environment influences the risk of a broad range of diseases including asthma, allergies, diabetes, obesity and its many complications. ORIGINS will recruit women (and the father of their baby) early in pregnancy and collect data on their health, diet, physical activity patterns and a range of factors in their environment. We will then assess how these early life exposures influence their child's growth, development, and health (including neuro-development, evidence of allergies, infections, and other medical history).

Pregnant women and their partners planning to deliver their baby at the Joondalup Health Campus will be eligible to participate in ORIGINS. Recruitment will take place at their first antenatal clinic visit at the Joondalup Health Campus. In addition to routine care, participants will be involved in internet-based communications with the Project team, including questionnaires, Project updates, and timely reminders for health-based events such as immunisations and child health clinic visits. At 1, 2½ and 5 years of age, ORIGINS children will be invited to attend Joondalup Health Campus for a 1 hour health check with a developmental

paediatrician and Project team members. This detailed follow-up should provide early detection of developmental issues and referral to services where appropriate.

#### ORIGINS will provide:

- a stronger focus on a 'healthy start' for short and long term disease prevention; and,
- a deeper understanding of the common early biological pathways that lead to disease.

#### Directors

Prof Susan Prescott, Prof Desiree Silva

#### Program Manager

Dr Lyn Colvin

#### Working Group

Dr Debra Palmer, Dr Lisa Gibson, Sarah Miller, Dr Erika Hagemann, Rebecca Vincent, Lynda Miller, Dr Ravish Srinivas Jois

## Sub-studies within ORIGINS

### THE SYMBA STUDY: PROMOTING GUT HEALTH (SYMBIOSIS) WITH PREBIOTIC FIBRE FOR PREVENTION OF ALLERGIC DISEASE

Will commence recruitment in May 2016.

#### Chief Investigators

*Prof Susan Prescott, Dr Debra Palmer, Prof Desiree Silva, A/Prof Michael Clarke, Prof Charles MacKay, Prof Jeffrey Keelan, Prof Karen Simmer, A/Prof Richard Allcock, Dr Timo Lassmann, Dr Lyn Colvin, Prof Johan Garssen, A/Prof Rae-chi Huang, Prof Maria Jenmalm, Prof Harald Renz, Dr Ravish Srinivas Jois, A/Prof Christina West*  
*Allergic diseases, including eczema, asthma, hay fever and food allergies, affect 30-40% of the Australian population. One in every four children will suffer from eczema and asthma, while one in every ten children will have at least one food allergy.*

We now know that a baby's immune system begins to develop even before birth, and that the mother's diet and her environment in pregnancy can have an important influence. Research shows that the mother's gut health may have important effects on the immune development of her baby.

'Prebiotics' is a general term for non-digestible dietary fibre that promote health and well-being by inducing the growth and/or activity of beneficial gut bacteria. Prebiotics occur naturally in grains, legumes, vegetables, fruit and breast milk. The supplement and

dose to be used in this study has the demonstrated prebiotic properties of a high fibre diet, including favourable effects on gut bacteria and immune health.

This project will recruit pregnant women (during their routine antenatal visits to Joondalup Health Campus) to receive either a prebiotic supplement or a placebo supplement. They will be asked to take the supplement from 18-20 weeks gestation until their baby is 6 months of age. The study will then examine whether supplementing the mother's diet during pregnancy and breastfeeding with the prebiotic fibre will reduce the development of allergies in her child.

#### Funders of the project

Telethon Perth Children's Hospital Research Fund 2014 - \$200,000  
NHMRC Project Grant 2015 - \$1,681,512

#### External collaborators

- Joondalup Health Campus
- Western Diagnostic Pathology
- Danone, The Netherlands
- Prof Johan Garssen, Utrecht University, The Netherlands
- Prof Maria Jenmalm, Linköping University, Sweden
- Prof Harald Renz, Philipps-University Marburg, Germany
- A/Prof Christina West, Umeå University, Sweden

### PLAN: PREGNANCY LIFESTYLE ACTIVITY AND NUTRITION

Commenced recruitment in December 2015.



## Chief Investigators

*A/Prof Rae-Chi Huang, Prof Susan Prescott, Dr Lisa Gibson, Prof Desiree Silva, Dr Cliff Neppe, Prof Lawrie Beilin, Dr Lyn Colvin, A/Prof Gina Ambrosini, Dr Hayley Christian*

We know that we are facing an obesity epidemic that is costing Australians \$58 billion per annum. Rates are continuing to rise with obesity projected to affect 75% of the Australian population by 2030. This unsustainable burden of disease will only increase unless the cycle of obesity is broken.

Evidence shows that maternal excess weight gain during early pregnancy (i.e. first trimester) has been identified as a critical window of opportunity for short term interventions to break the “transmission” of obesity from one generation to the next. Recruitment for the PLAN Project will take place at 6-8 weeks gestation and follow a 12 week lifestyle intervention program in conjunction with routine antenatal care for private and public patients.

The aim of the PLAN project is to test whether a lifestyle intervention in early pregnancy reduces offspring adiposity. Taking advantage of the growing advancements in medical technology, this project will use smartphone web based applications to deliver diet, physical activity and wellbeing advice to women who begin their pregnancy overweight (pre-pregnancy BMI > 25). Participants will have access to a live graph to maintain their weight gain according to Institute of Medicine guidelines. We hope to optimise gestational weight gain and provide a platform for a healthy pregnancy for women.

The PLAN project will examine epigenetic biomarkers (differential DNA methylation), determining if these are modified by optimisation of gestational weight gain or associated maternal lifestyle changes. Even small changes in infant adiposity have the potential to change future obesity trajectory, leading to a lifetime of cost savings.

## Funders of the project

Telethon Kids Institute Focus Area Seed Grant 2015 - \$24,821

## External collaborators

Joondalup Health Campus

## 2015 Success

### AWARDS AND PRIZES

Stephanie Dimitrov, Student Vacation Scholarship - \$1,200

### EXTERNAL COMMITTEES

#### International

Prof Susan Prescott: DOHaD ANZ (Founding President 2013-); DOHaD International Council.

#### Local

Prof Desiree Silva: Head of Paediatric Department, JHC (2007-); Professor of Paediatrics, UWA (2011-); Nature Play WA (Board member 2015-); Consultant Paediatrician, Rural Paediatric Service (Pilbara 1997-); St Mary's Anglican Girls School (Council member 2012-);





# RESPIRATORY HEALTH

## Cystic Fibrosis

### Overview

Imagine a world where you often have to miss school, playing sport and fun times with friends because your lungs don't work properly. You have to spend hours each day having treatments and getting a cold could potentially mean having to be admitted to hospital. This is what life can be like if you are child with cystic fibrosis (CF). CF is the most common chronic, life-shortening genetic condition affecting Australians. Approximately 1 in 25 people carry a CF-causing gene, resulting in around 1 in 2000 babies being born with the disease. CF affects many body systems, but is most devastating in the lungs, reducing a child's quality of life, and eventually leading to premature death. AREST CF is a collaborative group of over 30 doctors, allied health professionals and researchers dedicated to improving the respiratory health of children with CF by translating scientific research into tangible clinical outcomes. The WA arm of the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) is based at the Telethon Kids Institute and is led by Professor Stephen Stick. Research by our group and others has shown that infants and children with CF exhibit reduced lung function and evidence of inflammation and infection at a very early age. This highlights the need for new treatments that can be given from time of diagnosis to prevent and/or reverse the damage.

## Research Projects

### EARLY SURVEILLANCE PROGRAM (ESP)

The ESP is the platform upon which the AREST CF research program is based. Children attending CF clinics in Perth and Melbourne participate in the ESP from the time of diagnosis onwards. The ESP includes bronchoalveolar lavage (BAL, to assess airway inflammation, infection and other markers of disease), imaging (CT scan, to measure structural lung disease) and lung function measurements. Researchers are able to track the progress of lung disease through a comprehensive longitudinal set of biological samples, images and data archives. The ESP is now embedded in standard clinical practice in both Australian centres, and is in the process of being adopted by centres in the Netherlands and Switzerland. Since 2012, Professor Stick and A/Prof Sarath Ranganathan (Melbourne) were supported by a US Cystic Fibrosis Foundation Therapeutics grant to maintain and expand this program.

### Funders of the project

NHMRC, US Cystic Fibrosis Foundation Therapeutics

### EARLY DISEASE MECHANISMS

A better understanding of the significant contributing factors to the establishment and progression of CF lung disease will enable researchers to identify key targets

for new treatments. Our research into early disease mechanisms combines data and samples from the ESP with cutting edge technologies for measuring airway biology and infection. New research projects initiated since 2012 include investigations into mucus, hypoxia and the respiratory microbiome in progressive CF lung disease with the University of North Carolina, USA and the role of bioactive lipids in resolution of inflammation and tissue remodelling with Erasmus Medical Centre, Netherlands. Many factors contribute to exaggerated inflammatory responses observed in the CF lung; we have observed dysfunctional immune responses to common viruses and using systems biology approaches, we are identifying responses to viruses and bacteria that are pro-inflammatory and modifiable with existing and novel agents. Our data confirm that these are present soon after diagnosis, associated with disease progression and present a range of therapeutic targets.

### **Funders of the project**

NHMRC, NIH

### **PREDICTORS AND ENDPOINTS**

The premise that underpins this research area is the identification of early predictors of adverse pulmonary outcomes in children with CF. This will allow treatments to be targeted at those who will benefit the most. Development of objective novel, safe and potentially more informative methods will allow clinicians to identify progressive lung disease earlier and prevent or delay the onset of abnormal lung structure and function. These methods can then be

incorporated as outcome measures in clinical trials of new therapeutics. In 2013, in a landmark paper, we published the first data demonstrating that a biomarker measured at 3 months can predict structural lung disease outcomes at 1 and 4 years of age. We have also developed the first outcome measure (a quantitative CT method) to accurately reflect early structural disease in CF that can pave the way to regulatory studies of new therapies in young children with CF; an editorial in a major journal described this work as a step forward to “create a more targeted approach toward personalized medicine” *Editorial. Am J Resp Crit Care Med. 2015;191(1):1098-1099.*

We are actively pursuing research to better understand the:

- Evolution of airway function and inflammation in early CF lung disease. The combined measurements of respiratory function and inflammation will help detect and monitor the presence of lung disease early in the life of infants and young children with cystic fibrosis.
- Long term outcomes of infant lung function in CF. The data will inform the clinical importance of measuring lung function during infancy in CF and the role of these lung function tests in proposed early intervention studies.
- Viral pathogenesis of early CF lung disease. The investigation of viral infections in infants with CF will help determine the effect on the early origins and progression of CF lung disease.
- Clinical utility of LCI in early CF lung disease. This study will assess the clinical utility of lung clearance index (LCI) to detect lung damage, infection and



inflammation in preschool children with CF.

Prof Graham Hall's paediatric Respiratory Physiology team is a key element of this research, and partnering with A/Prof Sarath Ranganathan and Professor Harm Tiddens (Erasmus MC, Netherlands) the team has been successful in obtaining funding from various sources since 2012 to investigate different aspects of lung structure/function and disease progression.

### **Funders of the project**

NHMRC, NIH, US Cystic Fibrosis Foundation Therapeutics

## **DEVELOPING AND TRIALING NEW TREATMENTS AND INTERVENTIONS**

We are actively pursuing research to better understand the disease mechanism, with the goal to identify and develop new therapeutic targets for treatments and interventions.

Some examples of this research include:

- Investigating free protease activity in infancy as a strong predictor of subsequent lung damage and attenuation of this protease activity as a therapeutic target.
- Studying cells from the lungs and nose of young children with CF and investigating whether drugs that correct the underlying genetic disease can also correct the responses of these cells to virus infections.
- Investigating the optimal use of Human aortic endothelial cells (hAECs) to restore airway surface liquid (ASL), as a strategy to break the cycle of

mucus retention, inflammation and airway infection. This cellular therapy approach has the potential to engraft in the CF airway and correct the consequences of abnormal CFTR function in the lung and to prevent end-stage lung disease in CF.

This program is being led by A/Prof Anthony Kicic, in partnership with national and international collaborators.

### **Funders of the project**

NHMRC, US Cystic Fibrosis Therapeutics, Institute of Respiratory Health, Future Health WA Merit Awards, Telethon New Children's Hospital Research Fund

## **PSYCHOSOCIAL EFFECTS OF EARLY INTERVENTIONS**

Little is known about the psychological, social and economic effects on families of children undergoing early interventions for CF. Examination of the risks, burdens and benefits for families will inform improved future strategies for appropriate clinical and pastoral care. Translation of this research will also impact on content and delivery of education, nature of support services offered and development of relationships between families and providers, improving service delivery and potentially health outcomes for children with CF. Collection of qualitative and quantitative data from parents and care-givers of children participating in the ESP commenced in 2012 at Princess Margaret Hospital. Our psychosocial data have begun to identify significant impacts on children with CF and their families. These data provide important,

unique opportunities to assess child and family psycho-social distress, quality of life, anxiety on academic achievement and other outcome measures and to develop effective interventions.

### **Funders of the project**

NHMRC, WA Department of Health

## **2015 Success**

### **THESES PASSED**

Dr Luke Garratt PhD, University of Western Australia, "Neutrophil elastase mediated disruption of airway epithelial repair."

### **AWARDS**

Stephen Stick, Richard C. Talamo Distinguished Clinical Achievement Award (Cystic Fibrosis Foundation)

Graham Hall, Leadership WA: Signature Leadership Program

Graham Hall, Fellow, TSANZ

Luke Garratt, VERTEX Cystic Fibrosis Research Award (Thoracic Society of Australia and New Zealand (TSANZ))

### **EXTERNAL COMMITTEES**

#### **International**

Steve Stick, Scientific Board - Sophia Foundation, Rotterdam

Graham Hall, ERS College of Experts

#### **National**

Steve Stick, Grant Review Panel – NHMRC  
Anthony Kicic, TSANZ National ASM organising committee

Anthony Kicic, Deputy Convenor of the TSANZ Cell Biology & Immunology Special Interest Group

Anthony Kicic, TSANZ Research sub-

committee

#### **Local**

Luke Garratt, TSANZ Associates committee

Anthony Kicic, TSANZ Executive committee

Kelly Martinovich, TSANZ Associates committee (President)

Kelly Martinovich, Telethon Kids Institute Student Leader

### **INVITED PRESENTATIONS**

Stephen Stick, Invited Presentation, North American CF Conference, 8-10 October

Stephen Stick, Invited Presentation, European Respiratory Symposium, Amsterdam, 26-30 September

Stephen Stick, Plenary, 11th Australasian CF conference, Sydney, 15-18 August

Stephen Stick, Invited Presentation, 11th Australasian CF conference, Sydney, 15-18 August

Graham Hall, 2015 WA ANZSRS Annual scientific meeting



# EPITHELIAL RESEARCH GROUP

## Overview

Airway epithelium defends the lungs against inhaled irritants and pathogens. Its damage usually triggers a cascade of events that lead to rapid and efficient repair. We discovered that airway epithelial cells (AEC) isolated from asthmatics display defective cell migration properties in response to injury. Our discoveries of intrinsic biochemical and functional differences and dysregulated epithelial repair have identified a possible new asthma endotype and provide an opportunity to pursue new approaches to asthma management, independent to conventional treatments that have typically focus on combatting the symptomatic outcomes of an exacerbation (e.g. inflammation and bronchial constriction).

## Research Groups

### **DEFECTIVE CELL MIGRATION AS A MECHANISM OF DYSREGULATED ASTHMATIC AIRWAY REPAIR**

*Anthony Kicic, Stephen Stick*

Our research group has previously demonstrated in primary tissue samples from a paediatric population that dysregulated wound repair is a feature of asthmatic epithelium (Stevens et al. 2008, Kicic et al. 2010). Aberrant wound repair of asthmatic epithelium has been confirmed by others in adult primary tissue

and minimally transformed asthmatic cell lines (S Randell, personal communication). We believe that a failure of the epithelium to repair appropriately in asthma is an important component of an asthma endotype that renders the epithelium susceptible to injurious environmental triggers such as viruses and that can contribute to a chronic inflammatory response and remodelling in the airways.

Our group has made the exciting discovery that epithelial cells from young children with asthma display inherent biochemical and functional differences compared to similar cells from non-asthmatic children (Kicic et al. 2006, Stevens et al. 2008, Kicic et al. 2010). Further analysis by our group has revealed that asthmatic epithelial cells exhibit dysregulated responses to injury (Stevens et al. 2008). Furthermore, our recent discoveries have provided the basis for our overarching hypothesis that dysregulated repair is an innate feature of asthmatic epithelial cells. Our most recent findings demonstrate that the dysregulated repair in asthmatic epithelium is caused by a defective migratory capacity. Findings generated from this study are contributing to a fundamental shift in our approach to asthma, specifically, from one that focuses on the responses to injury to one addressing prevention of injury, restitution of normal repair and maintenance of epithelial integrity.

This project uses primary airway epithelial cells (pAEC), obtained by gently brushing the main airway of children (unselected population of mild asthmatics and non-asthmatics) undergoing non-respiratory elective surgery (e.g. tonsillectomy) at Princess Margaret Hospital and St.

John of God Subiaco. Cells are grown in the laboratory and then wounding experiments are conducted to assess their migration patterns and reparative capacity in vitro. In order to measure responses to wounding; we are using established methods as well as RNA-Sequencing analysis coupled with systems biology that assesses global gene expression. Systems biology allows us to map all the genes in the pathways involved in cell migration response and identify which particular genes in asthmatic pAEC are associated with the observed dysfunctional repair. We will then screen for known drugs or natural products that are able to target these genes with the hope of identifying new therapeutic targets to aid in the effective restitution of the asthmatic airway epithelial layer and prevent subsequent lung inflammation and remodeling.

### **Plain Language summary**

The findings from this study show that in children with asthma this protective barrier is different from children without asthma. It is leakier making it easier for viruses and toxins to enter the cells. Viral infections makes this leakiness worse. We also observed that the cells did not fully repair after injury, due to a lack of specific growth compound and the abnormal production of anchoring protein that helps the cell move. We also compared how these repair responses changed with age and severity of asthma, by comparing cells sampled from children and young adults. We have shown that this failure to repair happened very early in asthma and was sustained in adulthood.

### **Funders of the project**

NHMRC

### **External collaborators**

Clinical Professor Francis Lannigan; Head of Paediatrics, SJOG

Prof Darryl Knight, University of Newcastle, NSW

Associate Prof Paul Rigby, CMCA, WA

### **THE ASTHMATIC EPITHELIUM FROM CHILDHOOD TO ADULTHOOD**

*Stephen Stick, Anthony Kicic,*

*Anthony Bosco*

Our research team and others have demonstrated airway epithelium as an important contributor to disease pathogenesis. We have observed intrinsic biochemical and functional differences between lower airway epithelial cells from children with asthma and healthy controls (Kicic et al, 2006; Kicic et al, 2010), and that asthmatic epithelium exhibits dysregulated repair following injury (Stevens et al, 2008). Using global gene expression analyses we have also observed pathways that are down-regulated in asthma, independent of atopy. Furthermore, we have confirmed intrinsic epithelial properties including the basal cell phenotype in asthma that are conserved from children to adults (Kicic et al, 2006; Hackett et al, 2009).

Recently a study by Lopez-Guisa et al (2012) demonstrated that nasal epithelium from children with asthma have similar key characteristics to lower airway epithelium including cytokine and growth factor productions. Together all these data and our ability to obtain lower airway sampling from children and adults as well as the more readily accessible sampling from



the upper airway make it attractive to use this resource to develop a simple tool to identify individuals with intrinsic airway epithelial characteristics that predate expression of an asthma phenotype based on nasal epithelial gene expression.

We hypothesise that there is an epithelial gene expression signature in childhood asthma and that this signature is conserved in adults with asthma and in the nasal epithelium. To test this hypothesis we aim to (i) measure global gene expression in AEC from adults with asthma and healthy controls, (ii) measure gene expression in nasal epithelium from adults and children with asthma and healthy controls, and (iii) determine using system biology tools the pathways that characterise a specific asthma signature in the lower airway and nasal epithelium from children and adults with asthma.

### **Plain Language summary**

The cells lining the airways in the lungs are called epithelial cells. Once thought to be a simple barrier to the external environment, epithelial cells are involved in many repair and inflammatory processes that occur in childhood airway diseases. However, most research has been done in epithelial cells obtained from adults and may not reflect what happens in the airways of children. Our aim is to set up a program to obtain epithelial cells from children. This will enable us to understand how these cells behave in early childhood respiratory diseases such as asthma and cystic fibrosis, how they respond to different types of infection, and to identify new therapies to prevent or reduce childhood respiratory disease.

### **Funders of the project**

Asthma Australia

### **External collaborators**

Prof. Darryl Knight, University of Newcastle, NSW Australia

Assoc. Prof. Peter Wark, Hunter Medical Research Institute, NSW Australia

## **CULTURES OF HRV-C FOR INVESTIGATIONS OF PATHOGENESIS IN CHILDREN**

*Anthony Kicic, Ingrid Laing, Belinda Hales*

Human rhinovirus (HRV) has been identified as the most common respiratory virus in many respiratory studies, including neonatal intensive care (Zinna 2014 BMJ), acute asthma (Bizzintino 2010 ERJ), recurrent acute otitis media (Wiertsema 2011 J Med Virol), cystic fibrosis (Flight 2014 Thorax), lung transplantation (Noell 2013 Transplant Proceed) and COPD exacerbations (Wu 2014 Molec Biol Reports). HRV is also an important cause of bronchiolitis, croup and acute lower respiratory infection (Miller 2013 P Infect Dis J). Traditionally, HRVs have been grouped into A and B species according to phylogenetic classification. The advent of molecular diagnostic techniques for detecting HRV genome has led to the discovery of novel rhinoviruses designated HRV-C (aka HRV-A2 or HRV-X). Overall, there are more than 150 strains of HRV, of which at least 60 belong to the HRV-C species. Due to the inability to identify HRV-C receptor, HRV-C was not previously detected in clinical specimen via cell culture methods.

Recently, the techniques to successfully

culture HRV-C have been developed by CIs Gern and Bochkov (Department of Pediatrics, School of Medicine and Public Health, UW, Madison, Wisconsin, USA). As part of a recently established collaboration, CI Gern has agreed to provide us with the HRV-C15 plasmid, which will enable us to culture HRV-C15 at the Telethon Kids Institute. Full length of cDNA copy of HRV-C15 genome was cloned into a plasmid, and transformed into E.Coli for bulk production and the recombinant HRV-C15 is isolated via sucrose gradient purification. HRV-C15 can be inoculated onto differentiated primary epithelial cell cultures grown in air liquid surface interface. Recent work by CIs Gern and Bochkow has identified the HRV-C's receptor, Cadherin-related family member 3 (CDHR3) which was highly expressed in differentiated air-liquid interface culture and mediates HRV-C binding as well as replication.

We aim to develop HRV-C culture methods at the Telethon Kids Institute to facilitate HRV-C15 virus of sufficiently high titre that can be used for downstream experiments to enable study of the biological characteristics of HRV-C strains and development of treatment models for childhood respiratory disease.

### **Plain Language summary**

HRV is the most common pathogen detected in many childhood respiratory diseases. Emerging evidence suggested the importance of HRV-C species associated with acute asthma and induction of severe wheeze in children. However, traditional culture method has failed to produce sufficient HRV-C for downstream study. In order to study

the mechanism of HRV-C induced respiratory diseases, we sought to emulate the technique of culturing HRV-C to achieve adequate amount of HRV-C for our experiment and development of treatment models.

### **Funders of the project**

Westfarmers Centre of Vaccines and Infectious Diseases Seed Funding

### **External collaborators**

Dr Yuri Bochkov, University of Wisconsin, Madison, WI, USA.

Prof. James Gern, Uni of Wisconsin, Madison, WI, USA.

## **2015 Success**

### **THESES PASSED**

Dr Kevin Looi PhD, University of Western Australia, "Epithelial barrier integrity and function in paediatric asthma."

### **AWARDS AND PRIZES**

Thomas Iosifidis, Fiona Staniforth PhD Top-Up Scholarship (Asthma Foundation WA)  
Thomas Iosifidis, School of Paediatrics and Child Health Presentation Award (CAHS, Perth WA)

Thomas Iosifidis, Travel Grant (TSANZ)  
Thomas Iosifidis, New Investigator Award (TSANZ – Western Australian Scientific Meeting)

Thomas Iosifidis, Convocation Postgraduate Research Travel Award (UWA)

Kelly Martinovich, Travel grant (TSANZ)  
Liz Starcevich, Travel grant (TSANZ)



## EXTERNAL COMMITTEES

### National

Anthony Kicic, TSANZ National ASM organising committee

Anthony Kicic, Deputy Convenor of the TSANZ Cell Biology & Immunology Special Interest Group

Anthony Kicic, TSANZ Research sub-committee

### Local

Luke Garratt, TSANZ Associates committee

Anthony Kicic, TSANZ Executive committee

Kelly Martinovich, TSANZ Associates committee (President)

Kelly Martinovich, Telethon Kids Institute Student Leader

# PAEDIATRIC RESPIRATORY PHYSIOLOGY

## Overview

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

## Research Areas

### INDOOR AIR POLLUTION

#### **Impact of exposure to air pollutants during the prenatal period on lung function in infancy**

*Graham Hall, Peter Franklin, Zoltan Hantos, Shannon Simpson, Mark Tan and Naomi Hemy with the Peel Child Health Study ([www.peelchildhealthstudy.com.au](http://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

#### **Plain language summary**

The overall aim of this project is to assess the impact of prenatal environmental exposures e.g. indoor air pollution, on lung function in infancy.

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

### PRETERM

#### **BRONCHOPULMONARY DYSPLASIA: IDENTIFYING CARDIORESPIRATORY CONSEQUENCES AND TARGETS FOR**

## **PREVENTION AND INTERVENTION.**

*Jane Pillow, Graham Hall, Andrew Wilson, Zoltan Hantos, Shannon Simpson, Andrew Gill, Naomi Hemy, Nada Townsi*

Bronchopulmonary dysplasia (BPD) remains the most significant chronic lung complication of preterm birth and the most common form of chronic lung disease in infancy. Although BPD is often assessed in relation to the lung alone, the clinical picture is more of a complex multisystem disorder with multiple antecedent contributory factors and extrapulmonary manifestations including abnormal cardiac, pulmonary vascular, chest wall and respiratory muscle development as well as neurodevelopmental impairment. There are few data to indicate the frequency or severity of abnormal cardiac, pulmonary vascular, chest wall and respiratory muscle outcomes after very preterm birth, and their contributions to respiratory problems in very preterm infants are unknown. We will approach BPD as a clinical disorder resulting from abnormal function of the integrated thoracic unit. We will quantify the contributions of cardiovascular, respiratory muscular and pulmonary contributions to the development and persistence of the new BPD clinical phenotype in a large (n=500) regional cohort of very preterm infants by performing comprehensive lung, cardiac and diaphragmatic function testing prior to initial hospital discharge and again at 12 months. Risk indices for perinatal adverse exposures and abnormal function of each system will be used to develop a predictive model for moderately severe BPD. The identification of a significant incidence of cardiovascular, chest wall or respiratory muscle contributions

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

### **Plain language summary**

Bronchopulmonary dysplasia (BPD) is a significant chronic lung complication of preterm birth and the most common form of chronic lung disease in infancy. This study aims to quantify other contributory health factors to the development and persistence of BPD in children born less than 32 weeks of completed gestation. Information gathered from this study will help in the identification of infants at high risk who may benefit from early intervention and for the development of guidelines for additional screening and monitoring of these children.

### **Funders of this project**

National Health and Medical Research Council of Australia

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

*Graham Hall, Andrew Wilson, Jane Pillow, Andrew Maiorana, Shannon Simpson, Karla Logie, Chris O'Dea, Maureen Verheggen.*

Bronchopulmonary dysplasia (BPD) remains the most significant chronic lung complication of premature birth. Contemporary BPD is dominated by peripheral lung abnormalities including



failed alveolarisation with a decreased number of large and simplified alveoli and abnormal pulmonary vascular development. The few studies to examine the long term respiratory outcomes in new BPD have demonstrated impaired gas transfer reduced cardiopulmonary exercise capacity, gas trapping and increased respiratory morbidity. None of these studies undertook a comprehensive assessment of lung structure, peripheral lung function and respiratory morbidity and examined the influence of neonatal history on the long term outcomes of new BPD. Studies of this nature are essential and will provide an improved understanding of the pathology of new BPD and its long term outcomes and allow a more targeted approach to the treatment and management of infants with BPD through the neonatal period and into childhood. Key outcomes include

- Nearly all preterm children have abnormal lung structure, irrespective of the presence of BPD. More structural abnormalities on chest CT are associated with lower lung function in preterm children at 9-12 years of age.
- Children with a history of BPD more likely to exhibit exercise flow limitation when compared to preterm children without BPD and healthy children.
- All pre-term children have a reduced exercise capacity, and children with BPD have an altered ventilatory pattern to exercise.
- Preterm children (with and without BPD) had reduced lung function. Specifically, significant reductions in spirometry, gas trapping and altered peripheral lung mechanics.
- Respiratory Symptoms are increased in preterm children irrespective of a diagnosis of BPD. Children with

respiratory symptoms in the last year had worse lung function outcomes than children without recent symptoms.

### **Plain language summary**

The lungs of children who were born preterm grow differently than those children born at term. They also experience more breathing problems and respond differently to exercise. Therefore, it is important to monitor the long-term lung health outcome of these children. This study assessed school-aged children who were born preterm, to see how well their lungs are functioning.

Funders of this project: This project is funded by the National Health and Medical Research Council of Australia, Raine Foundation and Princess Margaret Hospital Foundation

### **LONGITUDINAL LUNG FUNCTION IN VERY PRETERM CHILDREN**

*Graham Hall, Andrew Wilson, Shannon Simpson, Karla Logie, Chris O'Dea, Maureen Verheggen.*

Rates of preterm birth have increased in almost all countries over the past 20 years, including Australia, and now account for more than 11 % of births globally. Bronchopulmonary dysplasia (BPD) remains one of the most significant complications of preterm birth. Significant improvements in neonatal critical care occurred during the 1990s; most notably the implementation and standardisation of postnatal surfactant therapy, increased use of antenatal maternal corticosteroids, and the development

of less aggressive ventilation strategies. These drastic changes have given rise to a contemporary pathophysiology, termed new BPD. The natural history and outcomes beyond infancy are largely unknown, although as the oldest survivors of new BPD are reaching their 20s, it is becoming clear that survivors are at increased risk of significant respiratory disease later in life. This longitudinal study of lung function in very preterm children aims to track lung function from the preschool years to mid-childhood utilising previously collected lung structure and function data.

Preliminary analysis suggests that preterm children with BPD are experiencing a decline in lung function between 5 and 10 years of age. Increased decline is associated with tobacco smoke exposure and particular structural changes to the lung that may indicate ongoing disease process.

### **Plain language summary**

Many children born preterm experience respiratory problems as a result of their preterm birth. Improved critical intervention immediately after birth have resulted in better lung health outcomes for these children and it is important to assess lung function outcomes of these children in later life. This study aims to evaluate the long-term lung health outcomes of children born preterm, specifically from preschool years to mid-childhood. Early results of this study suggest that children born preterm who experience lung disease as babies have lung function that gets worse through childhood. Further work is needed to understand the implications for these declining lung

function in later life

Funders of this project: This project is funded by the National Health and Medical Research Council of Australia, Raine Foundation and Princess Margaret Hospital Foundation

## **THE CONTRIBUTION OF DYSPHONIA TO RESPIRATORY SYMPTOMS IN VERY PRETERM CHILDREN**

*Shannon Simpson, Zoe Champion, Victoria Reynolds, Noel French, Graham Hall,*

Children born very preterm (<32 weeks) often experience dysphonia, likely due to laryngeal damage sustained during the neonatal period. We aimed to determine if laryngeal dysfunction is linked to the respiratory symptoms and reduced lung function often reported in very preterm children. Preliminary findings suggest that many very preterm children have dysphonia, which is associated with increased respiratory symptoms. Therefore, the upper airway may be involved in the respiratory symptoms in the very preterm child, particularly symptoms on exercise, and should be considered when these children present to clinicians.

### **Plain language summary**

Children born less than 32 weeks gestation (very preterm children) often experience voice impairment that is likely due to damage to the voice box sustained during the neonatal period. We aimed to determine if voice box dysfunction is linked to the respiratory symptoms and reduced lung function often reported in very preterm children. Preliminary findings suggest that many very preterm children have voice impairment which



is associated with increased respiratory symptoms. Therefore, the upper airway may be involved in the respiratory symptoms in the very preterm child, particularly symptoms on exercise, and should be considered when these children present to clinicians

## CYSTIC FIBROSIS

### **EVOLUTION OF AIRWAY FUNCTION AND INFLAMMATION IN EARLY CF LUNG DISEASE**

*This project is currently active*

*Graham Hall, Stephen Stick, Sarath Ranganathan (VIC), Rachel Foong, Alana Harper, Tim Rosenow and Kathryn Ramsey, as part of the AREST CF collaboration ([www.arestcf.org](http://www.arestcf.org))*

Cystic Fibrosis (CF) is a condition of chronic inflammation and infection resulting in destruction of lung architecture eventually leading to death. We and others have shown that infants and young children with CF show evidence of early inflammation and infection and reduced lung function. This highlights this period of life as a critical period for the development of new treatments to prevent progression or even reverse lung disease. However, the development of lung disease in early infancy is poorly understood and ongoing relationships between peripheral lung function and measurements of pulmonary inflammation or infection remain unknown. The goals of this study are to evaluate objective measurements of respiratory function and their combined ability to detect and

monitor the presence of lung disease early in the life of infants and young children with cystic fibrosis.

### **Plain language summary**

Cystic Fibrosis (CF) is a chronic disease that affects lung structure and function and can eventually lead 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. However, we do not fully understand the development of CF-related lung disease in infancy. This study aims to evaluate 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

### **Funders of the project**

The National Health and Medical Research Council of Australia (NHMRC) and the USA Cystic Fibrosis Foundation

### **External collaborators**

Riley Hospital for Children, Indianapolis, USA and Royal Children's Hospital, Melbourne

### **LONG TERM OUTCOMES OF INFANT LUNG FUNCTION IN CYSTIC FIBROSIS**

*This project is currently active.*

*Graham Hall, Stephen Stick, Sarath Ranganathan (VIC), Rachel Foong, Alana Harper, Tim Rosenow and Kathryn Ramsey as part of the AREST CF collaboration ([www.arestcf.org](http://www.arestcf.org))*

As part of the AREST CF collaboration

we have developed a unique and internationally recognised early surveillance program for the detection of lung disease in CF that includes complex measurements of lung function obtained in infants newly diagnosed with CF following newborn screening (NBS). We are the only group in the world to have comprehensively studied population-based cohorts of children diagnosed by NBS using such tests. In this project we aim to evaluate the longer term lung structural and functional outcomes associated with lung function measurements made during infancy. These data will inform the clinical importance of measuring lung function during infancy in CF and also the role of the tests in proposed early intervention studies in CF. Such data are eagerly anticipated by the global CF community. Plain language summary: Our team is part of the Australian Respiratory Early Surveillance Team and has developed an internationally recognized early surveillance program for the detection of lung disease in infants newly diagnosed with CF. In this project we aim to evaluate the longer term outcomes of lung function and structure, associated with lung function measurements made during infancy. These data are very important to the global CF community. The data will inform the clinical importance of measuring lung function during infancy in CF and the role of these lung function tests in proposed early intervention studies. Funders of the project: The National Health and Medical Research Council of Australia (NHMRC)

#### **External collaborators**

Royal Children's Hospital, Melbourne

## **VIRAL PATHOGENESIS OF EARLY CYSTIC FIBROSIS LUNG DISEASE**

*This project is currently active.*

*Graham Hall, Stephen Stick, Sarath Ranganathan (VIC), Rachel Foong, Stephanie Davis, Tom Ferkol, Alana Harper and Kathryn Ramsey as part of the AREST CF collaboration ([www.arestcf.org](http://www.arestcf.org))*

Infectious insults can profoundly change the trajectory of CF lung disease. Virus infections can lead to significant morbidity, but their effect on the early origins and progression of CF pulmonary disease is ill-defined. In this project, powerful nucleic acid-based detection approaches will be used to prospectively characterize infections in infants, and determine the impact of viruses on bacterial colonization, airway inflammation, physiological measures, and structural changes, thus elucidating early pathogenic events in CF lung disease. Plain language summary: Infections can profoundly impact and change the path of CF lung disease. Viral infections can lead to significant morbidity but their effect on the early origins and progression of CF lung disease is not well known. In this project, we will describe infections in infants with CF and determine the impact of viruses on lung health outcomes. Funders of the project: The National Institute of Health (USA) and National Health and Medical Research Council of Australia.

#### **External collaborators**

Riley Hospital for Children, Indianapolis, USA and Royal Children's Hospital, Melbourne



## **IDENTIFYING THE CLINICAL UTILITY OF MBW IN EARLY CF LUNG DISEASE**

*This project is currently active.*

*Graham Hall, Stephen Stick, Sarath Ranganathan (VIC), Rachel Foong, Alana Harper, Tim Rosenow as part of the AREST CF collaboration ([www.arestcf.org](http://www.arestcf.org))*

The number of children with CF that develop lung damage increases dramatically in the preschool period. As a result, this is a critical time in terms of intervening to prevent the development of permanent lung disease. The lung clearance index (LCI) is a marker of how well air mixes within lungs and can be easily measured in young children. There are a number of studies showing that LCI offers significant advantages in monitoring lung damage in school aged children with CF. However, there no studies of this kind in preschool children. Our understanding of whether or not LCI can be used to track pulmonary inflammation and/or infection in young children is also limited. It is critical that the ability of LCI to detect lung damage, infection and inflammation in preschool children with CF is examined. If LCI is sensitive to lung damage in this age group it may suggest that it could be used as a clinical monitoring tool and in new clinical trials in early CF lung disease. Plain language summary: The number of children with CF that develop lung damage increases dramatically in the preschool period. As a result, this is a critical time for interventions to prevent the development of permanent lung disease. The lung clearance index (LCI) is an outcome of lung function tests that tells us how well air mixes within the lungs and can be easily measured in young children. There are a number of studies showing

that LCI offers significant advantages in monitoring lung damage in school aged children with CF. However, there are no studies of this kind in preschool children. Our understanding of whether or not LCI can be used to track lung inflammation and/or infection in young children is also limited. Therefore, this study aims to use assess the clinical utility of LCI to detect lung damage, infection and inflammation in preschool children with CF.

### **Funders of the project**

USA Cystic Fibrosis Foundation

### **External collaborators**

Riley Hospital for Children, Indianapolis, USA and Royal Children's Hospital, Melbourne

## **ANAESTHETICS**

### **OBESITY: THE MECHANICS OF LUNG FUNCTION IMPAIRMENT AND RISKS RELATED TO PRAE**

*This project is currently active*

*Graham Hall, Britta Regli-von Ungern-Sternberg, Anoop Ramgolam, Zoltan Hantos, Lliana Slevin, Lara Oversby and Debbie Cooper*

In paediatric anaesthesia, obesity is a significant problem with obese children not only having anaesthesia-relevant co-existing diseases like asthma or hypertension, but also having a higher incidence of anaesthesia related complications. Perioperative Respiratory Adverse Events (PRAE) are amongst the

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

Plain language summary: Childhood obesity is a significant problem with serious health impacts including a higher occurrence of anaesthesia-related complications. This project is looking at how obesity impacts lung function and the risk of respiratory complications during surgical procedures. Specifically, we are assessing lung function changes as well as the occurrence of respiratory adverse effects from surgical procedures, in

healthy and overweight/obese children. We expect that adverse effects will be higher in the obese/overweight children and knowledge gathered from our study will help to improve the management of this high risk category of patients.

### **Funders of the project**

NHMRC, ANZCA

### **External collaborators**

PMH, Uni of Szeged, hungary

## **NORMAL VALUES OF LUNG RESISTANCE; AN EVIDENCE-BASED GUIDELINE FOR PAEDIATRIC ANAESTHESIA**

*This project is currently active*

*Graham Hall, Britta Regli-von Ungern-Sternberg, Anoop Ramgolam, Lliana Slevin, Lara Oversby and Zoltan Hantos*

Paediatric patients undergoing elective or emergency surgery, or who have been admitted to the Neonatal/Paediatric Intensive Care Unit (NICU/PICU), often require mechanical ventilation. During the perioperative period, these patients are at risk of several types of lung injury, including atelectasis (collapse of lung tissue), pneumonia (disease marked by inflammation of the lungs), pneumothorax (presence of air within the pleural cavity leading to lung collapse), Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS). Anaesthetic management can contribute to these injuries, exacerbate any underlying lung conditions or even improve outcomes, depending on the specific situation. Moreover, several studies have shown



that pulmonary complications, more specifically respiratory failure requiring ventilation, are associated with high morbidity and mortality along with increased health-related costs and greater length of hospital stay. Ventilation mode (volume, pressure or dual), modality (controlled, assisted, support ventilation) and respiratory parameters (e.g. tidal volume and respiratory rate) are the most important factors of mechanical ventilation. An important aspect of ventilation strategies is to optimise respiratory mechanics. A critical part of this process is knowing the normal range of respiratory mechanics during ventilation. This allows clinicians to define ventilation such that the respiratory mechanics can be maintained at a level expected for that particular patient and therefore protect against over- or under ventilation and thus minimise potential harm. While the normal ranges of a variety of respiratory outcomes during mechanical ventilation have been assessed in adults, there are no normal reference ranges of values available for the paediatric population. This precludes the formulation of clear evidence-based ventilation guidelines in children. We are thus aiming at collecting lung function outcomes (respiratory resistance and pulmonary compliance) in healthy children aged between 1 and 15 years old undergoing surgery under general anaesthesia and requiring mechanical ventilation. The data and demographic information collected will then be used to develop robust prediction equations and nomograms that define the values of physiological parameters to be programmed in the mechanical ventilators for optimal lung function in anaesthetised children having surgery.

Plain language summary: The risk of lung injury associated with mechanical ventilation during surgery can be further complicated by anaesthetic management and it is important to know the normal range of respiratory mechanics during ventilation. This project aims to collect lung mechanics data in healthy kids (weight-wise) to build normal reference ranges in this population. This will provide anaesthetists with vital information, allowing them to improve airway management strategies during anesthesia and the use of mechanical ventilators.

#### **Funders of the project**

ANZCA

#### **External collaborators**

PMH, Uni of Szeged

## **ASTHMA**

### **WESTERN AUSTRALIA PREGNANCY (RAINE STUDY) COHORT 22 YEAR FOLLOW-UP**

*This project is not currently active.*

*Graham Hall, Elisha White*

The Western Australian pregnancy cohort (Raine study) is a community based, longitudinally studied birth cohort in Perth, Western Australia. The cohort was followed through pregnancy, birth, and at 11 follow-ups between ages 1 and 22 years, including major respiratory assessments at ages 5, 14 and 22 years. This project has focused upon the respiratory follow-up of the 22 year old

participants, with spirometry, forced oscillometry technique, exhaled nitric oxide and mannitol bronchial challenge testing performed. Active data collection for this project finished late 2014, and 2015 has seen the collation and analysis of this data, with several papers currently in progress.

### **Plain Language summary**

The Western Australian pregnancy cohort (Raine study) is a community cohort of young adults based in Perth, Western Australia. The cohort participants have been followed through pregnancy, birth, and at 11 follow-ups between ages 1 and 22 years, including major respiratory assessments at ages 5, 14 and 22 years. This project has focused upon the respiratory follow-up of the 22 year old participants, with a number of lung tests performed looking at respiratory disease and asthma.

### **Funders of the project**

The 22 year Raine Study follow-up was funded by NHMRC grant 1021858 and project grants 1027449, 1044840. GL Hall was funded by NHMRC Fellowship 1021855.

### **External collaborators**

Zoltan Hantos, Szeged University, Hungary;  
Peter Sly, Queensland Children's Medical Research Institute, Queensland.

## **MEASUREMENT OF BRONCHIAL HYPER-RESPONSIVENESS IN YOUNG CHILDREN: MANNITOL AND EXERCISE CHALLENGE TESTING**

*Prof Graham Hall, Dr Shannon Simpson,*

*Prof Stephen Stick, Dr Afaf Albloushi, Ms Georgia Banton and Mr Mark Kendall*

The addition of objective measures of bronchial hyper-responsiveness (BHR) to current clinical practice may result in improved diagnosis and management of young children with exercise related symptoms. This project aims to determine the feasibility of BHR testing using the forced oscillation technique (FOT) as a primary outcome of the mannitol challenge test in pre-school children with exercise induced symptoms. In addition we aim to determine the agreement of the mannitol challenge test and exercise challenge test in these children. We found that 85% of children aged three to seven years and 100% of children aged 4-7 years were able to complete the mannitol challenge using FOT as the outcome measure. The three children that failed to complete the test were three years of age and did not complete due to difficulty sustaining attention. Further research comparing mannitol and exercise challenge tests and to define appropriate cut off levels to support the diagnosis of exercise induced bronchoconstriction in young children is ongoing.

### **Funders of the project**

Asthma Foundation of WA and, Australian and New Zealand Society of Respiratory Science  
Collaborators, PMH



## 2015 Success

### THESES PASSED

Rhea Urs,  
Bachelor of Science (Hons) University  
of Western Australia, Exhaled breath  
condensate: Measuring inflammation and  
oxidative stress in preterm infants.

### AWARDS AND PRIZES

Rachel Foong,  
Dr Louisa Alessandri Memorial Fund Prize  
for Scientific Publication  
British Association for Lung Research Travel  
Prize

Nada Townsi,  
(With Ingrid Laing, Glenys Chidlow,  
Shannon Simpson, Graham Hall and  
Jane Pillow) \$15,000 Wesfarmers Centre  
of Vaccine and Infectious Diseases seed  
funding  
3 minute thesis award at Wesfarmers  
Centre of Vaccine and Infectious Diseases  
Research Retreat  
\$2500 Doctorate Excellence Award from  
the Saudi Cultural Mission in Australia

Rhea Urs,  
Young Investigator Award Annual Rottneest  
Respiratory Seminar

### EXTERNAL COMMITTEES

#### International

Graham Hall

- Joint American Thoracic Society -  
European Respiratory Society Working  
Party on Infant Lung Function Testing  
(2003-ongoing)
- Editorial Advisory Panel; Expert Review  
of Respiratory Medicine (Oct 2006 –

- ongoing)
- Secretary; Paediatric Respiratory  
Physiology Group, European  
Respiratory Society (Sep 2012 – Sep  
2015)
- Series Editor; Respirology (Jan 2014 –  
Jan 2015)
- Chair; Paediatric Respiratory Physiology  
Group, ERS (Sep 2015 – ongoing)
- Member; ATS/ERS Task Force on  
Standards for the Forced Oscillation  
Technique (Mar 2015 – ongoing)
- ERS College of Experts (Oct 2014 –  
Ongoing)
- Co-Chair; ATS/ERS Task Force – Gas  
Transfer Global Lung Initiative (Jan 2013  
– ongoing)
- Member; USA Cystic Fibrosis  
Foundation: State of Art for  
measurement of LCI (Oct 2013- Oct  
2015)

Shannon Simpson,  
ATS/ERS Taskforce for a Technical  
Statement of the Forced Oscillation  
Technique

#### National

Graham Hall,

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

Elisha White,

Australia & New Zealand Society of  
Respiratory Science, Regional Chair for  
Western Australia.

#### Local

Graham Hall,

Asthma Foundation of Western Australia  
Board member (2010 –ongoing)  
Medical and scientific advisory  
committee, Asthma Foundation of

Western Australia, Chair.

Elisha White,  
Thoracic Society of Australia &  
New Zealand WA branch, ANZSRS  
representative.

Rachel Foong,  
Child and Adolescent Cystic Fibrosis  
Consumer Reference Group of WA

## **INVITED PRESENTATIONS**

Graham Hall

“Reference equations and Indigenous  
Australians: can we do better?” WA  
ANZSRS Annual Scientific meeting

Tim Rosenow,  
Imaging the CF lung in young children:  
developments in CT and MRI, 29th  
Annual North American Cystic Fibrosis  
Conference, Phoenix Arizona, October  
8-10, 2015.

Nada Townsi,  
The Impact of Respiratory Viruses during  
the First Year of Life among Preterm  
Infants, Inspired by Infectious Diseases,  
Telethon Kids Institute, 3 September 2015  
Early Life Viral Infections in Preterm Infants,  
Scientific Innovation Gallery during  
the Saudi National Day celebration in  
Canberra 29 September 2015

# Respiratory Environmental Health

## Overview

Our group conducts research in three inter-related research themes: 1) early life determinants of lung growth, 2) respiratory environmental health and 3) mechanisms of airway dysfunction in asthma. These research themes underpin our overall goal to understand the early life factors that contribute to respiratory disease. The Developmental Origins of Health and Disease (DOHaD) concept describes how maternal and environmental factors interact during development to have long-term consequences on later health and disease. The main focus of DOHaD has been on how early-life nutritional insults manifest as chronic disease in adult life, however there is increasing evidence that in utero and early postnatal life exposure to environmental insults, such as air pollution, tobacco smoke, pathogens and allergens is involved in the early programming of asthma and other respiratory diseases. This evidence is based on epidemiological studies, but is confounded by the complex milieu of inter-related exposures that humans experience during development. Thus, a significant knowledge gap exists with regards to the mechanistic basis for associations between environmental exposures and the development of asthma. By understanding key lung development processes we aim to design interventions that will ultimately prevent the onset of respiratory disease and



improve lung health in the community. Our research relies heavily on mouse models of environmental exposures 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). Our group possesses a range of pre-clinical exposure models which can be readily modified and adapted to allow us to explore the mechanisms underlying respiratory dysfunction. Our approach to research is multi-disciplinary 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.

Highlights for 2015 include Dr Kimberley Wang receiving a NHMRC Peter Doherty - Australian Biomedical Fellowship, the passing of Dr Rachel Foong's PhD thesis and the fostering of collaborations with the National Measurements Institute and the Australia Competition and Consumer Commission with respect to our electronic cigarette research.

## Research Projects

### **VITAMIN D DEFICIENCY AND LUNG GROWTH**

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

There has been a dramatic increase in recent decades in the prevalence of vitamin D deficiency in Australia and worldwide. Vitamin D deficiency is associated with a number of diseases including, 1) the bone disorder rickets (due to the importance of vitamin D in calcium homeostasis), 2) autoimmune disorders and 3) cardiovascular disease. Recent prominent publications have also implicated vitamin D in the pathogenesis of obstructive lung diseases such as asthma and COPD. Additionally, epidemiological studies have shown a strong association between serum vitamin D levels and lung function suggesting an important link between vitamin D status and lung health. However, there had been no study showing a direct link between vitamin D deficiency and lung growth/structure/function. In 2010 we published a study in the leading respiratory journal (*American Journal of Respiratory and Critical Care Medicine*) on the lung structure and function of mice raised on vitamin D deficient and replete diets. We showed for the first time that vitamin D deficiency alters lung structure resulting in significant deficits in lung function. This study received considerable public interest resulting in an international media release by the American Thoracic Society and interviews for ABC Radio National. These studies are ongoing and we now plan to identify the mechanism of vitamin D deficiency induced alterations

in lung growth. This work is being pursued by Rachel Foong who began a PhD in 2011 examining the role of vitamin D deficiency airway remodelling in chronic lung disease. Rachel has published work showing that vitamin D deficiency causes airway hyperresponsiveness and increases airway smooth muscle mass in female mice. These are central features of many chronic lung diseases and may explain the link between vitamin D deficiency and chronic lung diseases. She has also published results showing that in utero vitamin D deficiency is sufficient to alter lung structure and function and differentially regulate genes important in lung development. Finally, she has also demonstrated in a mouse model of chronic allergic asthma that vitamin D can modulate asthma-related genes and contribute to asthma symptoms. This work is included in Rachel's PhD thesis, which has been submitted and passed.

### **Funders of the project**

NHMRC Project Grant (2013-2015).

## **ENVIRONMENTAL HEALTH OF REMOTE ABORIGINAL COMMUNITIES**

*Holly Clifford, Graeme Zosky (University of Tasmania), Roz Walker, Glenn Pearson, Janessa Pickering (UWA Paediatrics and Child Health), Lea-Ann Kirkham, Ruth Thornton*

There is a significant gap in health between Aboriginal and non-Aboriginal Australians. This is particularly true for respiratory health and in individuals living in remote communities. In 2011 we commenced a research program designed to assess the role of the

environment, with a focus on water quality and dust exposure, in contributing to poor lung health in these communities. We have travelled to several communities of the Martu people in the eastern Pilbara as well as Bidyadanga in the Kimberley region. We have collected water and dust samples for analysis of heavy metal contamination and we have now begun expanding this program to conduct real-time monitoring of the inhalable dust with a view to estimating exposure levels in the communities. We have also begun investigating the role of iron in dust and how this contributes to the severity of the response to respiratory infection. In 2015 we examined the specific effects of community-sampled dust on the cells of the human airway, with a view to investigate how dust exposure contributes to more common and severe bacterial infections in Aboriginal children. We found that exposure to dust affected the course of one of the most common bacterial infections seen in Aboriginal children – *Haemophilus influenzae* – by increasing bacterial attachment and invasion of airway epithelial cells and altering the inflammatory immune response during infection. We have also published two papers in 2015 – a paper detailing the effects of dust exposure on influenza infection in a mouse model in *Science of the Total Environment*, and a review in the *Australian Indigenous Health Bulletin* discussing environmental health challenges in remote Aboriginal Australian communities.

### **Funding**

BrightSpark Foundation; The Raine Foundation



## **AIRWAY SMOOTH MUSCLE AS AN INDEPENDENT PREDICTOR OF ASTHMA**

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

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

This NHMRC funded project began in 2012. The first stage of the project was to have the required mouse genotypes re-derived and sent to our Perth laboratory. The mouse models were characterised by our collaborator Professor Timothy LeCras in his Ohio (USA) based laboratory. The required mouse genotypes have now been successfully re-derived and the mouse colony established at TICHR. In 2012-2013 we exposed mice to doxycycline, which upregulates TGF $\alpha$

expression in the airways, producing ASM growth in mice that are Egr-1 deficient. We have established that in Egr-1 deficient mice exposed to doxycycline for 10 days demonstrating greater ASM mass, increased airway narrowing and lung resistance to methacholine challenge. We also found that ASM mass also correlates to baseline resistance.

In 2015, we have combined this non-inflammatory transgenic mouse model of ASM remodelling with an established allergic mouse model. We found that allergic inflammation and increased thickness of the ASM layer have independent and additive effects on airway responsiveness (narrowing and closure). This may be analogous, in patients with asthma of varying severity, to the varying levels of response of lung function to corticosteroid therapy.

### **Funders of the project**

NHMRC Project Grant (2012-2015)

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

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

Epidemiological studies have demonstrated that growth restriction in the womb (termed intrauterine growth restriction; IUGR) is associated with respiratory disease (including asthma) in childhood and persistent chronic lung disease in adulthood. However, it is still not known why growth restriction in early life can lead to respiratory disease. Our

hypothesis is that IUGR is associated with increased airway smooth muscle at birth and this represents an independent risk factor for the development of asthma.

In this study, we collaborated with Professor Sandra Davidge and Dr Jude Morton (University of Alberta) and together we have established a BALB/c mouse model of maternal hypoxia-induced IUGR. We found that maternal hypoxia induced IUGR offspring were smaller at birth but exhibited 'catch up' growth, as is often reported in clinical cohorts. Retardation of fetal growth altered airway and lung mechanics in adulthood and may predispose offspring to respiratory conditions such as airway hyperresponsiveness.

#### **Funders of the project**

New Investigator Research Award, WA Asthma Foundation (2015-2016)

### **TRANSFORMING GROWTH FACTOR ALPHA EXPRESSION IN A TRANSGENIC MOUSE MODEL IMPAIRS LUNG AND DIAPHRAGM MECHANICS**

*Kimberley Wang, Christine Astell, Philip Wijesinghe, Alexander Larcombe, Gavin Pinniger, Brendan Kennedy, Graeme Zosky, David Sampson, Alan James, Timothy Le Cras, Peter Noble*

Transforming growth factor alpha (TGFA) is increased in the lung tissue of patients with chronic respiratory disease. Animal models show that deficiency in the early growth response (Egr-1) gene accelerates the disease process. In this study, we collaborated with A/Prof Gavin Pinniger and Dr Brendan Kennedy to examine the effects of TGFA on lung and diaphragm

mechanics. We found that increased expression of TGFA impairs respiratory function characterised by increased lung loading and compromised diaphragm mechanics. Findings support a role of TGFA in chronic lung disease.

#### **Funders of the project**

NHMRC Project Grant (2012-2015)

### **EFFECT OF PRENATAL HYPOXIA-INDUCED GROWTH RESTRICTION ON LUNG STRUCTURE IN ADULT RATS**

*Kimberley Wang, Jude Morton, Sandra Davidge, Alexander Larcombe, Alan James, Peter Noble*

Intrauterine growth restriction (IUGR) is associated with asthma in childhood and adulthood. Abnormalities in airway and lung structure accompanying IUGR may predispose children to the development of asthma. I was awarded a Barbara May Scholarship from the institute to formalize an international collaboration with Prof. Sandra Davidge's laboratory at the University of Alberta, Edmonton, Canada to determine the structural consequences in the lungs of adult offspring born from IUGR pregnancies using a maternal hypoxia-induced IUGR rat model. I was able to undertake an observership of established methods for inducing IUGR by maternal hypoxia and sampling of fetal mouse organs. We were also able to establish methods of tissue storage in order to facilitate a tissue exchange program. From this study, we found that in utero growth restriction resulted in a more heterogeneous distribution of airway lumen calibre with potential implications for ventilation. The increased number of



lung macrophages in adulthood indicates a phenotypic change that has a fetal origin and warrants further investigation.

### **Funders of the project**

Barbara May Scholarship, Telethon Kids Institute (2014-2015)

## **THE HEALTH EFFECTS OF ELECTRONIC CIGARETTES**

*Alexander Larcombe, Peter Franklin (Department of Health, Western Australia), Ben Mullins (Curtin), Bill Musk (Sir Charles Gairdner Hospital), Rachel Huxley (Curtin University)*

Electronic cigarettes ("e-cigarettes") heat and atomize a liquid solution ("e-juice") producing an aerosol which is inhaled. They are a new technology and their use is widespread and increasing rapidly especially in adolescents. In many countries, the number of people regularly using e-cigarettes is doubling annually, and there are an estimated 200,000 current Australian users. Despite this, the potential for e-cigarette use to impact health is virtually unknown. This knowledge gap has been recognized as a research priority by international medical associations and it is this knowledge gap that our proposed research aims to help fill. The limited data on e-cigarettes that exist suggest that: (i) they are likely to have a negative impact on health, especially in situations of pre-existing respiratory disease, (ii) pregnant women are more likely to use them compared with conventional cigarettes and (iii) the type of e-cigarette e-juice can significantly influence health outcomes. In Australia, the laws surrounding the importation, sale

and use of e-cigarettes are vague, and hard-data on their potential to impact health are urgently required to guide policy makers.

In 2014 we received Department of Health, Western Australia funding to perform the first study investigating the long term respiratory health effects of electronic cigarette vapour exposure. Mice were exposed to one of four different e-cigarette vapours, cigarette smoke or clean air for 8 weeks and functional, inflammatory and lung structure outcomes were compared. Mice exposed to cigarette smoke showed increased inflammation and responsiveness to methacholine, compared to air controls. Mice exposed to e-cigarette vapour did not have increased inflammation, but did display decrements in parenchymal lung function at both functional residual capacity and high transrespiratory pressures. Mice exposed to vegetable glycerin based e-cigarette vapours were also hyper-responsive to methacholine (similar to tobacco smoke exposed mice) regardless of the presence or absence of nicotine. We showed that chronic exposure to e-cigarette vapour is not harmless to the lungs, and results in significant impairments in lung function. We also showed that the e-cigarette excipient used is important, with the most severe impairments seen in mice exposed to vegetable glycerin based vapour. These data were published in a Health Department of Western Australia report in 2015.

We also recently received an Asthma Foundation of Western Australia Project Grant in 2015 to study the potential for e-cigarettes to exacerbate asthma. This

study is nearing completion and our results to date show that acute e-cigarette vapour exposure can exacerbate early phase asthmatic responses in a mouse model. We found that mice exposed to 1 minute of VG base e-cigarette vapour experienced almost immediate bronchoconstriction and that this response was more severe in mice previously made “asthmatic” via our standard ova sensitization and challenge protocol. We have also performed a number of studies investigating the effects of e-cigarette vapour exposure on the late phase asthmatic response. Data analyses from these experiments are underway.

### **Funders of the project**

Asthma Foundation of Western Australia, Department of Health, Western Australia, Australian Competition and Consumer Commission, National Measurements Institute.

## **UNDERSTANDING HOW VIRAL INFECTION IN EARLY LIFE IMPACTS ON LUNG FUNCTION IN ADULTHOOD.**

*Alexander Larcombe, Anthony Bosco*

Environmental exposures in early life can have dramatic consequences for development and physiological function in adulthood. To study this phenomenon, we have developed a mouse model of respiratory viral infection, in which infected neonates have impaired lung function as adults, long after the infection has cleared. Using this model, we seek to identify the molecular changes (set of genes) that are altered by viral infection, which in turn lead to impaired lung development and function. Then, we seek

to identify Food And Drug Administration-approved drugs that can reverse these molecular changes, to determine if we can restore normal lung development and function. Our hypothesis proposes that the molecular changes which are brought on by viral infection causing developmental and physiological changes are reversible with FDA-approved drugs. In 2015 we received Telethon Kids Institute Blue Sky funding to explore this hypothesis. Initially, we infected neonatal mice with Influenza A and then at specific time-points after infection we harvested lung tissue for gene expression profiling studies (RNA-Seq). RNA-Seq is a powerful tool for transcriptomics, which employs next generation sequencing technologies to measure gene expression levels at single base resolution. In 2015 we collected and purified our samples and sent them to the Australian Genome Research Facility for RNA-Seq analysis on the Illumina platform (HiSeq 50-bp single end reads, 20 – 30 million reads per sample). The data were recently returned to us and are currently being analysed.

### **Funders of the project**

Telethon Kids Institute Blue Sky Grant.

## **VIRAL INDUCED AIRWAY HYPERRESPONSIVENESS**

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

These studies span a number of different projects and involve infecting mice with respiratory viruses (primarily rhinovirus and influenza) at different ages and under



different conditions (e.g. in the presence of other respiratory insults). In recent years we have made significant progress in our studies on how rhinovirus infection alters the development of pathogenesis of allergic airways disease. This was prompted by recent studies which show that rhinovirus (HRV) infections account for ~90% of asthma exacerbations. We infected mice with HRV in early life and studied the effects of this infection on lung function, and responsiveness to methacholine in adulthood. We also superimposed mouse models of allergic airways disease (house dust mite) onto HRV infection to assess whether early life HRV infection potentiates asthma development. The greatest effects were seen in HDM exposed mice which had altered lung mechanics, AHR and increased inflammation. There were limited effects of HRV alone, however in adult mice, additive effects of HDM and HRV contributed to neutrophilic inflammation and there was an interaction between HDM and HRV in some parameters of lung function. These data, formed the basis of a 1st class honours project and were published in PLoS One in 2014. In neonatal mice, more macrophages were seen in mice exposed to both respiratory insults compared with either insult alone. Exacerbation of some allergic airways disease symptoms was seen due to the combination of HDM and HRV. Our manuscript on this topic was published early in 2016.

### **Funder**

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

## **2015 Success**

### **THESES PASSED**

Rachel Foong, PhD, University of Western Australia. Vitamin D deficiency is associated with airway remodelling and altered lung structure and function.

### **AWARDS AND PRIZES**

Alexander Larcombe, Telethon Kids Institute Early Environment Working Group Project Funding - \$9,998

Alexander Larcombe, Telethon Kids Institute Blue Sky Grant - \$30,000

Alexander Larcombe, Asthma Foundation of Western Australia Project Grant - \$23,700

Alexander Larcombe, Asthma Foundation of Western Australia Project Grant - \$24,800

Kimberley Wang, NHMRC Peter Doherty - Australian Biomedical Fellowship (2015-2018) - \$309,436.

Kimberley Wang, The University of Western Australia Vice Chancellor's Research Award for Early Career Investigators - \$1,500.

Kimberley Wang, Australian Society for Medical Research (ASMR) Research International Award - \$5,000.

Kimberley Wang, The Ian Potter Foundation Travel Grant - \$2,500.

Kimberley Wang, Institute for Respiratory Health Junior Travel Award - \$1,750.

Kimberley Wang, The TSANZ Janet Elder International Travel Award - \$2,500.

Kimberley Wang, The TSANZ Travel Grant - \$520.

Kimberley Wang, Asthma Foundation Western Australia New Investigator Grant (2015-2016) - \$24,300.

Rachel Foong - Dr Louise Alessandri

Memorial Fund Prize for Scientific  
Publication - \$1,000.  
Rachel Foong - British Association for Lung  
Research Travel Prize - £100.

## **EXTERNAL COMMITTEES**

### **National**

Alexander Larcombe - NHMRC Early  
Career Fellowships Panel  
Alexander Larcombe – Rebecca L Cooper  
Medical Research Foundation Scientific  
Review Committee  
Kimberley Wang, NHMRC Postgraduate  
Scholarships Panel

### **Local**

Alexander Larcombe - University  
of Western Australia Animal Ethics  
Committee.  
Kimberley Wang, Australian Society for  
Medical Research (ASMR) WA branch  
committee member, 2013-present.

## **INVITED PRESENTATIONS**

Kimberley Wang, The early life origin  
of airway smooth muscle thickening in  
asthma pathogenesis, Sandra Davidge's  
laboratory, University of Alberta,  
Edmonton, Canada, June 2015



# WESFARMERS CENTRE FOR VACCINES AND INFECTIOUS DISEASES

## Aboriginal Ear Health

### Overview

**Otitis Media (OM)** refers to disease of the middle ear. It is a common illness in young children, peaking in infancy and again in pre-school years. Otitis media is best described as a spectrum of disease, ranging from Acute OM (which may cause pain but in Aboriginal children is commonly asymptomatic) to Acute OM with perforation to Otitis Media with Effusion (OME, also known as 'glue ear') in which there is fluid present in the middle ear and fluctuating hearing loss, through to chronic suppurative otitis media (CSOM) when there is recurrent ear discharge through a perforated tympanic membrane associated with hearing loss. Otitis media can seriously affect speech, ability to learn language, childhood development, school performance and subsequent social and economic well-being.

In the general population, episodes of OM tend to resolve though a substantial number of children do require surgery. However, in Aboriginal children the disease starts within weeks of birth and chronic disease with hearing loss is common. The prevalence of CSOM is very

high, up to 40% in some remote Aboriginal communities, well above the World Health Organization (WHO) threshold of 4% constituting "a public health emergency" requiring immediate attention.

Coordinated by Peter Richmond and Deborah Lehmann, the Wesfarmers Centre of Vaccines and Infectious Diseases Aboriginal Ear Health project hosted a Stakeholder meeting in March 2015. Acknowledging the enormous efforts in ear health programs across WA, the roundtable brought together more than 50 local and interstate health care professionals, researchers and people living and working in communities where children are most affected by ear infections. Chaired by Professor John Finlay-Jones and facilitated by Distinguished Professor Charles Watson, the stakeholder meeting attempted to unravel the problems of preventing, treating and managing otitis media and consequential hearing loss in Aboriginal people around WA. Representatives of Aboriginal communities, Aboriginal Health Workers, other health professionals, health administrators and researchers, came together in the one place in the hope that by working together we could uncover better ways of preventing and treating otitis media and the effects it may have across a lifetime. Outcomes of the meeting was general agreement

on a number of ways to address gaps in ear health programs, the way we deliver these programs and deficiencies in our understanding of otitis media. The areas identified for priority attention were:

1. Improving monitoring and evaluation of ear health programs
2. Identifying gaps in knowledge
3. Addressing social marketing from a local community perspective

The Ear Health project is being done in the context of a national collaboration around ear health research and advocacy that will be coordinated through the recently awarded NHMRC Centre of Research Excellence in Indigenous Ear health.

## Research Areas

### MONITORING AND EVALUATION

Three areas have been the focus of activities this year:

- Development of a WA Ear Health Strategy
- Development of an improved data management system
- Establishment of a metropolitan ear health research program

### WA EAR HEALTH STRATEGY

In June 2015 a working group was established to develop a WA Ear Health Strategy which aims to provide a clear framework that supports government and non-government agencies to work collaboratively to better deliver evidence-based, sustainable ear health services to WA children. Members include West Australian Country Health Services (WACHS), Rural Health West, Community

and Child Health, Child and Adolescent Health Service (CACH), Aboriginal Health Council of WA (AHCWA), Dept. of Health - Aboriginal Affairs and the Telethon Kids Institute. The working group is independently chaired by Dr Peter Richmond. Telethon Kids Institute's involvement emphasises the need for an evidence-based approach to develop recommendations.

### DEVELOPMENT OF AN IMPROVED DATA MANAGEMENT SYSTEM(S)

The possibility of an improved data management system(s) that would enable real-time access to a database by multiple service providers is also being investigated through the WA Ear Health Strategy process and by maintaining close links with those developing the comprehensive Northern Territory data system. The possibility of a pilot project in one region of WA is under discussion.

### ESTABLISHMENT OF A METROPOLITAN EAR HEALTH RESEARCH PROGRAM

Acknowledging the large Aboriginal population living in Perth metropolitan area, and the dearth of data on both the burden of otitis media in 0-5 year olds and access to optimal health services in the metropolitan area, under the direction of Associate Professor Deborah Lehmann, we are undertaking the ground work needed to establish an urban-based research program. In particular, this has involved consultation with numerous community-based organizations, researchers and providers.



**Urban audit.** An audit was started to identify what ear health services are available for Aboriginal children, who provides them and how.

**Hearing for Learning. OM from an urban Aboriginal perspective.** Rosemary Walley, a Whadjuk Nyoongar woman from the Swan coastal plains joined the team in the middle of the year. Rosemary will to conduct her Masters Research project addressing the social and cultural circumstances around Aboriginal people accessing care and the impact of otitis media on children and their families. We have secured funding through the Centre of Research Excellence in Otitis Media of Aboriginal and Torres Strait Islander Children (CRE\_ICHEAR) to support Rosemary's work. Associate Professor Cheryl Kickett-Tucker, Research Director of Pindi Pty Ltd, is also an investigator in this project.

**Cohort study of OM in young urban Aboriginal children.** A grant application has been submitted to Telethon Perth Children's Hospital Research Fund, to support research in determining prevalence of and risk factors for OM in children aged less than 12 months within the Perth metropolitan area. The study will also explore health literacy amongst Aboriginal families around ear problems, and early language and communication skills that are of value to Nyoongar people.

## IDENTIFYING GAPS IN KNOWLEDGE

We have completed mapping the evidence-based recommendations

for prevention and treatment of OM as documented in the Recommendations for Clinical Care Guidelines on the Management of Otitis Media in Aboriginal and Torres Strait Islander Populations, 2010. A draft paper identifying priorities for further research in primary prevention is being prepared. This manuscript will link outcomes of the evidence-based mapping exercise with the gaps identified by stakeholders, to help identify priorities in both research and in health care activities for improving ways of preventing otitis media and hearing loss in Aboriginal people.

The paper is being prepared in collaboration with Karen Edmond, Natalie Strobel and Kimberley McAuley from the CRE entitled "Improving Health Services for Aboriginal and Torres Strait Islander Children (ISAC)", Rosemary Walley and the Menzies School of Health Research (Menzies). It is worth noting that as part of the current CRE\_ICHEAR grant, the National OMATSI guidelines will be reviewed and revised in 2016-17 and many of those contributing to this process also attended the Stakeholder meeting in March 2015. The findings of our gaps and priorities work will feed into this review process.

## ADDRESSING SOCIAL MARKETING FROM A LOCAL COMMUNITY PERSPECTIVE

A working group is being established to address social marketing from a local community perspective. The group will be

tasked with developing a model of how we can better engage and empower local communities to improve community understanding of ear health and what the implications of poor ear health are across a life span. The group will develop a draft model that addresses local community values once these have been obtained and will use at least one metropolitan area (e.g. Midland or Kwinana/Rockingham) to pilot the model. The model may be most relevant to other urban centres but we acknowledge that a model developed in an urban area may not be immediately relevant to rural and remote communities. Furthermore, acknowledging the similar pathways to poor ear, lung and skin health, the Telethon Kids Institute has a working group seeking to identify programs which can address all these infectious diseases in a holistic manner.

## **THE KALGOORLIE OTITIS MEDIA RESEARCH PROJECT – AN INVESTIGATION INTO THE CAUSAL PATHWAYS TO OTITIS MEDIA IN ABORIGINAL AND NON-ABORIGINAL CHILDREN**

*Deborah Lehmann, Peter Jacoby, Wenxing Sun, Alicia Annamalay, Ruth Monck, Fiona Stanley, in collaboration with Bega Garnbirringu Health Services, Ngunytju Tjitji Pirmi Inc, Harvey Coates, Christine Jeffries-Stokes, Annette Stokes, Daniel McAullay, Dimity Elsbury, Janine Finucane (deceased), Thomas Riley, Sharon Weeks, Allan Cripps, Jennelle Kyd, Jacinta Bowman, Gerry Harnett, David Smith, Glenys Chidlow, Denise Murphy, Kylie Carville, Stefano Occipinti, Amanda Leach, Nevada Pingault, Eileen Dunne.* Otitis media (OM, middle ear infection) can seriously affect childhood

development, school performance and subsequent social and economic well-being. The Kalgoorlie Otitis Media Research Project was established in 1999 to investigate the causal pathways to OM and, specifically, to identify demographic, socio-economic, environmental, microbiological and immunological risk factors for OM in Aboriginal and non-Aboriginal children in order to develop appropriate interventions. We followed 100 Aboriginal and 180 non-Aboriginal children from birth to age two years. Field work was completed in 2004 and data cleaning completed in April 2005. Analysis of association between bacterial carriage and mucosal immunity is ongoing and a manuscript reporting characteristics of pneumococcal carriage isolates has been submitted for publication.

### **Major findings**

- The peak prevalence of OM in the Kalgoorlie-Boulder area was 72% in Aboriginal children aged 5-9 months and 40% in non-Aboriginal children aged 10-14 months.
- Almost one-third of Aboriginal children and 5% of non-Aboriginal children had a perforated ear drum at least once by age 2 years.
- 65% of Aboriginal children and 23% of non-Aboriginal children have some degree of hearing loss at age 12-17 months.
- Measurement of otoacoustic emissions in early infancy can identify children at subsequent risk of OM.
- Exposure to environmental tobacco smoke is an important risk factor for OM.
- Crowding is the strongest and most consistent predictor of carriage of OM-associated bacteria (pneumococcus,



nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis*) in the URT, but living in a larger house attenuates this effect in Aboriginal children.

- Daycare attendance predicts carriage of OM-associated bacteria in non-Aboriginal children while exclusive breastfeeding for the first 6-8 weeks of life protects children from carriage of *Staphylococcus aureus*.
- Rhinoviruses (HRV) and adenoviruses were commonly identified in asymptomatic children, more commonly in Aboriginal than non-Aboriginal children and are frequently associated with bacterial carriage.
- Human rhinovirus A is the most common virus type identified in healthy children and HRV C is associated with presence of upper respiratory symptoms and carriage of bacteria associated with OM.
- Early carriage of non-typeable *H. influenzae* increases risk of OM in Aboriginal children, while early carriage of *M. catarrhalis* increased risk of OM in non-Aboriginal children.
- A large proportion of *M. catarrhalis* strains were resistant to ampicillin and/or co-trimoxazole. Therefore, current therapeutic guidelines, which recommend 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*.
- A broader range of pneumococcal serotypes is seen in the upper respiratory tract of Aboriginal than non-Aboriginal children, reducing coverage afforded by pneumococcal conjugate vaccines.
- Different antimicrobial susceptibility patterns of carriage strains of

pneumococci are seen in Aboriginal than non-Aboriginal children with a multiresistant serotype 6B clone only identified in non-Aboriginal children.

## TRANSLATION

A health promotion study and program followed on from this research (Preventing Otitis Media to Give a Sound Start to School)

## FUNDERS OF THE PROJECT

Western Australian Health Promotion Foundation (Healthway); NHMRC Project Grant #212044 and as part of the NHMRC Program Grant #353514.

## EXTERNAL COMMITTEES

Ear Health Steering Committee for Stakeholder Forum:

- Deborah Lehmann, Telethon Kids Institute
- Peter Richmond, School of Paediatrics and Child Health, University of Western Australia and Paediatrician & Paediatric Immunologist, Princess Margaret Hospital for Children
- Ms Victoria Stroud, Telethon Kids Institute

Goldfields Ear Health Stakeholders Group

- Ruth Monck

### International

Deborah Lehmann, Member of Conference Committee for the 19th International Symposium on Recent Advances in Otitis Media (RAOM) (2012-)

### National

CRE in Otitis Media of Aboriginal and

Torres Strait Islander Children Face-to-Face meeting, 27-29 April 2015, Menzies School of Health Research, Darwin

- Deborah Lehmann, Telethon Kids Institute
- Peter Richmond, School of Paediatrics and Child Health, University of Western Australia and Paediatrician & Paediatric Immunologist, Princess Margaret Hospital for Children
- Rosemary Walley, Telethon Kids Institute
- Ms Victoria Stroud, Telethon Kids Institute

### Local

Deborah Lehmann, Data safety monitoring board

- Dissolving the glue in glue ear: Assessment of the use of Dornase alfa as an adjunct therapy to ventilation tube insertion, 2013 -

WA Ear Health Strategy Working Group

- Deborah Lehmann
- Peter Richmond (Chair)
- Victoria Stroud





# WESFARMERS CENTRE FOR VACCINES AND INFECTIOUS DISEASE

The Wesfarmers Centre of Vaccines and Infectious Diseases was initiated in 2014 through funding received from Wesfarmers Limited. Infectious diseases are the number one killer of young children worldwide and the main reason for childhood hospitalisations in Australia. The Centre's mission is to reduce the burden of serious childhood infectious diseases by finding better prevention and treatment solutions. Reducing the burden of serious infections in Aboriginal children in Western Australia has our particular attention.

Research conducted under the umbrella of the Centre is focused on finding new solutions to improve the prevention and treatment of serious infections experienced by children or adolescents in WA and beyond. The breadth of research goes from bench to bed, including laboratory-based discovery and preclinical research, epidemiology and surveillance, clinical trials and implementation research.

The Centre aims to advance the research excellence and output of associated investigators, initiate novel high potential research ideas and attract and keep talented researchers through activities stimulating and facilitating new collaborations, connecting the bench and bed, facilitating community, partnerships and supporting training activities.

In 2014 research associated with the Centre's activities could be grouped into the following themes: Group A Streptococcal Diseases; Ear Health; Infectious Disease Epidemiology & Surveillance; Vaccine Clinical Research (the Vaccine Trials Group); Implementation Research; and the Infectious Diseases Community Reference Group.

Many studies happening under the umbrella of the Wesfarmers Centre address Aboriginal child health. In Australia, Group A Streptococcal disease now predominantly affects Aboriginal people. Middle ear infections occur in non-Aboriginal but more frequently and in a chronic form in Aboriginal children often leading to lifelong hearing loss. The epidemiological data-linkage studies use total population, mostly state wide data and include identifiers for Aboriginality, which makes it possible to assess and compare the burden of disease and risk factors for WA Aboriginal children and non-Aboriginal children separately. And the Implementation Research Team is conducting clinical trials in the Northern Territory aimed at improving rotavirus vaccination strategies and gastroenteritis treatment options in Aboriginal children.



# Infectious Diseases Data Linkage

## Research Projects

### **USING TOTAL POPULATION DATA TO DESCRIBE THE CHARACTERISTICS OF RESPIRATORY INFECTIONS IN ORDER TO PREDICT FUTURE EPIDEMICS AND RECOMMEND VACCINATION STRATEGIES FOR WESTERN AUSTRALIAN CHILDREN**

*Hannah Moore, Nicholas de Klerk, Peter Jacoby, Denise Anderson*

Acute lower respiratory infections, or chest infections, such as bronchiolitis, influenza, pneumonia and whooping cough are a major cause of morbidity in children. This project follows on from previous work of the infectious disease epidemiology research group to investigate the pathogen-specific burden of respiratory infections, in particular bronchiolitis which is predominantly caused by respiratory syncytial virus. This project uses a linked dataset of respiratory syncytial virus detections in children from 2000 to 2005 to develop a mathematical model of virus transmission dynamics. These models aim to mathematically describe the flow of individuals in a population through a pre-infectious (susceptible) state, infectious state and then recovered or immune state. They can be used to characterise seasonal epidemics of pathogens by estimating and predicting certain parameters. Once models have been developed that accurately mimic the seasonal patterns of respiratory syncytial virus, different intervention strategies can be tested to predict what likely impact

they will have on disease burden. In collaboration with researchers at the National Centre for Epidemiology and Population Health at Australian National University, we have extended our base model for respiratory syncytial virus activity to the whole of Western Australia. This model identifies associations between viral detections and specific weather variables such as minimum and maximum temperature and relative humidity. These results have been submitted for publication in 2015 and we anticipate further analyses to continue in 2016.

#### **Plain Language summary**

Respiratory syncytial virus is one of the most common viruses found in children with chest infections. The majority of these infections generally occur in winter with a similar pattern each year. By using data stored on public records over a 6 year period, we have developed a model based on mathematical equations that mimics the seasonal patterns of this virus in children. We can now use this model to try to understand why we see so many infections in winter and why seasonal patterns of this virus might differ across different areas of Western Australia.

#### **Funders of the project**

NHMRC Early Career Fellowship (HM)  
APP1034254

#### **External collaborators**

Collaborators – Alexandra Hogan, Kathryn Glass (Australian National University, ACT, Australia)

## **IDENTIFYING OPPORTUNITIES FOR PREVENTING RESPIRATORY INFECTIONS IN CHILDREN THROUGH INTEGRATING POPULATION-BASED HEALTH AND LABORATORY DATA (TRIPLE I PROJECT)**

*Hannah Moore, Christopher Blyth, Peter Jacoby, Faye Janice Lim, Parveen Fathima, Tasnim Abdalla, Nicholas de Klerk, Deborah Lehmann, Kim Carter, David Hendrickx.*

This project further investigates the epidemiology of acute lower respiratory infections in young children. The pathogens most commonly associated with acute lower respiratory infections include respiratory syncytial viruses, influenza viruses, parainfluenza viruses, rhinoviruses, adenoviruses, *Streptococcus pneumoniae* and *Bordetella pertussis*. Some pathogens are found simultaneously in children with respiratory infections (known as co-infection) and there is mixed evidence to suggest that co-infection results in worse clinical outcomes than single infection. This project will use data linkage to investigate the pathogen-specific burden of acute lower respiratory infections in terms of hospitalisations and emergency department presentations between 1996 and 2012 in a total population cohort of Western Australian children.

The specific aims of this project are:

- 1) to quantify the pathogen-specific burden of acute lower respiratory infections in Western Australia using individually-linked laboratory, hospitalisation, emergency department and disease notification datasets;
- 2) to assess the impact of viral-viral and viral-bacterial co-infections on

respiratory infection outcomes and document the relative contribution of individual respiratory pathogens to these outcomes and;

- 3) to evaluate the direct and indirect population impact of paediatric immunisations on hospitalisations and emergency department presentations for acute lower respiratory infections, their related conditions (such as febrile convulsions) or other vaccine-preventable infections by conducting pre- and post-vaccination introduction temporal trend analyses.

To help inform the analyses, we established a Triple I Scientific Steering Committee consisting of all the named investigators and other key stakeholders with an interest in acute lower respiratory infections. In 2015, we convened one meeting of the Scientific Steering Committee focused around decisions for data cleaning and analyses. Data cleaning were completed in 2015 and preliminary analyses relating to Aim 3 of this project have been completed. Data analyses will continue in 2015 and we anticipate that we will results from these analyses in 2016.

### **Plain Language summary**

Chest infections, like influenza and pneumonia, are a major cause of illness in children, particularly in Aboriginal children. By bringing together information that is stored on public records, we will describe the viruses and bacteria that are associated with chest infections in Western Australian children over a 16 year period. We will look at how multiple infections (when two or more viruses or bacteria are found at the same time) affect the severity



of illness. This information will identify areas or sub-groups of the population where better targeted interventions are needed and will be most effective. This will help to reduce the amount of children who suffer from chest infections.

### **Funders of the project**

NHMRC New Investigator Project Grant  
APP1045668

### **External collaborators**

Collaborators – Alexandra Hogan, Kathryn Glass (Australian National University, ACT, Australia)

## **LINKAGE OF THE AUSTRALIAN CHILDHOOD IMMUNISATION REGISTER (ACIR) AND STATE-BASED REGISTERS TO EVALUATE AND INFORM AUSTRALIA'S IMMUNISATION PROGRAM**

*Hannah Moore, Christopher Blyth, Nicholas de Klerk, Peter Richmond, Parveen Fathima, Tom Snelling*

Infectious diseases are the most common reason for children to be admitted to hospital. Immunisation represents the most important public health intervention to prevent infection. Despite the success of immunisation programs, outbreaks of vaccine-preventable diseases such as pertussis (whooping cough) continue to occur, with Aboriginal and Torres Strait Islander children, those living in remote areas, and those with underlying illnesses suffering a disproportionate burden of preventable disease. Accurate information on whether children are being vaccinated, the timing of their vaccination and how well the vaccines are working

to reduce disease in the community overall, and in specific populations are required. Currently, this information is derived from stand-alone databases such as the Commonwealth funded- Australian Childhood Immunisation Register (ACIR) and compared to separate state-based databases of disease notifications or hospitalisations. While analysing these datasets in isolation is useful, their linkage would allow more accurate studies on the relationship between vaccination, timeliness of vaccination, and development of disease in various population sub-groups.

This study links data that are stored on administrative databases for children born in NSW and WA from 2000 to 2012. The following records have been linked: births and deaths, immunisation, hospitalisation, emergency department visits, and infectious disease notifications (e.g. whooping cough, pneumococcal disease and influenza). By bringing together all this information, we aim to:

- Determine whether there are particular characteristics that identify children who are not receiving vaccinations on time;
- Calculate the effectiveness of vaccinations in reducing disease;
- Compare the effectiveness of vaccinations in reducing disease between different risk groups, over time, and between NSW and WA.

The linked data was made available through the Secure Unified Research Environment (SURE) in February 2015. The data cleaning has been completed and preliminary analysis of immunisation coverage in an at-risk population (children born pre-term) has been completed. Pneumococcal vaccine effectiveness

analyses are in progress.

### **Plain Language summary**

In order to optimise the health and cost benefits of Australia's immunisation program, accurate data are required about how well the program is performing. Currently, information about this is limited. In this study we will for the first time bring information together for a population of births in WA and NSW on immunization records, hospital admissions, disease notification records, laboratory records and birth records. We will use this information to accurately determine how many infants and children are receiving their recommended vaccinations on time and if they are working to reduce the amount of infections that infants and young children suffer.

### **Funders of the project**

NHMRC Project Grant APP1082342

### **External collaborators**

Heather Gidding, Bette Liu, Louisa Jorm, Lisa McCallum – University of NSW, NSW  
Peter McIntyre – National Centre for Immunisation Research & Surveillance of Vaccine Preventable Diseases (NCIRS), NSW

Ross Andrews – Menzies School of Health Research, Queensland

## **THE PATHOGEN SPECIFIC BURDEN OF HOSPITALISATION FOR ENTERIC AND BLOOD STREAM INFECTION IN CHILDREN AND YOUNG PEOPLE IN WESTERN AUSTRALIA**

*Hannah Moore, Tom Snelling, Claire Waddington, Christopher Blyth, Deborah*

*Lehmann, Parveen Fathima, Julie Marsh*

Enteric infections cause significant mortality and morbidity worldwide, in both resource rich and poor settings. In WA, enteric infection is one of the leading causes for infection-related hospitalisations in children under the age of 2 years and Aboriginal infants are 8 times more likely to be admitted for enteric infections than non-Aboriginal infants.

Although enteric infection is usually self-limiting in healthy children, it can lead to acute morbidity through dehydration and chronic morbidity through failure to thrive and under-nutrition. Furthermore, some enteric pathogens can translocate into the normally sterile bloodstream causing bloodstream infection (BSI) and sepsis. The causative pathogens of enteric infection are geographically, seasonally and temporally variable. Rotavirus infection has been the single most important cause of enteric disease in WA as with elsewhere in Australia and globally, but bacterial enteric infection due to *Campylobacter* spp., *Salmonella* spp., *Shigella* spp. and parasites are also frequently reported in infants in the Northern Territory, and those aged less than 5 years in remote WA, especially in Aboriginal infants.

Rotavirus vaccination commenced in WA in mid-2007 and has been accompanied by a reduction in rotavirus-specific and all-cause gastroenteritis hospitalisations. We hypothesise that rotavirus immunisation has not only had a direct impact on rotavirus gastroenteritis, but it also has an indirect impact on non-rotavirus enteric pathogens by reducing their transmission. There are a number of observations arising from the field trial and post licensure



experience with rotavirus vaccines which support this hypothesis and yet it has never been formally tested. These observations include the disproportionate impact of vaccination observed against severe diarrhoea and diarrhoea-related mortality. Because of its capacity to directly link hospitalisation with pathogen-specific pathology data, WA is in a unique position to address this hypothesis. The results are highly significant for understanding the overall impact of rotavirus vaccination, especially among Aboriginal children and in resource-poor settings where non-rotavirus pathogens account for a significant proportion of the total diarrhoeal disease burden.

Accurate data on causative pathogens for community-acquired enteric infection are needed to guide medical management and further public health interventions. Pathogen data relevant to WA are limited. WA is climatically diverse, and has a large remote Aboriginal population among whom enteric disease causing pathogens differ from those in the non-Aboriginal population. A recent study has shown diverging temporal trends in gastroenteritis hospitalisation rates in Aboriginal and non-Aboriginal children in the different geographical regions of WA. We need to study the changes, if any, in the prevailing enteric pathogens over time to determine if they are driving these trends.

In this project, we propose to investigate the pathogen-specific burden of community-acquired enteric and bloodstream infection in Aboriginal and non-Aboriginal populations, focusing on children presenting to Emergency Department facilities or being hospitalised

across the state of Western Australia. The results will allow us to evaluate the overall impact of WA's rotavirus vaccination program and will inform future preventive and management strategies.

#### Specific aims of this project are:

1. To characterise the epidemiology and pathogen-specific burden of disease for community-acquired enteric disease including enteric bloodstream infection among Western Australian (WA) children
2. To describe the changes over time in the prevalent enteric pathogens causing presentations for diarrhoea and blood stream infection (BSI), and to compare overall and pathogen-specific rates of infection pre and post rotavirus vaccine introduction, using non-enteric BSI (Staphylococcus, Pneumococcus and Group A Streptococcus) as a control outcome.
3. To determine the demographic and clinical risk factors for community-acquired infection with enteric pathogens in WA.
4. To assess the impact of co-morbidities on disease outcome measured by 30 day mortality and duration of hospitalisation.
5. To correlate location specific rates of enteric diseases with publicly available data on location specific vaccine coverage.
6. To determine the reduction in emergency presentations and hospitalisations attributable to the rotavirus vaccine program.
7. To characterise changes in antimicrobial susceptibility of enteric pathogens over time.
8. To prioritise future public health interventions to address the residual

burden of enteric diseases in WA.

We received part of the linked data in August 2015. Data cleaning of these datasets has been completed and preliminary analysis of the data is underway.

### **Plain Language summary**

Enteric (gut) infections are a major cause of illness in children and young adults. Aboriginal children suffer from more gut infections compared with non-Aboriginal children. In addition to dehydration, severe gut infections can give rise to bloodstream infections (BSI) and other nutrition/growth related health problems. By bringing together the birth, hospitalisation, and laboratory records of children across Western Australia over the last 10 years, we will investigate which pathogens (bacteria, viruses or parasites) are responsible for enteric infection related health care presentations in children, who are most at risk and what factors (such as age, region of residence, infant low birth weight, maternal age etc) predicts the severity of illness. We will assess the overall impact of the rotavirus vaccination program introduced for children in Western Australia in 2007. This will help us to better target further prevention and management strategies for these infections.

### **Funders of the project**

Princess Margaret Hospital Foundation  
New Investigator Project Grant 2013

### **External collaborators**

Thomas Riley (UWA)

## **EVALUATING THE USE AND EFFECTIVENESS OF PASSIVE IMMUNIZATION IN REDUCING RSV-ASSOCIATED MORBIDITY IN HIGH RISK INFANTS**

*Hannah Moore, Tasnim Abdalla, Thomas Snelling, Nicholas De Klerk*

Respiratory syncytial virus is one of the main causes of acute lower respiratory infections leading to a substantial health and economic burden on national and global levels. Infants in the first 2 years of life in particular are at increased risk of morbidity and mortality caused by this virus. Clinical characteristics such as prematurity, chronic lung conditions or congenital heart disease further increase the susceptibility of infants to respiratory syncytial virus infections. In Australia the risk of serious respiratory syncytial virus -associated disease among high risk infants is controlled by the use of the monoclonal anti-RSV antibody, palivizumab. Palivizumab is administered as monthly injections during the respiratory syncytial virus season, usually extends from May to October. Although licensed by the Therapeutic Goods Administration, no uniform national guideline or policy governs the use of palivizumab in Australia. Few studies conducted in other developed countries have showed that the use and compliance with monthly injections of palivizumab have led to significant reduction in respiratory syncytial virus confirmed infections and associated hospitalisations. In Australia there has never been an evaluation of palivizumab efficacy in preventing respiratory syncytial virus. Thus, the aim of this data linkage cohort study is to provide an evaluation of the use and compliance with palivizumab, and the effectiveness of



its induced immunoprophylaxis in reducing the burden of respiratory syncytial virus and associated respiratory infections. The cost-effectiveness of palivizumab will also be analysed. We will utilize existing data stored in the Neonatal Clinical Care Unit Database (NeoBase), Midwives Notification System, Princess Margaret Hospital and King Edward Memorial Hospital Dispensary Databases, Death Register, Hospital Morbidity Database System, Emergency Department Data Collection, and the PathWest Laboratory Database. The NeoBase will be used to identify high risk infants born between 1st January 2002 and 31st December 2013 and admitted to Level 3 Neonatal Intensive Care Unit at KEMH and PMH. Funding was received for this project in mid-2014 and the application for linked data was submitted at the end of 2014. All of the project approvals have been obtained in July 2015 with receipt of linked data anticipated to be late 2016.

### **Plain Language summary**

Respiratory syncytial virus is a major cause of chest infections in young children and causes many children to go to hospital. Children who are born preterm are at particular high risk of infection with this virus. Currently there no vaccination against RSV infections and the only intervention available to protect high risk infants is the passive immunisation induced through a drug called palivizumab, which is given every month over the winter period. The effectiveness of palivizumab in preventing respiratory syncytial virus infections among high risk children has been demonstrated by other studies conducted in other developed countries,

but never in Western Australia. By bringing together information on hospital, pharmacy, laboratory and birth records, we will be able to measure how effective palivizumab is in reducing the number of infections caused by this virus. The study findings will provide valuable information to inform future health policy regarding the use of palivizumab.

### **Funders of the project**

Telethon-Perth Children's Hospital Research Fund Grant 2013

### **External collaborators**

Tobias Strunk (KEMH & PMH), Anthony Keil (PathWest, PMH & KEMH), Peter Richmond (PMH & UWA).

## **TRENDS IN ADMISSIONS FOR ACUTE RESPIRATORY INFECTIONS IN CHILDREN: AN INTER-COUNTRY COMPARISON BETWEEN WESTERN AUSTRALIA AND ENGLAND**

*Hannah C Moore, Tasnim Abdalla, Christopher C Blyth*

Acute respiratory infections (ARI) including bronchiolitis, pneumonia and influenza are a major cause of hospital admissions in children worldwide. In England, the hospital admissions rate for LRTI increased by 40% between 1999 and 2010 among children aged less than 15 years, and in Western Australia hospital admissions for LRTI doubled between 1992 and 2000 in non-Aboriginal children. This project will utilize existing administrative health data to examine the similarities and differences in temporal and seasonal trends of ARI admissions using linked datasets in Western Australia and England. The availability of comparable data items in each

jurisdiction will be used to characterize and compare the epidemiology of paediatric respiratory infections over a 13 year period. Identical coding and data cleaning principles will be applied to both datasets. Hospital admission for ARI in children aged <5 years between 2000 and 2012 were identified using International Classification of Diseases diagnosis codes. The descriptive comparative analysis will include comparing the hospitalization rates per 1000 child-years by age, gender and admission year in each jurisdiction. The differences in coding practices, seasonality and risk factors such as socio-economic deprivation and prematurity will be also be investigated. Area-level deprivation indicators are available in both countries and will be used to examine trends and compare seasonal peaks across levels of socio-economic deprivation. Furthermore, linked laboratory data for respiratory study will enable greater understanding of the burden of ARI in children and the impact of different child, maternal and social risk factors on the observed trends of infection. Funding for this project was received in 2014. The de-identified data accessed for the Triple I project (received in 2014) will be used in this study.

### **Plain Language summary**

Acute respiratory infections are major cause of hospital admission in young children despite the availability of childhood vaccination programs. By bringing together existing administrative data in England and Western Australia, we will able to compare the trends, risk factors and the effectiveness of different vaccination policies and interventions, in each jurisdiction. Better understanding of

the differences and similarities between the two countries will provide insights for preventing the high admissions due to chest infections in children.

### **Funders of the project**

UWA Research Collaboration Awards (RCA) 2015

### **External collaborators**

Collaborator – Pia Hardelid, Ruth Gilbert (University College London, London, UK)

## **2015 Success**

### **AWARDS AND PRIZES**

Hannah Moore, 2015 Woodside Early Career Scientist of the Year  
Faye Lim, The University of Western Australia representative for the C9-Go8 PhD Forum on Big Data

### **EXTERNAL COMMITTEES**

#### **Local**

Hannah Moore; Telethon Kids Institute Early Environment Research Focus Area Steering Committee, Started: 2014  
Hannah Moore; Telethon Kids Institute Early-Mid Career Research Council; Started: 2012  
Faye Lim; Telethon Kids Institute Early-Mid Career Research Council; Started: 2015  
Faye Lim; Telethon Kids Institute Student Reference Group; Started: 2013

### **INVITED PRESENTATIONS**

Hannah Moore; Science and research in WA; Young Professionals Roundtable with



the WA Premier; Perth, Australia; 9 Dec 2015

Faye Lim; My research in 5 minutes; UWA Early Career Researcher Community Engagement Initiative; Perth Modern School; 24 Feb 2015

## Group A Streptococcal Diseases

### Overview

The Group A Streptococcal (GAS) diseases team are a multidisciplinary team of researchers working to reduce the burden of GAS diseases, with a particular focus on RHD. Acute rheumatic fever (ARF) and RHD are most common in developing countries and in vulnerable populations in high income countries. In Australia, Aboriginal and Torres Strait Islanders live with a substantial burden of RHD. Our research is focused on reducing this burden through basic science, implementation science and policy advocacy. Our core team are physically located at the Telethon Kids Institute in Perth with a number of remote staff and large number of national and international research collaborators.

The GAS team had a number of highlights for 2015. These include receiving \$2.5 million from the NHMRC for the END Rheumatic Heart Disease Centre of Research Excellence, being awarded \$1.2m for stage one of Coalition to Advance New Vaccines Against Group A Streptococcus (the CANVAS initiative)

and the publication of the revised Jones criteria for diagnosing acute rheumatic fever.

## Research Projects

### **THE END RHD CRE: DEVELOPING AN END GAME FOR RHEUMATIC HEART DISEASE IN AUSTRALIA**

*Prof Jonathan Carapetis (CIA), Professor Bart Currie (CIB), Professor Graeme Maguire (CIC), Professor Dawn Bessarab (CID), Dr Dan MaAullay (CIE), Ms Heather D'Antoine (CIF), Professor Alex Brown (CIG), Professor Karen Edmond (CIH), Associate Professor Andrew Steer (CII), Professor Nicholas de Klerk (CIJ), Associate Professor Vicki Krause (AIA), Professor David Atkinson (AIB), Dr Gavin Wheaton (AIC), Doctor Thomas Snelling (AID), Dr Anna Ralph (AIE), Dr Stephanie Trust (AIF), Ms Claire Boardman (AIG), Dr Rosemary Wyber (AIH), Dr Samantha Colquhoun (AII), Professor Christopher Reid (AIJ)*

The END RHD CRE is a five year Centre of Research Excellence funded by the National Health and Medical Research Council Australia in 2014. The END RHD CRE brings together 20 investigators from 16 institutions to develop a strategy for how Australia can eliminate RHD as a public health problem (the "endgame report"). At the end of 5 years, the END RHD CRE will provide a stepwise roadmap to ending RHD in Australia and aim to produce a clear vision for achieving measurable disease control targets. The END RHD CRE will undertake a number of projects across several disciplines of research including epidemiology, biomedical sciences; implementation and translation; and understanding the

RHD community with a special focus on documenting the experiences of those living with the disease.

### **Plain Language Summary**

In Australia, RHD is essentially a disease of the past for all but Indigenous populations and some groups living in poverty. The END RHD CRE provides an opportunity to build a comprehensive, evidence based strategy for ending RHD and represents an untold opportunity to tackle the disparity between Indigenous and non-Indigenous Australians. We will undertake a number of projects across several disciplines of research with a special focus on documenting the experiences of those living with RHD. At the end of 5 years, the END RHD CRE will provide a roadmap to end RHD in Australia.

### **Funders of the project**

NHMRC

### **External collaborators**

Menzies, RHD Australia, Baker IDI, UWA, SAHMRI, MCRI, University of Melbourne, KAMS, NT CDC, Women's and Children's Hospital Adelaide, Monash University

## **COALITION TO ADVANCE VACCINES AGAINST GROUP A STREPTOCOCCUS (CANVAS): A TRANS-TASMAN INITIATIVE AGAINST RHEUMATIC FEVER**

*Professor Jonathan Carapetis and Professor John Fraser (Dean, Faculty of Medical & Health Sciences, University of Auckland)*

CANVAS is a Trans-Tasman initiative funded by the governments of Australia

and New Zealand; aimed at accelerating the development of a vaccine for rheumatic fever prevention and reducing the burden of GAS associated diseases. The CANVAS program offers the opportunity to leverage public funds to take a vaccine through the initial stages of clinical development to the point of an efficacy study for GAS pharyngitis, in the expectation that this early stage "de-risking" will allow partners in industry and significant international organisations to enter the development program with confidence. CANVAS program incorporates an objective pre-clinical and clinical evaluation of leading GAS vaccine candidates currently in development. GAS is diverse with over 200 distinct strains identified to date. A successful vaccine must confer protection against the vast majority of GAS strains circulating in a target population, with different geographical regions having a different range of predominant strains. Furthermore, a GAS vaccine must not cause autoimmune cross reactivity with human tissue that is the hallmark of acute RF. In order to collectively address the hurdles associated with GAS vaccine development, three major research focuses involve selection of minimal strain set that will represent a wide range of disease manifestations. Lead vaccine candidate will be selected on the basis of efficacy against the selected GAS strains. Finally, a health economic evaluation of interventions to control GAS infections to rationalize the investment in GAS vaccine development is also being undertaken.

### **Plain Language summary**

CANVAS is a commitment by the Governments of Australia and New



Zealand to advance the development of a vaccine against GAS infection, which can cause rheumatic fever.

The CANVAS program is evaluating potential vaccines currently under development to identify at least one that could proceed to clinical trials. The 3 main components to the CANVAS program are:

- obtaining a selection of the most common GAS strains
- testing potential vaccines against these strains
- undertaking an economic analysis to evaluate if vaccination is cost-effective.

### **Funders of the project**

NHMRC and Health Research Council (New Zealand)

### **External collaborators**

University of Auckland, AU and NZ Governments, University of Otago, NZ Environmental Science and Research, MCRI, UQ, Menzies School of Health Research, Harvard, University College London

## **DEVELOPMENT OF A LONGER ACTING FORMULATION OF PENICILLIN G FOR THE TREATMENT AND PREVENTION OF ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE**

*Jonathan Carapetis, Meru Sheel, Ben Boyd, Mark Sullivan, Glenn Pearson*

ARF and RHD are rare in developed countries, prevalence and associated morbidity and mortality is high within

developing countries. Most recent figures show the global prevalence of RHD to be as high as 34 million and number of deaths due to RHD to be greater than 345,000. In Australia and New Zealand, the disease burden amongst the indigenous communities is one of the highest in the world. The most effective recommended treatment of ARF requires four-weekly intramuscular injections of 1.2 million units of benzathine penicillin G (BPG). Secondary prophylaxis for ARF and RHD with BPG is recommended for a minimum of 10 years, and in some cases even for a life time. Adherence to secondary prophylaxis is low and can be attributed to a combination of factors including, frequency and duration of injection, pain at injection site, access to health care providers (especially for those living in poor remote settings). This projects aims at developing a longer acting formulation of penicillin G, such that frequency of the injection can be increased up to 3-6 months. It is hoped that the total direct and indirect cost of the new formulation would be equal to or lesser than the annual cost of delivering current forms of secondary prophylaxis. The new formulation of penicillin will also aim at targeting the issues of poor quality of BPG available in developing countries.

### **Plain Language summary**

The most effective recommended treatment to prevent RHD requires monthly injections of penicillin. These injections are painful and difficult to administer and as such many patients do not adhere to their treatment plan. This projects aims to develop a longer acting formulation of penicillin, such that frequency of the

injection can be increased up to 3-6 months. This will provide a practical, less painful method of treatment and vastly increase the number of patients being successfully treated.

### **Funders of the project**

Telethon - New Children's Hospital  
Research Fund

### **External collaborators**

Monash Institute of Pharmaceutical  
Sciences, Medicines Development Limited

## **IMPROVING DELIVERY OF SECONDARY PROPHYLAXIS FOR RHEUMATIC HEART DISEASE**

*Jonathan Carapetis, Graeme Maguire,  
Ross Bailie, Bart Currie, Adrienne Kirby,  
Vanessa Johnston, Keith Edwards, Anna  
Ralph, Alex Brown, Marea Fittock, Christine  
Connors, Rosalie Schultz, Suzanne Belton*

Rheumatic heart disease (RHD) is a major health problem in Indigenous communities. Continued progress in controlling RHD requires an understanding of how to improve delivery of regular injections of penicillin - secondary prophylaxis (SP). Due to proven benefit and demonstrated cost effectiveness, secondary prevention of RHD remains the focus of most RHD control strategies. Secondary prophylaxis involves a four-weekly administration of penicillin for at least 10 years to all people with a history of ARF or RHD to control and reduce their chance of progressing to established, or more severe disease outcomes. This study will evaluate whether an intervention designed to optimize health systems improves the delivery of SP, using

a stepped-wedge trial in 10 communities in the Northern Territory of Australia. A detailed mixed-methods evaluation will be undertaken to ascertain the degree to which adopting the systems-based intervention improves processes of RHD care and adherence to SP and which elements of the intervention are most effective in activating change. If successful, this model will provide a practical and transferable model for improving SP delivery.

### **Plain Language summary**

Rheumatic heart disease (RHD) is a major health problem in Indigenous communities. Continued progress in controlling RHD requires an understanding of how to improve delivery of regular injections of penicillin - secondary prophylaxis (SP). We will evaluate a systems-based approach to improving delivery of SP, in 10 communities in NT. If successful, this model will provide a practical and transferable approach that can be adopted nationally.

### **Funders of the project**

NHMRC

### **External collaborators**

Menzies School of Health Research , Baker  
IDI, University of Sydney, Northern Territory  
Department of Health



## **EVALUATING THE GENETIC CONTRIBUTION TO RHEUMATIC HEART DISEASE PATHOGENESIS IN AUSTRALIAN ABORIGINAL AND TORRES STRAIT ISLANDER COMMUNITIES**

*Jonathan Carapetis, Michael Inouye, Steven Tong, Heather D'Antoine, Andrew Steer, Paul de Bakker, Dawn Bessarab, Jenefer Blackwell, Ngjare Brown, Bo Remenyi*

Although poorly understood, the pathogenesis of RHD appears to involve infections with “rheumatogenic” strains of Group A Streptococcus in a host with inherited susceptibility resulting in an abnormal immune response and the development of autoimmunity. This project aims to identify regions of the human genome that confer susceptibility to rheumatic heart disease (RHD) in Australian Aboriginal and Torres Strait Islander populations. Results may lead to improved diagnostics, therapeutics and vaccines for RHD. The project will enroll approximately 500 remote Aboriginal people with RHD and 1,000 community-matched controls across the Northern Territory. A major component of this study is to explore better ways to undertake community consultation and gain informed consent for genetics research in Aboriginal people, and to develop appropriate mechanisms for governance of the use of data and samples in the long term. The study will be a model for the conduct of genetic studies in Aboriginal populations.

### **Plain Language summary**

Rheumatic heart disease is highly prevalent in Aboriginal people in Australia and leads to early cardiac

disease. Despite decades of research, the underlying genetic mechanisms for why it occurs are not well understood. We are conducting a genetic study to better understand why some people are susceptible to RHD and others are not. The study will involve substantial Aboriginal leadership and consultation and will be a model for the conduct of genetic studies in Aboriginal populations.

### **Funders of the project**

NHMRC

### **External collaborators**

Menzies School of Health Research (Menzies), Charles Darwin University, Walter & Eliza Hall Institute of Medical Research (WEHI), University of Melbourne, Murdoch Childrens Research Institute, Harvard Medical School, USA

## **RHEACH (RHEUMATIC HEART DISEASE. EVIDENCE. ADVOCACY. COMMUNICATION. HOPE)**

*Jonathan Carapetis, Liesl Zuhlke, Rosemary Wyber*

RhEACH is a technical support and policy translation initiative to amplify rheumatic heart disease control efforts locally, regionally and globally. We aim to identify, describe and disseminate solutions for this neglected disease and to reduce burden on vulnerable populations around the world.

As a collaborative organization, we partner with a broad range of stakeholders – including clinicians, other disease communities, academics, funders, governments, industry and people living

with RHD – to achieve our common goals. RhEACH focuses in three key domains:

- Collating & disseminating information
- Technical support for RHD control programs and service providers.
- Policy focused research to inform disease control efforts

### **Plain Language summary**

RhEACH is a technical support and policy translation initiative to amplify rheumatic heart disease control efforts locally, regionally and globally. RhEACH aims to identify, describe and disseminate solutions for this neglected disease and to reduce burden on vulnerable populations around the world.

As a collaborative organisation, we seek to partner with a broad range of stakeholders - including clinicians, other disease communities, academics, funders, governments, industry and people living with RHD - to achieve our common goals.

### **External collaborators**

University of Cape Town, South Africa

## **RHD ACTION**

RHD Action is the name given to the global movement to reduce the burden of rheumatic heart disease (RHD) in vulnerable populations of all ages throughout the world. Initiated in September 2014 under the auspices of the UN Every Woman Every Child (EWEC) commitment, this movement will add to ongoing global efforts contributing to the World Health Organization (WHO) and World Heart Federation (WHF) goals to reduce premature mortality by the

year 2025. The driving force behind this global movement is the RHD Action Alliance – a coalition of three global organizations – Medtronic Philanthropy, the World Heart Federation and RhEACH – working together toward the shared goal of ending RHD. Critically reinforcing this global movement are the RHD Action Countries – a cohort of countries wherein government and partner institutions are actively engaged in achieving specific RHD targets within their geographies, while also strengthening their health systems.

### **Plain Language summary**

The RHD Action Alliance (RHDA) is a coalition of global organisations including Medtronic Philanthropy, the World Heart Federation and RhEACH. RHDA will work together to establish a scientific and technical support community available to all countries, draw on this technical knowledge to advocate for policy change for better heart health, support and empower all people living with RHD and to foster multi-sectoral partnerships to support and sustain the global movement.

### **Funders of the project**

Medtronic Foundation

### **External collaborators**

RhEACH, World Heart Federation, Medtronic Foundation



## 2015 Success

### THESES PASSED

- Dr Asha Bowen, PhD (CDU) awarded 2015. Principal supervisor – Jonathan Carapetis
- Ms Samantha Colquhoun, PhD (CDU) awarded 2015. Principal supervisor – Jonathan Carapetis

### AWARDS AND PRIZES

- Rebecca Seth - Mike Schon-Hegrad Incentive Award
- Judith Katzenellenbogen – Heart Foundation Future Leader Fellowship – awarded in 2015 to commence in 2016.
- Clancy Read - Allegra Scafidas Development Award

### EXTERNAL COMMITTEES

#### International

Jonathan Carapetis:

- Editorial Board Member, Heart Asia, British Medical Journal, 2015-
- Editorial Board Member, Global Heart Journal, World Heart Federation and Elsevier, 2011-
- Working Group on Rheumatic Fever and Rheumatic Heart Disease, World Heart Federation, Geneva, 2011-
- Board Member, One Disease at a Time Foundation, 2010-
- Expert Group Core Member and Head, Expert Group on Rheumatic Heart Disease, Cardiovascular Diseases Expert Group, Global Burden of Diseases, Injuries, and Risk Factors Study, 2008-

#### National

Jonathan Carapetis:

- Member, Association of Australian Medical Research Institutes (AAMRI) Board, 2014-
- Fellow and Council Member, Australian Academy of Health and Medical Sciences (FAHMS), 2014
- Member, Program Management Committee, RHD Australia, 2012-
- National Committee for Medicine, Australian Academy of Science, 2007-

Asha Bowen:

- Member, Australian and New Zealand Paediatric Infectious Diseases (ANZPID) special interest group of ASID and a committee member of the ASID Clinical Research Network (CRN).

#### Local

Jonathan Carapetis:

- Member, RHD Australia Advisory Committee (ARC), 2015-
- Member, NHMRC Australia Council, 2015-
- Member, The University of Western Australia, Forrest Foundation Selection Committee, 2015-
- Member, WA Health Translation Network (WAHTN) Executive Board, 2015-
- Member, Department of Corrective Services WA, Youth Justice Board, 2014-
- Member, Western Australian Immunisation Strategy Implementation Steering Committee (WAISISC), 2013-
- Chair, Clinical Advisory Group, WA RHD Control Program, 2013-
- Member, Western Australian State Health Research Advisory Council (SHRAC), 2012-2015
- Executive Director, Telethon Kids

Institute Board of Directors, 2012-

Asha Bowen:

- Member, Australasian Society of Infectious Diseases Clinical Research Network
- Chair, scientific committee for the upcoming 2016 Infection and Immunity in Childhood: Perth course
- Member of the Australian and New Zealand Paediatric Infectious Diseases (ANZPID) special interest group of ASID and a committee member of the ASID Clinical Research Network (CRN).

## INVITED PRESENTATIONS

Jonathan Carapetis:

- CEDA – The Committee for Economic Development of Australia Futures Series, Perth, WA.
- Australian Medical Students Association Global Health Conference, Perth, WA.
- Walter & Eliza Hall Institute of Medical Research Centenary Symposium, Melbourne, VIC.
- Leadership WA Seminar, Curtin University of Technology, Perth, WA.
- Infection and Immunity in Children International Congress of Paediatric Infectious Disease, Oxford, United Kingdom. (29 June – 01 July)
- Resident Medical Officer Teaching Program, Princess Margaret Hospital for Children, Perth, WA.
- Science on the Swan, Inaugural Conference, Perth, WA.
- Australasian Society for Infectious Diseases Annual Scientific Meeting, Auckland, NZ
- Pan-African Society of Cardiology (PASCAR), Addis Ababa, Ethiopia

Rosemary Wyber and Judith Katzenellenbogen – NHMRC Masterclass, Sydney, 2015. (Katzenellenbogen, J. Wyber, R. Dimer, L. Haynes, E. Shilton, T. Bessarab, D. Carapetis, J. Thompson, SC. Aboriginal health health: achieving local and national research impact. NHMRC Research Translation Symposium, October 2015)

# Implementation Research

## Overview

The Implementation Research team is part of the Wesfarmers Centre of Vaccines and Infectious Diseases which reports to the Early Environment RFA. We conduct research which aims to find the best way to implement strategies to improve the wellbeing of children. The team collaborates widely and uses a range of methods, including pragmatic randomised controlled trials, observational comparative effectiveness studies and data linkage studies.

## Research Projects

### **A RANDOMISED, PLACEBO-CONTROLLED TRIAL OF ORAL NITAZOXANIDE FOR THE EMPIRIC TREATMENT OF ACUTE GASTROENTERITIS AMONG AUSTRALIAN INDIGENOUS CHILDREN**

*Tom Snelling<sup>1</sup>, Claire Waddington<sup>1</sup>, Asha Bowen<sup>1</sup>, Ross Andrews<sup>2</sup>; Peter Morris<sup>2</sup>, Mark Naunton<sup>3</sup>, Julie Marsh<sup>1</sup>*



<sup>1</sup>Telethon Kids Institute; <sup>2</sup>Menzies School of Health Research, Darwin; <sup>3</sup>University of Canberra

Aboriginal children experience a large burden of disease from gastroenteritis. Those living remotely have a particularly high burden of disease, and frequently require aero-medical retrieval to hospital for management of gastroenteritis. There are few effective treatment options for acute diarrhoeal illness in children. Management is limited to supportive care with fluid and electrolyte replacement to prevent life-threatening dehydration, correct electrolyte imbalances and improve nutritional status.

Nitazoxanide (NTZ) is an antimicrobial with broad-spectrum activity against many of the pathogens implicated in acute gastroenteritis in high-burden settings, including in remote Aboriginal children. In other settings, NTZ treatment has been successfully used to treat gastroenteritis caused by a wide range of pathogens.

Our team successfully obtained an NHMRC project grant to conduct a pragmatic, placebo controlled, randomised clinical trial to investigate the potential benefit of using NTZ as an empiric treatment strategy in Aboriginal children hospitalised with acute gastroenteritis. This study is currently recruiting participants and is planned to finish in the next two years.

### **Plain Language summary**

The study aims to assess the impact of oral nitazoxanide (antimicrobial) on the length of symptoms among Aboriginal children admitted to hospital with gastroenteritis

aged between three months and five years old. A total of 400 children will be enrolled from the Royal Darwin Hospital and Alice Springs Hospital. The children receive the nitazoxanide treatment or a placebo for three days. We follow up the children for 60 days and at completion we will assess any differences between the two groups.

### **Funders of the project**

NHMRC project grant

### **External collaborators**

Peter Morris – Menzies School of Health Research, Darwin, NT

Mark Naunton – University of Canberra, Canberra, ACT

Ross Andrews – Menzies School of Health Research, Darwin, NT

Keith Grimwood – Griffith University, Qld

Roy Robins-Browne – University of Melbourne, Melbourne, Vic

Carl Kirkwood – Gates Foundation, Seattle, USA

Robert Baird – Northern Territory Government Pathology Services, Darwin, NT

Deborah Fearon – Alice Springs Hospital, Alice Springs, NT

## **A RANDOMISED CONTROL TRIAL OF NOVEL TREATMENT STRATEGY FOR THE TREATMENT OF BRONCHIOLITIS IN INFANTS**

*Claire Waddington<sup>1</sup>, Tom Snelling<sup>1</sup>, Meredith Borland<sup>2</sup>, Andrew Martin<sup>2</sup>, Christopher Blyth<sup>1,2</sup>*

<sup>1</sup>Telethon Kids Institute; <sup>2</sup>Princess Margaret Hospital for Children/UWA School of Paediatrics and Child Health

By the time they reach their first birthday, 3-5% of all infants have been hospitalised with bronchiolitis, a condition caused by virally induced inflammation of the lower respiratory tract, resulting in breathing difficulties, cough, poor feeding, irritability and occasionally apnoea. There are no proven treatments for bronchiolitis and despite considerable effort vaccines for the most important cause, Respiratory Syncytial Virus (RSV) remain elusive. RSV monoclonal antibody is of benefit for preventing bronchiolitis in extremely high risk infants, but management is otherwise limited to supportive care with fluids, oxygen and ventilatory assistance, with admission to intensive care in severe cases.

Novel approaches that are effective, affordable, and well tolerated are desperately needed to reduce the huge morbidity, economic cost and social burden of bronchiolitis. The broad-spectrum anti-viral activity of a novel anti-infective agent has recently been described, including against the principal viral aetiological agents of bronchiolitis (especially Paramyxoviridae, including RSV, human metapneumovirus [hMP], parainfluenza viruses and the Orthomyxoviridae, including Influenza viruses A and B). As such, this treatment may provide a significant and much needed advance in the management of infant bronchiolitis. This project will examine the effect of this treatment compared to placebo on the duration of significant illness in West Australian infants hospitalised with bronchiolitis, to determine if its use as empiric treatment for bronchiolitis is beneficial. Following award a successful funding application in mid-2014, this project is currently in the

set-up phase.

### **Plain Language summary**

Bronchiolitis, a virus infection of the lungs and airways, is one of the most common reasons for babies to need admission to hospital. A new medicine appears effective for killing the viruses which cause bronchiolitis in the laboratory. The medicine has been shown to be safe in young children when used for other infections. We will test this new medicine in babies who have bronchiolitis, to see if it is safe and to see if these babies recover faster than babies who receive a placebo (dummy medicine).

### **Funders of the project**

Telethon-Perth Children's Hospital Research Fund

### **External collaborators**

Meredith Borland, Princess Margret Hospital, Perth, WA  
Andrew Martin, Princess Margret Hospital, Perth, WA  
Christopher Blyth, Princess Margret Hospital, and School of Paediatrics and Child Health, University of Western Australia, Perth, WA  
Peter Richmond - School of Paediatrics and Child Health, University of Western Australia, Perth, WA

## **DETERMINANTS OF INCOMPLETE VACCINATION AND NON-VACCINATION AMONG WA CHILDREN**

*Claire Waddington<sup>1</sup>, Tom Snelling<sup>1</sup>, Paul Effler<sup>2</sup>, Julie Leask<sup>1</sup>, Hal Willaby<sup>3</sup>*

*<sup>1</sup>Telethon Kids Institute; <sup>2</sup>Communicable*



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for Immunisation Research (NCIRS),  
Sydney*

Vaccination is an enormously successful public health intervention. Not only does vaccination protect the individual against disease, it provides population level (herd) protection and engages young children with primary health care during their most vulnerable years of life. Data from the Australian Childhood Immunisation Register (ACIR) show that vaccination rates in Western Australia (WA) are the lowest for any Australian state with approximately one in ten children incompletely vaccinated.

Determinants of vaccine uptake and timeliness in WA are unknown. A wide range of social, demographic, maternal and infant related factors have been identified as important in other settings but their importance in WA is unclear. Understanding determinant factors in WA is critical to identify interventions needed to ensure all children in WA are protected against vaccine preventable disease. Experience from elsewhere has shown that co-ordinated, targeted approaches can successfully increase vaccination rates. Potential low cost interventions to improve uptake, applicable at a population level, include the use of text message reminders for routine vaccination. As well as being effective, the use of modern technologies for vaccination reminder and recall is supported by parents.

This project will identify the determinants of vaccination in WA that will be used design and inform a targeted approach to increase vaccine coverage in WA

using modern technology (such as the use of text message reminders). The impact of the approach will be assessed in a randomised control trial. These data are an essential step in ensuring that all children in WA are fully protected for vaccine preventable disease.

Primary data collection for this study has ended. We are using sophisticated Bayesian network approaches to understand how specific beliefs and attitudes drive under vaccination.

### **Plain Language summary**

Incomplete uptake of vaccination remains a problem, with vaccine preventable diseases still occurring in Australia and other countries despite routine provision of childhood vaccination. Understanding which parental beliefs contribute to incomplete vaccination might help to identify and prioritise opportunities to intervene. This project has surveyed WA parents to better understand beliefs and attitudes towards vaccination.

### **Funders of the project**

WA Department of Health

### **External collaborators**

Paul Effler – Communicable Diseases Control Directorate, WA Department of Health, Perth, WA

Julie Leask – School of Public Health, University of Sydney, NSW

Harold Willaby – School of Public Health, University of Sydney, NSW

## **THE SAFETY AND ACCEPTABILITY OF MIXED WHOLE CELL/ACELLULAR PERTUSSIS VACCINE SCHEDULES IN INFANTS TO PREVENT SENSITISATION TO FOOD ALLERGENS: A PILOT STUDY**

Tom Snelling<sup>1</sup>, Peter Richmond<sup>1,2</sup>, Susan Prescott<sup>1,2</sup>, Patrick Holt<sup>1</sup>

<sup>1</sup>Telethon Kids Institute; <sup>2</sup>UWA School of Paediatrics and Child Health

Atopic disease (encompassing eczema, asthma, rhinoconjunctivitis, and food allergy), represents a significant disease burden in Australia and around the world. Rates of IgE mediated food allergy appear to be increasing since the late 1990s, with marked increases in the reported rates of food allergy, increases in the incidence specialist referrals for food allergy, and increases in hospital admissions for food allergy.

This 'allergy epidemic' is proposed to have been triggered by one or more environmental factors or lifestyle changes. A decrease in exposure to microbes has been suggested to have caused the observed increases in atopy. Known as the 'hygiene hypothesis', cleaner environments and altered microbiota are hypothesised to lead to dysregulation of the immune system and subsequent atopy. This does not, by itself, explain the abrupt uptick in food allergy seen in Australia.

A marked temporal association exists between the rapid increase in hospitalisations due to food allergy anaphylaxis in Australia from the late 1990s and the phase out of whole cell pertussis vaccine (wP) in favour of acellular pertussis vaccine (aP). Previous

research by our group suggests that wP vaccination may protect against the development of the Th2-skewed immune phenotype which predisposes some children to allergy, including food allergy.

This pilot randomised controlled trial will have 2 arms, with some infants receiving the standard Australian schedule of 3 priming doses of aP at approximately 6 weeks, 4 months and 6 months old, and half receiving an initial dose of wP instead of aP at approximately 6 weeks followed by 2 scheduled doses of aP.

We hypothesise that a single first dose of wP followed by two doses of aP may allow a more Th1/Th2 balanced immune response, and protection from subsequent food allergy. Although a full wP vaccine course is more reactogenic than a full aP vaccine course, this may not be true for a single dose of wP given in early infancy. Furthermore, substitution of the first aP dose with wP may significantly reduce the frequency of extensive limb swelling observed after the 18 month and 4 year old booster doses of aP. An assessment of the immune responses of contemporary Australian infants primed with either a mixed wP/aP or the current aP-only schedule is warranted.

The development of IgE levels in infants following vaccination as an indicator of developing atopy will be monitored. Tetanus specific IgE levels will be assessed following the first and third pertussis vaccine doses, and skin prick tests (SPT) to a range of common food allergens will be tested at 18 months of age. The reactogenicity and parental acceptance of both the wP/aP and the aP-only schedules will also be assessed.



### Plain Language summary

Whooping cough is reemerging as a serious health problem in Australia. There is a growing body of evidence that suggests the whole cell vaccine against pertussis that used to be used in Australia may be better at protecting against whooping cough than the acellular vaccine currently in use. In addition, there is evidence to suggest that the whole cell vaccine might protect against the development of allergy in children. However, the vaccine was discontinued in Australia due to undesirable side effects. This is a pilot study to assess the acceptability of reintroducing one dose of the whole cell vaccine into the child immunisation schedule, and to assess the development of allergic potential among children receiving either the whole cell or acellular vaccine.

### Funders of the project

Telethon-Perth Children's Hospital Research Fund and UWA/WA Health 'near-miss' funding

### External collaborators

Peter Richmond - School of Paediatrics and Child Health, University of Western Australia, Perth, WA  
Susan Prescott – School of Paediatrics and Child Health, University of Western Australia, Perth, WA

## THE ROLE OF MIDWIVES IN TACKLING VACCINE HESITANCY

Katie Attwell<sup>1</sup>, Tom Snelling<sup>2</sup>, Claire Waddington<sup>2</sup>, Julie Leask<sup>3</sup>, Kerrie Wiley<sup>3,4</sup>

<sup>1</sup>Murdoch University (Perth, WA); <sup>2</sup>Telethon Kids Institute; <sup>3</sup>University of Sydney;

<sup>4</sup>National Centre for Immunisation Research and Surveillance.

Parental hesitancy around the decision to vaccinate their children ('vaccine hesitancy') represents a major threat to public health and our ability to prevent unnecessary deaths from infection. Midwives have an increasingly integral role in immunisation advice and provision, but may abstain from advocating for immunisation for a variety of reasons such as limited understanding of vaccines, lack of access to education resources, or philosophical objections linked to views around bodily autonomy and preference for 'natural' processes. There is evidence that expectant mothers want childhood immunisation information early, which midwives are ideally placed to give. Health care providers, including midwives, have significant influence on parental immunisation decisions. To date, there has been little research on understanding midwives' perspectives and practices on immunisation, and how they might be better engaged as advocates of immunisation for expectant and new parents. This research aims to explore the evidence around the role of midwives in vaccine education and provision, and how vaccination may be optimally framed to resonate with both midwives and their audience of birthing mothers.

### Plain Language summary

Midwives, like other healthcare providers, are an important information source regarding vaccination for parents and expectant parents. Information and attitudes matter in an age where some parents are worrying about vaccinating their children. This project reviewed the

existing literature from developed world settings, generating an overview of what we know about midwives' attitudes towards vaccination.

### **Funders of the project**

Wesfarmers Centre of Vaccines and Infectious Diseases seed funding

### **External collaborators**

Katie Attwell, Murdoch University, Perth, WA

Julie Leask – School of Public Health, University of Sydney, NSW

Kerrie Wiley, University of Sydney, NSW; National Centre for Immunisation Research and Surveillance, NSW

## **TESTOV PNEUMO- EVALUATION OF THE EFFECTIVENESS OF THE 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE AGAINST PNEUMOCOCCAL PNEUMONIA IN CHILDREN**

Adam Jaffe<sup>1</sup>, Tom Snelling<sup>2</sup>, Stephen Lambert<sup>3</sup>, Lyn Gilbert<sup>4</sup>

<sup>1</sup>University of New South Wales, Sydney;

<sup>2</sup>Telethon Kids Institute; <sup>3</sup>University of Queensland, Brisbane; <sup>4</sup>University of Sydney

*Streptococcus pneumoniae* (pneumococcus) causes a range of infectious diseases, including pneumonia and invasive pneumococcal disease (IPD), and remains a leading cause of childhood morbidity and mortality globally. Paediatric pneumococcal vaccines provide coverage against a limited number of serotypes. The real world impact of these vaccines on IPD and pneumonia has been mixed, with

paradoxical increases in some outcomes, notably for complicated pneumonia in Australia. One explanation for this is that vaccination results in a decrease in nasal carriage of vaccine serotypes, opening up a biological niche that allows non-vaccine serotypes to infect ('serotype replacement'). Some of these

replacement serotypes may be even more pathogenic than the serotypes they replace.

This study will assess the contribution of *S. pneumoniae* to hospitalisation for pneumonia in Australian children in the post-vaccine era; determine the factors that contribute to these infections; and evaluate the real world effectiveness of the vaccination program in preventing hospitalisation. Children with pneumonia and empyema will be recruited from 13 tertiary paediatric hospitals. Blood, pleural fluid and nasopharyngeal swabs will be tested for *S. pneumoniae* (including serotyping), and other bacteria and respiratory viruses using molecular techniques. The vaccination status of these cases will be compared with matched children from the Australian Childhood Immunisation Registry to determine vaccine effectiveness. It is anticipated that this will be the most comprehensive evaluation of the impact of a national pneumococcal vaccine program on hospitalised pneumonia and that the results will directly influence Australian and international vaccine policy and vaccine development.

### **Plain Language summary**

Children receive three doses of vaccine during the first six months of life to prevent



diseases caused by the pneumococcus bacteria including pneumonia. However, the effectiveness of the vaccine against pneumonia has not been well assessed. We are conducting this study to compare the vaccination status of children hospitalized with pneumonia to that of other children, to assess the vaccine effectiveness. We expect this study data will be useful to develop new vaccines to ensure better protection against childhood pneumonia.

### **Funders of the project**

NHMRC project grant

### **External collaborators**

Adam Jaffe - University of New South Wales, NSW

Lyn Gilbert - University of Sydney, NSW

Stephen Lambert - University of Queensland, Brisbane, Qld

Melanie Wong - Sydney Children's Hospital Network, Sydney, NSW

## **A PHASE IV, DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED CLINICAL TRIAL TO OPTIMISE THE DELIVERY OF RV1 ROTAVIRUS VACCINE TO NORTHERN TERRITORY ABORIGINAL INFANTS**

*Claire Waddington<sup>1</sup>, Tom Snelling<sup>1</sup>, Ross Andrews<sup>2</sup>, Carl Kirkwood<sup>3</sup>, Margaret Danchin<sup>3</sup>*

<sup>1</sup>*Telethon Kids Institute; <sup>2</sup>Menzies,*

<sup>3</sup>*Murdoch Childrens Research Institute*

Diarrhoea kills more than half a million children under five years old every year, predominantly in resource-poor settings. Rotavirus is the leading cause of severe, dehydrating diarrhoeal disease

in children, and accounts for almost one-third of these deaths. Consequently, safe and effective rotavirus vaccines have been a longstanding public health need. Field trials of two oral attenuated rotavirus vaccines demonstrating high efficacy against severe rotavirus disease were therefore a major step forward in the battle to reduce the global burden of diarrhoeal disease. Unfortunately, more recent data have shown that both vaccines have substantially lower efficacy, and a more rapid waning of protection, in low-resource settings. We have observed similar results among Australian Indigenous infants. Indeed, the discrepancy in the rate of rotavirus hospitalisations between Indigenous and non-Indigenous children has actually increased since vaccine introduction. The underlying reasons for this are not completely known, but both reduced vaccine immune responses and low vaccine coverage are likely to be important factors. Pragmatic and timely solutions to the reduced effectiveness of rotavirus vaccines are needed to overcome both the absolute disease burden and the disparity between Indigenous and non-Indigenous children. Administering an additional dose and/or relaxing the requirement to complete the rotavirus vaccine course before six months of age represent two highly feasible but untested solutions. This study will appraise the potential impact that these strategies could offer Indigenous children in the Northern Territory.

### **Plain Language summary**

Since the introduction of the rotavirus vaccine in 2006 the discrepancy in the rate of rotavirus hospitalisations between

Indigenous and non-Indigenous children has actually increased. The underlying reasons for this are not completely known, but both reduced vaccine immune responses and low vaccine coverage are likely to be important factors. This study will assess the likely impact of an additional scheduled rotavirus vaccine dose between 6 to 12 months of age on the burden of diarrhoeal disease in Australian Indigenous children in the Northern Territory.

### **Funders of the project**

NHMRC project grant

### **External collaborators**

Ross Andrews – Menzies School of Health Research, Darwin, NT

Carl Kirkwood – Murdoch Children's Research Institute, Melbourne, Vic

Margaret Danchin – Murdoch Children's Research Institute, Melbourne, Vic

## **CASE-COHORT STUDY OF THE ASSOCIATION BETWEEN PERTUSSIS VACCINATION IN INFANCY AND THE RISK OF IGE-MEDIATED FOOD ALLERGY**

*Tom Snelling<sup>1</sup>, Dianne Campbell<sup>2</sup>, Michael Gold<sup>3</sup>, Claire Waddington<sup>1</sup>, Sarah Sheridan<sup>4</sup>, Marie Estcourt<sup>1</sup>.*

<sup>1</sup>Telethon Kids Institute; <sup>2</sup>University of Sydney, <sup>3</sup>University of Adelaide,

<sup>4</sup>Queensland Children's Medical Research Institute

We hypothesise that before it was phased out in the late 1990s, the whole cell pertussis vaccine (wP) partly protected children against the development of food

allergies. This project uses a retrospective case-controlled trial design, targeting cases of previously diagnosed food allergy, and comparing case vaccination history to that of the whole population.

This is a retrospective individually-matched case-control study of Australian children born during the period of transition from use of wP vaccines to aP vaccines. IgE mediated food allergy cases will be drawn from allergy clinics associated with tertiary teaching hospitals around Australia. The odds ratio of wP versus aP vaccination will be compared for cases and their matched cohort controls. This will effectively approximate the relative risk of the development of food allergy among children receiving wP compared with aP vaccines. If whole cell vaccination is found to have a protective association against the development of allergy, this is likely to impact on vaccine policy in Australia and around the world.

### **Plain Language summary**

In the late 1990s the type of pertussis vaccine (against whooping cough) used in Australia was changed from a whole cell vaccine to an acellular vaccine. During this time period a rapid increase in the number of reported food allergy cases among children was also observed. This is a retrospective study looking at children diagnosed with food allergy and the type of vaccine they received. This study aims to see if whole cell vaccine was protective against the development of food allergy. If this older vaccine is found to be associated with protection against allergy this is likely to impact vaccine policy in Australia and around the world.



## Funders of the project

NHMRC project grant

## External collaborators

Dianne Campbell – University of Sydney, NSW

Michael Gold – University of Adelaide, SA

Sarah Sheridan – University of Queensland, Qld

## PARENTS' IMMUNISATION NEEDS AND ATTITUDES - ANTENATAL (PINA-A SURVEY)

Margaret Danchin<sup>1</sup>, Katie Attwell<sup>2</sup>, Jessica Amato<sup>3</sup>, Harold Willaby<sup>4</sup>, Kerrie Wiley<sup>5</sup>, Michelle Giles<sup>6</sup>, Helen Marshall<sup>7</sup>

<sup>1</sup>Murdoch Childrens Research Institute,

<sup>2</sup>Telethon Kids Institute <sup>3</sup>Royal Children's

Hospital, Melbourne, <sup>4</sup>University of Sydney,

<sup>5</sup>National Centre for Immunisation

Research and Surveillance, <sup>6</sup>The Alfred

Hospital, Victoria, <sup>7</sup>Women's and

Children's Hospital, Adelaide.

To ensure that parents are fully informed about childhood vaccination parents need independent, accurate, objective and accessible information. Information pertaining to the risk and benefits of vaccination, the purpose of vaccination and what to expect following administration of a vaccine could be considered a minimum requirement for any parent for any parent to make an informed choice about childhood vaccination. It has been suggested that the process of parent education should commence in the antenatal period, but there is currently insufficient resources to provide this. Further, accurate information is needed to facilitate the process of informed parental

consent is required prior to administration of any childhood vaccine, but this requires information that is specific to the vaccine schedule used in any particular setting. This project will focus on building the information resources related to vaccination that can be used in Western Australia.

## Plain Language summary

To understand the information needs and attitudes of pregnant women with regards to vaccination during pregnancy and after birth, we are surveying them in hospital during antenatal appointments. Later, we contact them again to find out what vaccination decisions they have made after their babies' births.

## Funders of the project

Wesfarmers Centre of Vaccines and Infectious Diseases seed funding

## External collaborators

Margaret Danchin – Murdoch Children's Research Institute, Melbourne, Vic

Jessica Amato – Royal Children's Hospital, Melbourne, Vic

Harold Willaby – School of Public Health, University of Sydney, NSW

Kerrie Wiley – University of Sydney, NSW; National Centre for Immunisation Research and Surveillance, Sydney, NSW

Michelle Giles – The Alfred Hospital, Melbourne, Victoria

Helen Marshall – Women's and Children's Hospital, Adelaide, SA

## **SMS REMINDERS TO IMPROVE VACCINATION RATES: A SIMPLE 'NUDGE' FOR A COMPLEX PROBLEM**

*Claire Waddington<sup>1</sup>, Tom Snelling<sup>1</sup>, Julie Marsh<sup>1</sup>, Grace Currie<sup>1</sup>, Yue Wu<sup>1</sup>, Paul Effler<sup>2</sup>, Alan Leeb<sup>3</sup>.*

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In many parts of Australia under-vaccination and delayed vaccination is putting children at unnecessary risk of infections (e.g. whooping cough). Our research has shown that although vaccine decision making is complicated, most WA parents support vaccination, including parents of under-vaccinated children. Simply reminding parents of due or overdue vaccinations may be an effective 'nudge' to boost vaccination rates in WA.

In the last decade, mobile phone ownership has rapidly increased in Australia with approximately 94% of adult Australians owning a mobile phone. The wide-spread popularity of mobile phones is an excellent opportunity to reach parents to remind them of upcoming or overdue vaccinations. SMS reminders are also relatively cheap to send and the instant delivery of messages allows parents to schedule a vaccination without delay.

Sending simple reminders to parents using SMS, has been shown to improve vaccine uptake and timeliness in other countries like the United States. Previous research has suggested that educational or motivational reminders, emphasising the importance of vaccination or the risks of catching disease, may be more effective than traditional appointment

scheduling reminders. Considering the risks and consequences of under-vaccination and delayed vaccination, it is important to develop communication strategies that encourage vaccination acceptance and positive health behaviours.

SMS reminders for childhood vaccination has never been trialled before in Australia. We believe that providing timely reminders to parents when a vaccine is due will be an effective nudge to improve vaccination rates and timeliness. The effectiveness of this modern and powerful technology will be assessed using an adaptive clinical trial design to inform the roll-out of automated SMS software across GP clinics in Australia. This project is currently in the set-up phase and aims to begin recruitment in July 2016.

### **Plain Language Summary**

New and modern strategies are needed to improve childhood vaccination rates and encourage parents to vaccinate their children on time. The rapid increase of mobile phone ownership in Australia has created a promising means of communication to notify parents of due or overdue vaccines. This trial is the first of its kind in Australia and will assess whether simple strategies, such as SMS reminders, are an effective way of improving vaccine coverage in WA.

### **Funders of the project**

WA Department of Health

### **External Collaborators**

Paul Effler – Communicable Diseases Control Directorate, WA Department of Health, Perth, WA

Alan Leeb – Illawarra Medical Centre,



Perth, WA

Ian Peters – Datavation, Perth, WA

## **THE PATHOGEN SPECIFIC BURDEN OF HOSPITALISATION FOR ENTERIC AND BLOOD STREAM INFECTION IN CHILDREN AND YOUNG PEOPLE IN WESTERN AUSTRALIA**

*Hannah Moore<sup>1</sup>, Tom Snelling<sup>1</sup>, Claire Waddington<sup>1</sup>, Christopher Blyth<sup>1,2</sup>, Thomas Riley<sup>3</sup>, Deborah Lehmann<sup>1</sup>, Parveen Fathima<sup>1</sup>, Julie Marsh<sup>1</sup>*

*<sup>1</sup>Telethon Kids Institute; <sup>2</sup>Princess Margaret Hospital for Children/UWA School of Paediatrics and Child Health; <sup>3</sup>University of Western Australia*

Enteric infections cause significant mortality and morbidity worldwide, in both resource rich and poor settings. In WA, enteric infection is one of the leading causes for infection-related hospitalisations in children under the age of 2 years and Aboriginal infants are 8 times more likely to be admitted for enteric infections than non-Aboriginal infants.

Although enteric infection is usually self-limiting in healthy children, it can lead to acute morbidity through dehydration and chronic morbidity through failure to thrive and under-nutrition. Furthermore, some enteric pathogens can translocate into the normally sterile bloodstream causing bloodstream infection (BSI) and sepsis.

The causative pathogens of enteric infection are geographically, seasonally and temporally variable. Rotavirus infection has been the single most important cause of enteric disease in WA as with elsewhere in Australia and

globally, but bacterial enteric infection due to *Campylobacter* spp., *Salmonella* spp., *Shigella* spp. and parasites are also frequently reported in infants in the Northern Territory, and those aged less than 5 years in remote WA, especially in Aboriginal infants.

Rotavirus vaccination commenced in WA in mid-2007 and has been accompanied by a reduction in rotavirus-specific and all-cause gastroenteritis hospitalisations. We hypothesise that rotavirus immunisation has not only had a direct impact on rotavirus gastroenteritis, but it also has an indirect impact on non-rotavirus enteric pathogens by reducing their transmission. There are a number of observations arising from the field trial and post licensure experience with rotavirus vaccines which support this hypothesis and yet it has never been formally tested. These observations include the disproportionate impact of vaccination observed against severe diarrhoea and diarrhoea-related mortality. Because of its capacity to directly link hospitalisation with pathogen-specific pathology data, WA is in a unique position to address this hypothesis. The results are highly significant for understanding the overall impact of rotavirus vaccination, especially among Aboriginal children and in resource-poor settings where non-rotavirus pathogens

account for a significant proportion of the total diarrhoeal disease burden.

Accurate data on causative pathogens for community-acquired enteric infection are needed to guide medical management and further public health interventions. Pathogen data relevant to WA are limited. WA is climatically diverse,

and has a large remote Aboriginal population among whom enteric disease causing pathogens differ from those in the non-Aboriginal population. A recent study has shown diverging temporal trends in gastroenteritis hospitalisation rates in Aboriginal and non-Aboriginal children in the different geographical regions of WA. We need to study the changes, if any, in the prevailing enteric pathogens over time to determine if they are driving these trends.

In this project, we propose to investigate the pathogen-specific burden of community-acquired enteric and bloodstream infection in Aboriginal and non-Aboriginal populations, focusing on children presenting to Emergency Department facilities or being hospitalised across the state of Western Australia. The results will allow us to evaluate the overall impact of WA's rotavirus vaccination program and will inform future preventive and management strategies.

We received part of the linked data in August 2015. Data cleaning of these datasets has been completed and preliminary analysis of the data is underway.

### **Plain Language summary**

Enteric (gut) infections are a major cause of illness in children and young adults. Aboriginal children suffer from more gut infections compared with non-Aboriginal children. In addition to dehydration, severe gut infections can give rise to bloodstream infections (BSI) and other nutrition/growth related health problems. By bringing together the birth, hospitalisation, and laboratory records of children across Western Australia over

the last 10 years, we will investigate which pathogens (bacteria, viruses or parasites) are responsible for enteric infection related health care presentations in children, who are most at risk and what factors (such as age, region of residence, infant low birth weight, maternal age etc.) predicts the severity of illness. We will assess the overall impact of the rotavirus vaccination program introduced for children in Western Australia in 2007. This will help us to better target further prevention and management strategies for these infections.

### **Funders of the project**

Princess Margaret Hospital Foundation  
New Investigator Project Grant 2013

### **External collaborators**

Thomas Riley – University of Western Australia, Perth, WA

## **2015 Success**

### **THESES PASSED**

Kaylin Hooper, BMedSci candidate, University of Western Australia, Development of a clinical trial to assess strategies to optimise rotavirus vaccination  
Muatasem Muhsen, MSc candidate, University of Western Australia, Developing a clinical trial protocol to assess the efficacy of whole cell versus acellular pertussis vaccination  
Antony Kurishungal Aloysius, University of Western Australia, assessing the impact of pneumococcal vaccination on nasopharyngeal carriage in WA children



## AWARDS AND PRIZES

Tom Snelling, University of Western Australia Vice-Chancellor's Early Career Investigators Award

Tom Snelling, WA Department of Health New Independent Researcher Infrastructure Support (NIRIS) Award

Claire Waddington, Early or Mid Career Researcher Award for Research Excellence, Telethon Kids Kudos Award Program

Claire Waddington, Telethon Fellowship Award

## EXTERNAL COMMITTEES

### International

Julie Marsh, member of International Biometrics Society.

### National

Tom Snelling, Pharmaceutical Benefits Advisory Committee (PBAC), 2014-current

Tom Snelling, Economics Subcommittee of the PBAC, 2012-2015.

### Local

Tom Snelling, Aboriginal Health Research Focus Area steering committee, Telethon Kids Institute, co-chair

Tom Snelling, Antimicrobial stewardship committee chair, Princess Margaret Hospital

Tom Snelling, WA Committee on Antimicrobials, WA Health

Tom Snelling and Claire Waddington, Biological Hazards Committee, Telethon Kids Institute

Tom Snelling and Claire Waddington, WA ACTA

Julie Marsh, UWA Mathematics & Statistics Outreach Committee

## INVITED PRESENTATIONS

Tom Snelling, From Chumps to Champs? The early years of stewardship at PMH 2015. Western Australian Committee for Antimicrobials Symposium (WACA), Perth (WA), 29 June 2015

Tom Snelling, Childhood Respiratory Infection- Pertussis - Where we are heading. RNIG/WA (Professional Development Day for Respiratory Nurses), Perth (WA), 26 June 2015

Claire Waddington, From random care to randomized care, Australian Medical Students' Association's (AMSA's) Global Health Conference, Perth (WA), 28 August 2015

## Infectious Diseases Community Reference Group

### Institute members

*Anita van den Biggelaar, Glenn Pearson, Heid Hutton, Anne McKenzie*

An Infectious Diseases Community Reference Group (CRG) has been meeting at the Institute four times a year since it was convened in 2007. The group is comprised of community members, representatives from the Western Australian Department of Health, the Meningitis Centre, the Institute's Consumer and Community Advisory Council and Institute researchers. Community members provide input and advice to researchers presenting their proposed research studies to the group and identify areas of particular community concern. Presentations to the CRG are part of informing the wider community about

infectious disease research conducted both within the Institute and externally. This year (on April 1 2015), the Wesfarmers Centre of Vaccines and Infectious Diseases and IDCRCG organized a Community Conversation at the Leederville Community Centre to get the community's perspective on the Wesfarmer Centre's research program. The event was advertised widely through the Consumer and Community Partnership's emailing list; flyers at Princess Margaret Hospital; a Telethon Kids enews invitation to over 1700 email addresses of community members who have subscribed through the Institute website and the Parents and Babies Expo; Facebook; and an interview with Geoff Hutchison on ABC radio. The intended program was adapted following the death of a 1-month old infant at PMH of whooping cough and the media attention following this. **Community participants were asked to rotate between four tables to talk about the following topics:**

- What information does the community need to better understand the effective use of antibiotics, and how should this be made available?
- What can be done to increase the confidence of the community about the safety and necessity of vaccinating?
- What information will help women be confident to make a decision to have recommended vaccines for influenza / whooping when pregnant?
- How can we support greater involvement of the community in our infectious disease research program?

**Key messages arising from this Community Conversation were:**

- There is a huge gap in (grand) parents knowledge on vaccines and

antibiotics

- People vaccinate because they get a reminder, or because they go by government/GP recommendation ("passive")
- With strong communication from the anti-vaccine lobbyists and a lack of information on the need to vaccinate, people start doubting and evading: Information & communication on vaccination needs to be: ongoing, not reactive; transparent (upfront on the risks); adapted for different target populations; consistent and simple
- Lack of knowledge, lack of time and personal opinions are identified as major deficiencies of GPs in advising parents on childhood and maternal vaccinations.
- There is a need for a medium where parents can directly ask questions
- There is a need for a direct approach through child health nurses, antenatal classes and play groups

### **Funders of the project**

Wesfarmers Centre of Vaccines and Infectious Diseases

## **Pneumococcal Vaccine Trials in PNG Research Projects**

### **A STUDY TO DETERMINE THE SAFETY AND IMMUNOGENICITY OF 10-VALENT AND 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINES IN PAPUA NEW GUINEAN**



## CHILDREN

Deborah Lehmann<sup>1</sup>, Andrew Greenhill<sup>2</sup>, Peter Richmond<sup>1,3</sup>, Lea-Ann Kirkham<sup>1,3</sup>, Peter Siba<sup>4</sup>, William Pomat<sup>4</sup>, Audrey Michael<sup>4†</sup>, Celestine Aho<sup>4</sup>, Rebecca Ford<sup>4</sup>, Tilda Orami<sup>4</sup>, Vela Solomon<sup>4</sup>, Geraldine Masiria<sup>4</sup>, William Lagan<sup>4</sup>, Trevor Duke<sup>5</sup>, Megan Passey<sup>6</sup>

<sup>1</sup>Telethon Kids Institute; <sup>2</sup>Federation University, Ballarat, Victoria; <sup>3</sup>UWA School of Paediatrics and Child Health; <sup>4</sup>PNG Institute of Medical Research, Goroka, Papua New Guinea; <sup>5</sup>University of Melbourne; <sup>6</sup>University of Sydney

Approximately 800,000 children die annually from pneumococcal disease worldwide, the majority in early infancy. Pneumococcal conjugate vaccines (PCVs) have been introduced into routine immunization programs in many industrialised countries and an increasing number of third world countries. The Global Alliance for Vaccines and Immunisation (GAVI) and the World Health Organization (WHO) have committed to the introduction of PCV for infants in GAVI-eligible countries (including PNG). No pneumococcal vaccine was available in PNG until 13vPCV was distributed in 2014. The primary aim of this study, which began in November 2011, is to determine whether the 10-valent (PCV10) or 13-valent (PCV13) pneumococcal conjugate vaccines (which include 10 or 13 pneumococcal serotypes, respectively) given in a 1-2-3-month schedule are safe and immunogenic in Papua New Guinean infants. This is an open randomised trial. We aim to enrol 260 children at age 1 month: half are randomised to receive PCV10 and the other half PCV13 in a 1-2-3-month schedule. At age 9 months

half in each group are randomised to receive the 23-valent pneumococcal polysaccharide vaccine (PPV) and the other half no PPV. To address the possibility of hyporesponsiveness following PPV, all children will receive a challenge dose (0.1ml) of PPV at age 23 months. Enrolment of 262 children has been completed, and more than 200 children have completed 9- and 10-month follow-up visits and 170 received a challenge dose at 23 months. The last follow-up at 24 months is due in March 2016. Assays measuring pneumococcal serotype-specific IgG and culture of pernasal swabs have been completed on all samples collected at ages 1 (pre-PCV) 4 months (one month post-dose 3 PCV), 9 months (pre-PPV/no PPV) and 10 months (one month PPV/no PPV). A total of 1225 pernasal swabs, 1216 serum samples and 672 PBMC samples have been collected to date.

Both PCV10 and PCV13 are immunogenic in PNG infants under the 1-2-3 month schedule for VT with good antibody persistence to 9 months of age though immunogenicity varies between serotypes. PPV responses are consistent with priming for immunologic memory. Pneumococcal carriage rates increased from 65% at age 1 month to 88% thereafter with no difference between the vaccine groups. Approximately 50 different pneumococcal serotypes have been identified to date. Preliminary results were presented at Annual meeting of the Medical Society of Papua New Guinea in Port Moresby in September 2015 and at the 9th World Congress of the World Society for Pediatric Infectious Diseases in Rio de Janeiro in November 2015.

## Project funding

Exxon-Mobil Governance and Public Affairs  
Papua New Guinea Institute of Medical Research Internal Competitive Research Award Grant  
NHMRC

## NEONATAL IMMUNIZATION WITH PNEUMOCOCCAL CONJUGATE VACCINE IN PAPUA NEW GUINEA

*Deborah Lehmann, Pat Holt, Peter Richmond, Anita van den Biggelaar, in collaboration with William Saila Pomat, Peter Siba, Suparat Phuanukoonnon, Andrew Greenhill, Celestine Aho, Tilda Orami, John Reeder, Amanda Leach, Ingrid Laing.*

Throughout the world approximately 800,000 children die annually from pneumococcal disease, the majority in early infancy in third world countries. This study was designed to investigate the safety, immunogenicity and priming for immunologic memory of pneumococcal conjugate vaccine (PCV) in Papua New Guinean infants at 1-2-3 months of age and to find out whether neonatal immunisation in the first week of life would provide earlier protective antibody responses. We have assessed the impact of neonatal immunisation on humoral and cellular immune responses to concomitant vaccines (diphtheria toxoid, tetanus toxoid and measles) and whether PCV interferes with normal maturation of the immune system. Manuscripts are in preparation on the impact of a 7-valent PCV (7vPCV) on early pneumococcal nasopharyngeal colonisation and on mucosal immune responses. Further immunological analyses are planned. A

total of 318 children were enrolled; 80% completed follow-up at 18 months of age.

### Results to date show:

- No deleterious effect of neonatal 7-valent PCV (7vPCV).
- 7vPCV is immunogenic in PNG neonates and young infants.
- 7vPCV in a neonatal (0-1-2 months) or early infant (1-2-3 month) schedule primes for immunologic memory for 7vPCV serotypes with booster response to 23-valent pneumococcal polysaccharide vaccine (PPV) at age 9 months. Serotype-specific antibody concentrations are generally sustained to age 18 months.
- PPV induces good antibody responses for some non-PCV pneumococcal serotypes which commonly cause disease.
- 60% of infants were colonised with *Streptococcus pneumoniae* by age 1 month.
- 54 different pneumococcal serotypes have been identified in the upper respiratory tract.
- At age 9 months, 68-78% of pneumococci in the upper respiratory tract were non-7vPCV serotypes.
- At age 9 months, non-7vPCV serotypes are more commonly carried in the upper respiratory tract of children who received 7vPCV than in controls.
- Early pneumococcal carriage may result in enhanced disease susceptibility and suboptimal vaccine responses by modulating the development of pneumococcal immune responses.
- Analysis of cellular immune responses has shown that neonatal PCV vaccination is safe and not associated with immunological tolerance.
- Preliminary analysis of saliva samples



shows that 7vPCV generally primes mucosal immune responses for boosting by pneumococcal polysaccharide vaccine at age 9 months. A manuscript is in draft form. A manuscript describing impact of 7vPCV on carriage is in final draft form.

In an extension of this project IA Laing investigated the contribution of human genetic susceptibility to nasal bacterial carriage, development of immune/vaccine responses and the incidence of pneumonia in this population. Preliminary results from investigation of associations between genotype and acute lower respiratory infections (ALRIs) suggest that several genetic variants for known immune pathways may play a role in the frequency of lower respiratory tract infections in children in PNG.

### **Translation**

In addition to previous data demonstrating the enormous burden of pneumococcal disease in young children in PNG, the safety and immunogenicity data of PCV in a 1-2-3-month schedule provided important information resulting in the introduction of 13vPCV in PNG in 2014 with support from the Global Alliance for Vaccine and Immunisation (GAVI).

### **Funders of the project**

This study was funded by the NHMRC/ Wellcome Trust International Collaborative Research Grant #303123 and a Papua New Guinea Institute of Medical Research Internal Competitive Research Award Grant.

## **2015 Success**

### **EXTERNAL COMMITTEES**

#### **International**

Deborah Lehmann, Papua New Guinea Institute of Medical Research Buttressing Coalition, 1998-current

Deborah Lehmann, Member of Conference Committee for the 19th International Symposium on Recent Advances in Otitis Media (RAOM), 2012-current

Deborah Lehmann, Member of Local Organising Committee for the 11th Symposium on Pneumococci & Pneumococcal Diseases 2018 in Melbourne

#### **National**

Deborah Lehmann: Data safety monitoring board of CHIRRP "Combating H. influenzae related respiratory pathology" (2012-current)

#### **Local**

Deborah Lehmann, Meningitis Centre Management Committee (1998-current)

Deborah Lehmann, Infectious Diseases Community Reference Group (2008-2014)

Deborah Lehmann, Dissolving the glue in glue ear: Assessment of the use of Dornase alfa as an adjunct therapy to ventilation tube insertion, 2013 -current

Deborah Lehmann, Member of WA Ear Health Strategy Working Group 2015 –

# Vaccine Trials Group

## Overview

The Vaccine Trials Group, based at the Telethon Kids Institute, is staffed by a dedicated team of doctors, nurses, researchers, scientists, PhD, Honours and Masters students, phlebotomists and administration staff.

With infectious diseases still the most common cause of death in children, we are evaluating new vaccines for a range of diseases including influenza, pneumococcal, meningococcal and swine and bird flu.

## Research Projects

### **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.**

*Associate Professor Rachel Skinner and Dr Tanya Stoney*

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 worldwide, 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. Twenty Seven participants were recruited to the study since 2011.

### **Plain Language summary**

At the completion of the HPV 015 study the women who received the placebo during the study, were offered the Cervarix vaccine. If they were over the age of 45 years they needed to enrol in the HPV 066 study, as the vaccine is not licenced for use past this age. Safety data was collected during this study.

### **Funders of the project**

GlaxoSmithKline

### **THE VACCINE RESPONSE AND LONG-TERM ANTIBODY PERSISTENCE OF GSK BIOLOGICALS' MENACWY-TT VACCINE ADMINISTERED AS ONE DOSE AT 6 YEARS POST-MENC PRIMARY VACCINATION IN HEALTHY SUBJECTS AGED 12-18 MONTHS AT PRIMARY VACCINATION**

*Associate Professor Peter Richmond*

Children who were enrolled in a previous GSK combination HibMenC vaccine trial when they were 12 months of age were asked to be involved in this follow on study - The purpose of which is to evaluate the safety, immunogenicity and the long term antibody persistence at 2 and 4 years after the administration of a booster dose



of GSK Biologicals' MenACWY-TT vaccine. This vaccine was administered 6 years after the children received either a combined HibMenC vaccine or separate Hib and MenC vaccines at 12 months of age, co-administered with the MMR vaccine.

It is expected that the study vaccine will act as a booster for MenC conjugate vaccine and will enlarge the coverage to serogroups A, W135 and Y.

The vaccination phase of the study was in progress during 2013 and early 2014 and we enrolled 28 subjects in this trial. One subject has since withdrawn as they do not wish to participate in any further blood tests.

In 2015, most of the children have been seen for their visit 2 year post vaccination visit. At this visit a blood sample was taken to measure the levels of immunity to both the Hib and MenC component of the vaccine. These children are then due to return for their last visit with us in 2017.

### **Funders of the project**

GlaxoSmithKline

### **FOLLOW UP OF IMMUNOGENICITY AND SAFETY OF ACELLULAR PERTUSSIS VACCINE GIVEN AT BIRTH TO 4 YEARS OF AGE.**

*Associate Professor Peter Richmond, Dr Tanya Stoney, Dr Gabriela Willis*

This was an open labelled study which is following up children to 4 years of age following administration of pertussis (Pa) vaccine at birth. Participants received either the normal scheduled pertussis containing vaccine (Infanrix-IPV) with

Measles, Mumps Rubella (MMR) vaccine or the lower dose pertussis containing vaccine (Boostrix-IPV) with MMR vaccine at 4 years of age.

97 Children enrolled in the previous pertussis at birth study either received the pertussis vaccine at birth (4 doses of Pa by 12 months of age) or the normal infant immunisation schedule (3 doses of Pa vaccine by 12 months of age). Some of these children also received a booster dose of pertussis containing vaccine at 18 months of age.

There were 6 different groups, depending upon which vaccine schedule the child received in the previous studies. Comparison will be made between levels of protection against pertussis in these children when they receive their 4 year booster vaccines. Any adverse reactions following an alternate pertussis boosting schedule will be evaluated.

Parents of participants who had already received 4 year vaccinations or were not willing to participate in the study were asked to complete a brief telephone questionnaire about reactions that may have occurred after the 4 year old vaccinations.

The last subject's last visit was on 20 January 2016 with 26 participants enrolled in the study and 46 questionnaires completed for children who did not enroll in the study and received their 4 year vaccinations elsewhere.

### **Plain Language summary**

This study followed up children who participated in the Pertussis at Birth Study (received 4 doses of Pertussis vaccine

by 12 months of age) and those that participated in the Pertussis Follow on Study (received a booster dose of Pertussis containing vaccine). The levels of protection against pertussis in these children were compared when they received their 4 year booster vaccines. Any reactions that occur following vaccination at 4 years were also assessed.

### **Funders of the project**

National Health and Medical Research Council

## **EFFICACY, IMMUNOGENICITY, AND SAFETY STUDY OF CLOSTRIDIUM DIFFICILE TOXOID VACCINE IN SUBJECTS AT RISK FOR C. DIFFICILE INFECTION**

*Associate Professor Peter Richmond, Dr Tanya Stoney, Dr Gabriela Willis*

This study aims to assess the efficacy of a Clostridium difficile toxoid vaccine in preventing the onset of Clostridium difficile Infection (CDI) in adults aged  $\geq$  50 years who are at risk for CDI and have received at least 1 injection. The study is a randomized, observer blind, placebo controlled, multicentre, multinational Phase III trial in 15,000 subjects.

Adults aged  $\geq$  50 years are enrolled in 1 of 2 risk strata across the treatment groups. Risk Stratum 1: Has had at least 2 hospital stays, each lasting at least  $\geq$  24 hours, in the 12 months before enrolment and has received systemic (not topical) antibiotics in the 12 months before enrolment. Risk Stratum 2: Is anticipated to have an inpatient hospitalization for a planned surgical procedure within 60 days of enrolment.

Participants are randomly assigned in a 2:1 ratio to receive either vaccine or placebo. Vaccine or placebo is administered in a 3 dose schedule on Days 0, 7, and 30. All subjects are actively followed for efficacy throughout the follow up period, which may extend for up to 3 years after the last injection. To December 2015 there were 26 participants enrolled in the study at Vaccine Trials Group. Recruitment is challenging due to the selection criteria and lack of awareness of CDI within the target population.

### **Plain Language summary**

This study is investigating a trial vaccine that hopes to prevent Clostridium difficile Infection (CDI) in adults aged 50 years or greater who are at risk for CDI. Participants will be placed into 1 of 2 risk groups that reflect the risk factors for developing CDI including previous and proposed hospitalisation and antibiotics use. Participants will be followed for up to 3 years to determine the effectiveness of the vaccine in preventing CDI in these at risk adults.

### **Funders of the project**

Sanofi Pasteur

## **A PHASE IB, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY OF THE SAFETY, TOLERABILITY, PRELIMINARY EFFICACY AND PHARMACODYNAMICS OF BTD-001 IN YOUNG ADULTS AND ADOLESCENTS WITH DOWN SYNDROME.**

*Associate Professor Helen Leonard,*



Associate Professor Peter Richmond,  
Dr Tanya Stoney, Dr Gabriela Willis, Dr  
Kingsley Wong

The aim of this study was to evaluate the safety and tolerability of 50 and 100 mg BID and BTD-001 (pentylentetrazole) in persons with Down syndrome aged 13 to 35 years. In mouse studies, administration of PTZ led to sustained reversal of cognitive deficit associated with Down Syndrome. These data suggest that BTD-001 may improve function and cognition in persons with Down syndrome. The study doses are also consistent with available non-clinical toxicity and efficacy data.

In addition to safety and tolerability this study aimed to evaluate cognitive and behavioural/functional effects of BTD-001 in persons with Down syndrome as reflected by psychometric and functional measures this was a multi-centre, parallel group study. Subjects were recruited for study participation from Australia. Two dose levels of study drug were being evaluated in a placebo controlled design. Subjects (13 to 35 yrs. in age) were randomized with stratification in two levels by age (less than 18 or 18 and older). Prior to administration of first dose a visit took place to establish baseline measurements of cognitive function, adaptive behaviour scoring and evoked response measurements. Study drug was given for 12 weeks. Measurements of cognitive function, adaptive behaviour and ERP were made at 4 weeks, 12 weeks and 16 weeks. Safety was monitored throughout the study.

The study closed with 88 participants enrolled for a target of 90 in Australia. At

Telethon Kids Institute 26 participants were screened with 20 enrolled and completed in the study. The last visit was completed on 19 May 2015.

### Plain Language summary

This study was investigating a medicine called BTD-001 to determine if it is safe and effective in helping people with Down syndrome to improve their ability to think and solve problems. The medicine was taken with a juice flavoured drink once per day for 12 weeks. Participants were required to attend a screening visit to confirm eligibility for the study and if eligible, another 6 visits to assess general health and to complete psychological tests to assess thinking and problem solving.

### Funders of the project

Balance Therapeutics Pty Ltd

## **A PROSPECTIVE COHORT STUDY OF MOTHER-INFANT PAIRS ASSESSING THE EFFECTIVENESS OF MATERNAL INFLUENZA VACCINATION IN PREVENTION OF INFLUENZA IN EARLY INFANCY.**

Associate Professor Peter Richmond

The primary aim of the FluMum Study is to determine the effectiveness of maternal influenza vaccine in pregnancy against laboratory confirmed influenza among infant offspring during the first 6-months of life. Also while conducting this study we aim to:

- Establish the first national system of validated annual influenza vaccine uptake in pregnancy.
- Monitor annual changes in vaccine

uptake over time within each of the participating sites.

- Assess the factors that influence the decision to receive influenza vaccination during pregnancy and examine why women are not being vaccinated in pregnancy.
- Estimate the effectiveness of maternal influenza vaccine in pregnancy against laboratory confirmed influenza in the mother during pregnancy and hospitalization of the infant with acute lower respiratory infection (ALRI) during the first six months of life.

All 10,106 mother-infant pairs have been recruited in six study sites (Darwin, Brisbane, Sydney, Melbourne, Adelaide and Perth) this occurred over four consecutive influenza seasons (2012-2015). The 6 month follow up period continues for those infants born in 2015 to evaluate the levels of influenza.

### Funders of the project

National Health and Medical Research Council

## **CHIRRP - COMBATING HAEMOPHILUS INFLUENZA RELATED RESPIRATORY PATHOLOGY. A MULTI-CENTRE, DOUBLE-BLIND, RANDOMISED CONTROLLED TRIAL TO EVALUATE THE EFFICACY OF 10 VALENT-PNEUMOCOCCAL-PROTEIN D CONJUGATE VACCINE COMPARED TO QUADRIVALENT (ACYW135) MENINGOCOCCAL CONJUGATE VACCINE IN REDUCING RESPIRATORY EXACERBATIONS IN CHILDREN AGED ≥ 18 MONTHS AND <18 YEARS WITH SUPPURATIVE LUNG DISEASE**

*Dr Kerry-Ann O'Grady, Dr Andrew Wilson,*

*Associate Professor Peter Richmond, Dr Ruth Thornton, Dr Tanya Stoney, Dr Gabriela Willis*

Non-typeable *Haemophilus influenzae* is the most common bacterial pathogen associated with exacerbations (cough and infection) in chronic suppurative lung disease (CSLD). The aim of this study was to determine if a vaccine known as Synflorix, will reduce respiratory exacerbations in children with CSLD from this bacteria. In this double blinded randomised controlled trial, children between 18 months and 18 years of age are randomised to receive either the trial vaccine Synflorix (10 valent pneumococcal – Protein D conjugate vaccine) or the control vaccine Menactra (Meningococcal Groups ACWY 135 conjugated vaccine). This is a multi-centre trial with The Vaccine Trials group in Perth and other sites in Brisbane Sydney and Melbourne. The aim for the study was to enrol a total of 206 children across Australia.

The duration of this study for each participant was 14 months. During the study, there were 5 visits and fortnightly phone calls to go through a cough questionnaires. Each child had a minimum of 2 blood tests, and they also had a nasopharyngeal (nose) swab and saliva sample taken at each of their 5 visits to the clinic. The first participant for this study was enrolled on 26th March, 2013. Perth site enrolled 23 children in the study at The Vaccine Trials Group. Recruitment at the Perth Site ceased in August, 2014 with the last patient being recruited on the 11th August, 2015. All visits were completed by 14th October, 2015. Of the enrolled children, 20 completed all visits, 2 participants withdrew from the study and one participant was a screen failure.



Brisbane site ceased recruitment on 25th September, 2015 and have enrolled 38 participants, Sydney site ceased recruitment on 16 Feb 2015 and have enrolled 5 children. Melbourne is the only site yet to complete their last visits due mid-2016.

In order to answer the main aim of the study, 206 children were required to be enrolled in this study. After 2 years of recruitment, this target has not been achievable within the remaining resources available.

There are a number of reasons why we have not been able to meet this target, the main ones being the lack of children who have had 2 flare-ups in the 18 months prior to enrolment and other clinical trials underway in this population. However, the information from the participants and the specimens collected throughout the study will still provide very important, world first, information about flare-ups and immunity in children with recurrent wet coughs. This information will contribute to finding a way to preventing flareups in these children. The fortnightly follow-up data are also still of value with respect to better understanding flare-ups in children and in designing future studies and interventions. All samples will be analysed in the future and participants will be un-blinded in 2016.

### **Funders of the project**

National Health and Medical Research Council

## **DISSOLVING THE GLUE IN GLUE EAR: ASSESSMENT OF THE USE OF DORNASE ALFA AS AN ADJUNCT THERAPY TO VENTILATION TUBE INSERTION.**

*Associate Professor Peter Richmond, Dr Ruth Thornton, Clinical Professor Harvey Coates, Clinical Associate Professor Shyan Vijayasekaran, Mr Peter Jacoby, Dr Selma Wiertsema, Dr Lea-Ann Kirkham, Mr Paul Bumbak.*

Middle ear infections (otitis media, OM) are the most common reason a child will visit their doctor and be prescribed antibiotics. These often don't work on the chronic or recurrent nature of the infections and some children go on to require surgery. Our research group have demonstrated that the presence of bacteria in biofilm within the middle ear contributes to the persistence and recurrence of ear infections. We have also shown that these biofilms can stay in the ears in big nets of DNA that are produced by the children's own immune responses. This study is a Phase IIB trial to look at the safety, tolerability and efficacy of the off-licence use of Dornase alfa (an agent to cut up the extra DNA) in reducing future ventilation tube insertions in children with chronic otitis media effusion and recurrent acute otitis media.

We believe that the application of Dornase alfa into the middle ears of children at the time of Ventilation Tube insertion surgery will:

1. Reduce blockage of ventilation tubes and suppurative complications.
2. Delay the time to re-infection, thereby reducing the rate of repeat ventilation tubes in children.

To be eligible for this study the child must

be between 6 months-5years of age (not have had their 6th Birthday). To be undergoing surgery for ventilation tube insertion for recurrent acute otitis media and or otitis media effusion for the first time and have had bilateral fluid for 3 months or longer.

The study runs for 24 months involving 10 visits 3 months apart. Visit 1 is the day of surgery where a saliva swab is taken, then under anaesthetic a blood sample, nasopharyngeal swab, throat swab and adenoid biopsy (only if the child is having their adenoids removed) is collected. This study is double-blinded where the child will have the investigational treatment (Dornase alfa) administered in one ear and the same volume of 0.9% sodium chloride (salty water) administered to the alternate ear at the time of surgery. Follow up visits involve appointments at the Vaccine Trials group where a questionnaire is completed and the child will have their ear health checked. The recruitment target was 60 children which was achieved on the 8th April, 2014. The first participant was recruited on 24th May 2012 and last participant on the 8th April, 2014. 39 participants have completed last visit 10 with 11 visits remaining, 2 remaining to finish Visit 9. All visits should be completed by May 2016

### **Funders of the project**

State Health Research Advisory Council Grant, Princess Margaret Hospital for Children Translational Research Grant.

## **A PHASE III, RANDOMISED, OPEN, CONTROLLED, MULTICENTRE, PRIMARY VACCINATION STUDY TO EVALUATE THE IMMUNOGENICITY AND PERSISTENCE OF 1 AND 2 DOSES OF GLAXOSMITHKLINE BIOLOGICALS' MENINGOCOCCAL CONJUGATE VACCINE MENACWY-TT IN TODDLERS (AFTER 1MONTH AND UP TO 5 YEARS) AND TO DEMONSTRATE NON-INFERIORITY OF CO-ADMINISTRATION OF MENACWY-TT AND PFIZER'S 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE PREVENAR 13™ VERSUS SEPARATE ADMINISTRATION OF THE 2 VACCINES**

*Associate Professor Peter Richmond, Dr Tanya Stoney, Dr Gabriela Willis*

Meningococcus (*Neisseria meningitidis*) is a germ that causes serious diseases such as meningitis and blood infection. Different strains of this germ exist. The vaccine being trialled protects against four strains of meningococcus – A, C, W and Y – with C being the only strain that Australian children are currently vaccinated against under the National Immunisation Program at 12 months of age.

The study is being done to determine if toddlers should receive either 1 or 2 doses of the MenACWY vaccine and also if it can be given at the same time as another vaccine called Prevenar13 (Pneumococcal vaccine). In Australia Prevenar13 is offered to babies at 2, 4 and 6 months of age as part of the National Immunisation Program, however in Europe and America it is given at 12 months. We are hoping to see that giving this vaccine in a combination form does not impact on other vaccines given at the same time.



The study involves attending 5 or 7 clinic visits (depending on whether the child is allocated to receive 1 or 2 doses). After the initial visits the child is required for follow-up appointments 1, 3 and 5 years after the vaccine. This is an International study sponsored by GSK, where children have been recruited in multiple regions including Australia, North America and Europe.

There are 7 participants enrolled in Perth. The next visits are due in 2017.

### **Funders of the project**

GlaxoSmithKline Biologicals

### **A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 2-PART STUDY OF ORALLY ADMINISTERED ALS-008176 TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF SINGLE ASCENDING DOSING AND MULTIPLE ASCENDING DOSING IN INFANTS HOSPITALIZED WITH RESPIRATORY SYNCYTIAL VIRUS (RSV) INFECTION**

*Associate Professor Dr Peter Richmond, Dr Tanya Stoney, Dr Gabriela Willis*

Respiratory Syncytial Virus (RSV) is one of the viruses that cause the 'common cold', leading to coughing, fever, sore throat, and a runny nose that usually lasts for about 1-2 weeks. Most babies who get RSV recover fully to normal health after 1-2 weeks, but RSV infection can sometimes worsen and lead to severe cases of chest infection in children.

There are no vaccines approved for the prevention of RSV infection in healthy

children. There are no routinely used medications available for the treatment of RSV.

Pharmaceutical companies are trying to find new medicines to help these children get better quickly when they are sick with RSV infection.

This is a two part study. The first part of the study requires administration of a Single Ascending dose (SAD) of the medication to the participant and the second part of the study administers multiple ascending doses (MAD) of the medication 12 hourly over 5 days to the participant. The purpose of this research is to look at the effects of the new drug called ALS-008176, which Alios BioPharma Inc. (the Study Sponsor) is developing for use in children infected with RSV.

This study drug is considered an experimental medication as it is still being developed and has not yet been approved for sale by the Regulatory Authorities in the countries where this study is being conducted, including the Therapeutic Good Administration.

ALS-008176 is an antiviral medication (it attacks the RSV virus that causes the infection). It is given by mouth as a liquid. The study drug prevents the virus from dividing and making more copies of itself. In this way, it is hoped that the study drug may control the RSV infection and speed up recovery.

The study drug has been tested in adults who have been infected with RSV. In that study, the drug significantly reduced the amount of virus and also reduced the duration, signs and symptoms of RSV

infection.

Up to 144 participants will be enrolled into the first part of the study where infants will be given a single dose of study drug. Blood tests, nose swabs and an ECG are also required. This study will take 7 or 8 days to complete.

Up to 120 participants will be enrolled into the second part of the study where infants will be given 10 doses of the study drug over 5 days. This study will take 11 or 12 days to complete.

This is an International study with approximately 50 sites involved recruiting in Europe, Asia Pacific, South Africa, and North/Latin America. As of Dec 2015 67 participants have been enrolled in the SAD and 10 participants have been enrolled in the MAD with no safety concerns reported.

### Funders of the project

Alios BioPharma Inc

**HEALTH CARE WORKERS (HCWS) IN PAEDIATRIC HOSPITALS HAVE BEEN RECOMMENDED TO RECEIVE PERTUSSIS BOOSTER IMMUNISATIONS (AUSTRALIAN IMMUNISATION HANDBOOK 2013) AS THEY ARE BOTH AT INCREASED EXPOSURE TO PERTUSSIS IN THE HOSPITAL AND CAN CAUSE NOSOCOMIAL TRANSMISSION TO THEIR PATIENTS. IT IS NOW ALMOST 10 YEARS SINCE BOOSTRIX™ WAS INTRODUCED INTO WESTERN AUSTRALIA (2004) WITH HIGH UPTAKE BY EMPLOYEES AT PRINCESS MARGARET HOSPITAL**

**FOR CHILDREN IN PERTH AND HEALTH CARE WORKERS ARE BEING OFFERED REVACCINATION. LITTLE IS KNOWN ABOUT THE DURATION OF PERTUSSIS IMMUNITY IN ADULTS. NO STUDIES HAVE YET PROVIDED AN IN-DEPTH ANALYSIS OF THE IMMUNE RESPONSES INDUCED BY ACELLULAR PERTUSSIS VACCINES AND HOW FAST THESE MAY WANE OVER TIME. INVESTIGATIONAL MEDICINAL PRODUCT: ADULT FORMULATION DIPHTHERIA-TETANUS-PERTUSSIS VACCINE (BOOSTRIX™, DTPA 0.5ML)**

*Associate Professor Peter Richmond, Dr Tanya Stoney, Dr Gabriela Willis*

Despite long-term high pertussis vaccine coverage, Australia has the highest recorded all-age incidence of pertussis in the world. Little is known about the duration of pertussis immunity in adults. Health care workers (HCWs) in paediatric hospitals have been recommended to receive pertussis booster immunisations (Australian Immunisation Handbook 2013) as they are both at increased of exposure to pertussis in the hospital and have causing nosocomial transmission to their patients. It is now almost 10 years since Boostrix™ was introduced into Western Australia (2004) with high uptake by employees at Princess Margaret Hospital for Children in Perth and health care workers are being offered revaccination although little is known about the persistence of antibody and reactogenicity and immunogenicity of booster vaccination. We propose to use this unique opportunity of a cohort of HCWs being offered booster dTpa immunisation to study the duration of both serologic and CMI immunity in adults and the immunogenicity and reactogenicity to booster immunisation in comparison to HCWs and researchers working with



children receiving dTpa vaccine for the first time. The assays developed for assessment of B-cell and T-cell immunity in this study will also be able to be transferred to paediatric populations and should help guide development of optimal vaccine schedules and development of new vaccines to help prevent this serious infection.

The aim of the study is to recruit 150 healthy adult health care workers between the age of 23-64 years employed in the Child and Adolescent Health Service, University of WA School of Paediatrics and/or Telethon kids Institute. Participants will be allocated into 2 groups depending upon whether or not they have previously received a booster for pertussis. Group 1. Received dose in the last 5-10 years or Group 2. Not since <15 years.

There are 4 study visits. The licensed vaccine Boostrix (Tetanus, Diphtheria and Pertussis) will be given to both groups as a single intramuscular dose at the first visit. A diary card will be given at this visit and reviewed day 7 and day 28 for any adverse events. At each visit a blood test of approx. 25-30ml is also required to assess antibody response.

As of December, 2015 we have 1 participant enrolled in this study.

### **Funders of the project**

GlaxoSmithKline

### **PAEDIATRIC ACTIVE ENHANCED DISEASES SURVEILLANCE (PAEDS)**

*Dr Christopher Blyth, Associate Professor Peter Richmond, Dr Tom Snelling, Associate Professor Kristine McCartney, Professor Elizabeth Elliott, Associate Professor Yvonne Zurynski, Professor Peter McIntyre, Professor Robert Booy, Associate Professor Nicholas Wood, Dr Jim Buttery, Dr Nigel Crawford, Associate Professor Helen Marshall, Dr Michael Gold, Dr Julia Clark and Dr Anne Kynaston.*

Children's hospitals are uniquely placed to monitor key conditions or complications. Given the importance of vaccines in preventing childhood disease, key vaccine preventable conditions and severe side effects from vaccine are monitored in 5 paediatric hospitals in Australia. These data are compiled and used to inform public health authorities and the Australian Immunisation Program. Plain Language summary: In 2015, PAEDS continues to conduct surveillance for six main conditions, which are either vaccine preventable diseases (VPDs), potential adverse events following immunisation (AEFI) or other important conditions of importance from a public and child health perspective. These conditions are:

1. Acute flaccid paralysis (AFP) – 8 recruited by PMH & 46 Nationally
2. Acute childhood encephalitis (ACE) - 48 recruited by PMH & 217 Nationally
3. Influenza (via a collaboration with FluCAN) – 242 recruited by PMH & 2070 Nationally
4. Intussusception (ISS) – 18 recruited by PMH & 63 Nationally
5. Pertussis (PSS) – 4 recruited by PMH & 74 Nationally
6. Varicella/herpes zoster (from varicella zoster virus, VZV) – 9 recruited by PMH & 38 Nationally

Surveillance for febrile seizures, with a particular emphasis on those occurring following vaccination with measles-containing vaccines, ceased in mid-2014. PAEDS commenced a pilot study of capturing and assessing vaccine exposure in children admitted with severe Neurological Events (SNE), such as encephalitis, Guillian - Barré syndrome, transverse myelitis and hospitalised febrile seizures in May 2015. This surveillance helps provide reassurance to the public regarding vaccine safety, in conjunction with other systems for active prospective surveillance.

We are also preparing to implement active prospective surveillance for invasive meningococcal disease (IMD) in children. PAEDS is working with state health departments to ensure we can obtain rich clinical, demographic and vaccine data to better understand the burden of this serious disease.

### **Funders of the project**

Commonwealth Department of Health;  
WA Department of Health.

### **FLUCAN - A RAPID ALERT SYSTEM FOR SEVERE RESPIRATORY ILLNESS (THE FLUCAN SURVEILLANCE SYSTEM)**

*Dr Christopher Blyth, Allen Cheng, Paul Kelly, Tom Kotsimbos, Heath Kelly, Tony Korman, Deb Friedman, Louis Irving, Sanjaya Senanayake, Grant Waterer, Simon Brown, Mark Holmes, Cameron Hunter, Simon Bowler, John Upham, Graham Simpson, Stephen Brady, Saliya Hewagama, Dominic Dwyer, Jen Kok, Peter Wark, Kristine Macartney.*

The main aim of the study is to provide timely surveillance data to public health authorities on severe influenza. This complements data collected in sentinel general practices on influenza across Australia, and helps public health authorities form a picture of influenza activity.

In addition, we are also able to see if the seasonal influenza vaccine is protective against hospitalisation with influenza by collecting data on patients presenting with respiratory symptoms are diagnosed with and without influenza.

### **Plain language summary**

The number of admissions with confirmed influenza was the highest since we started in 2009 – across all sites in the 2015 season, 2070 cases of influenza were reported. Since April, around half of cases (46%) were >65 years of age, with 75% reporting known medical comorbidities. A high proportion of admissions were associated with influenza B (51%). This varied by hospital, with influenza B being the most common at Princess Alexandra Hospital (Qld; 70%) and the least com-mon at the Royal Hobart Hospital (37%). Overall, 7.6% of cases were admitted to ICU.

In an interim analysis, we estimated that vaccination with the 2015 trivalent seasonal influenza vaccine reduced the risk of hospitalisation with influenza by 43% in the 2015 influenza season. This is slightly lower than in previous years, this is due to the fact, in part, that two B strains that circulated where only one was covered by the trivalent vaccine.



## Funders of the project

Commonwealth Department of Health and Ageing

## **FEBRILE SEIZURES FOLLOWING VACCINATION IN CHILDREN: WHAT IS THE LONG-TERM CLINICAL AND DEVELOPMENTAL OUTCOME?**

*Associate Professor Peter Richmond*

### Plain Language summary

Febrile seizures are common in children aged 6 months to 6 years peaking in the second year of life and triggered by a sudden change in temperature. The aim of this study is to classify and describe the clinical, cognitive, behavioural and revaccination outcomes of children who have experienced a Febrile Seizure after vaccination. Secondly to determine if there are any genetic markers predisposing to febrile seizure. This will be compared to children who have had a vaccine distant febrile seizure and to those without a history of febrile seizure. Funders of the project: National Health and Medical Research Council

### External collaborators

The Children's Hospital at Westmead NSW, Royal Children's Hospital Vic, Epilepsy Research Centre, Women's and Children's Hospital SA

## **TESTOV PNEUMO- EVALUATION OF THE EFFECTIVENESS OF THE 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE AGAINST PNEUMOCOCCAL PNEUMONIA IN CHILDREN**

*Dr Thomas Snelling, Dr Andrew Martin*

## Plain language summary

Pneumonia remains a major cause of childhood morbidity and the number one cause of deaths of children globally. *Streptococcus pneumoniae* is the leading cause of pneumonia with over 90 strains. The aims of the study are to determine what the contribution of pneumococcus is to hospital presentations for pneumonia, in Australian children. To identify what are the factors that contribute to these infections. How effective is 13vPCV vaccination in preventing disease. Funders of the project: National Health and Medical Research Council

### External collaborators

Sydney Children's Hospital NSW, The Children's Hospital Westmead NSW, Lady Cilento Children's Hospital Qld, Royal Darwin Hospital NT, Women's & Children's Hospital SA, Royal Children's Hospital Vic, John Hunter Hospital NSW, Royal Hobart Hospital Tas, Monash Medical Centre Vic, Alice Springs Hospital NT

## **PNEUMOWA: A CASE-CONTROL STUDY OF THE ROLE OF VIRAL AND BACTERIAL PATHOGENS IN CAUSING PNEUMONIA AMONG WESTERN AUSTRALIAN CHILDREN**

*Dr Christopher Blyth, Dr Tom Snelling, Professor David Smith, Dr Andrew Martin, Associate Professor Meredith Borland, Associate Professor Peter Richmond*

### Plain Language summary

The primary aim of this study is to determine which specific viruses and bacteria contribute to childhood pneumonia in Western Australia. Additionally, to determine the frequency,

predictors and clinical significance of respiratory virus-bacterial co-infection. To assess whether there is a relationship between the loads of specific viruses and bacteria and to assess whether load varies between children with pneumonia (both mild and severe) and community controls. In the future, we wish to establish a biobank for future studies on childhood pneumonia and respiratory infections

### **Funders of the project**

Telethon-Perth Children's Hospital  
Research Fund

External collaborators: Sydney Children's  
Hospital NSW, PathWest Laboratory  
Medicine WA, Menzies School of Health  
Research NT

### **WEST AUSTRALIAN INFLUENZA VACCINE EFFECTIVENESS (WAIVE) STUDY**

*Dr Chris Blyth, Associate Professor Peter  
Richmond, Paul Effler, Anthony Keil, David  
Smith, Heath Kelly, Peter Jacoby, Hannah  
Moore, Avram Levy, Dr Gabriela Willis,  
Meredith Borland*

This prospective study is designed to evaluate the effectiveness of trivalent influenza vaccine (TIV) in young children and to assess the burden of influenza in young children and their families. Children aged between 6 months and 5 years presenting to Princess Margaret Hospital for Children (PMH) Emergency Department or admitted to a hospital ward with an influenza-like-illness (ILI) are eligible for enrolment. Children were swabbed to test for influenza and other common respiratory viruses, and influenza vaccination status was checked via

parental questionnaire and ACIR/GP verification. The study has been running since 2008.

In 2015 recruitment occurred only in the Emergency Department as hospitalised children with influenza were captured via another research project (FluCan). A total of 549 children were enrolled into the study between 15th June and 2nd November 2015, with 23 withdrawals, predominately because a respiratory sample was not taken after consent was obtained. Influenza was detected in 54 children (10.25%) and because of the low numbers there was insufficient power to calculate vaccine effectiveness for 2015. However, these numbers will add to the overall analysis, which now captures 7 influenza seasons (2008-2015).

With data collected over the influenza seasons, the WAIVE study has been able to demonstrate that the overall vaccine effectiveness of TIV is 65% in children. This is comparable to the effectiveness in young adults. It also has demonstrated that TIV is effective in children under 2 years of age. 2015 saw a slight increase in the uptake of the free influenza vaccine for children under 5 years of age. In the cohort 11.5% were fully vaccinated and 12.5% were partially vaccinated. Despite demonstrated vaccine effectiveness, vaccine uptake is still low. Data collected as part of this project has also been used to assess the impact of influenza illness in young children, the validity of the Australian Central Immunisation Register (ACIR) for influenza vaccine status in young children, and the attitudes of parents towards influenza illness and vaccine.



## Plain Language summary

Influenza vaccination is recommended for all children in Western Australia age 6 months to 5 years. To date, there has been little evidence demonstrating that influenza vaccination prevents influenza in very young children. The data from this study demonstrate that the influenza vaccination prevents 2 out of 3 children from presenting to hospital with influenza.

## Funders of the project

WA Department of Health

## AUSVAXSAFETY

*Kristine Macartney, Nick Wood, Gulam Khandaker, Alexis Pillsbury, Dr Christopher Blyth, Dr Tom Snelling, Associate Professor Peter Jacoby, Associate Professor Peter Richmond, Annette Regan, Alan Leeb, Paul Effler, David Durrheim, Patrick Cashman, Craig Dalton, Brendan McMullan, Nigel Crawford, Jim BATTERY, Peter Eizenberg, Michael Crampton, Susan Vlack, Kari Jarvinen, Michael Gold, Gabriella Lincoln and Rosalind Webby.*

Building upon the FAST study (2011-2013), this national collaboration undertook prospective parental survey to identify any significant increase in adverse events following a seasonal trivalent inactivated influenza vaccine (TIV). Parents of children receiving the flu vaccine received a SMS message three days after their child was vaccinated asking them whether the child experienced an adverse event following the immunisation. The number of children we have been able to follow up has greatly increased in the last two years due to some clever new technology called SmartVax developed by Dr Alan Leeb, a

Perth GP, and Ian Peters. This innovative tool uses SMS and smartphone technology to greatly reduce the manpower required to perform this essential surveillance. Between 1 April 2015 and 31 August 2015, a total of 4441 parents/carers were offered participation and 4396 (99.0%) participants were enrolled and sent SMS and/or emails. Of those enrolled, there were 3340 (76.0%) survey completions. Western Australia was the jurisdiction that provided the largest amount of surveys, with 2,434 children who received the flu vaccine completing surveys.

Overall, 11.5% (95% CI: 10.5–12.7) reported any systemic and/or local reaction within 3 days of receiving an influenza vaccine. Fever was reported in 4.4% and injection site reactions in 2.0%. Medical attention was sought in 1.1% of children following vaccination, and there were four serious adverse events (three children, all with underlying neurological condition and prior seizures, experienced seizures and attended an Emergency Department) More information can be found on the following website - [www.ncirs.edu.au/surveillance/ausvaxsafety/index.php](http://www.ncirs.edu.au/surveillance/ausvaxsafety/index.php)

## Plain language summary

This study follows up children who have had an influenza vaccine, and asks their parents (via SMS and email) whether the child had any reaction. The study shows only 11.5% have any side effects from the vaccine. Most of these are mild and last 1-2 days e.g. a sore arm or a fever. Only 1.1% attend a GP or ED after the vaccine. This study reassures us that flu vaccines are safe in young children.

## Funders of the project

Commonwealth Department of Health,  
WA Department of Health  
External collaborators: National Centre for  
Immunisation Research and Surveillance  
(NCIRS), NSW

## **EVALUATION OF A COMPLEX INTERVENTION TO INCREASE UPTAKE IN SCHOOL HPV VACCINATION PROGRAM**

*Rachel Skinner, Spring Cooper, Helen  
Marshall, Dr Tanya Stoney, Kevin  
McGeechan, David Regan and Patricia  
Whyte*

### **Plain Language summary**

The primary aim is to increase the school-based uptake of the human papillomavirus (HPV) vaccination. Secondary aims are to improve program logistical outcomes, knowledge and attitudes, decision making involvement and reduce fear in adolescents receiving the vaccine.

During 2013 and 2014 forty secondary schools across WA and SA participated in this study.

The schools were randomly allocated to the study intervention (receive intervention) or wait-list control (receive intervention the following year). The intervention consisted of adolescent education resources (in-school teaching with teacher training, take home information, app and website for use in schools and out); and methods for distraction/relaxation on vaccination day; an information brochure and decisional support tool for adolescents and parents; and logistical strategies targeting consent

form return rates, vaccination-room setup and in-school mop-ups.

Students at participating schools were invited to complete a questionnaire on 3 occasions throughout the school year (pre and post-vaccination) to determine changes in adolescent knowledge, confidence with vaccination and decision-making. Information about the school vaccination day was also collected by immunisation nurses and supervising school staff on the day. Finally another important aspect of the study was the qualitative component, which helps to “put meaning to the data”. The gathering of this information has been through interviews and focus groups with interested immunisation nurses, students, parents/guardians and school staff who have been involved in the Year 8 immunisation program.

It is hoped that the intervention will have a positive impact on vaccination coverage, adolescent HPV vaccination experience and ease of running the school-based vaccination program.

Analyses is on-going with preliminary results indicating that participants in the intervention group were more informed about HPV and vaccination, were slightly more involved in the decision making process about vaccination and reported less anxiety about vaccination.

### **Funders of the project**

National Health and Medical Research Council, bioCSL.



## **BRIGHTHEARTS: USING BIOFEEDBACK MEDIATED RELAXATION TECHNIQUES DURING VACCINATION OF CHILDREN AND ADOLESCENTS**

*Tanya Stoney, Cristyn Davies, Rachel Skinner, Kevin McGeechan, Angie Morrow, George Khut*

### **Plain Language summary**

This study aims to reduce student experience of pain, fear and anxiety associated with school-based vaccinations.

To address adolescent vaccine-related fear and anxiety, we are trialling the BrightHearts 'app' with students who are eligible for vaccination as part of the School-based Immunisation Program. BrightHearts is an award-winning artwork and mobile 'app', (2012 Australian Business Arts Foundation: Arts and Health Foundation Award, and 2012 National New Media Art Award, Queensland Art Gallery) developed at The Children's Hospital at Westmead, NSW, for the purpose of teaching children relaxation techniques to cope with pain. BrightHearts uses an iPad to display a colourful geometric artwork that responds to changes in heart rate transmitted by a wireless pulse monitor worn on a person's wrist. An auditory component responds to decreases in heart rate by producing musical sounds. Participants use slow exhalation and focus on relaxing feelings to decrease their heart rate and animate the sounds and visuals on the BrightHearts app. The goal of the interaction is to voluntarily decrease one's heart rate to change the colour on the screen – from orange to yellow, to green and eventually blue – indicating that the heart rate has

reached its lowest rate since the start of the session.

Our aim is to recruit a total of 120 students from three secondary schools. To date a total of fifty-five students have taken part with recruitment to conclude in March 2016. Consenting students are randomised to either use the App before and during their vaccinations or to follow the normal vaccination day processes. After vaccination all students complete a short questionnaire asking questions about how they usually feel and how they felt before and during vaccination, including whether they experienced any pain, fear or anxiety. If they use the BrightHearts app they will also be asked what they thought about this. Interviews have also been completed with immunisation nurses, school health nurses and teachers regarding their opinions about the app.

### **Funders of the project**

Princess Margaret Hospital Foundation Seeding Grant

### **A PHASE 2, RANDOMISED, CONTROLLED, OBSERVER-BLINDED STUDY , CONDUCTED TO DESCRIBE THE IMMUNOGENICITY, SAFETY AND TOLERABILITY OF A NEISSERIA MENINGITIDIS SEROTYPE B BIVALENT RECOMBINANT LIPOPROTEIN 2086 VACCINE (BIVALENT RLP2086) WHEN ADMINISTERED TO HEALTHY TODDLERS AGED 12 TO <18 MONTHS OR 18 TO <24 MONTHS**

*Associate Professor Peter Richmond, Dr Tanya Stoney, Dr Gabriela Willis*

The purpose of this study is to investigate a new vaccine against Meningococcal

B disease when administered to healthy toddlers aged 12-24 months. The trial will describe the immune response and evaluate the safety profile by comparing two different dose strength (60mcg & 120mcg) of the vaccine.

A vaccine against meningococcal B is not currently available on the Australian Immunisation Schedule but it is available privately (Bexsero).

Participants are randomly assigned in a 2:1 ratio to receive either the study vaccine or the control (HAV- Hepatitis A vaccine). Vaccine or control is administered in a 3 dose schedule at 0, 2 and 6 months.

At the end of 2015 there were 6 participants enrolled at the Vaccines Trial Group. Recruitment has been slower than expected initially due to Hepatitis A being used as a control. Many of the participants required Hepatitis A for travel to countries in the region. These participants had previously received Hepatitis A vaccine or required vaccination in the near future for planned travel. The study commenced in September 2015 and recruitment will continue until June 2016.

Lay summary for your project: The study is investigating a new vaccine against Meningococcal B disease in toddlers aged 12-24 months. Meningococcal B is a serious and rapid onset infection that can cause death within hours. Children are routinely vaccinated against disease caused by the C strain but not the B strain. The B strain is the most common in Western Australia. Children on the study are randomised to receive either the

study vaccine or a control (Hepatitis A vaccine). The study will collect information on the immune response (how well the child makes antibodies after having the vaccine) and safety (side effects) of the Meningococcal B Vaccine.

### **Funders of the project**

Pfizer

## **2015 Success**

### **THESES PASSED**

Pickering, Janessa - PhD, University of Western Australia, Diversity of nontypeable Haemophilus influenzae colonizing Australian Aboriginal and non-Aboriginal children.

Willis, Gabriela, Master of Public Health, University of Western Australia, The Impact of Influenza Illness in Young Children in metropolitan Western Australia

### **AWARDS AND PRIZES**

Blyth, Christopher - Vaccine Fellow Program (inaugural class) Edward Jenner Vaccine Society, Amsterdam, The Netherlands: This is one of 5 fellowships provided by the Edwards Jenner Society for young academics with interest and skills in vaccinology

Willis, Gabriela - The Australian Society for Microbiology Poster Prize, Combined Biological Sciences Meeting 2015

### **EXTERNAL COMMITTEES**

#### **International**

Richmond, Peter and Thornton, Ruth - Scientific committee member, Program committee, Australian Advisory



Committee. 19th International Symposium on Recent Advances in Otitis Media (RAOM), 4th to 8th June, 2017, Gold Coast Queensland.

Thornton, Ruth - Research Committee, International Society for Otitis Media, 2015-2017

### National

Richmond, Peter - Member, NHMRC Grant Review Panel for Clinical Trials (5E) August 2015

Richmond, Peter - Member, WA Health Translation Network, 2015-present

Richmond, Peter - Member, SmartVax Jurisdictional Advisory Committee, 2015-present

Richmond, Peter - Member, the University of Notre Dame and the Fremantle Hospital Research Foundation, 2015-present.

Richmond, Peter - Chair, ATAGI MMR-Varicella and Herpes Zoster Vaccine Working Party, 2006-present.

Richmond, Peter - Member, ATAGI Pneumococcal Vaccine Working Party, 2007-present.

Richmond, Peter - Member, Steering Committee Paediatric Trials Network of Australia (PTNA), 2010-present.

Richmond, Peter - Member, ATAGI Hib and Meningococcal C Vaccine Working Party, 2008-present.

Richmond, Peter - Member, ATAGI H1N1 Influenza Vaccine Working Party, 2009-present.

Blyth, Christopher - HRCNZ External grant reviewer - Health Research Council of New Zealand project grants

Blyth, Christopher - NHMRC Grant Review Panel Member – Microbiology and Virology

### Local

Richmond, Peter - Princess Margaret

Hospital for Children Ethics Committee, 2003-present.

Richmond, Peter - Princess Margaret Hospital for Children Medical Advisory Committee, 2007-2012.

Richmond, Peter - Chair, New Children's Hospital Research and Education Reference group, 2009-present.

Richmond, Peter - Chair, Child Health Research and Education Advisory Council, 2009-present.

Richmond, Peter - CAHS Activity Based Funding and Activity Based Management Steering Committee, 2012-present

Richmond, Peter - Member, CAHS/ Curtin Allied Health Standing Committee, 2014-present

Richmond, Peter - Member, Child Health Research Strategic Council, 2014-present

Richmond, Peter - Chair, Campus Child Health Research Committee, 2015-present.

Hutton, Heidi. Infectious Diseases Community Reference Group. February 2014

### INVITED PRESENTATIONS

Richmond, Peter - Australian and New Zealand Children's Haematology/ Oncology Group Annual Scientific Meeting: Protecting the vulnerable - immunisation for children with cancer. Perth, Western Australia. June 2015 (invited speaker).

Richmond, Peter - 2015 RACGP WA Medical Symposium: Paediatric ENT - placebo surgery or life-long benefits? Perth, Western Australia. June 2015 (invited panel member).

Richmond, Peter - Healthed 2015 Annual Women's and Children's Health Update - vaccination update: what's happening with fluvax? Perth, Western Australia.

August 2015 (invited speaker).  
Richmond, Peter - Papua New Guinea Biomedical and Social Sciences Society Specialty Meeting - prevention of pneumonia in early infancy: the potential of maternal immunisation. Port Moresby, Papua New Guinea. September 2015 (invited speaker).

Richmond, Peter - Interscience Conference on Antimicrobial Agents and Chemotherapy, and Richmond, Peter - International Congress of Chemotherapy and Infection 2015 Conference - preventing early pneumococcal disease: the potential role of maternal and neonatal immunisation. San Diego, USA. September 2015 (invited speaker).

Richmond, Peter - Australian Influenza Symposium – immunogenicity and clinical effectiveness of the trivalent inactivated influenza vaccine in immunocompromised children undergoing treatment for cancer. Geelong, Victoria. October 2015 (invited speaker).

Richmond, Peter - 3rd Neonatal and Maternal Immunisation Symposium 2015 - high and persistent antibody responses to monovalent acellular pertussis vaccine at birth: a large randomised controlled trial. The Gambia, West Africa. November 2015 (invited speaker).

Blyth Christopher - Influenza vaccine for healthcare providers: to push or to pull? Interscience Conference in Antimicrobial Agents. Interscience Conference on Antimicrobials Agents and Chemotherapy and International Congress of Chemotherapy, San Diego 2015

Blyth Christopher - Invasive fungal infection: Options for children failing therapy: Australian & New Zealand Children's Haematology Oncology Group Scientific Meeting, Perth 2015

Blyth Christopher - Influenza vaccine in

children: unanswered questions: Influenza Specialist Group Annual Scientific Meeting. Melbourne 2015

Thornton, Ruth - Lorne Infection and Immunity Conference 2015, Lorne, 18-20th February 2015, Lorne, Australia



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PRINCIPAL PARTNER



STRATEGIC PARTNER

