RAINE
MEDICAL RESEARCH FOUNDATION

Raine Medical Research Foundation

annual report
2017

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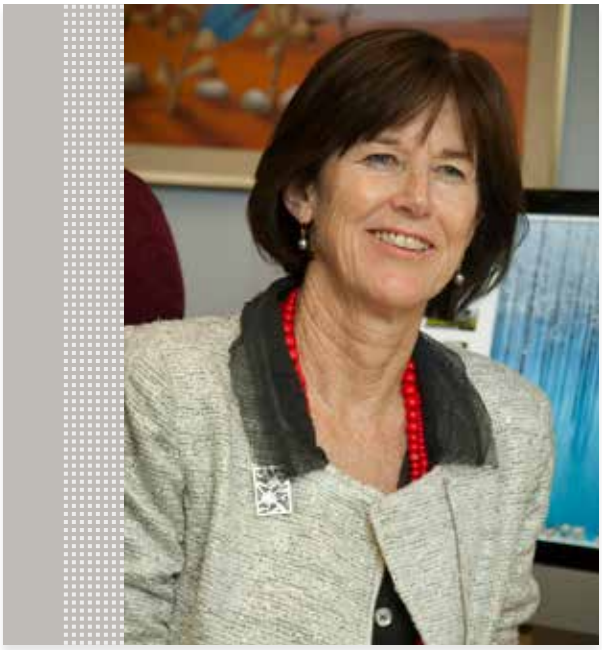
Chair's Address



It is with great pleasure that I present to you the 2017 Annual Report of the Raine Medical Research Foundation, including the activities of the Healy Medical Research Foundation.

2017 marked a major milestone in the history of the Raine Foundation with the celebration of its 60th Anniversary. It was in August 1957 that Mary Raine signed the Deed of Trust, bequeathing her property empire to the University of Western Australia for the purpose of funding medical research. This anniversary has provided a timely opportunity for us to reflect on the generosity and vision of Mary Raine, review the Foundation's financial contributions to medical research over the past 60 years and acknowledge the outstanding scientific achievements that have resulted from this generous bequest. The Raine Foundation has now passed the total distribution of $50m in support of more than 500 medical researchers in WA.

The Raine Foundation has a proud history of supporting scientific excellence, and particularly researchers at an early stage of their career. In 2017, the Raine Foundation distributed in excess of $2.1 million to the brightest and best young medical research minds in Western Australia. Additionally, the Healy Research Foundation distributed $19,500 towards Research Collaboration Awards. Congratulations go to the 23 recipients who were awarded a Priming Grant, Clinician Research Fellowship, Research Collaboration Award, Visiting Professor Award or Publication Prize across eight different funding programs. Special thanks goes to our partners and donors – the WA Department of Health, the University of Western Australia, the BrightSpark Foundation, the Jon and Caro Stewart Family Foundation, Charter Hall and the Rigby family, who are equally committed to encouraging and nurturing the careers of young medical research scientists to achieve better health outcomes for the wider community.

The strong alliance between the BrightSpark and Raine Foundations has ensured continued support for early career researchers who are striving to find answers for childhood disease. This BrightSpark Foundation provided support for a Raine Priming Grant in the area of child health to commence in 2018, which was awarded to Dr Tara Richman (*BrightSpark/Raine Fellow*) for her project entitled: *Modelling mitochondrial dysfunction in disease*. The Jon and Caro Stewart Family Foundation also continued to support the top grant in child health that was awarded for two years to commence in 2017 to Dr Melissa O'Donnell (*Stewart/BrightSpark/Raine Grant*) for her project entitled: *Alcohol-related harm in young people: Developing a longitudinal evidence base*.

The Clinical Research Fellowship program, in partnership with the WA Department of Health, entered its sixth round in 2017 and also continues to be a resounding success. Twenty-five Fellowships have now been awarded in support of top clinician researchers, with combined funding of over $6.2M. The impact of this program has been widespread, with research outcomes influencing new directions and improvements in health policy and clinical practice. Full details of the research supported by this program can be found on pages 41-66.

The Raine and Healy Foundation Research Committees are mindful of the importance of developing collaborative partnerships that will strengthen the knowledge and skills of our young scientists, and allow them to advance health and medical knowledge that improves the welfare of those suffering illness and disease. The Raine Management Office manages three successful Research Collaboration Award programs: the first is funded by the Healy Medical Research Foundation in support of early-career researchers in WA; the second is funded by the Edith E Cockell Bequest for research into mental health illness; and the third is funded

by the BrightSpark Foundation in support of research into childhood illness. Additionally, three Prizes are offered each year that reward early-career researchers for research that is published in top international journals. These Awards and Prizes were awarded to eight WA scientists in 2017, and have given them the opportunity to present their research findings, develop links with national and international collaborators and advance their research strengths.

Another esteemed program, the Raine Visiting Professor Awards, has been supported by the Raine Foundation since 1971, and has seen distinguished scientists from all over the world visit WA universities to enrich and advance our medical research knowledge and expand our collaborative networks. In 2017 we were privileged to welcome an exciting line-up of leading researchers from top international Universities, including the University of Cambridge, UK, the Chinese Academy of Sciences and the Israel Institute of Technology. The Visiting Professors were generous with their knowledge and time, conducting workshops and training sessions, presenting lectures, and providing mentoring to our WA researchers. Full details of the activities of the 2017 Raine Visiting Professors is on pages 68-73.

Another hugely successful partnership that the Raine Foundation is delighted to be part of is with the Charter Hall Group. In 2017, the Charter Hall Group (the property developers of Raine Square) announced their partnership with the Raine Medical Research Foundation as their charity of choice, undertaking a corporate commitment to help support the Foundation's future funding of medical research. Raine Square was officially opened in 1986 and named after Joe and Mary Raine, who owned and managed the Wentworth Hotel and various other hotels and properties in the Perth CBD. The significance of this partnership was captured by the Perth Heritage Days – Mary Raine Exhibition event that was hosted by Charter Hall in Bankwest Place, Raine Square in late 2017. The exhibition highlighted the astounding accomplishments of Mary Raine as a businesswoman during her lifetime and her enormous generosity and vision in establishing the Raine Medical Research Foundation.

There are a large number of people who volunteer their time to ensure that the Foundation achieves the very best research outcomes for the WA community. We have an outstanding team looking after our financial interests, headed by Mr Garry Prendiville and including the UWA Office of Treasury and Investment. I extend my personal thanks to the team at Treasury, Mr Trevor Crooke and Ms Rachel Wong for their hard work and guidance throughout the year. We also have many hard working and committed representatives on our Research Committee and Scientific Advisory Panels who give their time willingly and generously in the interest of medical research. I extend my personal thanks to this professional group that is comprised of scientists, clinicians and business consultants, who provide expert leadership and guidance to ensure that the Foundation retains its proud reputation and remains a major source of research funding in WA.

Special thanks goes to Professor Mariapia Degli-Esposti and Dr Sharan Dogra who at the conclusion of 2017 stood down from their roles on the Raine and Healy Research Committees. Professor Degli-Esposti has been with the committee for six years, during which time she has made an outstanding contribution in supporting both Raine and Healy Foundations, particularly as the Chair of the Raine Priming Grant Advisory Panel where her hard work and commitment to scientific excellence has been exemplary. Dr Dogra has also been a valued committee member and we thank her for her contribution to the Foundations.

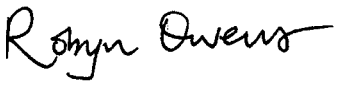
Finally, I would like to acknowledge the enormous contribution of our Director, Ms Lyn Ellis, who has managed the Raine and Healy Foundations for more than 23 years and who retired at the end of 2017. Lyn has a background in senior management at UWA that spans 30 years, and after a number of senior positions that include the University Library and School of Psychology, Lyn left the main campus in 1990 and moved to the QEII site to take up an executive appointment in the Faculty of Medicine and Dentistry. Included in her portfolio in the Medical and Dental Schools was responsibility for the Raine (and Healy) Medical Research Foundations. This was the first time that Lyn came to learn first-hand about the important role that the Raine Foundation played in supporting medical research in WA.

Lyn Ellis and Amanda Cleaver

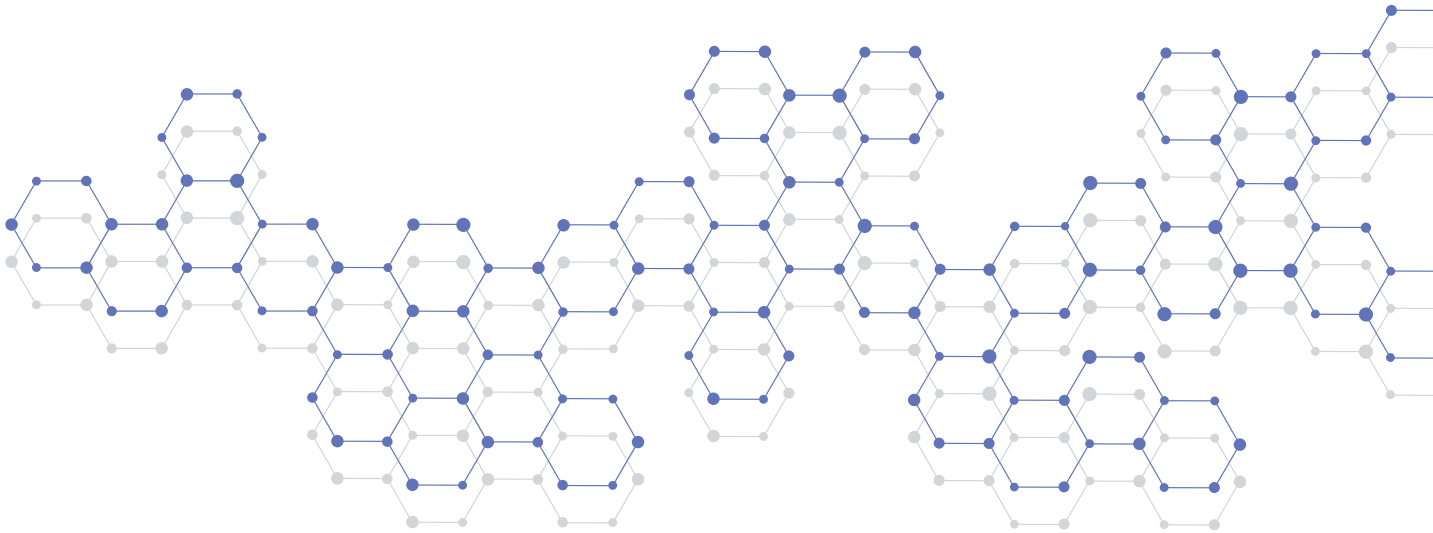
Since then, Lyn's role evolved as she directed the activities of the Foundation, overseeing a major portfolio of income and investments that has grown from $16m in 1995 to $38m in 2017. Lyn has meticulously implemented and managed the processes and programs that have given the Foundation its long-standing reputation for excellence. Lyn also steered the Foundation into highly successful partnerships and has always gone above and beyond with her personal commitment to the Foundation. On behalf of the Raine Research Committee, I would like to thank Lyn for

her passion and dedication to upholding Mary Raine's vision of advancing medical research in WA.

I would also like to welcome our incoming Director, Dr Amanda Cleaver, who has been working with Lyn and the Foundation for over two years, and brings with her more than 15 years of experience across the medical research and research management fields. We look forward to an exciting future for the Raine and Healy Foundations that will strengthen and grow partnerships and funding support for WA researchers to achieve medical research outcomes that have a positive impact on the health and wellbeing of all in the community.



Robyn Owens
Deputy Vice-Chancellor (Research)
Chair, Raine Medical Research Foundation
Chair, Healy Medical Research Foundation



Research Committee

The Raine Medical Research Foundation and the Healy Medical Research Foundation are governed by a Committee of Senate, constituted in accordance with the requirements of their respective Deeds of Trust.
The 2017 Research Committee consisted of the following members:

Professor Robyn Owens
Chair and UWA Deputy Vice-Chancellor (Research)

Professor David Joyce
Professor of Medicine

Professor Jeff Hamdorf
Professor of Surgery

Professor Alice Vrielink
Professor of Biochemistry

Dr Sharan Dogra
Fellow, Royal Australasian College of Physicians

Mr Peter Smith
Fellow, Royal Australasian College of Surgeons

Dr Richard Choong
General Practitioner, Australian Medical Association
WA Branch Representative

Professor Mariapia Degli-Esposti
Head – Experimental Immunology
Centre for Ophthalmology and Visual Sciences, Research Committee representative

Mr Garry Prendiville
Honorary Financial Consultant

Ms Lyn Ellis
Director

Dr Amanda Cleaver
Project Manager

BrightSpark/Raine Alliance Committee

The 2016 partnership of the BrightSpark Foundation and the Raine Medical Research Foundation has forged an outstanding alliance in support of child health research. The BrightSpark/Raine Alliance is now well established and focused on seeing our early-career researchers achieve success in their efforts to translate medical research into better health outcomes for young children.

The 2017 BrightSpark/Raine Alliance Committee consisted of the following members:

Mr Graham Dowland, Chair

Mr Geoff Anderson

Dr Richard Choong

Mr Tony Barber

Mr Garry Prendiville

Dr Elizabeth Davis

Mr Peter Smith

Mr Andrew Thompson

Ms Lyn Ellis

Dr Amanda Cleaver

Raine 60th Anniversay Oration

RAINE MEDICAL RESEARCH FOUNDATION | 60th ANNIVERSARY 1957 – 2017

CELEBRATING 60 YEARS OF RESEARCH EXCELLENCE

Mary Raine was a remarkable woman – well ahead of her time. She ruled over a successful hotel and property empire and was happily married. But unfortunately her husband, Joe, suffered a sudden and severe stroke that prematurely claimed his life. Mary was inconsolable and couldn't understand why doctors couldn't do more to save him. In her anguish, Mary believed that medical research was the key to preventing illness and finding cures to disease. This was her defining conviction 60 years ago in establishing the Raine Medical Research Foundation – she wanted to make sure that others did not lose their loved ones as she had lost Joe.

It was in 1957 that Mary Raine set up a Deed of Trust that formally bequeathed her property empire to The University of Western Australia for the purpose of establishing the Raine Medical Research Foundation. The Foundation has strived to fulfil the vision of Mary Raine, and to-date the Foundation has distributed more than $50 million in support of nearly 500 researchers in Western Australia. The Raine Honour Roll is impressive: it includes two Centres of Excellence, the well-known Busselton Population Study, the Fremantle Diabetes Study, The Raine Study, as well as scores of Grants, Fellowships, Scholarships and Visiting Professorships – to name but a few. The Foundation has supported many of our top scientists in WA and we hope to continue supporting future generations who will push the boundaries of medical science in the quest to "find answers" to imponderable questions – and ultimately, to translate those answers into better health outcomes for the community.

To mark this historic milestone in the history of the Raine Foundation, an Oration event was held on 2 May 2017. The Chair of the Raine Priming Grants Advisory Panel, Professor Mariapia Degli-Esposti, officially opened the event with an outstanding overview of the life of Mary Raine and the history of the Raine Foundation. She then introduced our guest speaker Professor Ian Frazer, AC, who presented a talk entitled *Translating research into practice: Lessons I've learnt*. Professor Frazer was named Australian of the Year in 2006 for his outstanding work in the development of a papillomavirus vaccine. He is the Director of The University of Queensland Diamantina Institute and Chief Executive Officer and Founding Director of the Translational Research Institute. He is also President of the Australian Academy of Health and Medical Science and of Cancer Council Australia. Overall the celebratory event was a resounding success.

Perth Heritage Days – The Mary Raine Exhibition

Charter Hall

As part of our 60th anniversary celebrations, the Raine Medical Research Foundation was proud to support an event hosted by Raine Square and Charter Hall in conjunction with Perth Heritage Days – The Mary Raine Exhibition.

The exhibition was open to the public from 14 October to 30 November 2017 in Bankwest Place, and showcased the life and history of our namesake Mary Raine – a business woman and philanthropist who shaped the beginnings of the Perth CBD, and whose generous donation created the Raine Medical Research Foundation.

Two public talks and several radio interviews were also presented by the Raine Foundation Director, Ms Lyn Ellis and Project Manager, Dr Amanda Cleaver. These presentations focused on the life of Mary Raine, the history of Raine Square and the achievements of the Raine Medical Research Foundation over the last 60 years. It was standing room only for those who came late!

'The Mary Raine Story – From Putney to Perth', a book written by Mary's close colleague and friend Meg Sangster, was also available for purchase at the presentations.

GRANTS

Raine Priming Grants

Twelve research projects were in progress in 2017. This includes two grants awarded for 2015/2016 that were extended to finish in 2017, five two-year grants awarded for 2016/2017, and five new two-year grants awarded for 2017/2018 to commence in 2017. In 2017 five Grants were awarded to commence in 2018, with a total funding allocation of $944,622.

Thank you to our partners the Jon and Caro Stewart Family Foundation and the BrightSpark Foundation for their support towards this Grant program.

2015 Raine Priming Grants
(Grants commenced in 2015 and approved for extension to finalise in 2017)

	Chief investigator	Project title
	Dr Coral-Ann Almeida School of Pathology and Laboratory Medicine The University of Western Australia	Stimulation of HIV-specific cytolytic effector function using allogeneic cell immunotherapy
	Dr Benjamin Mullin School of Medicine and Pharmacology The University of Western Australia	Role of genetic copy number variation in osteoporosis

2016 Raine Priming Grants
(Second year of Grant commenced in January 2017)

The top candidate, Dr Annette Lim relinquished her Raine Priming Grant as she was awarded another grant for the same research project. She retains the title of 'Honorary Raine/Robson Fellow'.

	Chief investigator	Project title
	Dr Gemma Cadby Centre for Genetic Origins of Health and Disease The University of Western Australia	The association of sleep apnoea and long-term health outcomes in Western Australian adults
	Dr Tristan Clemons School of Molecular Sciences The University of Western Australia	Nanoparticle-aided delivery of lysyl oxidase (LOX) inhibitors for the treatment of scarring
	Dr Elin Gray School of Medical and Health Sciences Edith Cowan University	Genetic analysis of circulating tumour cells and circulating tumour DNA for prognosis of uveal melanoma
	Dr Grand Roman Joldes School of Mechanical Engineering The University of Western Australia	Towards translating the benefits of patient specific biomechanics into clinical practice
	Dr Alison McDonnell School of Biomedical Sciences The University of Western Australia	Identifying immune biomarkers of response to chemotherapy in thoracic cancers

2017 Raine Priming Grants
(First year of Grant commenced in January 2017)

The top candidate, Dr Yit Heng Chooi, relinquished his Raine Priming Grant as he was awarded another grant for the same research project. He retains the title of 'Honorary Raine/Robson Fellow'.

A generous donation by the Stewart family, in partnership with the BrightSpark Foundation and the Raine Medical Research Foundation, made possible a Raine Priming Grant to be awarded to the top applicant in child health research. Dr Laurens Manning relinquished his Raine Priming Grant as he was awarded another grant for the same research project. He retains the title of 'Honorary Stewart/BrightSpark/Raine Fellow'. Dr Melissa O'Donnell was awarded the 'Stewart/BrightSpark/Raine Project' for her project in the area of child and youth health.

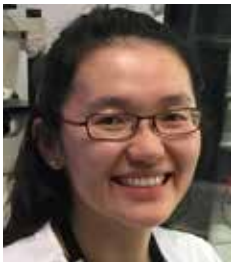
	Chief investigator	Project title
	Dr Mark Agostino School of Pharmacy and Biomedical Sciences Curtin University	Structural characterisation of the Wnt signalling pathway
	Dr Katrina Ellis School of Medicine and School of Biomedical Sciences The University of Western Australia	Novel aspects of the role of lipoprotein(a) in premature heart disease
	Dr Ashleigh Lin Telethon Kids Institute	The GENTLE project (GENder identiTy Longitudinal Experience)
	Dr Melissa O'Donnell **Stewart/BrightSpark/Raine Project** Telethon Kids Institute	Alcohol-related harm in young people: developing a longitudinal evidence base
	Dr Helena Viola School of Human Sciences The University of Western Australia	A novel approach for the prevention of hypertrophic cardiomyopathy

2018 Raine Priming Grants

Five new Priming Grants were awarded in December 2017 for 2018/2019 with a total funding allocation of $994,622. The top candidate, Dr Yu Yu was awarded the title of 'Raine/Robson Fellow'.

In partnership with the BrightSpark Foundation, the Raine Foundation awarded a Raine Priming Grant to the top candidate in child health research. Dr Tara Richman was awarded the title of 'BrightSpark/Raine Fellow'.

	Chief investigator	Project title
	Dr Gail Alvares Telethon Kids Institute	Childhood indicators of adult outcomes: A longitudinal follow-up of the WA Autism Register
	Dr Chandrakumar Balaratnasingam Lions Eye Institute	Improving diabetic retinopathy management through early detection of microvascular changes
	Dr Jonathan Chee School of Biomedical Science The University of Western Australia	Analysis of T cell receptor diversity in animal models of cancer
	Dr Rachel Foong School of Physiotherapy and Exercise Sciences Curtin University	Examining environmental risk factors for asthma in Western Australia

	Dr Tara Richman **BrightSpark/Raine Fellow** Harry Perkins Institute of Medical Research	Modelling mitochondrial dysfunction in disease
	Dr Yu Yu **Raine/Robson Fellow** Curtin Health Innovation Research Institute Curtin University	Enhancing current ovarian cancer response by inhibiting SYK

2017 Annual Research Reports
Raine Priming Grants

PROJECT TITLE
Structural characterisation of the Wnt signalling pathway

INVESTIGATORS
Dr Mark Agostino (Chief Investigator)
Professor Yvonne Jones (Associate Investigator)
Associate Professor Philip Thompson (Associate Investigator)

SCHOOL/INSTITUTE/CENTRE
School of Pharmacy and Biomedical Sciences, Curtin University

SUMMARY OF AIMS AND RESULTS
Wnt signalling pathways are of significant interest for their roles in embryonic development and cancer. Three Wnt pathways have been described, these being the canonical and non-canonical planar cell polarity, and calcium-dependent pathways. The first step in all of these pathways is characterised by the binding of a Wnt protein to the Frizzled (Fzd) receptor ectodomain, which is referred to as an Fzd-type cysteine-rich domain (CRD). The receptor is then activated, permitting subsequent binding of Dishevelled (Dvl), which then binds to different proteins depending on the specific pathway being activated. Secreted Frizzled-related protein 4 (sFRP4) has been identified as a potent inhibitor of the Wnt signalling pathway, indicating the potential for it, or its derivatives, to act as an anticancer agent. Understanding the structural basis of protein-protein interactions in these crucial first steps of the pathway would provide new opportunities for the structure-based design of agents modulating Wnt signalling.

This project addresses two key aims:

- Aim 1: Understanding the structural basis of Fzd receptor activation
- Aim 2: Understanding the structural basis of the Wnt antagonist activity of sFRP4

The primary focus of the past year has been to investigate Wnt-Fzd interactions and Wnt interactions with their natural antagonists – the secreted Frizzled-related proteins (sFRPs). As there are 19 Wnt proteins, 10 Fzd receptors and five sFRPs in humans, a potential combinatorial number of interactions could result. A model for calculating Wnt binding affinity with Fzd-type CRDs was developed and validated against a small set of experimentally determined affinities for mouse Wnt-CRD interactions, then applied to predict all Wnt-CRD binding affinities in mouse and human. The results demonstrate that Wnt-CRD binding affinity, in general, depends on the particular Fzd or sFRP being examined, with some Fzds/sFRPs binding promiscuously to most Wnts, while others binding to very specific Wnts. These results will be valuable to dictate future research efforts on this signalling pathway, as well as having implications for the computational study of protein-protein interactions that feature direct involvement of post-translational modifications that facilitate the interaction.

The structural basis of activation of the full-length Fzd7 is currently being investigated using molecular dynamics simulations conducted at the Pawsey Supercomputing Centre. A putative active state structure of Fzd7 was prepared by multi-template homology modelling against several structures of the Smoothened protein (the only class F G protein-coupled receptor (GPCR) for which a full-length structure is available), as well as the intracellular loop 3 and inner leaflet regions of helices 5 and 6 from an adenosine A2A receptor structure in an active conformation. A full-length putative inactive state Fzd7 structure has also been prepared against Smoothened structures. A variety of simulation approaches (including biased molecular dynamics (MD) and metadynamics) are being used to explore the possibility that Fzd7 activation follows a similar pathway to Class A GPCRs, as well as to refine the structure to identify likely Dvl-binding saddle points along the pathway. Once completed for Fzd7, it is intended to extend this to other Fzds, as well as to investigate the influence of lipid binding (and potentially Wnt binding) to the Fzd-type CRD on the activation pathway.

OUTCOMES

Publications

Agostino M, Pohl SOG, Dharmarajan A. Structure-based prediction of Wnt binding affinities for Frizzled-type cysteine-rich domains. *Journal of Biological Chemistry*. 2017; 292: 11218-11229

Conference Presentations

Agostino M. (Oral) Structure-based prediction of Wnt-Frizzled binding affinities. *Australian Society for Medical Research Western Australian Branch Annual Research Symposium*. 2017; Edith Cowan University, Mt Lawley

Agostino M. (Oral) The prediction of Wnt-Frizzled binding affinities using structure-based approaches. *CHIRI Cancer Workshop*. 2017; Curtin University, Bentley

Agostino M. (Oral) Development of a model for predicting Wnt-Frizzled binding affinities. *Molecular Modelling for the Life and Materials Sciences Conference*. 2017; Margaret River

Agostino M, Pohl SOG, Dharmarajan A. (Poster) Prediction of Wnt-Frizzled binding affinities using structure-based approaches. *Science on the Swan: One Health*. 2017; Fremantle

Grants

Agostino M. Characterising structural transitions in the Frizzled receptor. Curtin Institute for Computation Operational Research Support 2017 round; $10,000

PROJECT TITLE

Stimulation of HIV-specific cytolytic effector function using allogeneic cell immunotherapy

INVESTIGATORS

Dr Coral-Ann Almeida (Chief Investigator)
Associate Professor Lloyd D'Orsogna (Associate Investigator)
Associate Professor Mina John (Associate Investigator)

SCHOOL/ INSTITUTE/CENTRE

School of Pathology and Laboratory Medicine, The University of Western Australia

SUMMARY OF AIMS AND RESULTS

Although current anti-retroviral regimens have reduced the morbidity and mortality associated with HIV-1 infection, suppression of viral replication requires adherence to life-long therapy that itself carries the risk of drug associated toxicities. In the absence of an efficacious vaccine against HIV-1, investigations are underway to identify T cell responses that control viral replication. Adaptive CD8 T cell immunity mediates the natural control of HIV replication and is likely to be an important component of any effective preventative vaccine. Mechanisms that stimulate HIV-specific memory CD8 T cells could potentially lead to viral control and delay disease progression. The novel hypothesis investigated in this project is that heterologous immune responses, which arise when pathogen-specific memory CD8 T cells recognise and respond to unrelated pathogens or allo-antigens, can be used to induce or augment an HIV-specific CD8 T cell response.

Peripheral blood mononuclear cells were isolated from individuals enrolled in the Western Australian HIV Cohort Study. Multiple HIV-specific CD8 T cell clones were derived from 12 individuals with chronic HIV infection, specific for 13 different HIV group-specific antigens (Gags) and restricted to seven different human leukocyte antigen (HLA) molecules. The generated T cell clones were investigated for allo-reactive responses against a panel of single HLA class I expressing cell-lines (SALs). HIV-specific T cells that recognised at least one allogeneic HLA molecule were identified from seven of 12 patients

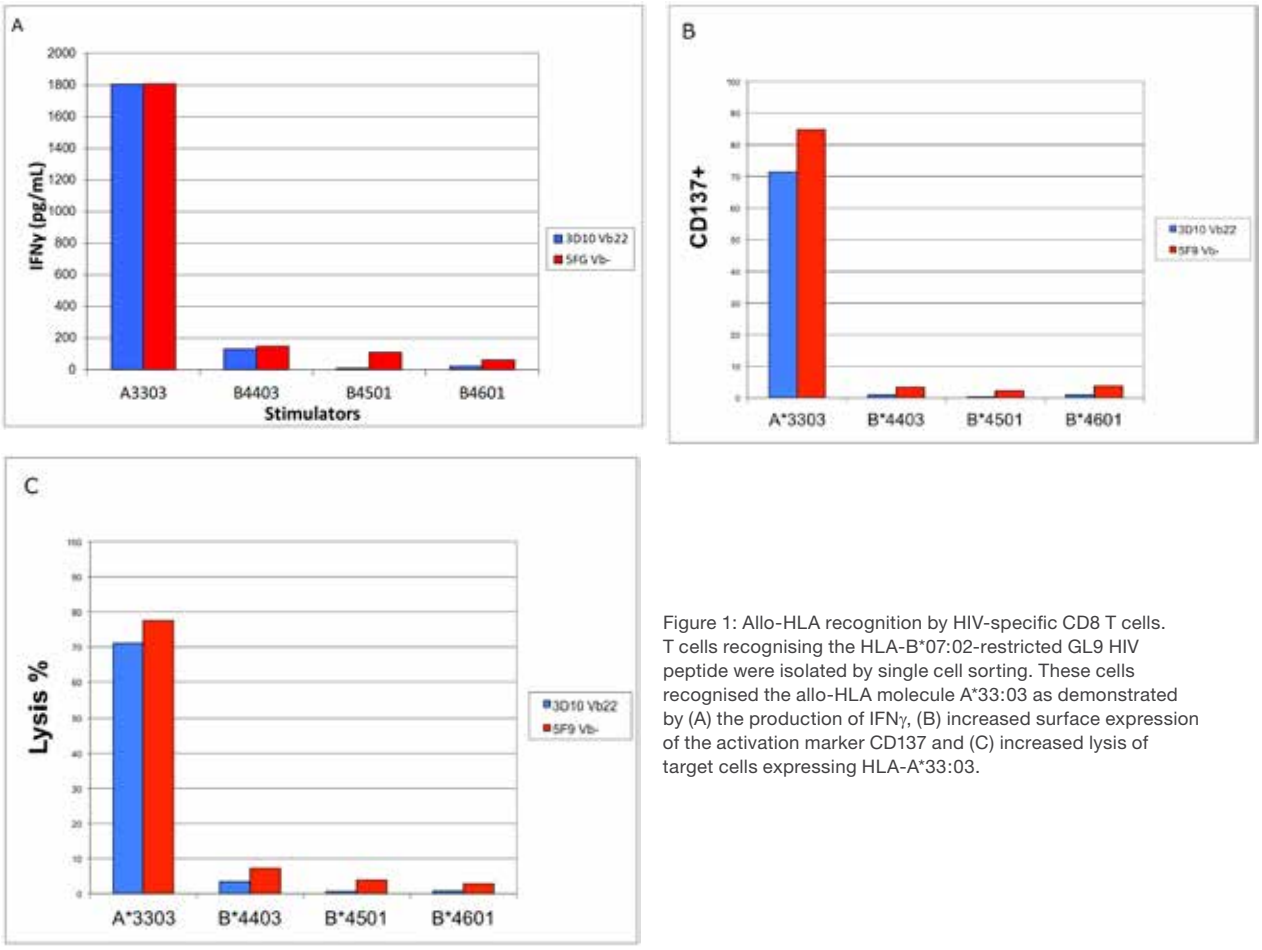


Figure 1: Allo-HLA recognition by HIV-specific CD8 T cells. T cells recognising the HLA-B*07:02-restricted GL9 HIV peptide were isolated by single cell sorting. These cells recognised the allo-HLA molecule A*33:03 as demonstrated by (A) the production of IFNγ, (B) increased surface expression of the activation marker CD137 and (C) increased lysis of target cells expressing HLA-A*33:03.

tested. Allo-recognition was associated with interferon gamma (IFNγ) cytokine production, CD137 up-regulation and cytotoxicity, suggesting high avidity allo-stimulation (Figure 1).

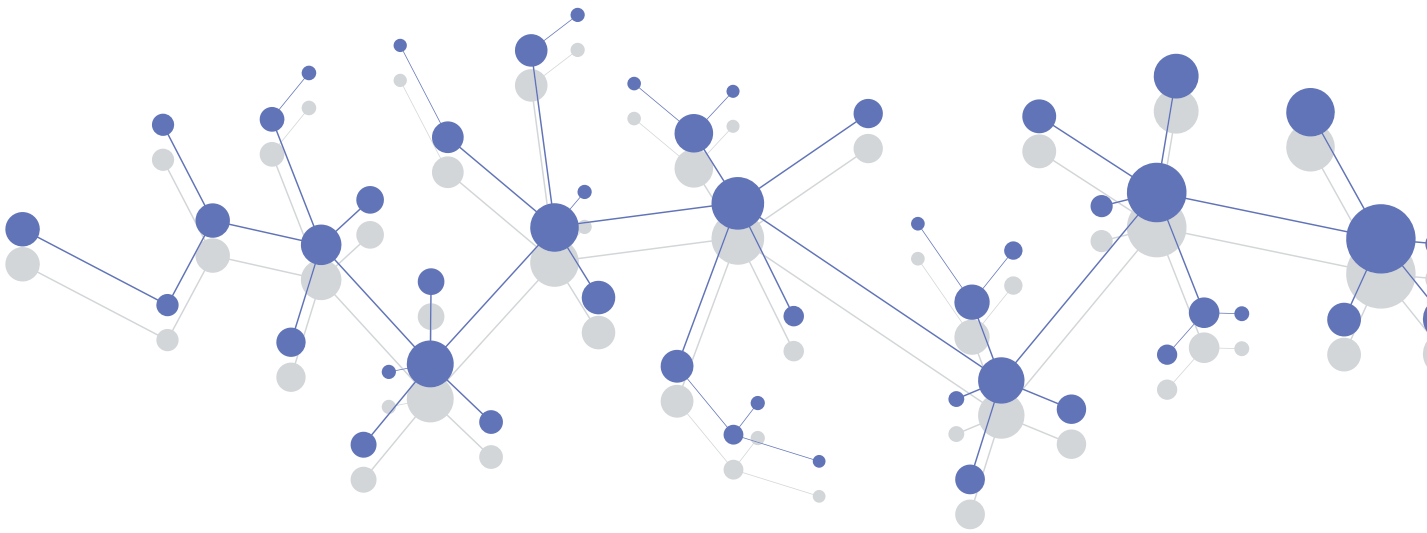
The allo-HLA response by HIV-specific CD8 T cells depended on the HIV target peptide, restricting HLA allele and the T cell receptor (TCR) Vγusage of the cells. This proof-of-principle study, therefore, confirms that HIV-specific T cell clonotypes can be specifically stimulated by allogeneic HLA molecules. These results could have potential future implications for HIV vaccine design and immunotherapy.

In collaboration with Dr Nicole Mifsud at Monash University, allo-reactive clones identified in this study have been sent to Melbourne to identify the cognate peptides that stimulate HIV-specific T cells. Future investigations will focus on the final aim of the project – the ability of these peptides to elicit an immune response in individuals uninfected by HIV. Additional investigations also include affinity and crystallography studies of allo-recognition by HIV clonotypes.

OUTCOMES

Publications

Almeida C, van Miert P, O'Driscoll K, Zoet YM, Chopra A, Watson M, *et al*. Stimulation of HIV-specific T cell clonotypes using allogeneic HLA. *Cellular Immunology*. 2017; 316: 32-40



PROJECT TITLE

The association of sleep apnoea and long-term health outcomes in Western Australian adults

INVESTIGATORS

Dr Gemma Cadby (Chief Investigator)
Professor Eric Moses (Associate Investigator)
Professor Joseph Hung (Associate Investigator)
Dr David Hillman (Associate Investigator)
Associate Professor Nigel McArdle (Associate Investigator)
Associate Professor Tom Briffa (Associate Investigator)

SCHOOL/INSTITUTE/CENTRE

Centre for Genetic Origins of Health and Disease, The University of Western Australia

SUMMARY OF AIMS AND RESULTS

Obstructive sleep apnoea (OSA) is a sleep-related breathing disorder that affects approximately 800,000 Australians, or 5% of the Australian population. OSA is characterised by the repetitive collapse of the throat and upper airway during sleep (sometimes occurring hundreds of times per night). The importance of sleep disorders, including OSA, are largely unrecognised and the health impacts are not properly appreciated.

OSA results in poor sleep quality, daytime somnolence (sleepiness), and inattention leading to work and motor vehicle accidents. The physiological effects of OSA include intermittent hypoxia and cortical arousals. These can lead to inflammation, metabolic dysregulation, sympathetic activation and angiogenesis, which can all have devastating consequences on the health of an individual, including hospital morbidity and mortality due to cardiovascular diseases, cancers, diabetes, motor vehicle accidents and mental health disorders.

This study focuses on the investigation of obstructive sleep apnoea (OSA) and its association with common health outcomes, such as cardiovascular diseases, cancers, diabetes, motor vehicle accidents and mental health disorders. In particular, the research team will investigate whether OSA severity is an independent risk factor for these outcomes after adjusting for known risk factors, such as obesity and blood lipids.

The aim of this study is to establish whether the presence and severity of OSA are independent risk factors for incident or recurrent health outcomes in a large consecutive cohort of patients who were referred for overnight sleep studies at a Western Australian sleep clinic from 1989 to 2013.

Changing trends of OSA

This study has identified approximately 26,500 individuals who underwent sleep studies at Sir Charles Gairdner Hospital (SCGH) between 1989 and 2013. Of these, approximately 21,000 patients had some level of OSA reported. The research team investigated the severity of OSA and its risk factors over time and identified that OSA severity and patient characteristics had changed during the period between 1989 and 2013. For example, approximately 10% of patients (with a clinical definition of OSA) in 1989 were female and this has increased to over 40% of patients in 2013. Similarly, body mass index (BMI) has increased over time, from approximately 32 in 1989 to 34 in 2013. In summary, between 1989 and 2013, the characteristics of patients presenting with OSA have changed and, on average, patients are heavier, more disadvantaged and likely to be female.

The investigators linked the cohort to the Western Australian Data Linkage System and received the health associated data in December 2017. This included data on hospital morbidity, deaths, cancer diagnoses, mental health records and motor vehicle accidents.

Cancer

Using the Western Australian Cancer Registry data, 4,234 (approximately 17%) individuals were identified who were diagnosed with cancer. The most common cancers diagnosed were prostate cancer, melanoma, blood/lymphatic cancers, colorectal cancer and breast cancer. The research team is currently in the process of determining whether the incidence of cancer is associated with OSA severity.

Motor vehicle accidents

In collaboration with Dr Kim Ward and Professor Lynn Meuleners, the investigators are studying whether the severity of OSA and associated excessive sleepiness is associated with motor vehicle accident-related injuries, using data from the Hospital Morbidity System, Death Registrations and the Insurance Commission of Western Australia.

Mental health disorders

Using the mental health data, approximately 4,700 individuals were identified with mental health disorders though the Mental Health Information System. The most common diagnoses are depression and anxiety. Dr Cadby *et al.* are currently in the process of determining whether the incidence of mental health is associated with OSA severity.

OUTCOMES

Conference Presentations

Singh B, Bond-Smith D, McArdle N, Ward K, King S, Noffsinger W, Mukherjee S, Palmer LJ, **Cadby G**. Changing trends of obstructive sleep apnoea in Western Australia from 1988 to 2014. *Journal of Sleep Research*. 2017; 26: 61

Grants

CI D Hillman, CI J Hung, CI L Palmer, CI B McQuillan, CIE S Dhaliwal, CIF N McArdle, CIG B Singh, CIH S Mukherjee, CII P De Chazal, **AI Cadby**. National Health and Medical Research Council "The interaction between obstructive sleep apnea and cardiovascular risk factors on cardiovascular disease". 2018-2021; $1.26M

Collaborations

Collaborations have been formed with Dr Kim Ward and Prof Lynn Meuleners from the Curtin Monash Accident Research Centre. Using grant funding from the Road Trauma Trust Account, administered by the Road Safety Commission, Dr Ward and Professor Meuleners will be investigating whether the severity of OSA and associated excessive sleepiness is associated with motor vehicle accident-related injuries.

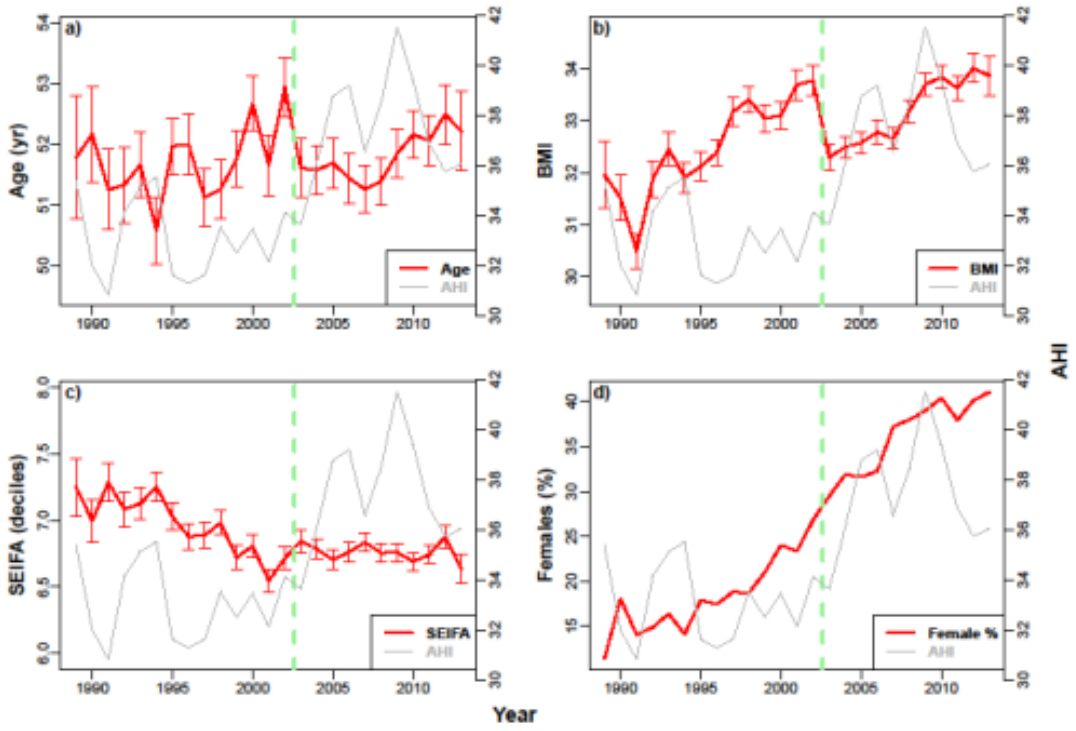


Figure 1. Distribution of age, body mass index, socio-economic status and gender over time.

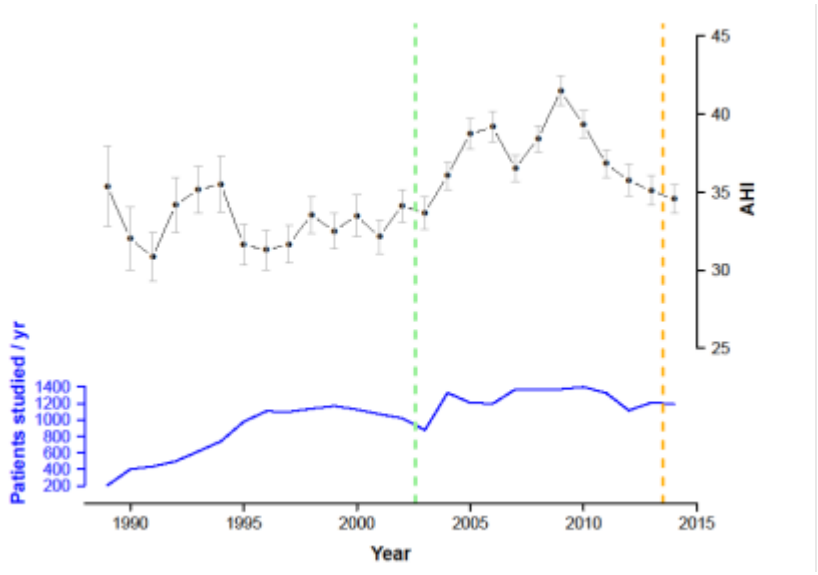


Figure 2. Distribution of sleep apnoea severity (apnoea-hypopnea index; AHI) and number of patients over time.

PROJECT TITLE

Nanoparticle-aided delivery of lysyl oxidase (LOX) inhibitors for the treatment of scarring

INVESTIGATORS

Dr Tristan Clemons (Chief Investigator)
Professor Fiona Wood (Associate Investigator)
Dr Wolfgang Jarolimek (Associate Investigator)
Dr Keith Stubbs (Associate Investigator)
Dr Mark Fear (Associate Investigator)
Professor Swaminathan Iyer (Associate Investigator)

SCHOOL/INSTITUTE/CENTRE

School of Molecular Sciences, The University of Western Australia

SUMMARY OF AIMS AND RESULTS

Skin injuries and subsequent scarring represents a huge global burden with billions of dollars being spent annually on the treatment of scars. In the developed world, 100 million people develop scars annually. With recent advances in care significantly decreasing mortality, the improvement of scar outcomes and recovery of patient function have become increasingly important. The link between the inhibition of lysyl oxidase (LOX), the family of enzymes responsible for the crosslinking of collagen in the scar matrix, and the improvement of scar architecture is well-established, making LOX inhibitors an attractive pharmaceutical target. The research team's patented nanoparticle (NP) delivery system has shown great promise in delivering a range of therapeutics, and in current work it has been successful in drug loading and the release of LOX inhibitors across the skin.

This project aims to use novel therapeutics to improve functionality and outcomes following burn injury and subsequent scarring. This will greatly improve the quality of life for people currently living with the debilitating side effects of severe scarring (e.g. both the psychological and physical distress that can result from significant burn injuries).

The aims of the project are:

- Aim 1: Generate polymeric multimodal nanoparticle delivery vehicles for the delivery of therapeutic lysyl oxidase (LOX) inhibitors to scar tissue
- Aim 2: Assess efficacy of therapeutic LOX inhibitor delivery in a clinically relevant porcine model.

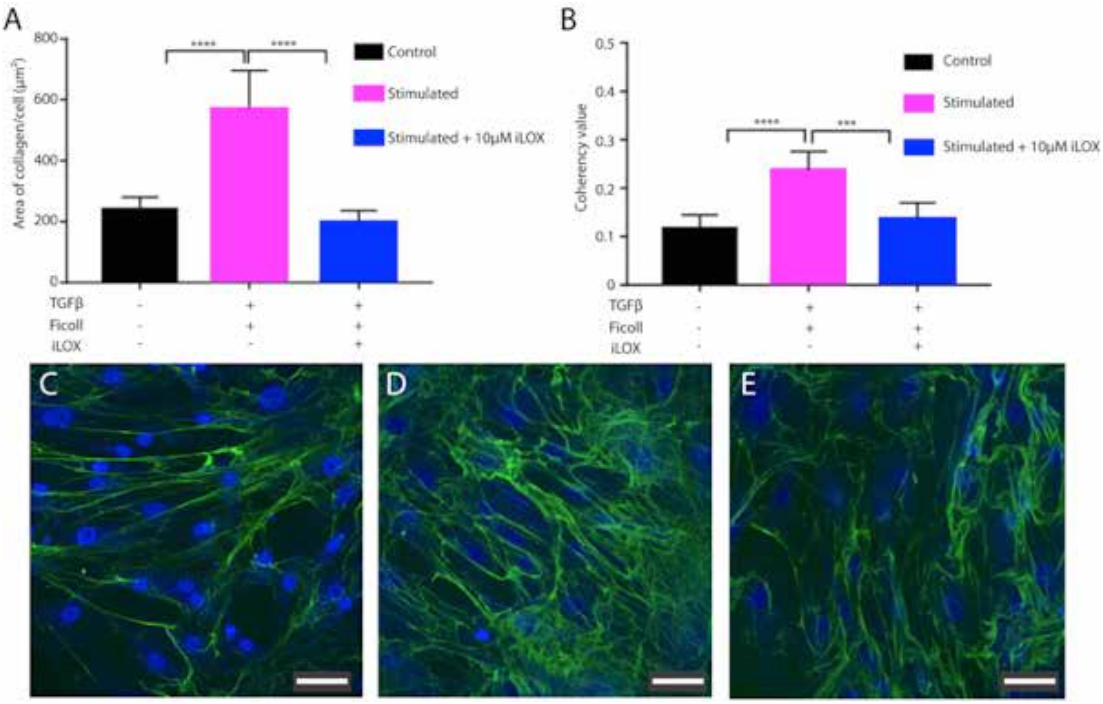


Figure 1. Scar in a jar assessment of iLOX inhibitors in primary human fibroblasts. (A) The area of collagen per cell and (B) the coherency of collagen deposition. Representative images of controls (C), stimulated (D) and stimulated + 10μM iLOX (E) by confocal microscopy are shown. Scale bars are 50 μm.

Through collaboration with Pharmaxis Pty. Ltd., the investigators have tested a range of inhibitors of lysyl oxidase (LOX) activity with *in vitro* models of scarring. The LOX inhibitors are effective *in vitro* at being able to reduce the amount of collagen production, as well as returning the coherency of the deposited collagen fibres to a random basket weave structure similar to controls (Figure 1). Following from this work a lead candidate was chosen to progress into *in vivo* testing.

Polymeric nanoparticles have been developed and tested for their ability to deliver therapeutic cargo suitable for application in a wound-healing model. For this work a mannose-6-phosphate analogue, developed by Pharmaxis, has been successfully delivered in culture to again reduce the amount of collagen deposition in an *in vitro* scar model, while also returning the coherency of the deposited collagen to architecture similar to that of controls. This work also clearly demonstrates the ability of the nanoparticles to be internalised by human primary fibroblasts, which is important in progressing this work forward for *in vivo* studies (Figure 2).

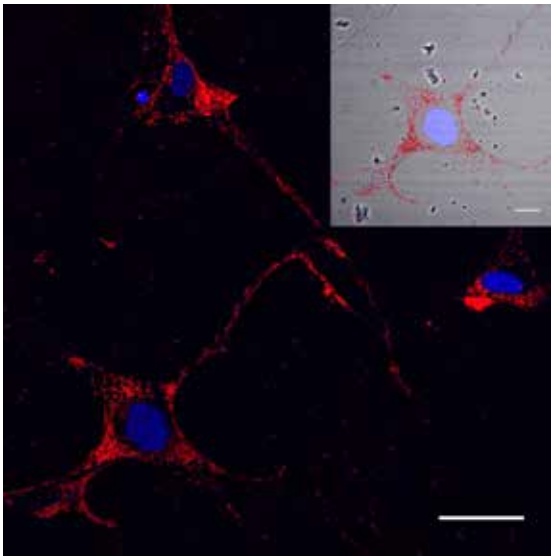


Figure 2. Fluorescent uptake of PGMA/PEI/RhB NPs following 48 h incubation with 10 ug/ml nanoparticles (NPs), as assessed by confocal microscopy, showing rhodamine-labelled nanoparticles (red) and Hoescht-labelled nuclei (blue). Inset: fluorescent overlay on a bright field image. Scale bars: 50 µm and 20 µm (inset).

The effectiveness of the lead LOX inhibitor candidate was investigated further in mice to determine an effective vehicle solution for the therapeutic and optimum timing of treatment. Scarring is an intricate process with collagen crosslinking being an important requirement in the healing wound. Hence, the application of LOX inhibitors too early could be detrimental to wound healing; likewise, application that is too late may limit the potential for scar remodelling. The effectiveness of the LOX inhibitors on actually inhibiting collagen crosslinking was assessed further by *in vivo* analysis with liquid chromatography mass spectrometry (LC-MS). LC-MS results depicted a time-dependant reduction of mature crosslinks (hydroxyproline (HYP) and pyridinoline (PYD)), and immature crosslinks (dihydroxylysinonorleucine (DHLNL) and hydroxylysinonorleucine (HLNL)) in the presence of the LOX inhibitors (Figure 3). Interestingly, if treatment had begun in the first week following injury, this would have resulted in elevated levels of crosslinks, thereby suggesting the wound was still in a healing phase compared to when treatment begun in the second week following injury. As such, crosslinks could have been restored to normal control levels (Figure 3).

OUTCOMES

Conference Presentations

N Chaudhari, P Toshniwal, V Plalnivelu, F Wood, **T Clemons**, A Stevenson, K. S. Iyer, M Fear. Development of a novel therapeutic to improve scar appearance, *Australasian Society for Biomaterials and Tissue Engineering 25th Annual Conference*. 2017; Canberra

Grants

Clemons T, Stupp. "Self-assembling peptide amphiphile based nanomaterials for wound healing". American Australian Association-Dow Chemical Company Scholarship. 2017

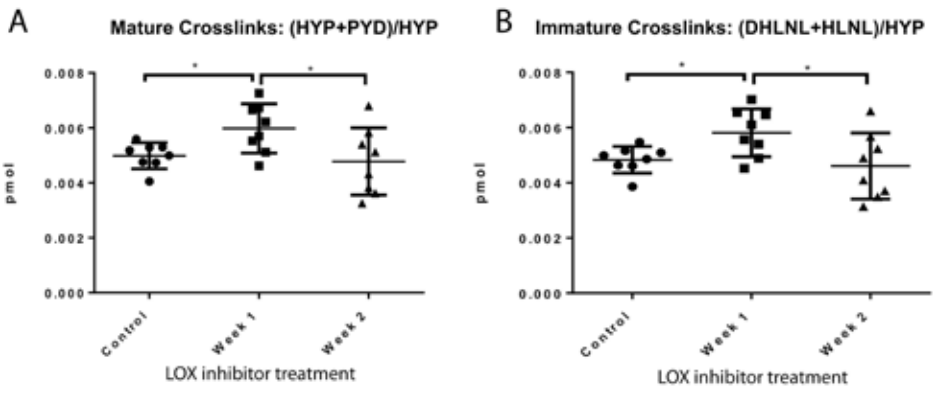


Figure 3. LC-MS analysis of collagen crosslinks in vivo. (A) Mature crosslinks (normalised with the total amount of hydroxyproline) for controls, treatment beginning in the 1st week post injury or the 2nd week post injury. (B) Immature crosslinks (normalised with the total amount of hydroxyproline) for controls, treatment beginning in the 1st week post injury or the 2nd week post injury. In both cases, collagen crosslinks in the week 1 treated group were significantly increased compared to both controls and the week 2 treatment group.

PROJECT TITLE

Novel aspects of the role of lipoprotein(a) in premature heart disease

INVESTIGATORS

Dr Katrina Ellis (Chief Investigator)
Professor Gerald Watts (Associate Investigator)
Professor Graham Hillis (Associate Investigator)
Dr Dick Chan (Associate Investigator)
Dr Jing Pang (Associate Investigator)
Professor Carl Schultz (Associate Investigator)

SCHOOL/INSTITUTE/CENTRE

School of Medicine and School of Biomedical Sciences, The University of Western Australia

SUMMARY OF AIMS AND RESULTS

Coronary artery disease (CAD) and its complications remain common in Australia. Despite significant advances in the treatment of acute and chronic CAD, incidence, prevalence and morbidity remain high, as do the associated economic costs. The high rates of initial and recurrent CAD events indicate the need for an improved model (beyond the current set of accepted risk factors) for predicting both the onset and progression of CAD. An improved approach for identifying those individuals at the greatest risk of CAD, particularly those with a strong family history, would allow for the targeting of clinical management to those with the greatest chance of suffering a cardiac event.

Lipoprotein(a) (Lp(a)) is comprised of a low-density lipoprotein (LDL)-like moiety covalently bound to apolipoprotein(a) (Figure 1). Elevated plasma levels of Lp(a) is a common and heritable risk factor for CAD that affects approximately 25% of the general population. Lp(a) promotes atherosclerosis by inducing atherothrombosis, which occurs as a result of adverse effects on endothelial function, inflammation, oxidative stress and plaque stability.

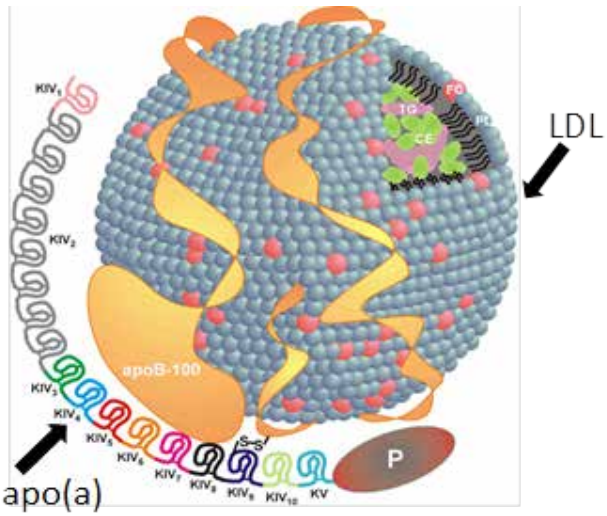


Figure 1. The Lp(a) molecule consists of an LDL particle covalently bound to an apolipoprotein(a).

Numerous genetic and epidemiological studies have demonstrated a robust curvilinear association between Lp(a) and incident CAD. Nevertheless, elevated Lp(a) is currently under-diagnosed and under-recognised, with routine screening for elevated Lp(a) not being carried out as part of standard clinical practice. Early detection is particularly important for genetically determined traits, such as elevated Lp(a), as the risk exposure in affected individuals begins from birth.

The aims of the project were to investigate two approaches for detecting elevated Lp(a). The first approach was to determine the detection rate of elevated Lp(a) in patients consecutively admitted to the coronary care unit (CCU) at Royal Perth Hospital. Secondly, the research team investigated the yield of cascade screening for elevated Lp(a) in families. Cascade screening is the systematic testing of close family members of an index case, which in this instance is defined as an individual with elevated Lp(a). For both screening approaches, the association between elevated Lp(a) and incident and recurrent CAD was also assessed.

To determine the frequency of elevated Lp(a) in patients admitted to the CCU, plasma Lp(a) concentrations were measured in consecutively admitted patients for a period of 6.5 months. During this period, 316 patients presenting with an acute coronary syndrome or prior history of CAD were screened. Elevated Lp(a) was common, present in 27% of admitted patients. A greater frequency of patients with premature CAD (32%) also had elevated Lp(a) when compared with patients without premature CAD (22%). These initial findings support the need for routine screening for elevated Lp(a) in the CCU, particularly among patients with premature CAD. The value of screening for elevated Lp(a) in the CCU would be for secondary prevention in patients with established CAD and for primary prevention in cascade screened relatives of index cases.

In order to investigate the second approach for detecting elevated Lp(a), the investigators are in the process of developing an Lp(a) cascade screening programme at Royal Perth Hospital and primary care: they have commenced testing for elevated Lp(a) in the families of several index cases (Figure 2). In addition to determining the detection rate of elevated Lp(a), the research team aims to characterise the spectrum of additional cardiovascular risk factors in individuals with elevated levels. This includes information pertaining to diet, exercise, smoking, body mass index, blood pressure, diabetes and cholesterol levels. Establishing the prevalence of these factors is important as it has recently been shown that the increased risk associated with elevated Lp(a) can be substantially reduced by intervening with secondary cardiovascular risk factors.

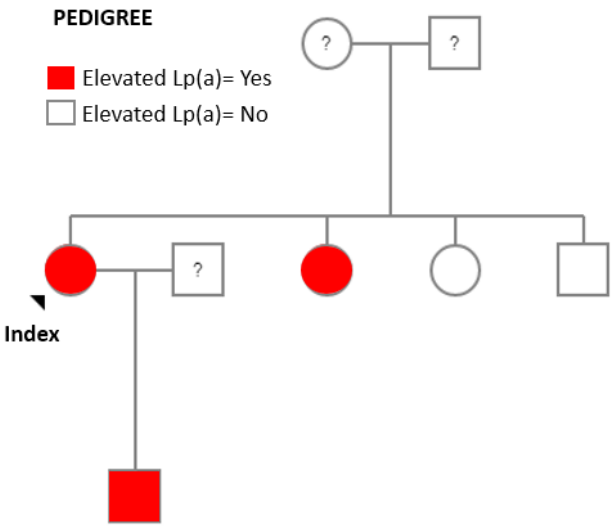


Figure 2. Example of a family cascade screened for elevated Lp(a) as part of the study. Of the relatives screened, 50% had elevated Lp(a).

OUTCOMES

Publications

Ellis KL, Pang J, Chieng D, Bell DA, Burnett JR, Schultz CJ, Hillis GS, Watts GF. Elevated lipoprotein(a) and familial hypercholesterolaemia in the coronary care unit: between Scylla and Charybdis. *Clinical Cardiology*. 2017; In Press

Ellis KL, Watts GF. Is lipoprotein(a) ready for prime-time use in the clinic? *Cardiology Clinics*. 2017; In Press

Ellis KL, Boffa MB, Sahebkar A, Koschinsky ML, Watts GF. The Renaissance of lipoprotein(a): Brave new world for preventive cardiology. *Progress in Lipid Research*. 2017; 68: 57-82

Conference Presentations

Ellis KL, Pang J, Bell DA, Burnett JR, Schultz CJ, Hillis GS, Watts GF. Isolated elevation of lipoprotein(a) is uncommon among patients admitted to coronary care. *Cardiac Society of Australia and New Zealand Scientific Meeting*. 2017; Perth

Ellis KL, Ooi E, Barrett H, Chan D, Hung J, Thompson P, Beilby J, Watts G, McQuillan B. Familial hypercholesterolaemia and lipoprotein (a) phenotypes in a community-based cohort: Associations with carotid intima-media thickness, focal plaque and cardiovascular outcomes. *Cardiac Society of Australia and New Zealand Scientific Meeting*. 2017, Perth

Chieng D, Pang J, **Ellis KL**, Bell D, Burnett J, Hillis G, Schultz C. Lipoprotein (a) level is associated with angiographic disease complexity (SYNTAX score) in patients with premature coronary disease. *Cardiac Society of Australia and New Zealand Scientific Meeting*. 2017; Perth

Ellis KL, Pang J, Bell D, Hooper A, Burnett J, Watts G. Systematic screening for familial hypercholesterolaemia and elevated Lp(a) in families. *Cardiac Society of Australia and New Zealand Scientific Meeting*. 2017; Perth

Ellis KL, Pang J, Bell DA, Burnett JR, Schultz CJ, Hillis GS, Watts GF. Elevated lipoprotein(a) and familial hypercholesterolaemia phenotypes in patients admitted to a coronary care unit with coronary artery disease. *European Atherosclerosis Society Meeting*. 2017; Prague, Czech Republic

Collaborations

The research team is actively collaborating with researchers from the SAFEHEART study in Spain on the investigation of the yield of cascade screening for elevated Lp(a). The SAFEHEART study is also undertaking cascade screening for elevated Lp(a), enabling them to combine data and compare findings between the Australian and Spanish screening programmes.

PROJECT TITLE

Genetic analysis of circulating tumour cells and circulating tumour DNA for prognosis of uveal melanoma

INVESTIGATORS

Dr Elin Gray (Chief Investigator)
Dr Tim Isaacs (Associate Investigator)
Associate Professor Fred Chen (Associate Investigator)
Dr Tersia Vermeulen (Associate Investigator)
Professor Wendy Erber (Associate Investigator)
Dr Jaqueline Bentel (Associate Investigator)
Professor Mel Ziman (Associate Investigator)

SCHOOL/INSTITUTE/CENTRE

School of Medical and Health Sciences, Edith Cowan University

SUMMARY OF AIMS AND RESULTS

Uveal melanoma (UM) is the most common primary intraocular malignancy and the leading cause of death due to primary intraocular disease in adults. Local control of UM can be achieved in the majority of cases. However, up to 50% of individuals who are diagnosed with UM will develop incurable metastatic disease despite local control of the tumour. The inability to safely obtain tumour tissue from eye melanomas is a major obstacle in providing accurate prognoses for patients. Specific genetic characteristics of the tumour can help to identify those patients that are likely to develop metastases, allowing more regular screening of high risk patients and earlier treatment. This study aims to develop methods that utilise cancer-derived DNA and cells found in blood to identify high risk genetic characteristics. Ultimately, the aim is to develop a blood test that will identify those high risk patients who will benefit from early preventative treatment.

Aim 1. To determine the frequency of circulating tumour cell (CTC) detection in UM patients at diagnosis

Thirty patients with primary localised UM were recruited into the study. CTCs were enriched by targeting melanoma-associated chondroitin sulphate proteoglycan (MCSP). Of the 26 cases in which CTCs were analysed, 15 had detectable CTCs (58%) ranging from 1 to 37 CTCs per 8 mL of blood. The investigators then evaluated the expression of a panel of melanoma markers (e.g. MCSP, MCAM, ABCB5, RANK, gp100, 5HT2B, MART-1, S100B and Nestin) in UM using a tissue microarray and 5 UM cell-lines. UM tumours and cell-lines exhibited a high heterogeneity of marker expression. Commonly used CTC markers such as MCSP, MCAM or surface gp100 were not expressed homogenously, while 5HT2B and ABCB5 were much better expressed in the tumours than in the cell-lines. These results demonstrate that the capture of CTCs with a single marker is not sufficient given the high heterogeneity of patients. As such, a multimarker approach could provide more efficient capture and identification of UM CTCs.

A multimarker approach was evaluated in which MCSP, MCAM, surface gp100, ABCB5 and 5HT2B were targeted to capture UM cells that were spiked into healthy controls blood. A recovery rate of 60-80% was observed for the markers alone or in combination. The research team are now comparing the number of CTC recovered using this multimarker approach to their previous rate where only MCSP was used to enriched CTCs. So far, the analysis of 10 UM cases have been completed.

Aim 2. To develop methodologies to identify metastatic UM by genetic analysis of CTCs

Two different whole genome amplification (WGA) kits were compared, PicoPlex WGA Kit (Rubicon Genomics) and Repli-G Single Cell Kit (Qiagen), for their ability to provide accurate copy number variation (CNV) information. WGA DNA, plus the corresponding genomic DNA, were whole genome sequenced using the Ion PGM System (Life Technologies) at an approximate depth of 0.1X. The PicoPlex Kit, but not the Repli-G kit, was able to whole genome amplify cells after fixation. WGA-DNA from single cells amplified using PicoPlex provided accurate genomic profiles concordant with parental cell-lines. Cytogenetic features of prognostic value, such as the loss of chromosome 3 and gain in 8q, was clearly distinguishable in all the samples analysed. The multimarker method described in Aim 1 was implemented with single cell WGA/low-pass sequencing to identify chromosomal aberrations associated with the metastatic risk of uveal melanoma patients. Currently, five patients have been processed using this method. Figure 1 exemplifies a case in which CNV from CTCs and the primary tumour were compared.

Aim 3. To evaluate whether circulating tumour DNA (ctDNA) analysis can be used to identify markers of metastatic UM

A panel of droplet digital assays (ddPCR) for the detection of ctDNA in UM was expanded to include not only GNA_q/GNA_{11} mutations, but also more rarely mutated genes like $PLC_\gamma 4$ and CYSLTR2, as reported in recent publications. Using a panel of eight ddPCR assays the research team detected ctDNA in eight of the 30 primary UM patients tested (23%, range 1.6-29 copies); two cases had a GNA_q Q209L mutation, two had a GNA_{11} Q209L mutation, one had a GNA_{11} Q209P mutation, one had a GNA_{11} R183C mutation, one had a $PLC_\gamma 4$ D630Y mutation and one had a CYSLTR2 L129Q mutation. Only four out of 30 patients had simultaneous detection of ctDNA and CTCs. In those with detectable mutations, ctDNA levels were correlated with tumour size. The investigators showed that ctDNA is not commonly detectable in the blood of patients with localised UM. By contrast, of the eight metastatic UM cases, all had detectable ctDNA consistent with a previous report. Nonetheless, longitudinal monitoring of two primary UM patients, that later developed metastatic disease, showed undetectable levels of ctDNA at baseline levels, but ctDNA was detected around the time of clinical confirmation of disease progression by PET scan (Figure 2). These findings indicate that low levels of detectable ctDNA in patients with primary disease are not suitable for the screening of patients at a high risk of developing metastasis. However, given the high proportion of hotspot mutations in UM, ctDNA analysis may be a feasible, minimally invasive method of monitoring metastatic disease burden and disease progression.

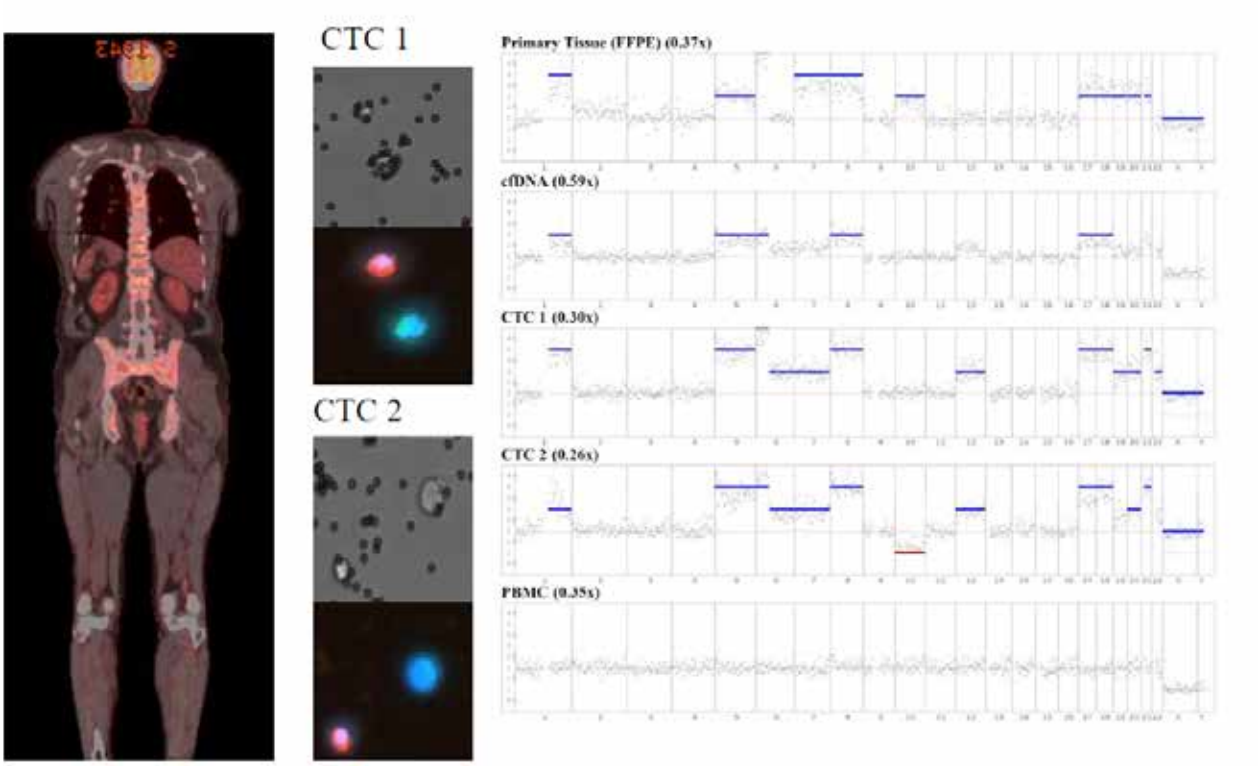


Figure 1. Comparison between the genetic profile of the primary tumour, cfDNA, two circulating tumour cells and a single peripheral blood mononuclear cell in a patient with metastatic uveal melanoma. Left panel: Whole-body FDG-PET of a UM patient at the time of blood collection. Middle panel: Brightfield and florescent images of the two CTCs used for somatic copy number alteration (SCNA) analysis. Cells were stained with a combination of antibodies against the melanoma markers MART1, gp100 and S100β (green); CD45 (red); and DAPI (blue), taken at X200 magnification. Right panel: Whole genome sequencing (WGS) SCNA profile of primary formalin-fixed, paraffin-embedded (FFPE) tumours, cfDNA, two CTCs and a single peripheral blood mononuclear cell (PBMC). The obtained sequence depth is indicated for each plot. Red and green bars represent chromosomal losses or gains, respectively.

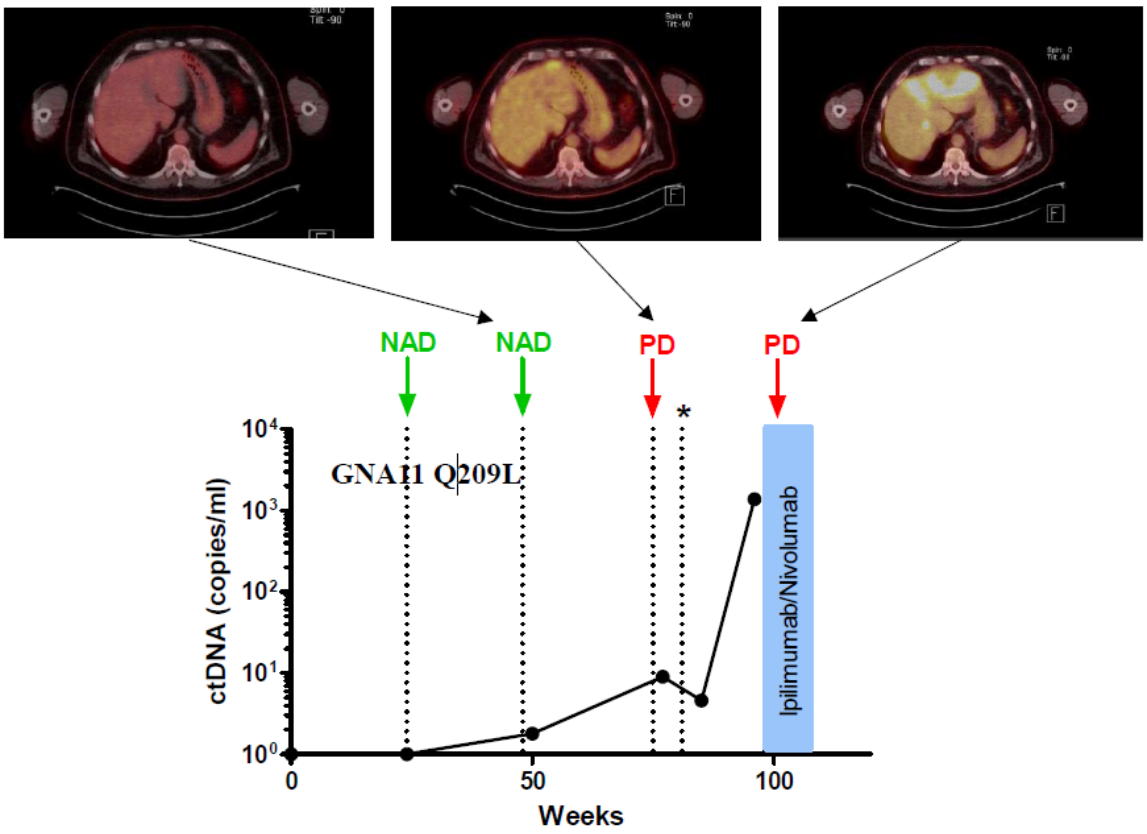


Figure 2. Analysis of ctDNA in patients with liver metastasis. Left panel: Comparison of ctDNA levels in primary (N=27) and metastatic (N=8) UM showed statistically significant differences; Student t-test p<0.001. Middle panel: Plasma ctDNA levels in longitudinally-collected samples from UM patient 656. Right panel: Plasma ctDNA levels in longitudinally-collected samples from UM patient 433, prior to and after the development of overt metastatic disease as shown by FDG-PET imaging of the liver. NAD, no active disease; PD, progressive disease.

OUTCOMES

Conference Presentations

Gray ES. Poster presentation at the *3rd ACTC Advances in Circulating Tumour Cells: Liquid Biopsy in Clinical Practice (ACTC 2017)*. 2017; Rhodes, Greece

Beasley A. Poster presentation at the *Society for Melanoma Research Congress*. 2017; Brisbane. Abstract published in the *Pigment Cell and Melanoma Research Journal*. 2018; 31: 125–230

Grants

Beasley A. Cancer Council WA, PhD Top-up Scholarships for 2017

Gray ES, Isaacs T, Ziman M. *Ophthalmic Research Institute of Australia*. 2018; $49,500

PROJECT TITLE

Towards translating the benefits of patient specific biomechanics into clinical practice

INVESTIGATORS

Dr Grand Roman Joldes (Chief Investigator)
Professor Karol Miller (Associate Investigator)

SCHOOL/INSTITUTE/CENTRE

School of Mechanical Engineering, The University of Western Australia

SUMMARY OF AIMS AND RESULTS

There is widespread international concern about the cost of meeting rising expectations for healthcare, particularly if large numbers of people require currently expensive procedures such as brain surgery. Costs can be reduced by using improved machinery to help surgeons perform these procedures quickly and accurately with minimal adverse effects. A novel partnership between surgeons and machines, made possible by advances in computing and engineering technology, could overcome many of the limitations of traditional surgery. By extending the ability of surgeons to plan and carry out surgical interventions more accurately and with less trauma, Computer Integrated Surgery (CIS) systems could help improve clinical outcomes and the efficiency of healthcare delivery. CIS systems could have a similar impact on surgery as has been realised with Computer Integrated Manufacturing.

The objective of this study was the development of algorithms that allowed the generation of computational models from medical images, as well as robust, fast and accurate solution methods. Specifically, the aim was to create a quick and robust method for generating patient-specific computational grids from diagnostic medical images, develop robust and accurate solution methods, create a fast updating procedure for high-resolution 3D images and reduce computation cost of the developed algorithms.

During the last 12 months, the development of computational algorithms for patient-specific biomechanical modelling has continued. These algorithms have been used to solve clinically relevant problems, such as brain deformation during electrode implantation for epilepsy treatment and blood flow within abdominal aortic aneurysms.

OUTCOMES

Publications

Joldes GR, Miller K, Wittek A, Forsythe RO, Newby DE, Doyle BJ. BioPARR: A software system for estimating the rupture potential index for abdominal aortic aneurysms. *Scientific Reports*. 2017; 7: 4641

Joldes GR, Chowdhury H, Wittek A, Miller K. A new method for essential boundary conditions imposition in explicit meshless methods. *Engineering Analysis with Boundary Elements*. 2017; 80: 94-104

Conference Presentations

Joldes GR, Smith DW, Gardiner BS. A discrete element framework for modelling cell and tissue behaviour with application to modelling chondrocyte migration. *Particles*. 2017; Hannover, Germany

Chowdhury H, **Joldes GR**, Wittek A, Miller K. An element free Galerkin framework for computing soft tissue deformation. *International Conference on Computational and Mathematical Biomedical Engineering*. 2017; Pittsburgh, USA

Joldes GR, Bourantas GC, Wittek A, Miller K, Smith DW, Gardiner BS. A discrete element method for modelling cell mechanics – application to the simulation of chondrocyte behavior in the growth plate. *Computational Biomachanics for Medicine, a MICCAI workshop*. 2017; Quebec, Canada

Bourantas GC, **Joldes GR**, Wittek A, Miller K. A flux-conservative finite difference scheme for the numerical solution of the nonlinear bioheat equation. *Computational Biomechanics for Medicine, a MICCAI workshop*. 2017; Quebec, Canada

Grants

K Miller, N Knuckey, A Nabavi, **G Joldes**, A Wittek, R Kikinis. "Resection-induced brain shift estimation: biomechanics-based approach". *NHMRC Project Grant APP1144519*. 2018-2020; $370,055

G Joldes. "Towards translation of patient specific biomechanics into clinical practice". *Department of Health WA Merit Awards*. 2016-2017; $25,000

G Joldes, S Warfield, G Bourantas. "Real-time brain deformation computation for accurate target localisation in epilepsy treatment": partner institution: Harvard Medical School. *UWA Research Collaboration Awards*. 2017; $21,420

A Wittek, K Miller, **G Joldes**, A Dyskin, E Pasternak, F Wang, Y Tang, Y Han, Q Peng. "Brain injury biomechanics in car crash: The brain–skull interface". *Fujian Province 100 Talent Team Program*. 2017-2018; $77,000

PROJECT TITLE
The GENTLE project (GENder identiTy Longitudinal Experience)

INVESTIGATORS
Dr Ashleigh Lin (Chief Investigator)
Professor Florian Zepf (Associate Investigator)
Dr Julia Moore (Associate Investigator)

SCHOOL/INSTITUTE/CENTRE
Telethon Kids Institute

SUMMARY OF AIMS AND RESULTS
Identification of a gender other than that matching the sex at birth is relatively common in adolescence. For example, in a 2012 survey of 8,166 New Zealand high school students, 1.7% described themselves as "transgender" and 2.5% described themselves as being "unsure about their gender". Young people may identify as trans, transgender, transsexual, gender queer, or simply as boy, girl, man or woman, where this gender identity differs from their natal sex.

For some gender dysphoric children, the prospect of pubertal development is extremely stressful and even unbearable, and can be a major contributor to poor mental health. It is well documented that transgender children and adolescents report alarmingly high rates of psychiatric morbidity compared to their cis-gender peers and are at extremely high risk for mortality by suicide. In contrast to the clear need for psychological and psychiatric intervention for this group of individuals, very few services in Western Australia specialise in the mental health of trans young people. There is also very limited support for the parents and families of trans and gender dysphoric young people who may be struggling with accepting the gender identity of their child.

The GENTLE project will investigate the health and wellbeing throughout the life span of people who accessed hormonal gender affirming treatment in adolescence. The primary aim is to establish a detailed database of adolescents attending the Princess Margaret Hospital-Gender Diversity Service (PMH-GDS) (i.e. the GENTLE database) and follow-up these young people one year later to examine their mental health outcomes. Secondary aims of GENTLE are:

1. To provide the foundation for future expansion and collaboration based on the GENTLE database, within Australia and internationally
2. To establish the GENTLE database as a rich information resource, which can be shared with researchers from diverse areas to address other important research questions

So far, 42 participants have been recruited to the GENTLE study, with only one patient at the Gender Diversity Service at PMH declining to participate. The research team foresee having consented all past and current patients by mid-2018. The GENTLE database is nearing completion and will be functional in March 2018. All data will be exported into the database, which can be used indefinitely both clinically and for research purposes. There is a PhD student working on GENTLE (Simone Mahfouda; The University of Western Australia), who will investigate the longitudinal mental health of gender diverse young people seen at the GDS. There is also a Masters in Clinical Psychology student working on GENTLE (Christina Panos, Murdoch University), who will investigate the overlap between gender diversity and autism spectrum disorders. Preliminary data analysis will be conducted in March.

OUTCOMES
Publications
Mahfouda S, Moore J, Siafarikas A, Zepf F, **Lin A**. Puberty suppression in transgender children and adolescents. *The Lancet Diabetes and Endocrinology*. 2017; 5; 816-826

Grants
Simone Mahfouda. Perth Children's Hospital fund PhD top-up scholarship

Collaborations
The GENTLE team are members of the Australian Children's Gender Clinics Network made up of clinicians and researchers in paediatric gender services in Australia. The Network meet every six months to discuss clinical issues and research. This link is vital for the rapid translation of findings from the GENTLE Cohort.

PROJECT TITLE

Identifying immune biomarkers of response to chemotherapy in thoracic cancers

INVESTIGATORS

Dr Alison McDonnell (Chief Investigator)
Professor Anna Nowak (Associate Investigator)
Adjunct Professor Richard Lake (Associate Investigator)
Professor Bruce Robinson (Associate Investigator)

SCHOOL/INSTITUTE/CENTRE

School of Biomedical Sciences, The University of Western Australia

SUMMARY OF AIMS AND RESULTS

The average survival from mesothelioma and advanced lung cancer is only 9-12 months and together these cancers account for 20-25% of cancer-related deaths in WA. New treatments are being developed that combine chemotherapy with drugs designed to activate the immune system; however, the successful combination of these treatments requires an understanding of how chemotherapy affects the immune system. This project examined how chemotherapy alters the immune response at the tumour site compared with blood, with a particular focus on T cells. The overall aim of this study was to identify novel immune markers in response to treatment. Specifically, the aims were as follows:

Aim 1. Characterise the phenotype and activation status of $CD8^+$ T cells at the tumour site (i.e. from pleural effusions (PE) and systemic peripheral blood (PB)).

Aim 2. Investigate and compare the T cell receptor (TCR) repertoire of lymphocytes within matched PE and PB samples.

Patient recruitment. The study population consists of patients with malignant mesothelioma and advanced non-small cell lung cancer with recurrent pleural effusion, undergoing standard care chemotherapy. The research team aimed to collect matched peripheral blood (PB) and pleural effusion (PE) samples from 35 patients across four time points (pre-treatment and three with treatment time points). While patient recruitment is currently ongoing, matched PB and PE samples from 31 patients (24 with mesothelioma and seven with lung cancer) have been collected and stored. However, serial samples from all of these patients could not be collected. Initially, this was due to problems with the sample collection protocols, whereas in the past six months there has been a change to the clinical management of pleural effusions associated with malignant mesothelioma for some patients. Thus far, baseline samples for all participants and serial samples from nine patients have been collected.

- Aim 1. Optimisation of mass cytometry protocols to examine the phenotype of T cells within PB and PE samples were delayed due to technical issues with the CyTOF 2 mass cytometer at UWA. This continued through the last year, however, the Centre for Microscopy, Characterisation and Analysis (CMCA; UWA) has been in negotiations with Fluidigm (the manufacturer) to upgrade the current machine to the new generation HELIOS mass cytometer. The inability to generate mass cytometry data has delayed the output and expected completion date for Aim 1. In lieu of access to CyTOF, the investigators designed and optimised three 15-parameter flow cytometry panels to look at the T cell subsets and have completed the analysis of matched samples from 17 patients thus far.

- Aim 2. This work is underway in collaboration with Associate Professor Mark Watson at the Institute for Immunology and Infectious Diseases (IIID) at Murdoch University. Bulk TCR sequencing of matched PB and PE samples has been conducted from one patient at one time point. The project is currently progressing towards single cell techniques to look at the T cells in more detail. The plan is to wait until the flow cytometry analysis is complete because initial results indicate TCR profiling a specific phenotype of T cells could yield more relevant information than bulk T cell subset analysis. This aim is moving forward well and exciting results are anticipated soon.

OUTCOMES

Conference Presentations

"Identifying immune biomarkers of response in malignant mesothelioma." *National Centre for Asbestos Related Diseases Annual Scientific Meeting*. 2017; Perth

Grants

McDonnell AM, Nowak AK, Lake RA, Robinson BWS, Cook AC. Identifying immune biomarkers of response to chemotherapy in malignant mesothelioma – a single cell study. *icare Dust Diseases Care Research Grant*, NSW Government. 2018-2019; $232,923

Collaborations

Dr McDonnell has established two new collaborations as a direct result of the work being conducted in this study. Together with Dr Sally Lansley of the Institute for Respiratory Health she is looking at modelling the T cell responses observed in the clinic in a mouse model of pleural effusion and mesothelioma. Also, the analysis of the immune response in the patient population of this study has led to a collaboration with exercise physiologist Dr Carolyn McIntyre from Edith Cowan University to explore the effect of exercise on the anti-tumour immune response in asbestos-exposed individuals and patients with mesothelioma and lung cancer.

PROJECT TITLE
Role of genetic copy number variation in osteoporosis

INVESTIGATORS
Dr Benjamin Mullin (Chief Investigator)
Associate Professor Scott Wilson (Associate Investigator)

SCHOOL/INSTITUTE/CENTRE
School of Biomedical Sciences, The University of Western Australia

SUMMARY OF AIMS AND RESULTS
As the Australian population ages, addressing issues related to osteoporosis become more imperative. Humans are living longer, with the frequency of age-related diseases such as osteoporosis increasing with the average lifespan. Studies have shown that there is a strong genetic influence on bone mass, bone loss and fracture rates. Genome-wide association studies have proven to be successful in identifying common genetic variants (with a minor allele frequency >5%) associated with bone mineral density and clinical endpoints (i.e. fragility fracture) for osteoporosis. However, the majority of the genetic variance for osteoporosis-related phenotypes remains unexplained. This study will help determine the role of copy number variations (CNVs) in osteoporosis, which could help explain some of the missing heritability for the disease.

- Objective 1: Perform genome-wide detection of genetic CNVs in whole-genome sequence data from 1,990 individuals
  - Genome-wide detection of CNVs in whole-genome sequence data from 1,990 individuals has been completed using the Genome STRiP (Genome STRucture In Populations) v2.00 software package, which is able to detect both duplication and deletion CNVs. The investigators have detected 30,182 CNV regions genome-wide with a minor allele frequency (MAF) ≥1%.

- Objective 2: Test common CNV in 56 loci with a known association with bone phenotypes for association with intermediate and clinical endpoints for osteoporosis
  - The research team has identified 1,533 CNV regions with a MAF ≥1% located within 1.2 Mb of 56 known bone loci. Analysis of these CNV for association with spine, femoral neck and total hip bone mineral density (BMD) was completed using PLINK 1.07. None of the CNVs were found to be significantly associated with BMD after correction for multiple testing (via Bonferroni statistical testing). However, interesting suggestive associations were identified between a series of CNVs located within the locus 12p11.22 and BMD at the spine, femoral neck and total hip sites (P=0.01, 0.01 and 0.007, respectively). This CNV region spans the last two exons of the *SMCO2* gene.

- Objective 3: Perform a genome-wide association study of common CNVs and phenotype data for intermediate and clinical endpoints for osteoporosis
  - A genome-wide association study was performed for all detected CNVs with a MAF ≥1% for association with spine, femoral neck and total hip BMD using PLINK 1.07. The analysis failed to identify any CNVs associated with BMD phenotypes at the genome-wide level after correction for multiple testing (Bonferroni). However, interesting suggestive associations were identified for CNVs at 9p21.1 (spine BMD, P=0.006), 10q11.22 (femoral neck and total hip BMD, P=0.02 and 0.004, respectively) and 11q11 (spine and total hip BMD, P=0.01 and 0.05, respectively).

- Objective 4: Replicate provisional associations from the discovery studies in an independent cohort comprised of 1,040 individuals genotyped using a commercial single-nucleotide polymorphism (SNP) array
  - Genome-wide marker array genotype data were generated using the Illumina OmniExpress 700K BeadChip for a replication population of 1,046 individuals with BMD data. Genome-wide detection of CNVs in this dataset was performed using the Illumina GenomeStudio v2011.1 software package utilising the cnvPartition v3.2.0 plugin, which is able to detect both duplication and deletion CNVs. The investigators detected 18,828 CNVs genome-wide with a MAF ≥1%. Statistical analysis was performed in this population using the PLINK 1.07 software. The *SMCO2* CNV was not detected in the replication cohort, however, the associations identified for CNVs at 9p21.1 (spine BMD, P=0.05) and 10q11.22 (femoral neck BMD, P=0.02) were replicated.

This study of CNVs has identified some interesting associations with BMD, while highlighting some of the challenges facing research in this area, such as consistency of CNV genotypes generated using different technologies. Future studies will include collaboration with other research groups possessing CNV genotype and BMD data to increase statistical power, and confirmation of the *SMCO2* gene CNV by direct genotyping using quantitative real-time PCR techniques.

The investigators plan to publish at least two more manuscripts on the findings from their osteoclast eQTL study and use these results as preliminary data to apply for NHMRC funding to perform genome-wide methylation studies in this cohort using the osteoclast DNA samples that are currently in storage. If funded, they will characterise regions of variable methylation in this cell type and investigate how they segregate with genetic variants and regulate the expression of nearby genes.

OUTCOMES

Publications

Mullin BH, Zhao JH, Brown SJ, Perry JRB, Luan J, Zheng HF *et al*. Genome-wide association study meta-analysis for quantitative ultrasound parameters of bone identifies five novel loci for broadband ultrasound attenuation. *Human Molecular Genetics*. 2017; 26: 2791-2802

Awards and Presentations

Mullin BH. Study of human osteoclasts identifies DNA variants associated with gene expression and disease pathways. *Sir Charles Gairdner Osborne Park Health Care Group (SCGOPHCG) New Investigator Awards*. 2017.

PROJECT TITLE

Alcohol-related harm in young people: developing a longitudinal evidence base

INVESTIGATORS

Dr Melissa O'Donnell (Chief Investigator)
Dr Michael Livingston (Associate Investigator)
Mr Scott Sims (Associate Investigator)
Dr Gavin Pereira (Associate Investigator)
Professor Fiona Stanley (Associate Investigator)

SCHOOL/INSTITUTE/CENTRE

Telethon Kids Institute

SUMMARY OF AIMS AND RESULTS

Globally, alcohol-related harm is a priority public health issue and in Australia a number of government strategies and initiatives are being implemented at the federal and state level to prevent and reduce it. Nationally, 5,534 deaths and 157,132 hospital admissions were attributed to alcohol in 2010 and an audit in 2014 showed that 13.8% of patients in emergency departments (ED) presented for alcohol-related reasons, with Western Australia (WA) higher than the average at 21%. Measuring alcohol-related harm has improved with the establishment of the National Alcohol Indicators Project (NAIP), which includes measures of alcohol attributable deaths and hospital admissions. However, there are limitations of individual indicators and divergent trends between surveys on alcohol consumption and alcohol-related harm.

This research aims to:

- Identify pathways through the health system for youths presenting with alcohol-relating harm or impacted upon by alcohol-related violence with a focus on:
  - Episodes of care, prognostic outcomes and points for early intervention
  - Mental health comorbidities and outcomes
  - Aboriginal youth
- Measure and geographically map the impact of changes in alcohol availability on alcohol-related harm. Spatial models will be used to map harm and explore the relationship between alcohol-related harm and alcohol availability, and model the risk of experiencing harm as a function of change in individual outlet exposure

In the last year, the research team has conducted analysis on health data to determine the trends in alcohol-related admissions and associated intentional and unintentional injuries. Alcohol outlet sales data have been received and the investigators have requested ambulance data in addition to the health datasets provided by the Department of Health. The police have also extracted their data on alcohol-related incidents and this will be provided shortly. The alcohol-related incident data from the police and St John Ambulance will allow for further analyses of the alcohol-related contacts for young people and their associated harm through linkage to health and mental health data.

The researchers will break down the data further into Aboriginal vs non-Aboriginal youth. They are currently mapping the health and alcohol-related outlet data to investigate this relationship.

Dr O'Donnell has been working with the ED data custodians to improve its collection through the implementation of recommendations to increase the number of diagnostic codes collected, as well as the development of mandatory external cause codes associated with injury presentations. She has also been a member of the Department of Health's working group on the Youth Health Policy in which Dr O'Donnell wrote the Youth Health Policy companion document. To further examine the relationship between risky drinking and mental health issues the research team has requested access to the Young Minds Matter: National Youth Mental Health Survey, which has been received and is currently being analysed.

OUTCOMES

Publications

O'Donnell M, Sims S, Maclean M, Gonzalez-Izqueirdo A, Gilbert R, Stanley F. Trends in alcohol-related injury admissions in adolescents in Western Australia and England: population-based cohort study. *British Medical Journal Open*. 2017; 7: e014913

Collaborations

Dr O'Donnell has made contacts and collaborations through attending the Western Australian Injury Prevention Summit and has attended regular seminars through Curtin University's National Drug Research Institute to forge further collaborations. She has also formed collaborations with Michael Livingstone (La Trobe University), Liz Geelhoed (UWA) and David Preen (Chair of Public Health, UWA).

PROJECT TITLE
A novel approach for the prevention of hypertrophic cardiomyopathy

INVESTIGATOR
Dr Helena Viola (Chief Investigator)

SCHOOL/INSTITUTE/CENTRE
School of Human Sciences, The University of Western Australia

SUMMARY OF AIMS AND RESULTS

Cardiovascular disease is the leading cause of death in Australia. It is a major human health issue and national health priority. In 2008-2009, the treatment of cardiovascular disease consumed $7.6 billion of all allocated healthcare expenditure (Australian Institute of Health and Welfare). Hypertrophic cardiomyopathy is a primary myocardial disorder that affects 1:200 of the general population. It is the leading cause of sudden cardiac death in the young. Drug therapy is used to manage symptoms in patients, but no treatment exists that can reverse or prevent cardiomyopathy. Determining new strategies to prevent the development of hypertrophic cardiomyopathy is critical for effective treatment of the disease.

This study represents a novel early-intervention approach to prevent the development of cardiomyopathy resulting from mutations in cTnI or β-MHC, which account for the majority of genotyped families with hypertrophic cardiomyopathy. It is anticipated that once translated, this will significantly reduce the incidence of sudden cardiac death and associated morbidity and mortality.

The cytoskeleton plays an important role in mediating alterations in mitochondrial function in response to changes in L-type Ca^{2+} channel activity. Dr Viola has previously demonstrated that the AID-TAT peptide slows the inactivation rate of the channel and decreases mitochondrial metabolic activity. It also improves contractility and prevents the development of cardiac hypertrophy following coronary artery occlusion, without decreasing blood pressure or altering calcium influx in cardiac myocytes. Therefore, the AID region of the L-type Ca2+ channel is a viable target for normalising mitochondrial function and for preventing the development of hypertrophic cardiomyopathy in *cTnI-G203S* and α*MHC403/+* cardiomyopathy, without causing negative ionotropic effects.

Aim 1: Determine the dose of AID-TAT required for optimal uptake into *cTnI-G203S* and α*MHC403/+* myocardium
It was anticipated that AID-TAT would last three to four days, which is consistent with the turnover rate of the L-type Ca2+ channel protein. Therefore, three days following treatment, the uptake and distribution of AID-TAT was assessed in the heart. The research team found that the administration of 10 μM AID-TAT was sufficient to result in the uptake into *cTnI-G203S* myocardium.

Aim 2: Determine the effect of *in vivo* treatment with AID-TAT on L-type Ca2+ channel activity and mitochondrial function in myocytes isolated from the hearts of *cTnI-G203S* and α*MHC403/+* mice
Cardiac myocytes were isolated from pre-cardiomyopathic *cTnIG203S* and αMHC403/+ mice three days following in vivo treatment with 10 μM AID-TAT (active or inactive control). The investigators found that mitochondrial function was significantly restored in myocytes isolated from mice treated with active AID-TAT versus inactive control AID-TAT.

Aim 3: Determine the efficacy of *in vivo* treatment with AID-TAT in preventing the development of hypertrophic cardiomyopathy in *cTnI-G203S* and α*MHC403/+* mice
Based on the findings from Aims 1 and 2, *cTnI-G203S* mice were treated with 10 μM AID-TAT three times per week for five weeks (until the establishment of hypertrophic cardiomyopathy). Remarkably, this treatment regimen was found to effectively prevent the development of cardiomyopathy in *cTnI-G203S* mice.

Aim 4: Determine if the beneficial effect of AID-TAT (i.e. preventing the development of hypertrophic cardiomyopathy) persists following completion of the treatment

The research team is now completing a study to determine the efficacy of the AID-TAT peptide on reversing hypertrophic cardiomyopathy in mice that have already developed the disease. They are also investigating toxicity of the peptide. These studies will be important in order to determine if the same peptide can be used to either prevent or reverse the disease in a safe/non-toxic way.

OUTCOMES

Conference Presentations

"Let's have a heart to heart". *UWA Research Week*, Speaker: Public Lecture (UWA). 2017; Perth

"Where are they now?". *UWA Faculty of Science Rising Star Winner*, Speaker (UWA). 2017; Perth

"Work Life Balance". Mentor-Mentee Dinner, Invited Speaker and Panellist. *CSANZ*. 2017; Perth

Invited talk (mini-oral): *ISHR*. 2017; Perth

Invited talk (poster presentation): "Excitation-contraction coupling". *Gordon Research Conference*. 2017; Les Diablerets, Switzerland (Figure 1)

Poster: "Excitation-contraction coupling". *Gordon Research Conference*. 2017; Les Diablerets, Switzerland

Poster: "Excitation-contraction coupling". *Gordon Research Seminar*. 2017; Les Diablerets, Switzerland

Grants

Viola (CIA). "Innovative use of hydrogel technology to recapitulate and investigate cardiac pathology." *NHMRC Project Grant - New Investigator (APP1143203)*. 2018-2020

Viola (CID). "How does sudden cardiac death occur in familial hypertrophic cardiomyopathy?" *NHMRC Project Grant (APP1143321)*. 2018-2021

Collaborations

Dr Viola has formed new collaborations with Professor Chris Semsarian, Centenary Institute, Sydney; Dr Yu Suk Choi, School of Human Sciences, UWA; and Associate Professor Evan Ingley, Harry Perkins Medical Research Institute.

Figure 1: Invited speaker at the *Gordon Research Conference*. 2017; Les Diablerets, Switzerland

FELLOWSHIPS

Government of **Western Australia**
Department of **Health**

RAINE MEDICAL RESEARCH FOUNDATION

WA Department of Health/Raine Clinician Research Fellowships

The Clinician Research Fellowship program was founded in 2012 by the WA Department of Health in partnership with the Raine Medical Research Foundation. The program aims to support talented clinicians and allied health professionals to establish and develop their research careers. The program has now supported 25 Clinician Research Fellowships with a funding commitment in excess of $6.2m.

Round 6 of the program was opened in 2017, for funding to commence in 2018. Fellowships are only offered to applicants demonstrating excellence in their research field, using highly rigorous and equitable assessment processes. Four Clinician Research Fellowships were awarded for Round 6 that focus on clinical research projects in the areas of child and youth health, transplant studies, and cancer. These projects aim to bridge the gap between research and clinical translation for improved clinical practice and better health care delivery that will benefit all in the WA community.

There were 13 Clinician Research Fellowships ongoing throughout 2017 from Rounds 2 - 5, including one project funded by the Department of Health Nurses and Midwives group. In 2017 four Fellowships were allocated for round 7 to commence in 2018, with a total funding allocation of $876,050.

2014 Clinician Research Fellowships (Round 2)

	Fellow	Project Title
	Clinical Associate Professor Gareth Baynam Princess Margaret Hospital for Children	1 in 12: Translational research for rare diseases
	Dr Brigitte Tampin Sir Charles Gairdner Hospital	The role of sensory parameters in predicting clinical outcome after lumbar discectomy

2015 Clinician Research Fellowships (Round 3)

	Fellow	Project Title
	Dr Edward Fysh St John of God Midland Public Hospital	Pleural effusions in intensive care patients: The physiological changes and clinical effects of drainage procedures
	Clinical Associate Professor Kwok-ming Ho Royal Perth Hospital	Detailed assessment of risks and benefits of inferior vena cava filters on patients with complicated injuries (the *da Vinci* Trial)
	Dr Thomas Snelling Princess Margaret Hospital for Children	Improving the West Australian immunisation program
	Mr Ulrich Steinwandel **Nurses and Midwifery Group** Fiona Stanley Hospital	Do ultrasound measurements of the inferior vena cava (IVC-US) by nursing staff improve assessment of intravascular volume status in the satellite haemodialysis clinic settings?

2016 Clinician Research Fellowships (Round 4)

	Fellow	Project Title
	Dr Martin de Bock Princess Margaret Hospital	Closed loop insulin delivery for patients with type 1 diabetes in free living conditions

	Dr Rishi Kotecha Princess Margaret Hospital for Children	Combinatorial therapeutics in high-risk infant acute lymphoblastic leukaemia
	Dr Annette Lim Sir Charles Gairdner Hospital	Mechanisms that facilitate the metastatic potential of oral cancer
	Dr Edmond O'Loughlin Fiona Stanley Hospital	Project 1: IronNOF – Intravenous Iron to reduce transfusion and improve post-operative haemoglobin in patients with fractured Neck Of Femur Project 2: PADDI – The Perioperative ADministration of Dexamethasone and Infection

2017 Clinician Research Fellowships (Round 5)

	Fellow	Project Title
	Dr Dimitri Azmanov PathWest	Diagnostic genomics applications for short stature
	Associate Professor Wai Lim Sir Charles Gairdner Hospital	Improving health outcomes of kidney transplant recipients
	Associate Professor Tobias Strunk King Edward Memorial Hospital for Women	Pentoxifylline to protect the preterm brain

2018 Clinician Research Fellowships (Round 6)

	Fellow	Project Title
	Dr Oyekoya Ayonrinde Fiona Stanley Hospital	The epidemiology, origins and associations of irritable bowel syndrome in adolescents
	Dr Nathan Harvey PathWest	Lymphovascular invasion of cutaneous squamous cell carcinoma in renal transplant patients
	Dr Andrew Martin Princess Margaret Hospital for Children	Feasibility and acceptability of screening children for inherited hypercholesterolaemia
	Dr Warren Pavey Fiona Stanley Hospital	Supercooled storage for extended preservation of hearts – A pilot study in a rodent model

2017 Annual Research Reports
Clinician Research Fellowships

PROJECT TITLE
1 in 12: Translational research for rare diseases

CLINICIAN RESEARCH FELLOW
Clinical Associate Professor Gareth Baynam

RESEARCH PROJECT OVERVIEW AND AIMS

The research conducted under this fellowship aimed to develop 3D facial analysis capacity for innovative solutions to improve the lives of individuals living with rare diseases and relatedly to support the development of rare disease knowledge management platforms. Health system outcomes included delivering 3D-FAST into clinical practice. The 3D-FAST tool was developed under the CliniFace program of works. Through iterative computer science developments enabled by expanding reference data sets and clinician and community engagement, the research team created a modular platform that is interoperable with different 3D imaging systems and 3D and 2D image formats, as well as being able to export data in multiple formats. 3D data can be visualised and analysed within the platform, which has been integrated into state-wide clinics through genetic services within Western Australia and is being increasingly integrated with the state-wide rare diseases knowledge management platform, Patient Archive-WA. This combines clinical data, such as text and 3D imaging at the clinical coal face. The first analysis modules focused on curvature, Human Phenotype Ontology (HPO) term extraction, and automated landmarking and measurements. HPO term extraction is being further refined to enable implementation with the global RD-Connect platform for integrative "omics" approaches. Further modules to deliver objective signatures of rare diseases are also being progressed. These tools are being used in clinical services, including the Undiagnosed Diseases Program WA, to improve rare diseases diagnosis and management.

ONGOING CLINICAL DEVELOPMENTS

Research Translation and Diffusion

- Rare and Undiagnosed Diseases Diagnostic Service (RUDDS): This service has trebled the rate of confirmed genetic diagnosis in clinical service. The RUDDS has continued from it initiation and implementation under this Fellowship
- The Undiagnosed Diseases Program (UDP) (http://www.kemh.health.wa.gov.au/services/genetics/#udp-wa): This was implemented at Princess Margaret Hospital as a novel and globally coordinated approach (The Undiagnosed Diseases Network International; http://www.udninternational.org/) for those with extraordinary clinical (diagnostic) need. To date it has achieved a definitive diagnosis for 2 out of 3 children seen. It involves multiple National Institutes of Health and their equivalents (e.g. US, Japan, Italy, Korea and others)
- Rare Diseases Data from WARDA (http://www.kemh.health.wa.gov.au/services/register_developmental_anomalies/): This has continued to provide world first population level information on the impact of rare diseases for health system planning for improved health care. This includes involvement in the RUDDS and the UDP, as well as obtaining baseline state-wide microcephaly data, covering the last 30 years, as preparation for Zikka virus and an expanding range of rare genetic microcephalies
- Cliniface (http://www.crcsi.com.au/research/4-4-health/completed-projects/4-406-cliniface/): Implementation of new 3D facial analysis tools in clinical practice

FELLOWSHIP OUTCOMES

Advancing Knowledge

Media Coverage/Publicity

The work has been disseminated through multiple articles published in state and national media, TV interviews and news broadcasts across Channels 7,9,10 and the ABC. Some examples include:

- The Australian – WA Undiagnosed Diseases Program Success (http://www.theaustralian.com.au/news/latest-news/wa-undiagnosed-diseases-program-success/news-story/e9faf0d678ea715f298a361db27759f7)
- ABC news – New expert panel hoping to unlock mysteries of undiagnosed Diseases (http://www.abc.net.au/news/2016-07-23/jessica's-mystery-disease-tackled-by-new-expert-wa-panel/7638750)
- Business News – 3D facial analysis to detect disease (https://www.businessnews.com.au/article/3D-facial-analysis-to-detect-disease)
- Pilbara Faces (https://www.youtube.com/watch?v=l9GV17EPleo)

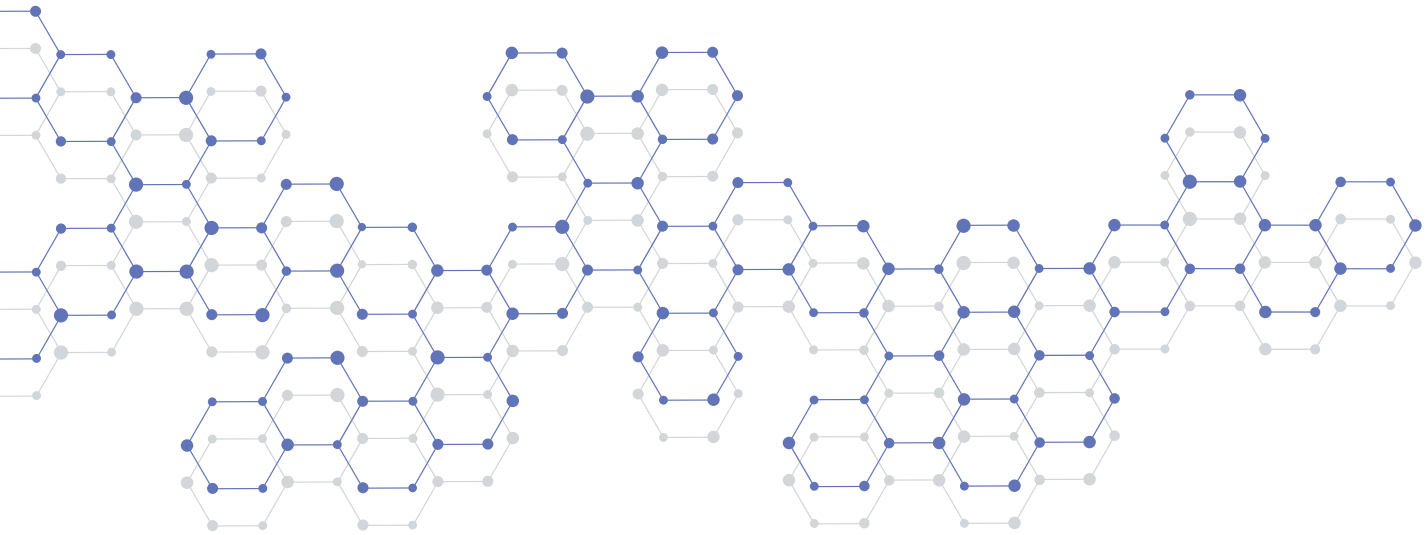
Capacity Building

Grants

- Principle Investigator, Cliniface Stage 2. Syndrome Classification and HPO Interoperability Extensions; $248,000
- Pilbara Faces; $298,000
- Principle Investigator, Goldfields Faces; $60,000
- Chief Investigator, NHMRC Centre for Research Excellence for Severe Neurocognitive Disorders; approximately $2.4M
- Chief Investigator, Center for Precision Medicine for Children, Telethon Kids Institute, Rare and Undiagnosed Diseases – creating a multi-omics pipeline; $501,000

ACKNOWLEDGEMENTS

Clinical Associate Professor Baynam would like to thank the WA Department of Health and the Raine Medical Research Foundation for the opportunity. This Fellowship has enabled a health system transformation under a precision public health paradigm, through a series of interwoven international collaborations and partnerships, and their implementation at the clinical interface.



PROJECT TITLE
Closed loop insulin delivery for patients with type 1 diabetes in free living conditions

CLINICIAN RESEARCH FELLOW
Dr Martin de Bock

RESEARCH PROJECT OVERVIEW AND AIMS

There are over 120,000 people in Australia with type 1 diabetes (T1D). Approximately 6,000 of these are children under 14 years of age and the incidence is increasing by around 3.5% each year, with over 1,000 patients up to the age of 18 in Western Australia with type 1 diabetes. Despite modern treatment, complications of T1D continue to be a reality for patients and attempts to aggressively manage blood glucose levels, in order to avoid long-term complications, are limited by the risk of hypoglycaemia. Severe, prolonged hypoglycaemic can lead to seizures, loss of consciousness and even death. This creates a fear of hypoglycaemia and anxiety for patients and their caregivers, which affects quality of life and promotes behaviours that are aimed at avoiding hypoglycaemia. These actions lead to hyperglycaemia, placing patients at a higher risk of developing long-term complications. Furthermore, type 1 diabetes affects cognitive function, social function, and places a large health and economic burden on their families and community. Indeed, in 2008-2009 $214 million of healthcare expenditure was for type 1 diabetes. Therefore, to address the unmet needs of patients with T1D, it is essential to develop new therapies.

Patients with type 1 diabetes are dependent on receiving insulin. Over the last decade advances in technology have seen the advent of insulin pumps that can deliver insulin continuously and glucose sensors that can measure glucose levels continuously. A closed loop system is where the information from the glucose sensor is communicated to the insulin pump, which then changes the amount of insulin delivered automatically in order to keep blood glucose levels in check. The aim of this study is to see how closed loop insulin delivery can improve the lives of patients with type 1 diabetes and their families in the community. The specific aims are to: (i) Define the improvements in glycaemic control due to hybrid closed-loop insulin delivery compared to sensor augmented insulin pump therapy with low glucose suspend (the current most advanced system available to patients) in true free-living conditions; (ii) Define the improvements in psychological and social well-being afforded by using hybrid-closed loop insulin delivery in true free-living conditions; (iii) Define “technology–user” interactions (“human factors”) to improve translational strategies; and (iv) Define the cost effectiveness of hybrid closed loop technology compared to sensor augmented insulin pump therapy with low glucose suspend.

ONGOING CLINICAL DEVELOPMENTS

Research Translation and Diffusion

At this stage of the project, the device is investigational and there is no ability to translate. However, as this is a multisite study and the device will come to market in Australia within the next two to three years, the research team has created a high degree of institutional knowledge across five sites in Australia, that account for approximately 50% of children with type 1 diabetes living in the country. This means that the research team will be in a better position to translate the technology into clinical practice when commercially available.

FELLOWSHIP OUTCOMES

Advancing Knowledge

Publications

- Dr de Bock’s research profile, assisted by this fellowship, has led him to be invited and contribute to international guidelines on diabetes technologies (publication pending)
- A protocol manuscript for the main trial is “In Press” with the *British Medical Journal Open*

Conference Presentations

- Presentations at the *Australasian Paediatric Endocrine Group (APEG)*. 2017; Hobart
- An abstract entitled “Performance of medtronic hybrid closed loop iterations, results from a randomized trial in adolescents with type 1 diabetes” has been accepted for presentation at the *Advanced Technologies and Therapeutics for Diabetes* conference. 2018; Vienna, Austria
- Dr de Bock was invited to speak at the largest diabetes conference in the world, the *American Diabetes Association* conference. 2018; Orlando, USA
- Oral presentation at *Directions in Diabetes*. 2018; Sydney

Media Coverage/Publicity

- A short term 1 week artificial pancreas study received great media attention with a front page picture and accompanying article in The Weekend West in September 2017.

Capacity Building

Workshops

- *Diabetes and Endocrine* workshop. 2018; Auckland, New Zealand
- *APS/ISPAD Diabetes* workshop. 2018; Melbourne

Collaborations

- A collaboration with the Cambridge artificial pancreas team, through Professor Katherine Barnard, has been created and will be built on in coming years

ACKNOWLEDGEMENTS

Dr de Bock would like to thank the WA Department of Health and the Raine Medical Research Foundation for this fellowship, without which this work would not have been possible.

The Weekend West

October 7-8, 2017

CELEBRATING 50 YEARS telethon 7

Teens take the leap in world-first medical trial

NEWS PAGE 17

Grace Popplewell, Jessica Kursar, Andrew Parsons, Matt Brown, Badon Rees-Wilmore, researcher Dr Martin De Bock and Callum Hughes at Woodman Point. Picture: Trevor Collens

PROJECT TITLE

Pleural effusions in intensive care patients: The physiological changes and clinical effects of drainage procedures

CLINICIAN RESEARCH FELLOW

Dr Edward Fysh

RESEARCH PROJECT OVERVIEW AND AIMS

Pleural effusions are common in intensive care, affecting 60% of patients, i.e. 68,000 patients per annum. While some small studies have shown improved oxygen levels after fluid drainage, they are not consistent. It is not known if pleural drainage is effective in Intensive Care Unit (ICU) patients, or what clinical benefits are achieved. Drainage procedures incur significant risk, especially since the majority of ICU patients are on positive pressure ventilation, increasing the risks of lung damage. This project will prospectively evaluate the physiological and clinical effects as well as complication rates of pleural effusion drainage in patients in two Australian ICUs. It will find predictors to select the best patients for drainage. Specifically, this project will provide for the first time: (i) The necessary understanding of the physiological and clinical benefits that may be conferred by pleural drainage; (ii) The complications associated with these procedures; (iii) Predictors of which patients benefit most from these procedures; and (iv) An evidence base on which to design guidelines for the management of over 68,000 patients in Australia, every year. These results will likely improve the burden of disease in intensive care units, the health outcomes of patients and the efficiency of healthcare delivery.

ONGOING CLINICAL DEVELOPMENTS

Research Translation and Diffusion

The study has shown that patients undergoing drainage of their fluid have significant improvements in their oxygenation and diagnostic accuracy compared to those undergoing expectant management. This does not appear to be at any increased penalties in terms of adverse events. While it would be inappropriate to change practice on the basis of interim findings, these results have sparked considerable interest and calls for randomised studies to confirm the outcomes seen. As such, this project has informed the design of the first randomised controlled trial in this field – the ESO-DICE or Efficacy and Safety Outcomes in Drainage of Intensive Care Pleural Effusions trial. Capacity to care for ICU patients has been increased through this study. Dr Fysh performs additional ultrasound-scans of patients with potential pleural effusions. Through this extra scanning, previously unrecognised diagnoses have been made, one of which (pericardial tamponade), resulted in improved patient care through enabling a life-saving procedure that otherwise may not have been performed. In further instances, Dr Fysh has been able to help guide treatment in emergencies.

Dr Fysh has also given multiple training talks and ultrasound practical sessions, upskilling the trainees and specialists in the three tertiary and one further secondary ICU. Every unit in Perth now has at least two Consultants and one Registrar at all times who are skilled in pleural procedures and ultrasound. The Clinician Research Fellowship has been critical in Dr Fysh being able to extend his work into new and exciting territory. This has resulted in the conferment of other awards that have allowed Dr Fysh to continue to build an independent, ground breaking research program that will add new knowledge to the care of patients with pleural disease and guide the management of these critically ill patients for years to come.

FELLOWSHIP OUTCOMES

Advancing Knowledge

Publications

- Thomas R, **Fysh ETH**, Smith NA, Lee P, Kwan BCH, Yap E, Horwood FC, Piccolo F, Lam DCL, Garske LA, Shrestha R, Kosky C, Read CA, Murray K, Lee YCG. Effect of an indwelling pleural catheter vs talc pleurodesis on hospitalization days in patients with malignant pleural effusion: The AMPLE randomized clinical trial. *JAMA.* 2017; 318: 1903-1912
- **Fysh ETH**, Thomas R, Tobin C, Kuok Y, Lee YCG. Air in the pleural cavity significantly enhances detection of pleural abnormalities by computerised tomography. *Chest.* 2018; In Press

Conference Presentations

- The interim findings of the project have been presented at international specialty society meetings in *Intensive Care and Respiratory Medicine* in Singapore and Sydney
- The protocol of this trial has been presented at the *Australia and New Zealand Intensive Care Society's Clinical Trials Meeting* in Wellington, where it received an Honourable Mention in the Best New Project Category, and two very senior and world-renowned intensive care researchers offered to support the trial by participating in the Data and Safety Monitoring Committee

Capacity Building

Grants

- Dr Fysh has been successful in securing an NHMRC Early Career Fellowship for four years to continue his research beyond the Clinician Research Fellowship, including the investigation of the impact and best management of pleural disease in patients requiring intensive care

ACKNOWLEDGEMENTS

This study could not be conducted without the support of the WA Department of Health and the Raine Medical Research Foundation.

PROJECT TITLE

Detailed assessment of risks and benefits of inferior vena cava filters on patients with complicated injuries (the *da Vinci* Trial)

CLINICIAN RESEARCH FELLOW

Clinical Associate Professor Kwok-ming Ho

RESEARCH PROJECT OVERVIEW AND AIMS

Venous thromboembolism (VTE), including pulmonary embolism (PE), is a major morbidity concern after severe trauma. Currently, the best way to prevent a fatal PE in patients who are at risk of bleeding after major trauma is uncertain. A filter placed inside the major vein of the abdomen has been widely used as a mechanical means to prevent PE for patients who cannot tolerate other means of preventing venous thromboembolism. This study compares the venous thromboembolism outcomes of patients who are randomized to receive the filter soon after their injury compared to those who do not receive the filters. Specifically, the project aims are as follows: (i) To assess whether the early use of inferior vena cava (IVC) filters can reduce the incidence of PE in patients who are at high-risk of developing deep vein thrombosis (DVT) and PE after major trauma; (ii) To assess the cost-effectiveness of IVC filters in preventing PE after major trauma; (iii) To assess whether IVC filters are effective in reducing symptomatic PE in patients who do not receive pharmacological DVT prophylaxis within the first seven days of major trauma; and (iv) To assess the incidence of complications of IVC filters in patients with major trauma, including whether IVC filters will increase the risk of DVT in the lower limbs, by using a proactive approach to investigate for these complications.

ONGOING CLINICAL DEVELOPMENTS

Research Translation and Diffusion

Recruitment of patients and control subjects has been completed, and the results of the study will be published within the next three months. Consequently, the study may change existing policies within the next six months. The initiation of the trial has already increased the awareness of the risk of venous thromboembolism in trauma patients. As a result, all severe trauma patients are now screened for contraindications to anticoagulation on admission to the study centres; this has increased the early initiation of pharmacological venous thromboembolism prophylaxis both in patients screened for the trial and those recruited into the trial.

FELLOWSHIP OUTCOMES

Advancing Knowledge

Publications

- **Ho KM**. Effect of non-linearity of a predictor on the shape and magnitude of its receiver-operating-characteristic curve in predicting a binary outcome. *Scientific Reports.* 2017; 7: 10155
- **Ho KM**, Rao S, Honeybul S, Zellweger R, Wibrow B, Lipman J, Holley A, Kop A, Geelhoed E, Corcoran T. Detailed assessment of benefits and risks of retrievable inferior vena cava filters on patients with complicated injuries: the da Vinci multicentre randomised controlled trial study protocol. *British Medical Journal Open.* 2017; 7: e016747
- Corcoran TB, Paech M, Law D, Muchatuta N, **Ho KM**, French M. Intraoperative dexamethasone alters immune cell populations in patients undergoing elective laparoscopic gynaecological surgery. *British Journal of Anaesthesia.* 2017; 119: 221-230
- Morgan DJ, Ho KM, Ong YJ, Kolybaba M. Out-of-office hours' elective surgical intensive care admissions and their associated complications. *ANZ Journal of Surgery.* 2017, 87: 886-892
- Hiller J, Sampurno S, Millen R, Kuruvilla N, **Ho KM**, Ramsay R, Riedel B. Impact of celecoxib on inflammation during cancer surgery: A randomized clinical trial. *Canadian Journal of Anesthesia.* 2017; 64: 497-505
- **Ho KM**, Lan NS. Combining Quick Sequential Organ Failure Assessment (qSOFA) with plasma lactate concentration is comparable to standard SOFA score in predicting mortality of patients with and without suspected infection. *Journal of Critical Care.* 2017; 38: 1-5
- Toner AJ, Ganeshanathan V, Chan MT, **Ho KM**, Corcoran TB. Safety of perioperative glucocorticoids in elective noncardiac surgery - a systematic review and meta-analysis. *Anesthesiology.* 2017; 126: 234-248
- McKenzie N, Williams TA, Tohira H, **Ho KM**, Finn JF. A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest. *Resuscitation.* 2017; 111: 116-126
- Silbert BI, **Ho KM**, Lipman J, Roberts JA, Corcoran TB, Morgan DJ, Pavey W, Mas E, Barden AE, Mori TA. Does furosemide increase oxidative stress in acute kidney injury? *Antioxidants and Redox Signaling.* 2017; 26: 221-226
- Cuadros L, Ismail H, **Ho K**. Evaluation of Reliability of MYZONE MZ-3 heart rate monitor: A study for the future of telephysiotherapy for preoperative prehabilitation in

cancer patients. *Telemedicine Journal and E-Health.* 2017; 23: 334-338

- Morgan DJ, **Ho KM**. Incidence and risk factors for deliberate self-harm, mental illness and suicide following bariatric surgery: a state-wide population-based linked-data cohort study. *Annals of Surgery.* 2017; 265: 244-252
- Morgan DJ, **Ho KM**. The incidence and outcomes after bariatric surgery in older patients: a state-wide data-linked cohort study. *ANZ Journal of Surgery.* 2017; 87: 471-476
- **Ho KM**, Pavey W. Applying the cell-based coagulation model in the management of critical bleeding. *Anaesthesia and Intensive Care.* 2017; 45: 166-176
- Honeybul S, **Ho KM**, Gillett GR. Reconsidering the role of decompressive craniectomy for neurological emergencies. *Journal of Critical Care.* 2017; 39: 185-189
- Harahsheh Y, **Ho KM.** Context-dependent risks and benefits of transfusion in the critically ill. *International Journal of Clinical Transfusion Medicine.* 2017; 5: 29-37
- Honeybul S, **Ho KM**, Lind CR, Gillett GR. The current role of decompressive craniectomy for severe traumatic brain injury. *Journal of Clinical Neuroscience.* 2017; 43: 11-15
- Richards S, Wibrow B, Anstey M, Sidiqi H, Chee A, **Ho KM**. Determinants of 6 month survival of critically ill patients with an active haematological malignancy: Response to letter. *Journal of Critical Care.* 2017; 39: 281
- Honeybul S, **Ho KM**, Blacker DW. Reply to letter to the Editor: ORACLE Stroke Study: Opinion Regarding Acceptable outCome folLowing decompressive hemicraniectomy for ischaemic stroke. *Neurosurgery.* 2017; 80: 237-238
- Pavey W, Raisis A, Dunne B, Van Laeken E, Jenkinson C, Vincent V, Baird P, Prince S, **Ho KM**, Merry C, Gilfillan I. The practicalities of establishing a porcine isolated heart model. *Perfusion*. 2017; In Press
- MacDonald S, Kinnear F, Arendts G, **Ho KM**, Fatovich D. Near-Infrared spectroscopy to predict organ failure and outcome in sepsis: the Assessing Risk in Sepsis using Tissue Oxygen Saturation (ARISTOS) study. *European Journal of Emergency Medicine.* 2017; In Press
- Harahsheh Y, **Ho KM**. Use of viscoelastic tests to predict clinical thromboembolic events: A systematic review and meta-analysis. *European Journal of Haematology*. 2017; In Press
- Parmar K, **Ho KM**, Bowles T. Delay in clearing cervical spine injuries in obtunded trauma patients and its implications. *Trauma.* 2017; In Press

Book Chapters

- **Ho KM**. Kidney and Acid-base. Chapter 5. *Oxford Textbook of Anaesthesia.* Oxford University Press. 2017
- **Ho KM**. Statistics. *Structured Oral Examination in Intensive Care Medicine.* Oxford University Press. 2018
- Honeybul S, Servadei F, **Ho KM**, Gillett G. Decompressive craniectomy for severe traumatic brain injury: Ethical considerations. *Decompressive craniectomy*. Nova Publisher. 2018

Conference Presentations

- **Ho KM**. Oral presentation: Resveratrol on coagulation and cardiovascular tolerance to massive blood loss. *76th National Scientific Congress, Australian Society of Anaesthetists*. 2017; Perth
- **Ho KM**. Oral poster presentation: Effects of resveratrol on coagulation, and risk of development of haemorrhagic shock and acute kidney injury: a randomised double-blinded canine study. *40th Annual Scientific Meeting, Shock Society.* 2017; Florida, USA
- **Ho KM**. Invited talk: Venous thromboembolism and central venous catheter: friend or foe? *World Congress in Vascular Access*. 2017; Perth

Capacity Building

Grants

- NHMRC Research Fellowship Merit Award, WA Health
- A multifaceted approach to improving outcomes of seriously injured patients. 2017; $25,000
- Thromboelastography in Blood Component Management Therapy by Haemonetic®
- Use of TEG5000 and TEG6S to identify critically ill patients with acquired coagulopathy requiring subsequent transfusion. 2017; $75,368
- Project Grant, MRF Royal Perth Hospital
- Effects of resveratrol on coagulation parameter in patients undergoing liver resection for cancers. 2018; $15,870

Awards

- Top Paper of the Year in Socioeconomic, Health, Policy, and Law by the Congress of Neurological Surgeons in the United States for the publication “ORACLE stroke study: Opinion regarding acceptable outcome following decompressive hemicraniectomy for ischaemic stroke” by Stephen Honeybul, **Kwok M Ho** and David W Blacker

ACKNOWLEDGEMENTS

Clinical Associate Professor Ho would like to thank the WA Department of Health and the Raine Medical Research Foundation for his Clinician Research Fellowship.

PROJECT TITLE
Combinatorial therapeutics in high-risk infant acute lymphoblastic leukaemia

CLINICIAN RESEARCH FELLOW
Dr Rishi Sury Kotecha

RESEARCH PROJECT OVERVIEW AND AIMS

Acute lymphoblastic leukaemia in infants has a significantly inferior outcome compared to older children, where the five year overall survival rate exceeds 90%. Infants diagnosed at less than one year of age have a five year event free survival (EFS) of less than 50%. For those with *KMT2A (MLL)* gene rearrangements that underpin their leukaemia or are at an age of less than 3 months at diagnosis, outcomes are dismal with a five year EFS of less than 40% and 16%, respectively. Patients are treated with up to ten potent chemotherapeutic drugs, yet more intensified therapy does not improve the outcome due to an increase in toxic death, as demonstrated in international trials. Therefore, novel therapies are desperately needed. The aims of the study are to: (i) Systematically identify synergistic drug combinations; and (ii) Test the efficacy of novel drug combinations *in vivo* using three iALL xenograft models.

ONGOING CLINICAL DEVELOPMENTS

Research Translation and Diffusion

Using a panel of infant acute lymphoblastic leukaemia (iALL) cell lines and high-throughput compound screening, Dr Kotecha identified several consistently effective FDA-approved drugs and targeted next-generation molecular inhibitors, such as the histone deacetylase inhibitor romidepsin, that are not currently used to treat iALL. Using an extensive preclinical testing pipeline, he demonstrated that romidepsin is highly effective in augmenting the cytotoxicity of cytarabine, one of the most critical drugs in the current therapy for iALL, thereby demonstrating the feasibility of combining this novel agent with a drug currently used to treat iALL. The overall outcomes of this study will be proposed for integration into upfront international clinical trials that will be used to treat infants with leukaemia in Western Australia.

Currently, it is too early for the project findings to inform policy or change clinical practice as the project is ongoing. Once the entire project has been completed, however, there is the potential for efficacious agents to be translated into upfront clinical trials by virtue of Dr Kotecha's position on the international infant acute lymphoblastic leukaemia clinical trial committee.

It should be noted that Dr Kotecha withdrew from the Clinician Research Fellowship after 15 months (with 21 months remaining), as he successfully secured a National Health and Medical Research Council (NHMRC) Early Career Fellowship. Due to the reduced timeframe the entire scope of the original proposal was not completed and the remainder of the project will be performed under the NHMRC Fellowship.

FELLOWSHIP OUTCOMES

Advancing Knowledge

Publications

- Stirnweiss A, Oommen J, **Kotecha RS**, Kees UR, Beesley AH. Molecular-genetic profiling and high-throughput *in vitro* drug screening in NUT midline carcinoma-an aggressive and fatal disease. *Oncotarget*. 2017; 8: 112313-112329
- Halliday GC, Miles GCP, Marsh JA, **Kotecha RS**, Alessandri AJ. Regular exercise improves the well-being of parents of children with cancer. *Pediatric Blood and Cancer*. 2017; 64; e26668

Conference Presentations

- Invited presentation. Identifying novel translatable treatments to improve the outcome for infants with acute lymphoblastic leukaemia. *Telethon Kids Research Cancer Centre Seminar*. 2017; Telethon Kids Institute, Perth

Media Coverage/Publicity

- Today Tonight Video: https://www.youtube.com/watch?v=rhlXun52jVg
- Raine Medical Research Foundation Video: "Supporting our Early Career Researchers": https://www.youtube.com/watch?v=4k4gnsUhg24 http://www.rainefoundation.org.au/research-stories/

Capacity Building

Grants

- National Health and Medical Research Council Early Career Fellowship (APP1142627). 2018; $344,657

Collaborations

This project has built capacity by facilitating a new and important collaboration with Professor Richard Lock from the Children's Cancer Institute in Sydney. Professor Lock is an internationally renowned expert with regards to the development and validation of patient derived xenograft models. Professor Lock was approached during the conception of this project to determine whether he could make his well characterised infant acute lymphoblastic leukaemia patient derived xenograft models available for use to achieve the project aims. Professor Lock exhibited a high level of interest in the project and has subsequently become a key collaborator for Dr Kotecha's preclinical research program

ACKNOWLEDGEMENTS

On a personal level, this fellowship has significantly assisted Dr Kotecha's research career by providing a platform for a successful National Health and Medical Research Council Early Career Fellowship application. This fellowship also made a significant contribution to his 2017 Early Career Cancer Researcher of the Year award by the Cancer Council of Western Australia. Dr Kotecha is eternally grateful to the WA Department of Health and the Raine Medical Research Foundation for providing him with the opportunity to further his research career as a clinical scientist.

PROJECT TITLE
Mechanisms that facilitate the metastatic potential of oral cancer

CLINICIAN RESEARCH FELLOW
Dr Annette Lim

RESEARCH PROJECT OVERVIEW AND AIMS

Head and neck cancer is the sixth most common cancer worldwide and despite technological advances, treatment failure rates approach 50%, with significant implications for cost, treatment-related toxicity and the lives of patients. The incidence of oral cavity squamous cell carcinoma (OCSCC) is increasing and predominantly affects young patients (<40 years) who develop tongue cancers without any known risk factors. Current staging criteria are not consistently able to identify patients with cancers at risk of treatment failure, nodal involvement or metastases. Current methods are also unable to identify premalignant lesions at risk of transformation. The identification of biomarkers that can predict a high risk of developing OCSCC will, therefore, significantly revolutionise patient care from primary to tertiary settings. Currently in WA, head and neck cancer patients are only cared for at two tertiary hospitals, thereby placing the state in a unique position where all public patients are able to benefit from an active state-wide collaborative research effort. Dr Lim's goals for this Clinician Research Fellowship include to: (i) Establish a comprehensive collaborative clinical research and translational research pipeline, encompassing primary (oral health) to the tertiary healthcare settings, for tumour streams that she is involved with; (ii) Offer patients the opportunity to participate in PI-PIII clinical trials, including investigator-initiated clinical trials with a translational component; (iii) Prospectively collect patient clinicopathological data into a comprehensive head neck cancer (HNC) database and establish collaborative multidisciplinary research from the same database; (iv) Attract undergraduate and postgraduate students, or clinicians for fellowship opportunities, within the collaborative group; (v) Establish sufficient peer-reviewed and clinically relevant published work, to be able to maintain funding for ongoing translational research; and (vi) Establish effective national research collaborative efforts to improve rapid translation of goals and cost-effectiveness of research endeavours.

ONGOING CLINICAL DEVELOPMENTS

Research Translation and Diffusion

Two head and neck cancer specific trials have been made available at Sir Charles Gairdner Hospital (SCGH), with numerous phase 1 trials recruiting head and neck cancer participants also available at Linear Clinical Research. Participant recruitment to this three year study is on target with nearly 80% of the cohort completed. Collaborative research partnerships with clinicians at SCGH, the Oral Health Centre of WA (OHCWA), St John of God Murdoch Hospital (SJOGMH) and Hollywood Private Hospital (HPH), have facilitated additional patient participation in the study. Dr Lim and her team are able to identify exosomes from blood samples with transmission electron microscopy to confirm the expected median size of particles at 139 nm. Quantification of exosomes has demonstrated a median of 4.87×10^9 exosomes/mL isolated from blood samples. Common known mutations in head and neck cancer and targetable mutations have been identified in both tumour tissue and exosomes, including mutations in *TP53*, *PI3K*, and *CDKN2A*. Ongoing analyses and validation are being performed to compare samples from participants from different disease stages and following treatment. Figure 1 below demonstrates the assessment of the immune CD4 T cell versus CD8 T cell ratio from a participant's blood sample, as determined by an Accuri Flow Cytometer. PathWest has been a crucial partner in the Next-Generation Sequencing (NGS) work, as well as UWA and Edith Cowan University collaborations. A Collaboration with the University of Notre Dame has been established for statistical input.

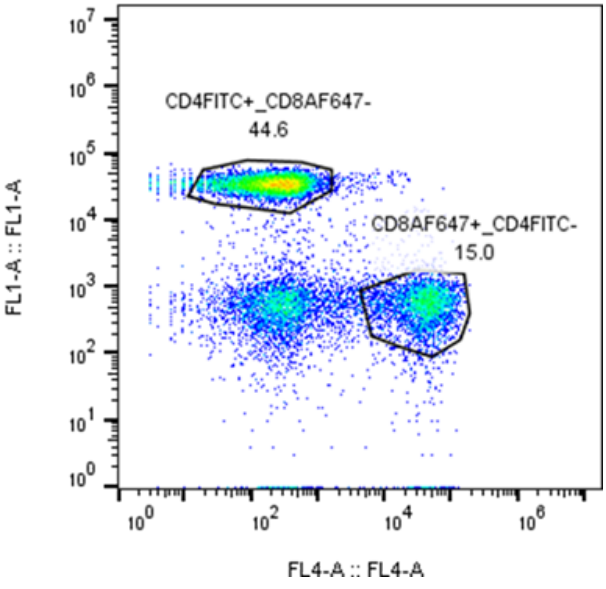


Figure 1. CD4 versus CD8 T cell ratio from a participant's blood sample, assessed on an Accuri Flow Cytometer.

A retrospective cohort of 100 patient tumour samples have undergone gene expression and protein analyses to comprehensively profile the role of a suppressed immune system in facilitating the development of more aggressive cancers. The laboratory analyses have been completed through collaborations with PathWest, Peter MacCallum Cancer Centre (Victoria) and UWA. Data analyses are currently underway. Additionally, exosomes from patients who receive immunotherapy as part of their standard treatment are being investigated for molecular signals that may herald an early sign of response.

FELLOWSHIP OUTCOMES

Advancing Knowledge

Publications

- Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD, Chung CH, Hernandez-Aya L, **Lim AM**, Chang ALS, *et al*. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *New England Journal of Medicine*. 2018; In Press

Conference Presentations

- Chaytor P, Meehan K, Thomas A, Leslie C, Robinson C, Amanuel B, Sader C, Friedland P, **Lim AM**. New blood based markers for monitoring and detecting oral cancers. *ASMR Medical Research Week, WA Scientific Symposium*. 2017; Perth
- Meehan K, **Lim AM**. The clinical potential of nanovesicles in head and neck cancer. *UWA-Sungkyunkwan University Collaborative Workshop*. 2017; South Korea
- Khan Y, Jacques A, Friedland P, Sader C, Tang C, Meyer C, Dewar J, **Lim AM**. Clinicopathological characteristics and outcomes for oral tongue squamous cell carcinoma (OTSCC) at a single Australian institution. *Medical Oncology Group of Australia ASM*. 2018; Adelaide

Capacity Building

Grants

- Institutional support from the Translational Cancer Pathology Laboratory was awarded by UWA for equipment and scientist support for this project

Awards

- Dr Lim was awarded a FutureHealth WA Department of Health Merit Award 2017

Workshops

- Tumour derived nanovesicles as potential biomarkers in oral cavity squamous cell carcinoma. *Honours Poster Presentation* by Phoebe Chaytor. 2017; UWA, Perth
- Cancer Council Western Australia (CCWA). *Head and Neck Cancer GP and Primary Care Event.* 2017

Collaborations

- Dr Lim secured the collaboration of two dedicated PathWest Pathologists for the pathological component of the project, the partnership of PathWest for NGS and an immunopathologist for the immune profiling work
- She has established a collaboration with the Institute for Health Research, University of Notre Dame, for the statistical analyses
- Two additional sites were added to the project, namely SJOGMH and HPH

ACKNOWLEDGEMENTS

Dr Lim is very grateful for the support of a Clinician Research Fellowship (CRF) received through the WA Department of Health and the Raine Medical Research Foundation, which has provided an invaluable opportunity to advance research for head and neck cancer patients. This project represents one of few in Australia that has a dedicated translational head and neck research team that involves clinicians, the state pathology service, multiple hospitals, local universities and interstate collaborations. It has provided cancer patients with more trial-based treatment opportunities and has enabled researchers to be involved in cutting-edge technology that aims to improve patient treatment. The CRF has also created opportunities for postgraduate researchers to be exposed to the needs of head and neck cancer patients, as well as providing collaborations in other fields.

PROJECT TITLE
Improving health outcomes of kidney transplant recipients

CLINICIAN RESEARCH FELLOW
Associate Professor Wai Lim

RESEARCH PROJECT OVERVIEW AND AIMS

The incidence of end-stage renal disease (ESRD) has reached global epidemic proportions, affecting 1 in 1000 people in 2014. Although kidney transplantation is the treatment of choice for patients with ESRD, long-term graft outcomes have remained unchanged, with graft loss secondary to rejection and/or disease recurrence being the most common. With the advancement of technology, combined with sophisticated statistical techniques, the gaps in transplant research may now be addressed. This project aims to promote the most advantageous allocation policies to achieve a balance between utility and equity and identify critical factors associated with graft loss after kidney transplantation. The specific aims are: (i) To establish the clinical significance of the association between extended immunological risk profiling and graft outcomes; (ii) To determine the incremental costs and benefits for alternative deceased donor allocation strategies that consider age-matching and extended immunological risk profiles; (iii) To develop a prognostic clinical and histological score to predict disease recurrence in patients with end-stage renal disease secondary to glomerulonephritis.

ONGOING CLINICAL DEVELOPMENTS

Research Translation and Diffusion

Several publications resulting from this fellowship have generated preliminary data for future research projects, as well as informing the discussion of the change in organ allocation and the assessment of immunological risk in Australia (through the Renal Transplant Advisory Committee and Clinical Immunology Department).

In particular, three additional projects will be undertaken over the next two years, including: (i) To determine differences and predictors of kidney transplant outcomes in indigenous and non-indigenous Western Australia kidney transplant recipients – a population cohort study; (ii) To evaluate interventions that aim to improve patient-oriented outcomes in kidney transplant recipients; and (iii) To determine factors associated with allograft and patient outcomes post-kidney transplantation using registry data.

FELLOWSHIP OUTCOMES

Advancing Knowledge

Publications

- Allen P, Chadban SJ, Craig JC, **Lim WH**, Allen R, Clayton PA, Teixeira-Pinto A, Wong G. Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes. *Kidney International.* 2017; 92: 461-469
- **Lim WH**, Badve S, Wong G. Long-term allograft and patient outcomes of kidney transplant recipients with and without incident cancer - a population cohort study. *Oncotarget.* 2017; 8: 77771-77782
- Selvey L, **Lim WH**, Boan P, Swaminathan R, Slimings C, Harrison AE, Chakera A. Cytomegalovirus viraemia and mortality in renal transplant recipients in the era of antiviral prophylaxis. Lessons from the Western Australian experience. *BMC Infectious Diseases.* 2017; 17: 501
- Krishnan A, Teixeira-Pinto A, Chan D, Chakera A, Dogra G, Boudville N, Irish A, Morgan K, Phillips J, Wong G, **Lim WH**. Impact of early conversion from cyclosporin to everolimus on left ventricular mass index: a randomized controlled trial. *Clinical Transplantation*. 2017; 31: 10
- Deering KE, Callan AC, Prince RL, **Lim WH**, Thompson PL, Lewis JR, Hinwood AL, Devine A. Low-level cadmium exposure and cardiovascular outcomes in elderly Australian women: a cohort study. *International Journal of Hygiene and Environmental Health.* 2017; S1438-4639: 30141-340144
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- Blekkenhorst LC, Hodgson JM, Lewis JR, Devine A, Woodman RJ, **Lim WH**, Wong G, Zhu K, Bondonno CP, Ward N, Prince RL. Vegetable and fruit intake and fracture-related hospitalisations: a prospective study of older women. *Nutrients.* 2017; 9: 5
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- **Lim WH**, Wong G, Lewis J, Lok C, Polkinghorne K, Hodgson J, Lim EM, Prince R. Total volume and composition of fluid intake and mortality in older women

– a cohort study. *British Medical Journal Open.* 2017; 7: e011720

- Ryding L, Wong G, Craig JC, Ju A, Williams N, **Lim WH**, Cross N, Tong A. Beliefs and attitudes to bowel cancer screening in patients with chronic kidney disease: a semi-structured interview study. *Clinical Journal of American Society of Nephrology.* 2017; 12: 568-576
- Touw WA, Ueland T, Bollerslev J, Schousboe JT, **Lim WH**, Wong G, Thompson PL, Kiel DP, Prince RL, Rivadeneira F, Lewis JR. Association of circulating Wnt antagonists with severe abdominal aortic calcification in elderly women. *Journal of Endocrine Society.* 2017; 1: 26-38
- **Lim WH,** Russ GR, Wong G, Pilmore H, Kannelis J, Chadban S. The risk of cancer in kidney transplant recipients maintained on everolimus and reduced exposure cyclosporine. *Kidney International.* 2017; 91: 954-963
- **Lim WH**, Wong G, McDonald SP, Pilmore H, Chadban S. Long-Term outcomes of people with type 2 diabetes mellitus who underwent kidney transplantation: a population-cohort study. *Lancet Diabetes and Endocrinology.* 2017; 5: 26-33
- Mincham C, Wong G, Teixeira-Pinto A, Kennedy S, Alexander S, **Lim WH**. Induction therapy, rejection and graft outcomes in paediatric and adolescent kidney transplant recipients. *Transplantation.* 2017; 101: 2146-2151
- **Lim WH**, McDonald SP, Kennedy S, Larkins N, Wong G. Association between slow and delayed graft function with graft outcomes in paediatric and adolescent deceased donor kidney transplant recipients. *Transplantation.* 2017; 101: 1906-1912
- Lewis JR, **Lim WH**, Wong G, Abbs S, Zhu K, Lim EM, Thompson PL, Prince RL. Association between high-sensitivity cardiac troponin I and cardiac events in elderly women. *Journal of American Heart Association.* 2017; 6: 8
- **Lim WH,** Duncan E. Is there a role or target value for nutritional vitamin D in chronic kidney disease (CKD)? *Nephrology.* 2017; 22 Suppl 2: 57-64
- Wong G, Au E, Badve SV, **Lim WH**. Breast cancer and transplantation. *American Journal of Transplantation.* 2017; 17: 2243-2253
- Allen P, Chadban SJ, Craig JC, **Lim WH**, Allen R, Clayton PA, Teixeira-Pinto A, Wong G. The authors reply. *Kidney International.* 2017; 92: 1291
- **Lim WH**, Johnson DW, Hawley CM, Pascoe E, Wong G. Impact of diabetes mellitus on the association of vascular disease before transplantation with long-term graft and patient outcomes after kidney transplantation – a population cohort study. *American Journal of Kidney Diseases*. 2018; 71: 102-111
- Yong K, Dogra G, Boudville N, **Lim WH**. Increased inflammatory response in association with the initiation of haemodialysis compared to peritonal dialysis in a prospective study of end-stage kidney disease patients. *Peritoneal Dialysis International.* 2018; 38: 18-23
- Chen JHC, Johnson DW, Hawley C, Boudville N, **Lim WH**. Association between causes of peritoneal dialysis technique failure and all-cause mortality. *Scientific Reports.* 2018; 8: 3980
- **Lim WH**, Wong G, Heidt S, Claas F. Novel aspects of epitope matching and practical application in kidney transplantation. *Kidney International.* 2018; 93: 314-324
- **Lim WH,** Wong G. The "cold" hard facts - seasonal variation in outcomes after kidney transplantation. *Transplantation International.* 2018; 31: 291-292
- Fidler S, D'Orsogna L, Irish AB, Lewis JR, Wong G, **Lim WH**. Correlation and agreement between eplet mismatches calculated using serological, low-intermediate and high resolution molecular human leukocyte antigen typing methods. *Oncotarget (Immunology)*. 2018; In Press
- Calisa V, Craig J, Howard K, Howell M, Alexander S, Chadban S, Clayton P, **Lim WH**, Kanellis J, Wyburn K, Johnson D, McDonald SP, Opdam H, Yang J, Chapman JR, Wong G. Survival and quality of life impact of a risk-based allocation algorithm for deceased donor kidney transplantation. *Transplantation.* 2018; In Press
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- Lewis JR, Schousboe JT, **Lim WH**, Wong G, Wilson K, Zhu K, Thompson PL, Kiel DP, Prince RL. Long-term atherosclerotic vascular disease risk and prognosis in elderly women with abdominal aortic calcification on lateral spine images captured during bone density testing: A prospective study. *Journal of Bone and Mineral Research.* 2018; In Press

Conference Presentations

- Outcomes from this fellowship have been presented at multiple national and international meetings throughout 2017.

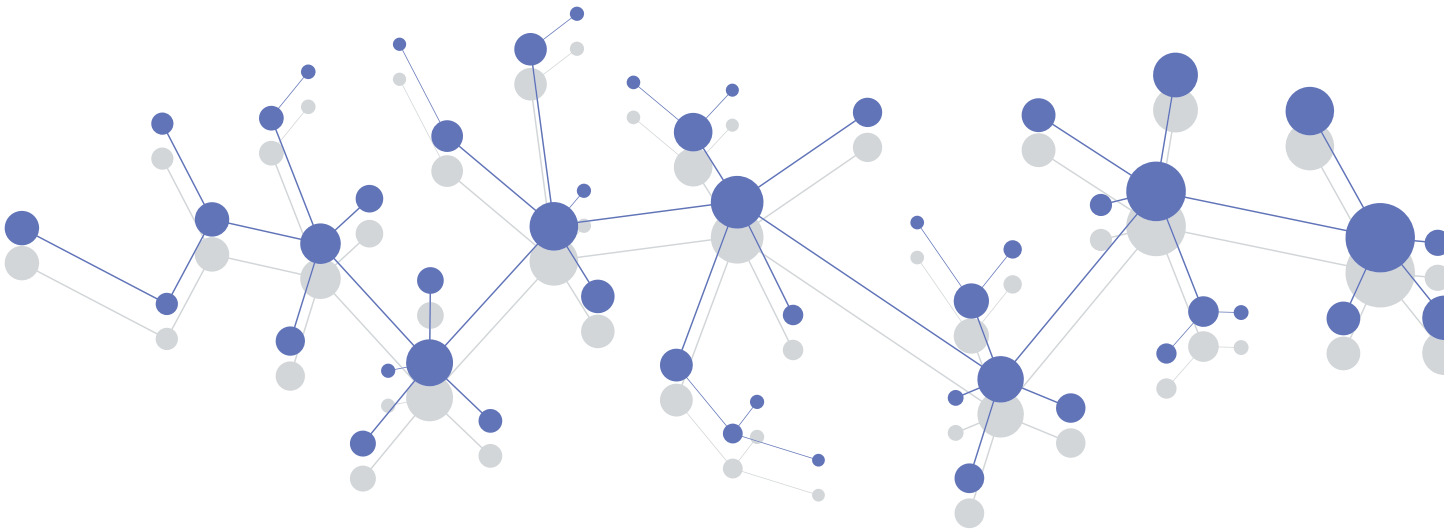
Capacity Building

Grants

- As a result of this research, Associate Professor Lim has been successful in obtaining further grant funding totalling almost $300,000.
- Telethon; $250,000
- Transplantation Society of Australia and New Zealand Mark Cocks Award; $10,000
- Sir Charles Gairdner Hospital Research Advisory Committee Grant; $37,000

ACKNOWLEDGEMENTS

Associate Professor Lim would like to take this opportunity to thank the WA Department of Health and the Raine Medical Research Foundation for continuing to support and further his research.



PROJECT TITLE

Project 1: IronNOF – Intravenous Iron to reduce transfusion and improve post-operative haemoglobin in patients with fractured Neck Of Femur

Project 2: PADDI – The Perioperative ADministration of Dexamethasone and Infection

CLINICIAN RESEARCH FELLOW

Dr Edmond O'Loughlin

RESEARCH PROJECT OVERVIEW AND AIMS

Two trials are underway to investigate the influence of intra-operative interventions on the longer term recovery and wellbeing of patients:

The IronNOF trial is investigating the potential role of iron given during surgery to fix hip fractures in elderly patients to reduce the need for blood transfusion, to facilitate recovery and impact mortality

The PADDI study is examining the influence of a commonly used anti-nausea drug, dexamethasone, on the rates of post-operative infection. Dexamethasone is very effective in preventing nausea, but its potential effects on surgical site infections are unknown.

ONGOING CLINICAL DEVELOPMENTS

Research Translation and Diffusion

The IronNOF trial has finished patient recruitment and data analysis is commencing. An offshoot of this project, the "Hepcidin Study", has examined iron levels in the bone marrow of patients taken at the time of surgery and has demonstrated very high levels of iron deficiency in this population. These results are being presented at a national level in 2018 and have resulted in changes to the way these patients are cared for. Blood testing for iron deficiency is no longer tested in this population, with the administration of intravenous iron to all of these patients during surgery, unless it is contraindicated.

The PADDI trial began recruiting patients in 2016 at the Alfred Hospital, Victoria, and has rapidly progressed to patient recruitment being conducted in 47 sites both in Australia and internationally. The research team has recruited approximately 44% of the 8,800 patients that are planned to be studied and have approximately 50 sites worldwide in the process of joining the study. Dr O'Loughlin hopes to finish recruiting for this study ahead of schedule and answer the important clinical questions in a timely fashion.

The Clinician Research fellowship has allowed Dr O'Loughlin time to concentrate on research and develop a fledgling research department at Fiona Stanley Hospital, as well as strengthening links between WA health organisations and those that are both local (e.g. Murdoch University) and international.

FELLOWSHIP OUTCOMES

Advancing Knowledge

Conference Presentations

- Oral presentation: PADDAG trial results (Breaking trials session). *ANZCA meeting*. 2017; Brisbane
- The "Hepcidin" study – assessing bone marrow iron stores in the NOF population. *ANZCA meeting*. 2018; Sydney
- Poster presentation: Iron Deficiency – Every Fractured Neck of Femur. *ANZCA meeting*. 2018; Sydney

Capacity Building

Grants

- An NHMRC grant submission for an international randomised controlled trial (RCT) is planned for 2019 based on the outcomes of the "Hepcidin Study"

Collaborations

- Dr O'Loughlin has developed broad-based engagement within the department, hospitals and with local universities
- A number of sub-studies and collaborations are continuing to develop within the background of the PADDI study, which further enhance research capacity locally and nationally

ACKNOWLEDGEMENTS

Dr O'Loughlin would like to thank the WA Department of Health and the Raine Medical Research Foundation.

PROJECT TITLE
Improving the West Australian immunisation program

CLINICIAN RESEARCH FELLOW
Dr Thomas Snelling

RESEARCH PROJECT OVERVIEW AND AIMS

Australia's National Immunisation Program represents the largest and fastest growing area of public health expenditure. The WA Immunisation Strategy 2013-2015 identified that WA continues to have the lowest vaccine coverage of any Australian jurisdiction. Of even greater concern than non-vaccination (or vaccine refusal), is late or delayed vaccination that undermines the impact of the program. Moreover the Horvath and other commissioned enquiries into the high rate of adverse reactions from influenza vaccination in WA in 2010 highlighted deficiencies in monitoring for vaccine adverse events. This suite of projects aims to improve the impact of the program and to improve mechanisms for monitoring for safety issues. Specific aims include: (i) Calculate the effectiveness of conjugate vaccination for preventing pneumonia and to determine the extent (if any) of "strain replacement" disease; (ii) Provide robust real time signal detection using aggregated national data; (iii) Demonstrate proof-of-principle for a fully powered multi-centre randomised controlled trial (RCT) using a pilot RCT with an immunological surrogate endpoint; and (iv) To partner with the Communicable Disease Control Directorate (CDCD) to conduct a pragmatic, adaptive designed RCT to study and optimise the effectiveness of text and/or phone-based reminders in a cohort of new parents in WA.

ONGOING CLINICAL DEVELOPMENTS

Research Translation and Diffusion

Over 30 safety reports have been provided to the Commonwealth Department of Health as part of the AusVaxSafety (a program of adverse event surveillance) project. These reports have confirmed the safety of seasonal influenza, pertussis and recently introduced zoster vaccine programs.

FELLOWSHIP OUTCOMES

Advancing Knowledge

Publications

- Britton PN, Blyth CC, Macartney K, Dale RC, Li-Kim-Moy J, Khandaker G, Crawford NW, Marshall H, Clark JE, Elliott EJ, Booy R, Cheng AC, Jones CA; Australian Childhood Encephalitis (ACE) Study Investigators, Influenza Complications Alert Network (FluCAN) Investigators, and **Paediatric Active Enhanced Disease Surveillance (PAEDS) Network**. The spectrum and burden of influenza-associated neurological disease in children: Combined encephalitis and influenza sentinel site surveillance from Australia, 2013-2015. *Clinical Infectious Diseases*. 2017; 65: 653-660
- Macartney K, Gidding HF, Trinh L, Wang H, Dey A, Hull B, Orr K, McRae J, Richmond P, Gold M, Crawford N, Kynaston JA, McIntyre P, Wood N; **PAEDS Network**. Evaluation of combination measles-mumps-rubella-varicella vaccine introduction in Australia. *JAMA Pediatrics*. 2017; 171: 992-998
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- Pillsbury A, Quinn H, Cashman P, Leeb A, Macartney K on behalf of the **AusVaxSafety consortium**. Active SMS-based influenza vaccine safety surveillance in Australian children. *Vaccine*. 2017; 35: 7101-7106
- Bellgard MI, Chartres N, Watts GF, Wilton S, Fletcher S, Hunter A, **Snelling T**. Comprehending the health informatics spectrum: Grappling with system entropy and advancing quality clinical research. *Frontiers in Public Health*. 2017; 5: 224
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- Newcombe J, Kaur R, Wood N, Seale H, Palasanthiran P, **Snelling T**. Paediatrician beliefs and practices around influenza vaccination. *Journal of Paediatrics and Child Health*. 2017; 53: 711-714
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of the effectiveness of pneumococcal vaccination in Australia. Proceedings of the International Population Data Linkage Network Conference. *International Journal of Population Data Science*. 2017; 1: 201

- Moore H, McCallum L, Fathima P, De Klerk Ni, Liu B, **Snelling T**, Blyth C, McIntyre P, Gidding H. Linking the Australian Childhood Immunisation Register to population-based perinatal datasets to assess coverage in at-risk groups. Proceedings of the International Population Data Linkage Network Conference. *International Journal of Population Data Science*. 2017; 1: 131
- Enkel SL, Attwell K, **Snelling TL**, Christian HE. 'Hesitant compliers': Qualitative analysis of concerned fully-vaccinating parents. *Vaccine*. 2017; In Press
- Estcourt MJ, Marsh JA, Campbell DE, Gold MS, Allen KJ, Richmond P, Waddington CS, **Snelling TL**. Case-cohort study of the association between pertussis vaccination in infancy and the risk of IgE-mediated food allergy. *British Medical Journal Open*. 2018; 8
- Berry N, Leask J, Danchin M, Witteman H, Kinnersley P, **Snelling T**. Sharing knowledge about immunisation: An exploration of parents' communication needs to inform development of a clinical communication support intervention. *Vaccine*. 2018; In Press

ACKNOWLEDGEMENTS

Dr Snelling would like to thank the WA Department of Health and the Raine Medical Research Foundation.

PROJECT TITLE

Do ultrasound measurements of the inferior vena cava (IVC-US) by nursing staff improve assessment of intravascular volume status in the satellite haemodialysis clinic settings?

CLINICIAN RESEARCH FELLOW

Dr Ulrich Steinwandel

RESEARCH PROJECT OVERVIEW AND AIMS

Previous research has shown that renal nurses have limited objective parameters available prior to the initiation of a haemodialysis session. These parameters are crucial when a renal nurse decides the treatment goals (fluid removal) for an individual. If these goals are chosen too high, episodes of low blood pressure (intradialytic hypotension = IDH) can occur subsequently. These episodes are the most common unwanted side effects of haemodialysis. It is also known that they can have a negative impact on various organ systems and the quality of life of patients with chronic kidney disease receiving haemodialysis. The study aims are: (i) To provide evidence of whether a renal nurse can reliably assess the intravascular volume status of haemodialysis patients during treatment using abdominal ultrasound on the inferior vena cava (IVC-US); (ii) To determine if renal nurses can draw the correct conclusions from these findings with the potential to amend treatment goals and to ultimately improve patient outcomes; (iii) To determine the prevalence rate of IDH in a local satellite haemodialysis clinic in the Perth metropolitan area. In this step, two fluid assessment methods, bioimpedance spectroscopy and IVC-US, will be compared to determine their usefulness as an additional parameter when made available to renal nurses; and (iv) To raise the awareness of the existence of the dilemma of IDH in the local and wider renal community, amongst stakeholders and to offer some potential solutions.

The findings could potentially be used by local senior nurses (e.g. Clinical Nurse Specialists, CNSs), staff development nurses and other stakeholders to inform policy, as well as changing current nursing practice. This study found that prevalence rates of IDH at local haemodialysis units remain unacceptably high, and more awareness about their negative consequences and measures for prevention are needed. The work further demonstrated that a renal nurse can be successfully trained and upskilled to perform IVC-US, drawing the correct conclusions, similar to other clinical experts. This additional skill has good potential to reduce adverse outcomes for haemodialysis patients when applied in dialysis clinics in the near future.

ONGOING CLINICAL DEVELOPMENTS

Research Translation and Diffusion

Research findings from this study have been presented and positively received by local stakeholders during medical meetings at Fiona Stanley Hospital (FSH) and at a local conferences for renal nurses. Follow-up conversations with individuals have shown that there is great interest (nurses and medical staff) in addresses the problem of IDH, an ongoing issue that the renal community is well aware of. To date, only one nurse has been educated to perform IVC-US; clearly, there is the need to educate more renal nurses and other healthcare professionals with the same skill to achieve better patient outcomes. Translation of research findings into clinical practice will need strong support on multiple levels. For this to be achieved, collaboration with local stakeholders of the renal community (clinical nursing educators, nurse unit managers (NUMs), CNS and medical staff) are required. The technique of IVC-US has also been practically demonstrated to medical staff at FSH, but it will need further education and repeated training of individuals to implement this method successfully in a local renal department of WA Health. Therefore, active support would be essential for the success and implementation of this novel technique in the hands of renal nurses.

In addition, existing ultrasound devices in the local renal units might also need to be equipped and upgraded with abdominal ultrasound probes to technically allow for IVC-US to be performed. Most current ultrasound machines readily available in the local renal units are commonly equipped with probes only suitable for cannulations of fistulas, but not for IVC-US. This project has shown that existing devices for fluid assessment (e.g. Body Composition Monitors (BCMs) using bioimpedance spectroscopy), are currently not being used, although they are available in some dialysis units (e.g. Fresenius Medical Care, a private company) and have been proven to be similarly effective as IVC-US. From discussions with renal nurses who work overseas (e.g. Europe), Dr Steinwandel learned that the use of IVC-US by renal nurses is more common and is successfully used in their units.

FELLOWSHIP OUTCOMES

Advancing Knowledge

Publications

- **Steinwandel U**, Gibson NP, Rippey JC, Towell A, Rosman J. Use of ultrasound by registered nurses-a systematic literature review. *Journal of Renal Care*. 2017; 43: 132-142
- **Steinwandel U**. Intradialytic hypotension – a daily challenge for each one of us – could ultrasound of the inferior vena cava provide us with a better understanding of the intravascular volume status *Renal Society of Australasia Communiqué.* 2017; 20: 11-12
- **Steinwandel U**, Gibson NP, Towell M, Rippey JJR, Rosman, J. Can a renal nurse assess fluid status using ultrasound on the inferior vena cava? A cross-sectional interrater study. *Hemodialysis International.* 2018; 22: 261-269
- **Steinwandel U**, Gibson NP, Towell M, Parsons R, Rippey JJ, Rosman J. (2018) Measuring the prevalence of intradialytic hypotension in a satellite dialysis clinic: Are we too complacent? *Journal of Clinical Nursing.* 2018; 27: e1561-e1570

Conference Presentations

- **Steinwandel U**. Ultrasound of the inferior vena cava for volume assessment – can renal nurses master this skill? *Renal Society of Australasia (RSA) Annual Conference*. 2017; Convention Centre, Sydney
- **Steinwandel U**. Ultrasound by nurses – meeting the challenge of fluid assessment. *Renal Society of Australasia (RSA) WA Branch Symposium 'Changing Climate'*. 2017; Parmelia Hilton, Perth

Capacity Building

Grants

One grant application for this project was successful in 2017, namely the "2017 Barry Marshall Travel Grant". These funds were used to attend a conference presentation in Sydney.

Collaborations

Throughout the project multiple local academic collaborations evolved. Dr Steinwandel was able to establish a strong collaboration with Professor James Rippey, an expert sonologist at the Emergency Department of Sir Charles Gairdner Hospital. He is also affiliated with UWA and with Professor Johan Rosman, Renal consultant at Royal Perth Hospital and Medical Director at Curtin University. Another strong partnership developed with Dr Richard Parsons, a senior statistician at Curtin University, who was frequently consulted and made significant contributions to this project. Finally, through Dr Steinwandel's PhD studies at Edith Cowan University, and the ongoing support of his supervisors Dr Nick Gibson and Dr Mandy Towell, this project has achieved strong relationships amongst mentors from several local universities.

ACKNOWLEDGEMENTS

Dr Steinwandel is sincerely grateful for the extraordinary opportunity provided by the WA Department of Health and the Raine Medical Research Foundation.

PROJECT TITLE
The role of sensory parameters in predicting clinical outcome after lumbar discectomy

CLINICIAN RESEARCH FELLOW
Dr Brigitte Tampin

RESEARCH PROJECT OVERVIEW AND AIMS
While surgery to relieve sciatic pain can result in less pain and a better quality of life, about one in three people still have pain. Some known psychological risk factors for pain persistency are the fear of moving, worry about the pain, catastrophic thinking and high distress. However, it is not known whether changes in sensory nerve fibres in people with sciatica are linked to pain that persists. Research suggests that certain people who demonstrate hypersensitivity to sensory stimuli, such as heat/cold or pressure, may be more vulnerable to developing ongoing pain. This study explored whether sensitivity may play a role in predicting poor outcome after back surgery. The aims of the study were to assess: (i) Sensory nerve function in people with sciatic pain before and after surgery; and (ii) If these changes in nerve fibre function are linked to patient quality of life three and 12 months after surgery.

ONGOING CLINICAL DEVELOPMENTS
Research Translation and Diffusion

The detrimental impact of neuropathic pain, i.e. pain associated with nerve damage, on the well-being, health and quality of life of patients has been widely documented and remains an area where improvements in clinical care are critically needed. The assessment of sensory nerve fibre function is a key element for the diagnosis of neuropathic pain, as loss of function is a core sign of nerve damage. While a traditional clinical sensory examination involves only the assessment of large fibres (touch sensation), this study clearly showed that small and large fibres can be affected in patients with sciatica. Specific tests for small fibre function (e.g. cold/warm detection or pinprick sensation) should be included in the standard neurological examination of a patient with back and leg pain.

This approach has been adopted by the Neurosurgery Spinal Clinic at Sir Charles Gairdner Hospital and has changed clinical practice accordingly. As Advanced Scope Physiotherapists, patients have to be assessed for their suitability for spinal surgery, and establish the presence of a possible nerve lesion/disease and neuropathic pain in order to recommend appropriate management to the patient as well as to the referring GP. The findings of the study have strengthened confidence in the adopted approach of patient triage and have assisted in informing the surgical care team for patients with compromised nerve roots. In the future, the use of electronic systems to streamline referrals to the Neurosurgery Department may be considered.

Overall, this study demonstrated that appropriate targeting of pain management, such as surgical intervention in case of nerve root compromise, led to a positive outcome in 83% of the cohort assessed. The positive outcomes, including patient quality of life, a return to work or the decreased need for health care, may translate into a reduced health economic burden on the WA health system.

FELLOWSHIP OUTCOMES
Advancing Knowledge

Publications

- Schmidt AB, Hayley L, **Tampin B**. Entrapment neuropathies: Challenging common beliefs with novel evidence. *Journal of Orthopaedic and Sports Physical Therapy*. 2018; 48: 58-62

Conference Presentations

- **Tampin B**, Slater H & Lind C. Significant changes in somatosensory profiles pre-post microdiscectomy. *Sixth International Congress on Neuropathic Pain (NeuPSIG)*. 2017; Gothenburg, Sweden

Capacity Building

Grants

- Research Advisory Committee Grant, Sir Charles Gairdner and Osborne Park Health Care Group
- Driving clinical improvement by implementing and evaluating a grading system for neuropathic pain. 2017; $22,701
- Additional research funding to set up a QST laboratory and a Neuropathic Pain Database at Sir Charles Gairdner Hospital according to the standards of the German Research Network on Neuropathic Pain (DFNS)
- Co-investigator in a funded study at Brighton University (UK) to improve clinical diagnoses for people with spinally referred leg pain

Workshops

- Session coordinator, chair and presenter of a symposium entitled “Radikuläre Schmerzen – ein Update zu Klinik und Management einer komplexen Symptomatik“ (Radicular pain – an update on clinics and management of a complex symptomatology) (2017) *Deutscher Schmerz Kongress (German Pain Congress)*, Mannheim, Germany
- Co-presented a topical workshop with Associate Professor Schmid, Neuroscience Nuffield Department of Clinical Neurosciences at the University of Oxford (UK), on the “Prognosis and neural regeneration capacity in patients with entrapment neuropathies: clinical and

molecular aspects" (2018) *World Congress on Pain of the International Association for the Study of Pain*, Boston, USA

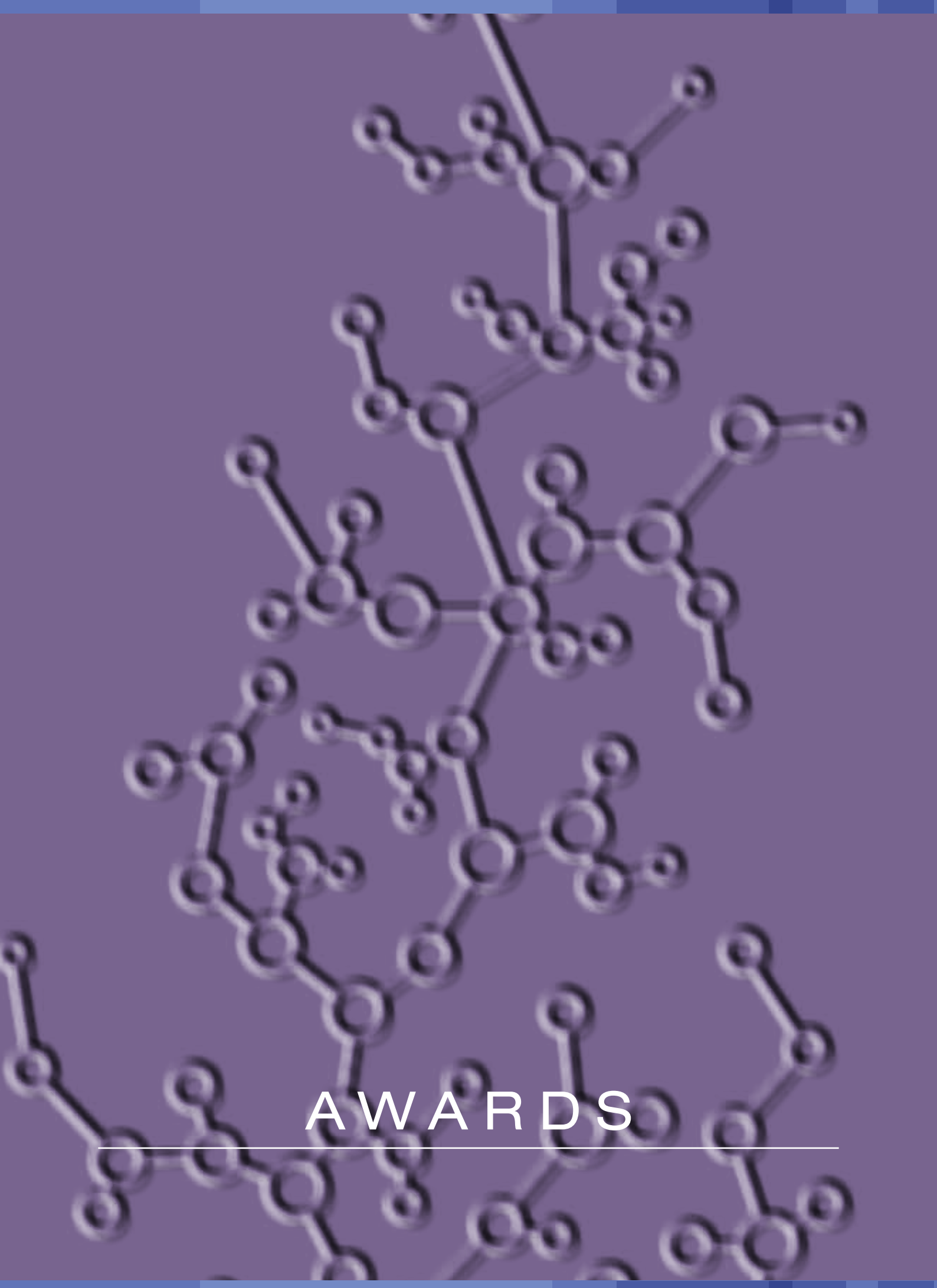
- Session coordinator, chair and presenter of a workshop abstract entitled "Radicular pain - an update on clinical presentation, classification and management of a complex condition", in collaboration with the Chair of the German Research Network on Neuropathic Pain (2018) *World Congress on Pain of the International Association for the Study of Pain*, Boston, USA

Collaborations

- As an Adjunct Senior Research Fellow at the School of Physiotherapy and Exercise Science, Curtin University, Dr Tampin has developed a strong collaboration with Professor Helen Slater
- In conjunction with the Pain Management Department at Sir Charles Gairdner Hospital, Dr Tampin and Professor Slater conducted a study last year entitled "Improving the clinical assessment and management of neuropathic pain"
- Dr Tampin has a longstanding research collaboration with Associate Professor Schmid at the Neuroscience Nuffield Department of Clinical Neurosciences, University of Oxford (UK), which resulted in a recently published view point paper on entrapment neuropathies and taught courses on this topic in the UK
- Through a professorship in Germany, partnerships with the QST training centre of the DFNS in Bochum have been extended in collaboration with Professor Dr Christoph Maier
- A collaboration with Dr Stefan Lauer, former employee at the Royal Perth Hospital Pain Management Department, now staff at the Pain Management Department at the Paracelsius Clinic in Osnabrueck (Germany), has been established
- At a local level, the Clinician Research Fellowship has strengthened a collaboration with Professor Christopher Lind and his research team (the Surgical NeuroDiscovery Group), who offered the use of research space at the Sarich Neuroscience Institute (SNRI)

ACKNOWLEDGEMENTS

Dr Tampin would like to acknowledge the WA Department of Health and the Raine Medical Research Foundation, as well as the School of Physiotherapy and Exercise Science at Curtin University, for the financial support of the study. She sincerely thanks Associate Investigators Professor Slater and Professor Christopher Lind for their invaluable contribution and collaboration. Also thanked are research assistants Ms Carly Pyne and Ms Stephanie Glass for their support in QST testing and the staff at the Physiotherapy Department, Pain Management Department and Neurosurgery Department at Sir Charles Gairdner Hospital for their support in recruitment of research participants, and organisational and administrative tasks. Finally, Dr Tampin would like to thank the staff at the Department of Research, Sir Charles Gairdner Hospital, for their assistance in all research-related matters.



AWARDS

Raine Visiting Professor Awards

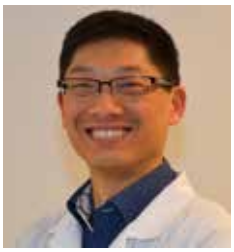
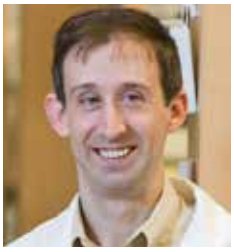
The Raine Visiting Professor Award program was introduced in 1971 to facilitate the visit of distinguished scientists to Western Australia. Visiting scientists bring many benefits to the WA scientific community including advances in health and medicine, cross-fertilisation of skills and ideas, networking and collaboration, as well as important reciprocal exchange programs. Visiting scientists also make a significant contribution to the teaching and research programs in their specialist field of medical research.

2017 Raine Visiting Professor Awards

The below Raine Visiting Professors visited Western Australia in 2017:

	Visiting Academic	Research Interests
	Professor Carol Brayne University of Cambridge, UK	Public health, ageing and dementia
	Professor Duanqing Pei Chinese Academy of Sciences, China	Stem cell biology
	Professor Shulamit Levenberg Israel Institute of Technology, Israel	Stem cells and vascular tissue engineering
	Professor Nicholas Topley Cardiff University, UK	Peritoneal dialysis (a treatment for end stage kidney disease) and peritoneal membrane function

The below Raine Visiting Professor Awards were awarded in 2017 for visits in 2018:

	Visiting Academic	Research Interests
	Professor Benjamin Chow University of Ottawa Heart Institute, Canada	Cardiac imaging and cardiac computed tomography (CT)
	Professor John Crispino Northwestern University, USA	Mechanisms of normal and malignant blood development
	Professor Freddie Fu University of Pittsburgh, USA	Anatomic anterior cruciate ligament (ACL) reconstruction, clinical outcomes and the bioengineering of sports-related problems

2017 Annual Reports
Raine Visiting Professors

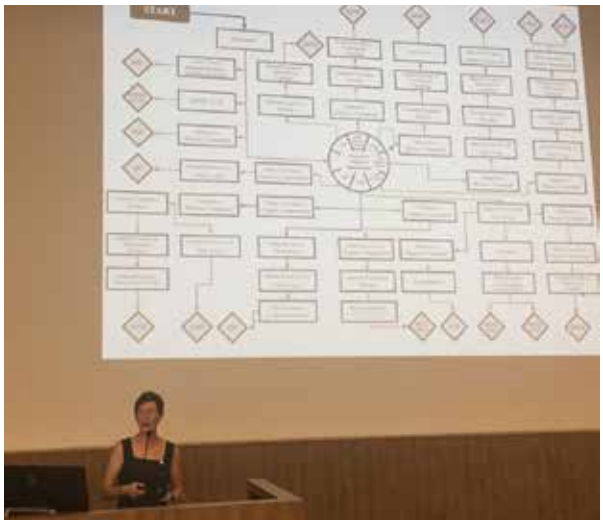
Professor Carol Brayne

In February 2017, the Raine Foundation was delighted to welcome Professor Carol Brayne to The University of Western Australia (UWA) as a Raine Visiting Professor and guest of Professor Leon Flicker at the UWA Centre for Medical Research within the Faculty of Health and Medical Sciences.

Professor Brayne is Professor of Public Health Medicine in the Department of Public Health and Primary Care at the University of Cambridge. She is Director of the Cambridge Institute of Public Health, where her research focuses on public health, ageing and the brain. Professor Brayne is a medically qualified epidemiologist and an internationally recognised leader in academic public health. She has made outstanding contributions to dementia research and to the understanding of the ageing brain. The studies she leads are acclaimed internationally and has been the prime moving force in major initiatives with national profiles. Professor Brayne has measured changing dementia prevalence, behavioural and psychiatric symptoms in dementia, and depression prevalence; research which is critical to defining long-term care needs for our population.

Specifically, Professor Brayne has pioneered the study of dementia in the general population, launching two major longitudinal studies of the health and cognitive functioning of 30,000 older people. The results underpin the understanding of dementia, showing (among many other things) that dementia can occur without the expected changes in brain pathology and that such alterations, when they do occur, do not invariably lead to dementia. Her studies provide the basis for planning long-term care needs in the UK and have recently shown that the prevalence of dementia at specific ages is declining.

Professor Brayne spent 17 days at UWA and was involved in many activities, including seminars, lectures, and research and government meetings. A major focus centred on liaising with researchers at all levels, ranging from early- to mid-career scientists, senior academics and a variety of medical professionals. For example, Professor Brayne hosted a special journal club session to staff entitled "*WA Centre for Health and Ageing Introduction*", and met with individual early career researchers to discuss research interests, synergies and methodologies on how to better engage with international scientists. These were followed by a one hour lecture to local medical professionals, as part of a fortnightly lecture series arranged by Professor Markus Schlaich, Dobney Chair in Clinical Research; the 2017 Dick Lefroy Annual Oration (which was recorded and can be viewed at https://www.perkins.org.au/wacha/news-events/; and a very well-received lecture ("*Dementia and our brains in contemporary ageing populations*") held at the



UWA University Club that was attended by 250 academics from UWA, Curtin University, clinicians from Royal Perth Hospital and Sir Charles Gairdner Hospital, numerous other stakeholder representatives, and interested community members. One of the major events was a presentation on the 15 February 2017 by Professor Brayne at the Harry Perkins Institute of Medical Research (HPIMR) that formed part of the prestigious Raine Lecture series. During her visit, Professor Brayne conferred new knowledge in the area of large population studies and the ageing brain to UWA researchers and Perth's health professionals, as well as upskilling staff on epidemiological studies.

On a higher professional level, Professor Brayne met with local health and ageing stakeholders over dinner; the Raine Chair Professor Robyn Owens and UWA Vice-Chancellor Professor Dawn Freshwater, who presented her with a Raine Visiting Professor Award medallion; and the then opposition Health Minister Hon Roger Cook. The latter encounter involved the sharing of views and methodology on how Professor Brayne's research findings affect health policy in the UK, with suggestions made for similar projects to be undertaken in Western Australia.

Overall, the visit was a great success with several proposed future initiatives, including a preliminary discussion regarding working with Professor Brayne and her team on a future grant application in the area of Indigenous health and ageing, thus allowing the research already completed in Australia to have a global perspective; long-term research collaborations between Professor Brayne, the host and other members of the WA Centre for Health and Ageing team, and UWA; and a planned visit to Professor Brayne's laboratory in the Cambridge Institute of Public Health, University of Cambridge, by UWA Research Analyst and Churchill Fellow Cath Josif.

Professor Shulamit Levenberg

Following a successful visit to UWA for 11 days in 2016, funded by a Raine Visiting Professor Award, Professor Shulamit Levenberg was welcomed back to The University of Western Australia (UWA) for three weeks in June and July 2017 after being awarded her second Raine Visiting Professor Award. On this occasion, Professor Levenberg, from the Biomedical Engineering Department, Technion Faculty, Israel Institute of Technology, was hosted by Professor George Yeoh at the Centre for Cell Therapy and Regenerative Medicine (CCTRM) within the Harry Perkins Institute of Medical Research (HPIMR).

Professor Levenberg conducts interdisciplinary research on stem cells and vascular tissue engineering. She conducted her PhD at the Weizmann Institute of Science, Israel, on cell adhesion and her post-doctoral research at Massachusetts Institute of Technology (MIT), USA, on stem cells tissue engineering with Professor Robert Langer, a world leader in biomaterials, drug delivery and tissue engineering. In 2004, she joined the Technion Faculty of Biomedical Engineering and spent a sabbatical year (2011 to 2012) as a visiting professor at the Wyss Institute for Biologically Inspired Engineering at Harvard University. In her research, Professor Levenberg studied the mechanical control of tissue assembly *in vitro* and *in vivo*, with a focus on vessel network formation and anastomosis in engineered tissues. She is also developing microbioreactors and nanolitre droplet devices for stem cell growth and manipulations, as well as for early diagnostic applications.

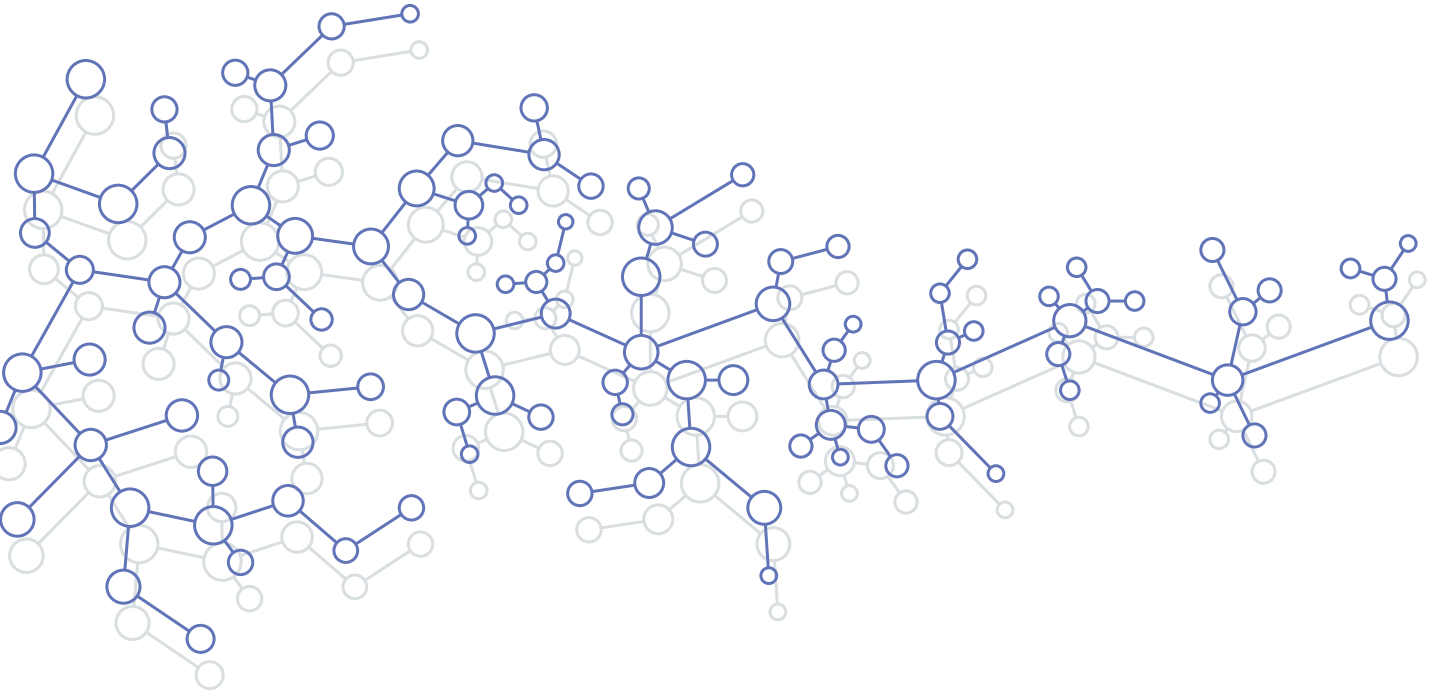
In 2006, Professor Levenberg received the Krill Prize for excellence in scientific research by the Wolf Foundation (Israel), and was named by Scientific American as a "Research Leader" in Tissue Engineering for her studies on the vascularisation of engineered tissues. Subsequently, Professor Levenberg obtained a European Research Council Starting Grant in 2011. Her major achievements have culminated in Professor Levenberg being included in a list of ten Israeli scientists by the Maariv, a daily Israeli newspaper, in 2013; being named as Woman of the Year by the Emuna Foundation; becoming the President of the Israel Stem Cell Society and a member of the Israel National Bioethics committee; and being listed as one of the ten top Israeli women in science and technology by the Israel Ministry of Education in 2014. To date, Professor Levenberg has delivered more than 80 talks as an invited or keynote speaker to international conferences, including the *Third Annual Cambridge Stem Cell Institute International Symposium* (Cambridge, UK; 2013); the *International Symposium on Engineering Complex Tissues* (Drexel University, USA; 2015); and the *Fourth TERMIS World Congress* (Boston, USA; 2015).

During her visit to Western Australia, a number of activities were undertaken by Professor Levenberg, many of which have resulted in several proposed future initiatives. Initially, Professor Levenberg met with Professor George Yeoh to engage in project discussions and conduct laboratory work, with some very promising results regarding the

development of hepatocytes and cholangiocytes from liver stem cells using scaffolds developed in the Levenberg laboratory. Then, a meeting with Dr Brendan Kennedy (laboratory head of Bioimaging Research and Innovation for Translational Engineering, HPIMR) took place that resulted in a new collaboration where Dr Kennedy and his postdoctoral fellow will travel to the Technion Faculty, Israel, to learn more about Professor Levenberg's research first-hand and to observe how to make engineered materials that can be constructed in Perth. Similarly, a PhD student of Professor Levenberg will visit Perth to ensure these materials are being generated correctly and to run a series of experiments. Professor Levenberg met twice with Professor Girish Dwivedi (HPIMR) to collaborate and explore the possibility of using adult vein endothelial cells seeded with myoblasts to produce "chimaeric" blood vessels in preclinical models and humans, a series of projects that have the potential to impact the treatment of conditions caused by heart disease. Professor Levenberg visited Curtin University in July to give a seminar presenting her exciting work on tissue vascularisation to a full house hosted by the School of Biomedical Sciences, followed by a round table discussion involving several research leaders, students and postdoctoral fellows with an interest in tissue engineering. As a result, two meetings occurred with Professor Fiona Wood to discuss a three-way collaboration between Professor Wood, and Associate Professor Pritinder Kaur, Curtin University, with a view to publish together and apply to the Human Frontier Science Program for future funding. There is potential for this collaboration to

be expanded to include Murdoch University, as well as Curtin University (via Associate Professor Guiseppe Verdile) and Imperial College London. A two-way location and engineered device exchange was discussed with Associate Professor Rod Dilley of the Ear Science Institute (ESI), UWA, as well as a private meeting with Mr John Schaffer, Chairman and Trustee of the ESI. Professor Levenberg attended a roundtable discussion, where Professor Kevin Pfleger will develop a mutual collaboration with the ARC Industrial Transformation Training Centre (ITTC) for Personalised Therapeutics Technologies, a joint venture between The University of Melbourne, UWA, Monash University, CSIRO, National University of Singapore and 16 partner organisations including several biotech companies. Other meetings of note took place with Dr Ionat Zurr and SymbioticA Director Oron Catts; Dr Judy Berman; members of the UWA Mifgash (a peer-to-peer organisation of young adult Israelis from around the world); Prof Ming-Hao Zheng and Paul Anderson, Managing Director of Orthocell, to discuss submission of an ARC Linkage Grant in 2017; an introduction of Associate Professor Cecilia Prele (Centre for Microscopy, Characterisation and Analysis, CMCA) to Professor Josue Sznitman from Technion BME to facilitate the potential for a collaboration on lung regeneration; and a student from the Lions Eye Institute who wishes to undertake a PhD in Israel.

Other important engagements included the conferment of a medallion by the Raine Chair Professor Robyn Owens and UWA Vice-Chancellor Professor Dawn Freshwater; an interview on the ABC's Radio National Breakfast program (http://www.abc.net.au/radionational/programs/breakfast/will-engineered-organs-ever-become-a-reality-in-medicine/8773910); the delivery of the prestigious Raine Lecture on "*Vascularisation dynamics in engineered tissues*" (jointly sponsored by UWA's Institute of Advanced Studies); and a presentation to the Centre for Entrepreneurial Research and Innovation (CERI) Bootcamp, where Professor Levenberg gave personal anecdotes to the group about her entrepreneurial journey and how she moved the translation of her research to be licensed. The great success of this Raine Visiting Professor Award has resulted in Professor Levenberg inviting Professor Robyn Owens and Christine Shervington, Project Manager, back to visit Technion, Israel, in 2018.

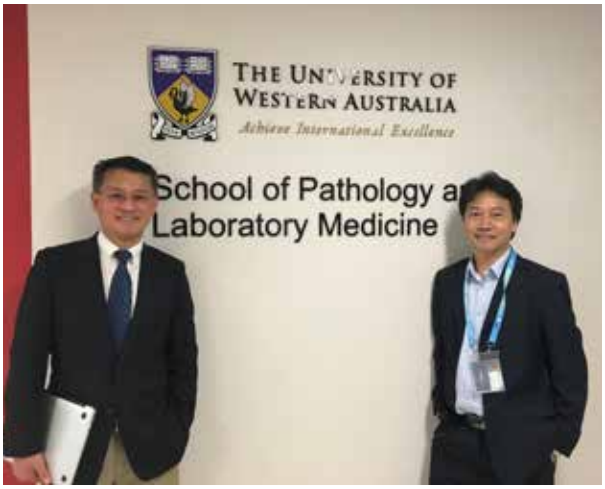


Professor Duanqing Pei

Visiting from the Guangzhou Institute of Biomedicine and Health (GIBH), Chinese Academy of Sciences, in China, the Raine Foundation was pleased to welcome Professor Duanqing Pei to The University of Western Australia (UWA) in February 2017. Hosted by Winthrop Professor Jiake Xu at Pathology and Laboratory Medicine, a part of the Medical School (Faculty of Health and Medical Sciences), Professor Pei was awarded a Raine Visiting Professor Award, which was accompanied by a medallion presented by the Raine Chair Professor Robyn Owens and UWA Vice-Chancellor Professor Dawn Freshwater.

Professor Pei is a Professor of Stem Cell Biology, but also serves as the Director General (President) of the GIBH in Guangzhou, China. He obtained his PhD from the University of Pennsylvania, USA, in 1991 and trained as a postdoctoral fellow at the University of Michigan. In 1996, Professor Pei became a faculty member at the School of Medicine, University of Minnesota, USA. He joined the Medical Faculty at Tsinghua University in Beijing, China, in 2002 and moved to the GIBH in 2004. His scientific interests are broad, with frequent changes in research disciplines. Currently, Professor Pei investigates the recent advances in stem cell research, in particular stem cell pluripotency and reprogramming, and their potential clinical applications. Recent publications from Professor Pei's laboratory include the discovery of vitamin C as a potent booster for induced pluripotent stem cell (iPSC) generation, and new ways to improve iPSC technology and their application to model human diseases *in vitro*.

During his 15 day visit, Professor Pei gave an enlightened Raine Lecture on "*Cell fate decisions during somatic cell reprogramming*" at the Harry Perkins Institute of Medical Research (HPIMR) and a keynote speech on the same topic at the inaugural *Australia-China Conference on Science, Technology and Innovation (ACCSTI)* at UWA (2-6 February, 2017). In addition, Professor Pei engaged in seminars, laboratory meetings, and conducted a roundtable discussion to all members of Winthrop Professor Xu's research group. Meetings were conducted between



Professor Pei and Faculty members to either commence or strengthen existing collaborations with Associate Professor Nathan Pavlos, Professor Grant Morahan and Associate Professor Julian Heng. As part of the collaboration with Professor Xu, Professor Pei gained new techniques into the programming and use of mouse iPSCs that will be of value to his research in China and ongoing joint ventures.

Outcomes from this successful visit include several proposed future initiatives and potential resultant publications, such as a joint research project to hunt for biomarkers present in osteonecrosis and collaborative research into the role of the protein sorting nexin 10 (SNX10) in bone homeostasis and stem cells, where SNX10 was first discovered by Professor Pei's group. Importantly, the Raine Visiting Professor Award supported a discussion on the potential for global networking opportunities, including the formation of a regenerative medicine network between UWA and GIBH. As such, Professor Xu undertook a collaborative visit to Professor Pei in March, 2017.

BrightSpark Research Collaboration Awards

The BrightSpark Research Collaboration Awards were established in 2016 and encourage early-career researchers in Western Australia to establish and develop research collaborations, both nationally and internationally, to seek a better understanding of the cause and treatment of childhood disease and illness.

In 2017 two Awards were allocated to commence in 2018, with a total funding allocation of $13,120.

2017 BrightSpark Research Collaboration Awards

	Chief Investigator	Project Title	Collaborating Institution
	Dr Laurence Cheung Telethon Kids Institute	Identification of novel drug combinations to cure high-risk infant leukaemia	University of New South Wales
	Dr Gavin Pieira School of Public Health, Curtin University	Heatwaves and Perinatal Morbidity – a combined observational and experimental study	The University of Western Australia Telethon Kids Institute

2018 BrightSpark Research Collaboration Awards

	Chief Investigator	Project Title	Collaborating Institution
	Dr Annette Regan School of Public Health, Curtin University	An international cohort study measuring child health following maternal immunisation	Children's Hospital of Eastern Ontario Research Institute, Canada
	Dr Nathanael Yates School of Human Sciences, The University of Western Australia	Developing preterm infant nutrition research capacity	University of Copenhagen, Denmark

2017 Annual Research Reports
BrightSpark Research Report

PROJECT TITLE

Heatwaves, stillbirth and perinatal morbidity – a combined observational and experimental study

INVESTIGATORS

Dr Gavin Pereira (Chief Investigator)
Dr Caitlin Wyrwoll (Collaborating Partner)
Dr Alex Larcombe (Collaborating Partner)

SCHOOL/INSTITUTE/CENTRE

School of Public Health, Curtin University
The University of Western Australia (Collaborating Institution)
Telethon Kids Institute (Collaborating Institution)

SUMMARY

This study examined the effects of elevated environmental or ambient temperatures on the survival of babies and stillbirth combining observational and experimental studies (i.e. a retrospective cohort study in humans with *in vivo* research in mice). The observational arm of the study was led by Curtin University (by Dr Gavin Pereira), whereas the *in vivo* part of the study was led by UWA (by Dr Caitlin Wyrwoll) and the Telethon Kids Institute (by Dr Alex Larcombe). A UWA medical student (Ms Emma McCormack) visited Curtin University and was supervised by Dr Pereira in data preparation for the observational study. Two honours students (Ms Karike Olivier and Ms Lauren Ashley Reinders) were supervised by Dr Wyrwoll on this project with input from Dr Larcombe. The titles of these projects were "*Heatwave exposure during late gestation alters the behavioural and physiological adaptations associated with mouse gestation*" and "*The effect of heatwaves in late gestation on fetal and placental development in mice*". Heatwave exposures were calculated for the human population at all Bureau of Meteorology sites in WA and used to define a heatwave for the *in vivo* studies (at 37°C). For the *in vivo* study, heatwave exposure in late gestation was associated with decreased maternal weight gain, increased rectal temperature, decreased nest building complexity and decreased food intake. Associations were not observed with genes related to the heat shock response. Heatwave exposure was associated, however, with reduced placental mass, a trend toward reduced fetal mass and down-regulation of the vascular endothelial growth factor a (*Vegf-a*) gene. Nutrient transporter genes were unaltered.

There were 680,799 births investigated in the human study. In observational studies, exposure can be assessed on a continuum. Unadjusted hazard ratios for stillbirth indicated an adverse effect of elevated daily maximum temperature, most notably around 37°C, and was, therefore, consistent with the perturbed placental growth and endothelial growth factor levels. Preliminary results indicate, however, that this effect is attenuated to statistical non-significance after adjustment. Adjusted models did not show an effect of heatwaves on the risk of stillbirth. This is likely because Aboriginal women and other vulnerable sub-populations in non-metropolitan areas are most predisposed to delivering a stillborn child and are located in regions of the state that experience higher temperatures. No unadjusted associations were observed between heatwaves and stillbirths. This is likely because the aforementioned finding is weakened as the heatwave definition was allowed to vary by location (95th and 99th centile of the closest Bureau of Meteorology site), which partially accounts for acclimatisation and adaptation.

OUTCOMES

Dissemination of Knowledge and Expertise

Preliminary results of the heatwave study will be shared by Dr Pereira to our community and a consumer reference group at the next meeting. *In vivo* results have been presented by the two honours students. Two manuscripts (one for the *in vivo* study and the other for the the observational work) will be submitted next year for publication in peer reviewed journals. Results from the study will be presented at the next national epidemiological conference.

This project contributed to the research training of two honours students and one medical student. The honours students both gained knowledge and experience in animal husbandry and surgery, molecular biology and physiological techniques, medical imaging, and oral and written scientific communication. The medical student gained experience in population-based studies and working with large epidemiological databases.

Collaboration

The project involved collaboration between Curtin University, UWA and the Telethon Kids Institute. The investigators on this project have put forward a research plan for the next three years. Two co-authored publications will be produced from this project: these manuscripts will establish a track record of collaboration for a joint submission of a national grant application in the next round. The study topic will be *"The role of placental development in explaining the adverse effects of ambient environmental exposures on pregnancy outcomes".* Again Dr Pereira will lead the observational study, Dr Wyrwoll will manage the *in vivo work* and Dr Larcombe will take charge of experiments related to exposure assessment and application, and biological interpretation. Smaller studies will be conducted in the interim. Dr Pereira has obtained observationally-linked health and medical records for all births in WA (1980 to 2016) and NSW (1994 to 2016). The equipment purchased for the heatwave study will be used for further studies by higher degree research students supervised by Dr Wyrwoll.

Conference Presentations

- Heat wave exposure during late gestation in mice alters maternal adaptations and decreases fetal and placental growth. *Society for Reproductive Biology. 2017. Perth, Australia*

Publications

- Honours dissertation: Heatwave exposure during late gestation alters the behavioural and physiological adaptations associated with mouse gestation
- Honours dissertation: The effect of heatwaves in late gestation on fetal and placental development in mice

Healy Research Collaboration Awards

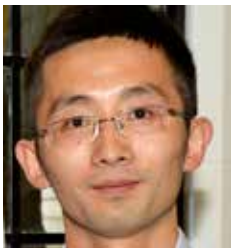
The Research Committee introduced the Healy Research Collaboration Awards in 2012 to encourage early-career medical research scientists to establish and develop national and international research collaborations. The Awards aim to increase opportunities for collaborative publications, joint grant submissions, sharing and advancement of research/clinical skills and industry linkages.

In 2017 there were three ongoing Awards, with one from 2015 given an extension to complete planned collaborative visits. In 2017 three Awards were allocated to commence in 2018, with a total funding allocation of $19,500.

2015 Healy Research Collaboration Awards

	Chief Investigator	Project Title	Collaborating Institution
	Dr Tristan Clemons School of Molecular Sciences, The University of Western Australia	Multifunctional targeted nanoparticles for the effective delivery of therapeutics in models of colorectal cancer	Cardiff University, UK

2017 Healy Research Collaboration Awards

	Chief Investigator	Project Title	Collaborating Institution
	Dr Peijun Gong School of Electrical, Electronic and Computer Engineering, The University of Western Australia	Optical imaging of conjunctival lymphatics for better glaucoma treatment	Lions Eye Institute Simon Fraser University, Canada
	Dr Iona Schuster Lions Eye Institute	Characterising innate lymphoid cells in steady state and infection	Memorial Sloan Kettering Cancer Centre, USA

2018 Healy Research Collaboration Awards

	Chief Investigator	Project Title	Collaborating Institution
	Dr Belinda Guo School of Biomedical Sciences, The University of Western Australia	Establishing cell culture models for fibrotic progression in patients with myeloproliferative neoplasms	Northwestern University, USA
	Dr Haibo Jiang Centre for Microscopy, Characterisation and Analysis, The University of Western Australia	Development of a multimodal mass spectrometry imaging platform for lipid analysis	University of California, USA National Physical Laboratory, UK
	Dr Samantha Lee Centre for Ophthalmology and Visual Sciences, The University of Western Australia Lions Eye Institute	Western Australia Atropine for the Treatment Of Myopia (WA ATOM) study	Dublin Institute of Technology

2017 Annual Research Reports
Healy Research Reports

PROJECT TITLE
Multifunctional targeted nanoparticles for the effective delivery of therapeutics in models of colorectal cancer

INVESTIGATORS
Dr Tristan Clemons (Chief Investigator)
Professor Alan Clarke (Collaborating Partner)

SCHOOL/INSTITUTE/CENTRE
School of Molecular Sciences, The University of Western Australia
The European Cancer Stem Cell Research Institute, Cardiff University, UK (Collaborating Institution)

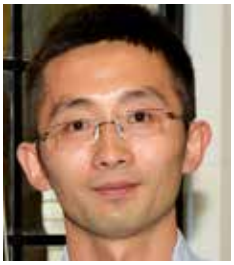
SUMMARY
This project aimed to develop a targeted nanoparticle delivery vehicle suitable for the delivery of chemotherapeutics in colon cancer. This nanoparticle will integrate the potential for multimodal imaging with magnetic resonance imaging (MRI) and fluorescence capabilities to target the epidermal growth factor (EGF) receptor (EGFR), which is overexpressed in a number of cancers, including colon cancer. The main aims were to: (i) Develop, synthesise and characterise a multifunctional polymeric nanoparticle system suitable for the targeted delivery of chemotherapeutics in cancer and (ii) Test the efficacy of this system in suitable *in vitro* models, as well as pilot test in a relevant *in vivo* mouse model.

OUTCOMES
Dissemination of Knowledge and Expertise
The rationale behind this work was to develop a multifunctional nanoparticle platform suitable for the targeted delivery and imaging of a chemotherapeutic. Unfortunately this project encountered some significant delays and disruptions. Sadly, a key collaborator, Professor Alan Clarke (Director of the European Cancer Stem Cell Research Institute), passed away suddenly in 2016. Fortunately during this period, a strong connection with Professor Clarke's lead postdoctoral researcher, Dr Trevor Hay, was maintained, who has been invaluable in ensuring the collaboration remained strong. However, Dr Hay was unavailable in 2017 for the majority of the year due to carers leave for his wife who was diagnosed with breast cancer. Hence, it is fitting to acknowledge where this work currently sits and the progress made to date with regards to how the work has progressed towards an application in treating breast cancer.

This work has been featured in a number of public events throughout the past two years. Dr Clemons is an advocate for promoting science and scientific research to school students and has presented his work to a number of schools in the Perth metropolitan area, as well as internationally with a presentation at the Amity University, India. The research of Dr Clemons has been featured in the Scitech "Beyond the Beaker Program", a scheme that travels to all corners of Western Australia and reaches over 10,000 school students per year. He was also a featured scientist for the Raine Medical Research Foundation's social media campaign in 2017. Recently, Dr Clemons was recognised as the WA Royal Australian Chemical Institute Bayliss Youth Lecture presenter. Such an accolade will take him across WA, as well as to the Northern Territory, to present on his research to broad public audiences and school students.

Collaboration
Future work in this area will involve a collaboration with Dr Anabel Sorrolla Bardaji at the Harry Perkins Medical Research Institute. Specifically, *in vivo* pilot assessments of these chemotherapeutic formulations will be made in xenograft breast cancer models. As the collaboration with the European Cancer Stem Cell Research Institute remains strong it is anticipated that future collaborations will continue with Dr Trevor Hay when he returns to work. The project will also be enhanced by a collaboration with the new director of the institute, namely Professor Matt Smalley, on the potential for applications in transgenic mouse models.

Conference Presentations
- Invited Talk: Multimodal polymeric nanoparticles – Applications in the treatment of cancer and prospects for burn injuries. Amity University. 2017; Noida, India
- Naidu P, **Clemons T**, Norret M, Dunlop SA, Fitzgerald M, Iyer KS. Enhancing the therapeutic efficiency of cancer treatment with doxorubicin using novel polymeric nanoparticles. *International Conference on Nanoscience and Nanotechnology (ICONN)*. 2018; Wollongong



PROJECT TITLE
Optical imaging of conjunctival lymphatics for better glaucoma treatment

INVESTIGATORS
Dr Peijun Gong (Chief Investigator)
Professor Marinko Sarunic (Collaborating Partner)
Professor Dao-Yi Yu (Collaborating Partner)

SCHOOL/INSTITUTE/CENTRE
Electrical, Electronic and Computer Engineering, The University of Western Australia
Simon Fraser University, Canada (Collaborating Institution)
Lions Eye Institute, Australia (Collaborating Institution)

SUMMARY
The imaging studies of the porcine conjunctival lymphatics provide high-resolution reference images for future studies with label-free optical coherence tomography lymphangiography (OCTL) imaging, thereby extending the knowledge of conjunctival lymphatics. The feasibility of OCTL for resolving conjunctival lymphatics was initially demonstrated in porcine eyes. This provided a necessary first step towards the ongoing adoption of OCTL to *in vivo* imaging of the human conjunctiva in both normal subjects and glaucoma patients.

OUTCOMES
Dissemination of Knowledge and Expertise

An updated optical coherence tomography (OCT) imaging system (MARS 3.0) was built by Professor Sarunic's team in Canada and then shipped to the Lions Eyes Institute (LEI) for the proposed imaging studies in collaboration with Professor Yu. Using the MARS OCT scanner, plus the TELESTO OCT scanner (kindly provided by the Optical and Biomedical Engineering Laboratory at UWA), the research team have imaged 31 porcine eyes *ex vivo* by acquiring 3D scans of the conjunctiva as a first step to study conjunctival lymphatics. Data processing and image analyses were performed to segment the lymphatic vessel network from conjunctival OCT scans, using the OCTL technique developed at UWA. Vessel images were presented to and analysed with both Professor Yu and Professor Sarunic during a visit to Canada by Dr Gong. This encounter assessed for image quality, and the interpretation of the vessel structures to build reference images of the lymphatic vessel network and identify the limitations of the current imaging techniques to guide the subsequent human eye imaging studies.

Upgrading of the TELESTO OCT scanner to address the OCTL imaging limitations has been performed, which has resulted in greater OCTL imaging capability to resolve small lymphatic vessels. Extended from the porcine studies, preliminary OCT scans of normal human eyes have been collected *in vivo* at the LEI and are currently being processed for OCTL imaging of the lymphatic system.

Ultimately, the goal of this project is to initiate the adoption of OCTL imaging for imaging the conjunctiva in human eyes and in particular patients with glaucoma. Within the scope of this project, the first step involving porcine eye studies has already led to the initiation of human eye imaging in normal subjects. It is anticipated that long-term, this work will be translated to the imaging of eyes in glaucoma patients. Such long-term work has been initiated by this collaboration, which has provided the instrumentation at the LEI, the data processing platform and the sharing of new knowledge among the collaborative research groups.

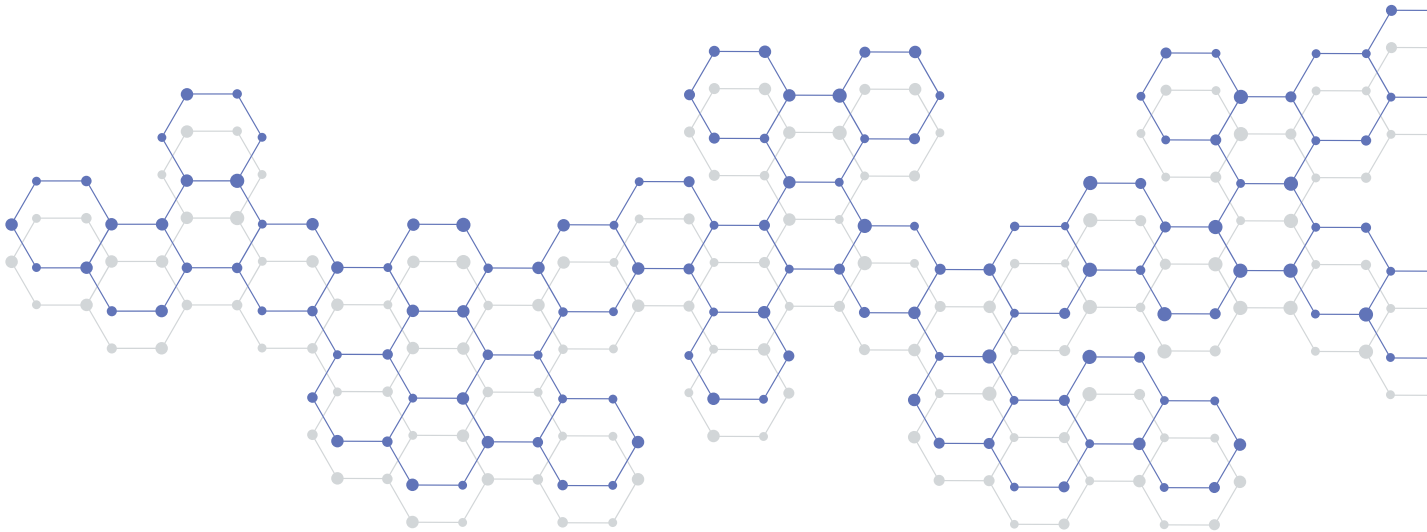
Collaboration

Dr Gong visited Professor Sarunic's research group, investigated their home-built OCT scanners and performed OCT scanning of patient conjunctivas *in vivo* in the Eye Care Center, Vancouver General Hospital. Indeed, several skills were acquired where artifacts due to the motion of the subjects during OCT scanning were reduced. Dardware and software developments were also learnt from techniques developed in Professor Sarunic's group. Taking further advantage of this visit, he also visited two other research groups at the University of Washington and the Oregon Health and Science University (OHSU), both of which specialise in OCT imaging of the human eye. The OHSU group is led by Professor David Huang, who pioneered the OCT imaging technique, and this encounter provided the research team with useful tools and solutions for the ongoing clinical imaging studies being conducted at the LEI.

Conference Presentations

The results from this collaborative work has led to three conference presentations, including:

- A poster presentation at the *5th International Conference on Biophotonics.* 2017; Perth
- An invited oral presentation at the prestigious *European Conferences on Biomedical Optics* conference. 2017; Munich, Germany
- An oral presentation at the *SPIE Photonics West BiOS conference*. 2018; San Francisco, USA. This is the largest conference in biomedical topics.



PROJECT TITLE
Characterising innate lymphoid cells in steady state and infection

INVESTIGATORS
Dr Iona Schuster (Chief Investigator)
Associate Professor Joseph Sun (Collaborating Partner)

SCHOOL/INSTITUTE/CENTRE
Experimental Immunology, Centre for Ophthalmology and Visual Science (COVS) & the Lions Eye Institute
Memorial Sloan Kettering Cancer Centre, USA (Collaborating Institution)

SUMMARY
The collaboration with Associate Professor Joseph Sun's laboratory at the Memorial Sloan Kettering Cancer Centre (MSKCC) in New York has focused on investigating group 1 innate lymphoid cells (ILCs), which are composed of natural killer (NK) cells and the recently identified type 1 ILCs (ILC1s). Specifically, the research team is interested in the identification of group 1 ILCs, their differentiation, and the role of these cells in the response to immunological challenges, including viral infections. In summary, this collaboration has produced a number of important new findings regarding the phenotypic characterisation and physiological importance of group 1 ILCs in steady-state conditions, as well as during a viral infection. This will allow for a better understanding of the respective contribution of the different group 1 ILC populations to immunological responses raised against pathogenic challenges, as well as their role in the regulation of adaptive immunity.

OUTCOMES
Dissemination of Knowledge and Expertise
To date, studies have generated a number of important findings, namely the identification of the cell surface protein CD200r as a specific marker for ILC1s in steady-state conditions, as well as with infection, in a number of different tissues. The identification of CD200r is an important finding since it allows the unequivocal identification of group 1 ILCs under inflammatory conditions. The researchers have found that the phenotypic markers commonly used to distinguish NK cells and ILC1s in steady-state conditions are significantly modulated during viral infections. As a result, CD200r is an invaluable marker for future studies aimed at understanding the respective contribution of group 1 ILC subsets to various immunological challenges. Using different routes of murine cytomegalovirus (MCMV) infection and models of influenza virus infection, the investigators have found that ILC1s are truly tissue-resident cells and are the first population to express interferon-gamma at initial sites of infection. This anti-viral response precedes that of NK and T cells, and is important to limit viral replication in the very early hours post-infection. This is the first demonstration that ILC1s contribute to the control of viral infections, thus providing important new insights into the physiological role of these cells. Finally, using the MCMV infection model, it has been demonstrated that group 1 ILCs are an important regulatory population that balance anti-viral T cell responses, thus preventing the generation of auto-immune responses in the salivary gland. Ongoing investigations are focused on group 1 ILC populations localised in and recruited to the salivary gland over the course of an infection; the identification of the specific subset regulating anti-viral T cell responses; and the cytokines and chemokines governing these regulatory responses.

Specifically, this collaboration has established novel intranasal infection protocols to target MCMV to the lung; shared salivary gland tissue dissection and analysis techniques with collaborators in New York; established *in vivo* leukocyte labelling techniques in Perth to differentiate between vasculature-associated and truly tissue-localised cells; and the planning, set-up and analysis of parabiotic mouse experiments.

Collaboration
Collaborations with Associate Professor Joseph Sun and Dr Timothy O'Sullivan are continuing, the latter investigator who is in the process of establishing his own research group at the University of California, Los Angeles (USA), on the investigation of group 1 ILC subsets, and their role in the response to and regulation of immunological responses to infection and disease. Meetings are planned for future international conferences and symposia, as well as the preparation of papers and the submission of a research grant. For example, a follow-up meeting with Associate Professor Joseph Sun at the ASI meeting in Brisbane to discuss continued collaboration on the investigation of salivary gland group 1 ILCs. The research team are continuing their collaboration with Dr Nadia Guerra, Imperial College London (UK), to further define the mechanisms underlying the NKp46-dependent regulation of tumour necrosis factor-related apoptosis-inducing ligand TRAIL expression.

Conference Presentations

- Invitation to present findings on the group 1 ILCs in the response to viral infection at the Infection and Immunity Workshop of the *Australasian Society of Immunology (ASI) Annual Meeting.* 2017; Brisbane

Publications

- Weizman OE, Adams NM, **Schuster IS**, Krishna C, Pritykin Y, Lau C, *et al*. ILC1 confer early host protection at initial sites of viral infection. *Cell*. 2017; 171: 795-808. This included the release of a press statement by the Lions Eye Institute on the *Cell* publication (http://www.medianet.com.au/releases/147105/)
- Sheppard S, **Schuster IS**, Andoniou CE, Cocita C, Adejumo T, Kung SKP, Sun J, Degli-Esposti MA, Guerra N. The murine natural cytotoxic receptor NKp46/NCR1 controls TRAIL protein expression in NK cells and ILC1. *Cell Reports***.** 2018; In Press

Cockell Research Collaboration Awards

The Cockell Research Collaboration Awards were established in 2015 from funds bequeathed to The University of Western Australia by the late Edith Elaine Cockell for the purpose of facilitating research into the cause and treatment of mental illness. These Awards provide an excellent opportunity for scientists working in the field of mental illness to develop national and international research collaborations. They facilitate cross-institutional ties with academic institutions or organisations that will lead to long-term alliances and advanced clinical knowledge into the cause and treatment of mental illness.

In 2017 there were seven ongoing Awards, with two from 2015 and two from 2016 given extensions to complete planned collaborative visits. In 2017 one Award was allocated to commence in 2018, with a total funding allocation of $13,650.

2015 Cockell Research Collaboration Awards

	Chief Investigator	Project Title	Collaborating Institution
	Associate Professor Julian Lk-Tsen Heng Harry Perkins Institute of Medical Research	Understanding how genetic mutations to gene regulatory proteins cause childhood brain disorder	University of Queensland
	Professor Florian Zepf School of Psychiatry and Clinical Neurosciences, The University of Western Australia	Studying the role of serotonin in anxiety in adolescence – An iterative translational research approach	Duke University, USA

2016 Cockell Research Collaboration Awards

	Chief Investigator	Project Title	Collaborating Institution
	Dr Wayne Davies School of Animal Biology, The University of Western Australia	Light therapy in the treatment of bipolar disorder	University of Oxford, UK

	Dr Kevin Runions Telethon Kids Institute	Social reward and impulsivity in disruptive behaviour problems: The roles of oxytocin and serotonin	The University of Sydney

2017 Cockell Research Collaboration Awards

	Chief Investigator	Project Title	Collaborating Institution
	Dr Ben Grafton School of Psychology, The University of Western Australia	Enhancing the treatment of depression through the delivery of attentional bias modification procedures	University of Exeter, UK
	Dr Benjamain Milbourn School of Occupational Therapy and Social Work, Curtin University	Mental health outcomes of adolescents with ASD as they transition to adulthood	Vanderbilt University, USA
	Associate Professor Lisa Wood School of Population and Global Heath, The University of Western Australia	Prevalence of mental illness and treatment pathways among people who are homeless in Perth, Western Australia	Royal Perth Hospital Pathway, UK

2018 Cockell Research Collaboration Awards

	Chief Investigator	Project Title	Collaborating Institution
	Dr Diane Dennis Intensive Care and Physiotherapy Department, Sir Charles Gairdner Hospital	Lessons learned following an episode of intensive care unit crisis: what experienced Intensivists can teach their peers	Hadassah University Hospital, Israel Austin Hospital

2017 Annual Research Reports
Cockell Research Reports

PROJECT TITLE
Light therapy in the treatment of bipolar disorder

INVESTIGATORS
Associate Professor Wayne Iwan Lee Davies FRSB (Chief Investigator)
Professor Russell Foster CBE FSB FMedSci FRS (Collaborating Partner)
Dr Katharina Wulff (Collaborating Partner)

SCHOOL/INSTITUTE/CENTRE
School of Biological Sciences, The University of Western Australia
University of Oxford (Collaborating Institution)

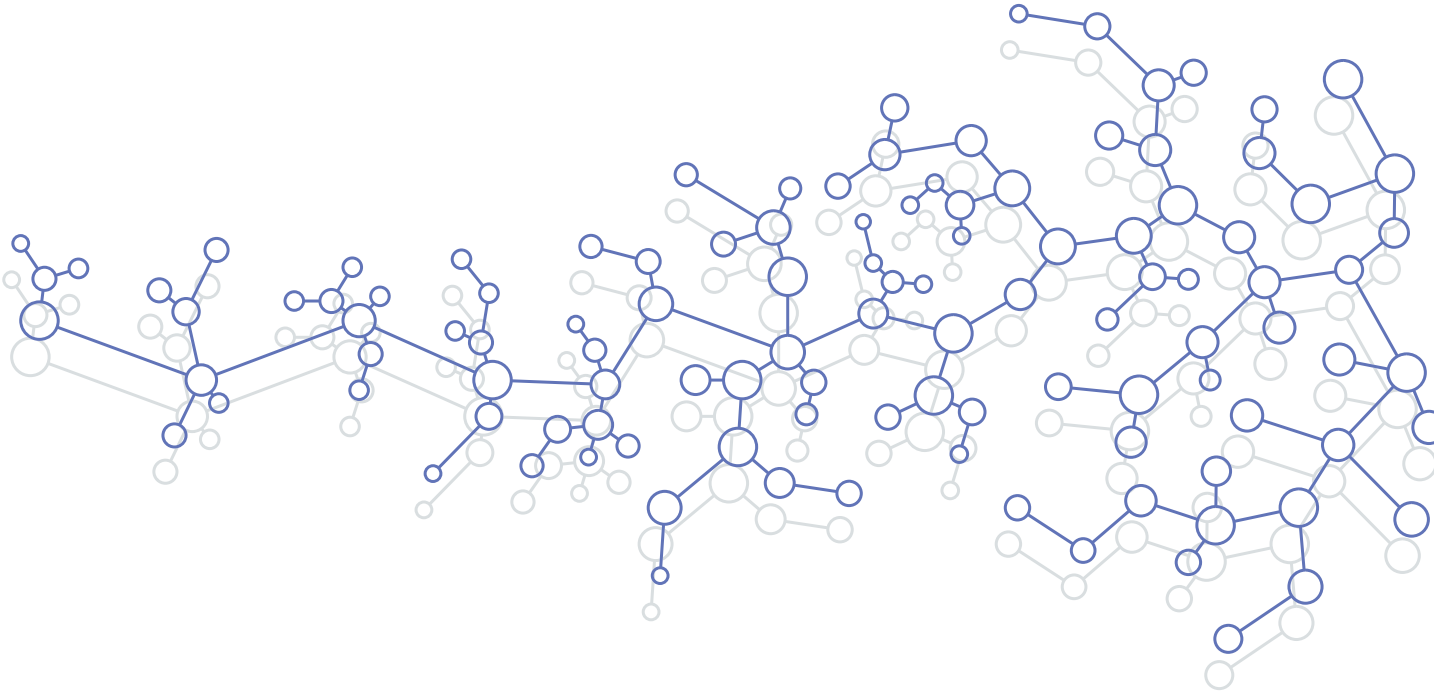
SUMMARY
Bipolar disorder (BD) is a mood disorder characterised by mania and depression, which often involves circadian dysfunction, irregular sleep patterns and suicide. It is feasible, therefore, that approaches that regulate biological rhythms and sleep will be effective treatments. This collaborative project aimed to study the use of light as a monotherapy for BD type II (BDII) depression, where current drug regimens are limited and accompanied by many side-effects and/or medication compliance issues. Mood and sleep cycles were monitored by questionnaires, actigraphy, and by assaying hormone levels in non-medicated participants subjected to green light. Although a pilot study, this was the first project of its kind to investigate light therapy as a non-invasive treatment for BD mood, secondary anxiety and sleep disturbances.

OUTCOMES
Dissemination of Knowledge and Expertise
When the Cockell Research Collaboration Award (CRCA) was awarded to Associate Professor Davies, a visit was arranged for him to meet Professor Foster (a world renowned circadian neuroscientist) and Dr Wulff (an expert in the link between sleep and mental health disorders) at the University of Oxford, UK. Although Associate Professor Davies and Professor Foster had worked together on previous projects looking at the evolution of non-visual systems, this was the first time they had collaborated on a human-based mental health study. In addition, this was the first time that Associate Professor Davies and Dr Wulff had formally collaborated. Specifically, Associate Professor Davies visited both the Nuffield Laboratory of Ophthalmology and the Sleep and Circadian Neuroscience Institute (SCNi) to discuss the phototherapy project in more detail and to finalise the experimental pipelines. With a strong track record in molecular biology and functional genomics of visual and non-visual systems (photobiology), this collaborative project meant that Associate Professor Davies was able to expand his research interests into human based studies, and in particular how to address mental health issues. More importantly, it meant that he could liaise and be trained by two international leaders in mental health disorders and sleep disruption. For a month, Associate Professor Davies met daily with Professor Foster and Dr Wulff (predominantly) and was trained in how to apply the correct questionnaires required to monitor mood, anxiety and subjective sleep. Being a major part of the proposal, Associate Professor Davies was also trained in actigraphy; this included how to accurately use actigraphy watches to measure changes in external lighting conditions (in RGB), and activity and sleep patterns every 24 h for the 8 weeks of the study pipeline. Alternate skills were gained in the measurement of cortisol and melatonin hormones to monitor stress/anxiety and objective sleep patterns via an introduction to researchers at the University of Surrey, UK. At the end of the project, Associate Professor Davies and the University of Oxford team met for a final time, where Associate Professor Davies was trained in advanced actigraphy analysis in preparation for future grant proposals. A major advantage of this proposal was the transference of new knowledge and advanced technical skills from the UK (University of Oxford and the University of Surrey) to Australia (UWA).

Post-training, Associate Professor Davies returned to UWA to conduct the pilot study. BDII individuals were recruited and subjected to the experimental pipeline, where the pilot results showed that with the onset of green light, baseline low mood levels in BDII patients increased by approximately 3-fold, which returned to baseline levels upon the removal of the light stimulus. Controls showed typical levels throughout the experiments and remained unaltered by light. Invariably, this work has the potential to lead to large-scale clinical trials and the application of phototherapies for other mental health conditions both nationally and internally. However, funding will be required to support further pilot studies (e.g. in major depressive disorder, MDD). In the long term, all of these will benefit UWA and Australian biomedical research in general.

Collaboration

Whilst at the University of Oxford, Associate Professor Davies met with many colleagues in the field of circadian neuroscience and sleep. Indeed, all were rather impressed and excited by the results presented to them, with many stating that this was critical work that very much needed to be funded and expanded further for the treatment of BD, but also other mental health disorders. As such, the UWA and University of Oxford teams formally submitted NHMRC Project grants in 2017. In 2018, a modified Project grant was resubmitted to the NHMRC with the addition of further UWA researchers as CI (e.g. Professor Sean Hood from the School of Psychiatry) and a number of mental health clinical staff as AIs. The team is also planning to extend this study pending further support by the application of additional grants (e.g. 2019 CRCA, larger grants administered by the Raine Medical Foundation Foundation, as well as more targeted mental health organisations). Without the support of the Raine Medical Research Foundation, this important work would not have been possible. As such Associate Professor Davies would like to offer his gratitude for the CRCA.



PROJECT TITLE

Enhancing the treatment of depression through the delivery of attentional bias modification procedures

INVESTIGATORS

Dr Ben Grafton (Chief Investigator)
Professor Ed Watkins (Collaborating Partner)

SCHOOL/INSTITUTE/CENTRE

School of Psychological Science, The University of Western Australia
University of Exeter, UK (Collaborating Institution)

SUMMARY

This Cockell Research Collaboration Award (CRCA) provided funding to support a strategic initiative, devised by Dr Grafton, to bring together investigators who specialise in basic cognitive-experimental research with expert clinical investigators. This collaboration aimed to establish a translational research enterprise that will systematically evaluate the capacity of novel computer-based cognitive technologies to enhance the efficiency and effectiveness of conventional cognitive behaviour therapy (CBT) interventions for emotional dysfunction. The work yielded important new findings, and, importantly, laid a strong foundation upon which to further develop and expand this strategic initiative in delivering significant ongoing benefits.

One key research aim was to carry out studies evaluating whether new cognitive bias modification (CBM) procedures, which have recently been developed, are more capable of therapeutically altering the patterns of biased cognitive processing known to underpin emotional dysfunction than current CBM approaches. Three such studies have now been completed, which revealed that these new CBM procedures are capable of more powerfully altering cognitive bias than existing CBM approaches. Given the considerable international interest in CBM research, and the strong focus within the literature on the importance of developing more robust CBM procedures, it can be anticipated that these findings will have a significant impact on the field in the years ahead.

A second key research aim was to conduct a small-scale intervention trial in which the therapeutic benefits of adding new CBM procedures to a conventional CBT group intervention were evaluated. Specifically, in late 2017, the UWA School of Psychological Science, the UWA Office of Student Life, and the UWA Student Guild, collaboratively launched the UWA Student Life Student Resilience Program. A key component of this program is to deliver conventional CBT group interventions to UWA students, and to help them build knowledge and skills that will optimise their resilience. The research team were presented with the unique opportunity to embed the present CRCA research within the UWA Student Life Student Resilience Program, which was eagerly embraced, as this will enable much greater visibility, penetration and impact. Dr Grafton has been working closely with colleagues from the UWA School of Psychological Science's Robin Winkler clinic to mount the UWA Student Life Student Resilience Program CBT group interventions. The generous support of the Raine Medical Research Foundation will be clearly acknowledged in the promotional and recruitment material for these CBT groups, which will be widely disseminated among the UWA student population.

OUTCOMES

Dissemination of Knowledge and Expertise

The work supported by this CRCA funding has produced four important outcomes: (i) The successful execution of studies that will result in high impact publications; (ii) An Australian Research Council grant application for a three-year research project involving Dr Grafton and Professor Watkins; (iii) The development of a collaborative research partnership with a new clinical investigator that will serve to expand the strategic initiative originally motivating this CRCA research; and (iv) The ongoing involvement of Professor Watkins, an internationally renowned clinician, in the delivery of CBT groups conducted within the UWA School of Psychological Science's Robin Winkler clinic. The novel findings of this study are being written up for publication in Behaviour Research and Therapy. Importantly, the outcomes will be built upon within a PhD research project that will be carried out by an outstanding new PhD student that Dr Grafton will supervise at UWA.

The manner in which this CRCA research project has been developed will ensure its sustainability over the long-term and enable it to be expanded in ways that will deliver ongoing benefits to Dr Grafton, other UWA early career researchers, UWA PhD/Masters students and UWA academic staff.

Collaboration

While in the UK, Dr Grafton also had the opportunity to meet with Professor Watkins' colleague, Dr Barney Dunn, an expert clinical investigator specialising in the treatment of anhedonia – an inability to feel pleasure in normally pleasurable activities and a hallmark symptom of depression. Dr Grafton, Professor Watkins and Dr Dunn worked together to develop a new collaborative research project, the first studies of which will be conducted with the input of future Honours student researchers. This project represents an important expansion of the strategic initiative of this CRCA.

Professor Watkins will travel to the UWA School of Psychological Science for a three-week research visit this year to meet extensively with Dr Grafton to further develop studies that will build upon the work carried out during this CRCA. He will also meet with other UWA early career researchers, UWA PhD/Masters students and academic staff at the UWA School of Psychological Science to identify new collaborative research projects. Professor Watkins will provide expert clinical guidance in an ongoing capacity to Dr Grafton and his UWA colleagues involved in the delivery of the CBT groups.

PROJECT TITLE

Understanding how genetic mutations to gene regulatory proteins cause childhood brain disorder

INVESTIGATORS

Associate Professor Julian Ik-Tsen Heng (Chief Investigator)
Dr Michael Piper (Collaborating Partner)

SCHOOL/INSTITUTE/CENTRE

School of Biomedical Sciences, The University of Western Australia
The Queensland Brain Institute, The University of Queensland (Collaborating Institution)

SUMMARY

The functions of the human brain are predicated on the appropriate production of nerve cells, and their assembly as functional circuits. Failures in these essential steps in foetal brain development can result in intellectual disability, a lifelong mental illness. This proposal will facilitate the research capabilities of two outstanding mid-career neuroscientists to establish the molecular basis for intellectual disability. The applicants will undertake reciprocal research exchange to acquire state-of-the-art research techniques to investigate how genetic mutations disrupt the formation of brain circuits. This collaboration will develop their joint capabilities as leaders in the fields of developmental neuroscience and mental health.

OUTCOMES

Dissemination of Knowledge and Expertise

In this funded project, Associate Professor Heng and Dr Piper investigated the molecular mechanisms which underlie the formation of neural circuits in the mammalian brain during foetal development. In particular, the investigators focussed on two candidate genes (*RP58* and *NFIX*) to ask how their presence is important to this process. In the last 12 months, both investigators have made significant progress on these parallel projects. They have published two manuscripts thus far.

Initially, Associate Professor Heng proposed to host a member of Dr Piper's laboratory to learn *in utero* electroporation, but technical difficulties and logistical challenges prevented this from occurring. However, electroporation experiments related to this interaction was undertaken by a member of Associate Professor Heng's laboratory instead, with the subsequent preparation of data carried out in Dr Piper's laboratory group. The collaboration grant has enabled both research laboratories to expand on their capacity to perform *in utero* electroporation experiments, as well as to broaden the capabilities for their respective groups to be able to analyse tissues collected from different stages of brain development, from foetal development through to postnatal development. This capability is crucial to both labs to support their complementary execution of such laboratory experiments, enabling Associate Professor Heng and Dr Piper to continue to publish research together for the foreseeable future.

Collaboration

Both investigators continue to collaborate on the development of a gene diagnostic panel test for neurological disorders. The interaction between both lab heads will also strengthen their complementary research strengths to understand the cellular and molecular basis for neural development and childhood brain disorders. The long-term goal of this collaboration is to foster linkages to develop a multi-site programme grant to investigate the genetic basis for childhood brain disorders.

Publications

- Clément O, Hemming IA, Gladwyn-Ng IE, Qu Z, Li SS, Piper M, **Heng JI**. Rp58 and $p27^{kip1}$ coordinate cell cycle exit and neuronal migration within the embryonic mouse cerebral cortex. *Neural Development*. 2017; 12: 8
- Clément O, Hemming IA, Gladwyn-Ng IE, Qu Z, Li SS, Piper M, **Heng JI**. Correction to: Rp58 and $p27^{kip1}$ coordinate cell cycle exit and neuronal migration within the embryonic mouse cerebral cortex. *Neural Development*. 2018; 13: 1
- Harris L, Zalucki O, Clément O, Fraser J, Matuzelski E, Oishi S, Harvey TJ, Burne THJ, **Heng JI**, Gronostajski RM, Piper M. Neurogenic differentiation by hippocampal neural stem and progenitor cells is biased by NFIX expression. *Development.* 2018; 145: dev155689

PROJECT TITLE

Social reward and impulsivity in disruptive behaviour problems: The roles of oxytocin and serotonin

INVESTIGATORS

Dr Kevin Runions (Chief Investigator)
Professor Mark Dadds (Collaborating Partner)

SCHOOL/INSTITUTE/CENTRE

Telethon Kids institute, The University of Western Australia
The University of Sydney (Collaborating Institution)

SUMMARY

Studying the epigenetic profiles of adolescents engaged in deliberate self-harm (DSH) builds upon insights provided by a growing body of research - of which Professor Dadds' work is at the forefront - that indicates that most mental health disorders involve epigenetic regulation of neuropsychologically relevant gene expression. Methylation - the binding of methyl molecules to gene CpG sites - can arise as a result of adverse childhood experiences and go on to alter gene transcription. Adolescents who engage in DSH are more likely to have been abused in childhood, and methylation may be the mechanism whereby social experiences are biologically embedded to affect subsequent mental health outcomes and DSH risk. To date, epigenetic markers of suicide risk have been identified, but little is known about the differential role of epigenetics of these sites in the heterogeneity of DSH and in the response to treatment of clients engaged in DSH. Thus, the proposed research aimed to map epigenetic markers associated with heterogeneity in DSH characteristics and treatment responses. This will form the background for a pilot study of methylation changes observed in clinical DSH. In summary, the collaboration with Professor Dadds has provided the conceptual groundwork for world-first research on the epigenetics of DSH.

OUTCOMES

Dissemination of Knowledge and Expertise

The Cockell Research Collaboration Award (CRCA) was aimed to provide a mechanism to engender collaboration between Perth-based researchers and a highly successful research team in Sydney led by Professor Mark Dadds. Despite some initial impediments, Dr Runions was able to initiate and see through several important activities. These include a continued collaboration with Professor Dadds and the establishment of an Australian Violence and Aggression Research Network.

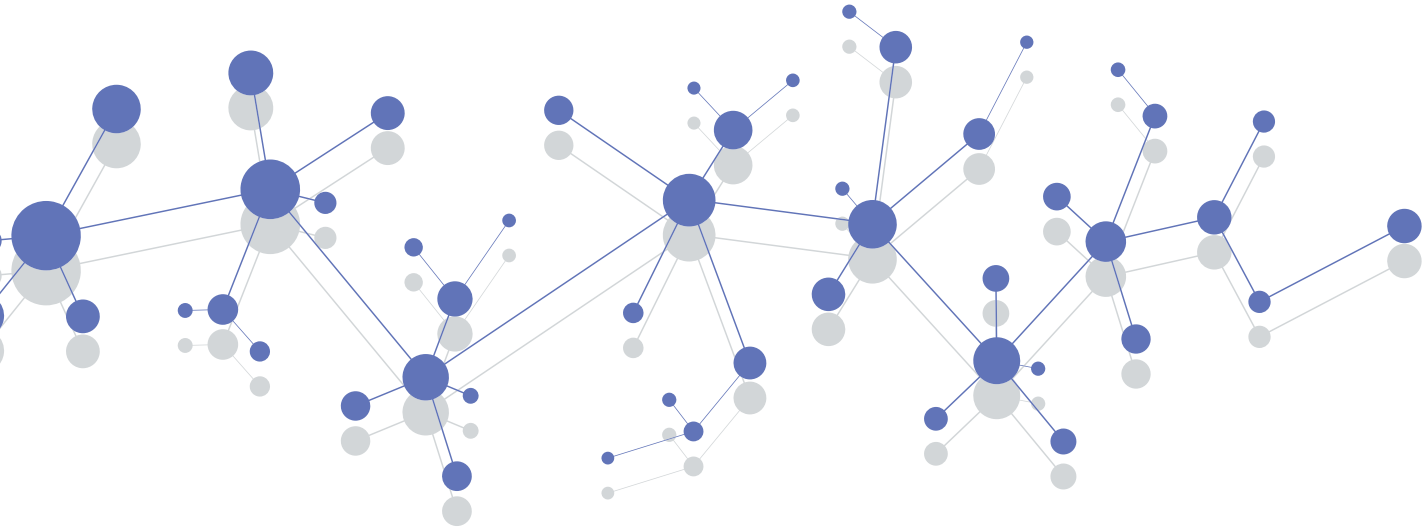
At the *International Society for Research on Aggression (ISRA)* meeting, it was agreed to conduct a survey of Australian-based researchers engaged in this area, where Dr Runions coordinated and implemented an online survey that was distributed by the ISRA coordinators and others. This resulted in responses from 66 researchers including psychologists, criminologists, educators, sociologists, undergraduate students and established research professors. The survey provided a snapshot of the current research foci of Australian researchers in terms of what aspects of aggression are studied (including modes or types of aggression, as well as contributors and processes involved) and what research methodologies are used, both with a view of identifying future growth areas. The resulting report was disseminated through networks, and included a list of names and contact details of 37 participants who were interested in future development of an Australian Violence and Aggression Research Network *(*AVARN). Subsequent to this, Dr Runions set up the Western Australian Violence and Aggression Research (WAVAR) working group at the Telethon Kids Institute. This group includes local researchers from UWA, Murdoch University, and stakeholders from the Department of Health (Child & Adolescent Mental Health Services) and the Department of Education (School of Special Educational Needs: Behaviour & Engagement), with the aim of developing applied research plans to enable improved collaborations in child and adolescent pathological aggression.

Collaboration

Steps have been implemented to ensure sustainability of the collaboration with Professor Dadds. For example, he was a recipient of Research Excellence and Culture funding from the Telethon Kids Institute to present at the Friday research seminars, which will also provide a mechanism for further face-to-face meetings to continue this work. A proposal to the Telethon Perth Children's Hospital Research Fund was submitted for a Strategic Initiative that would entail further collaboration. Recently, Dr Runions took up a position with Child & Adolescent Mental Health Services as a Research Psychologist. Specifically, this embeds him within a service that works with young people who are engaged in deliberate self-harm and have features indicative of borderline personality disorder. The collaborative relationships and expertise that were established via the CRCA have proven to be crucial in these activities. As part of the CRCA work, Dr Runions has been leading a systematic review of the role of serotonin in child and adolescent aggression. This paper will serve as a capstone to this funding, as it brings together research on epigenetics (with Professor Dadds), along with UWA's Professor Florian Zepf's research on serotonin challenge.

Conference Presentations

Following on from a meeting with Professor Dadds, Dr Runions convened a forum as part of the meeting of the 22nd world meeting of the *International Society for Research on Aggression (ISRA)* in Sydney. In collaboration with Dr Wayne Warburton and Associate Professor Kay Bussey (both at Macquarie University) and Dr Barbara Spears (University of South Australia), this forum established an Australian research network to pull together individuals and groups conducting research on aggression. Dr Runions presented a paper at this conference addressing the heterogeneity of aggression as it pertains to bully-aggression.



PROJECT TITLE

Prevalence of mental illness and treatment pathways among people who are homeless in Perth, Western Australia

INVESTIGATORS

Associate Professor Lisa Wood (Chief Investigator)
Dr Nigel Hewett OBE (Collaborating Partner)
Dr Amanda Stafford (Collaborating Partner)

SCHOOL/INSTITUTE/CENTRE

School of Population and Global Health, The University of Western Australia
Pathway, UK (Collaborating Institution)
Royal Perth Hospital (Collaborating Institution)

SUMMARY

The Cockell Research Collaboration Award (CRCA) enabled the research team to establish and consolidate collaborations with Dr Nigel Hewett OBE, as well as a network of affiliated researchers and organisations in the UK that are dedicated to improving the health of homeless people. As part of the award, Dr Hewett from Pathway, UK (https://www.pathway.org.uk/), visited Perth in 2017 and significantly expanded collaborations around homeless health in WA with the Royal Perth Hospital (RPH) Homeless Team (RPHHT), Homeless Healthcare and The East Metropolitan Health Service. These collaborations have a particular focus on quantifying the magnitude of health and mental health issues facing homeless patients of RPH and identifying intervention points to support these clients. Through the international and local collaborations that are being developed, the research team is amassing evidence to demonstrate the cost savings that can accrue to government when the mental and physical health needs of people who are homeless are addressed.

Pathway have published several reports and papers to date incorporating the use of hospital data to measure outcomes for their homeless clients: the WA research team is now in a position to apply some of the insights from Pathway's methodology and questions to local data in a project that has linked the records for 2,995 clients of Homeless Healthcare and Royal Perth Hospital. Data is being analysed for this client group from 2013 to 2017, including emergency department (ED) presentations, planned and unplanned hospital admissions (including psychiatric admissions), mental health diagnoses and status. Preliminary analysis highlights the magnitude of mental health need among this vulnerable population group, with ED presentations and unplanned inpatient admissions often associated with a mental health diagnosis. Untreated mental health conditions such as schizophrenia are also highly prevalent among this group, but some positive case studies have been collated on how mental health has stabilised once homeless people receive targeted healthcare and are connected to housing and other supports.

OUTCOMES

Dissemination of Knowledge and Expertise

"I think Nigel's perspective on how horribly inadequate our mental health system is with regard to homeless mentally ill people was a wakeup call…He said that in the UK, such people would be admitted to psychiatric institutions for treatment, but this did not appear to be available to them in Perth." Dr Amanda Stafford, RPH

Whilst in Perth, Dr Hewett participated in collaborative meetings with researchers, clinicians and policy makers and gave three major presentations all on the topic of integrated care for homeless people. The mental health needs of homeless people was a key focus. Key activities included: (i) A presentation with question time to over 40 researchers and academics at a UWA School of Population Health seminar; (ii) A keynote presentation to an audience of >70, including health professionals, the homelessness sector, and the general public, as part of the 2017 Social Impact Festival; (iii) An invited presentation to 25 senior staff and executives at the East Metro Health Service; and (iv) A private meeting with state Health Minister Roger Cook, who sought his advice on the UK experience around homelessness and health interventions. As a result of the CRCA, the investigators are currently working with Dr Stafford to build evidence and identify potential intervention points for a magnitude of mental health issues facing homeless people in WA.

Dr Hewett's presentations, mentoring and generous sharing of experiences has helped build research and evaluation capacity in the research team and local collaborating partners. Following his visit, the collaboration team sought to distil the elements of best practice healthcare for people who are homeless, with significant inputs by Dr Hewett and Dr Stafford. A short YouTube clip of an interview with Dr Hewett during his visit to Perth is currently being developed and is in final production. Towards the end of 2017, Dr Kevin Murray from the WA team was able to visit the UK and visit several researchers involved in Pathway, UK. Through the visit several joint papers have been instigated and advice sought on several methodological challenges.

Collaboration

The collaboration with Dr Hewett and Pathway, UK, has helped build team capacity in data linkage and analysis for a WA cohort of people experiencing homelessness. In particular, the collaboration has assisted in identifying key variables to include in hospital data requests, and prioritising health conditions and issues for the initial analyses. The research team continues to be in regular contact with collaborative partners and communicate around joint authorship opportunities, potential partnership grants, and advice on data analysis and research translation issues in this cohort.

Conference Presentations

- Wood L. "A place to call home – why housing stability matters for mental health". *WA Tenancy Conference.* 2017
- Conference abstract "Relevant, responsive, relational: accelerating evidence into action – lessons from homelessness and health". *Public Health Association Conference*. 2018; Cairns

Publications

- Stafford A, **Wood L**. Tackling health disparities for people who are homeless? Start with social determinants. *International Journal of Environmental Research and Public Health*. 2017; 14: 1535
- **Wood L**, Vallesi S, Flatau P. Harnessing the potential of linked administrative data for homelessness research. *Parity*. 2017; 30: 43

Grants

Two grants have been submitted: (i) A State Health Research Advisory Council (SHRAC) grant with clinician colleagues Dr Stafford and Dr Andrew Davies; and (ii) An ARC Linkage grant, partnering with Royal Perth Hospital, Homeless Healthcare, East Metropolitan Health Service, and Pathway as an international partner.

Dr Nigel Hewett presenting at the East Metropolitan Health Service Breakfast to Senior WA Health Executives

Dr Amanda Stafford introducing Nigel Hewett at the presentation

Dr Amanda Stafford and Dr Nigel Hewett at the 2017 Social Impact Festival

Screenshot from video clip of interview with Dr Nigel Hewett on his observations of the work of the RPH Homeless Team

Social Impact Festival Flyer

Dr Nigel Hewett meeting WA Minister for Health and Deputy Premier, Roger Cook

Snapshot summary of Dr Hewett's visit

PROJECT TITLE

Studying the role of serotonin in anxiety in adolescence – An iterative translational research approach

INVESTIGATORS

Winthrop Professor Florian Zepf (Chief Investigator)
Professor Cynthia Kuhn (Collaborating Partner)

SCHOOL/INSTITUTE/CENTRE

Department of Child and Adolescent Psychiatry, The University of Western Australia
Duke University, USA (Collaborating Institution)

SUMMARY

The purpose of this proposal was to develop the methodology to transiently decrease serotonin in the brain of adolescent rodents in order to investigate the role of serotonin in anxiety-like behaviours during adolescence. To accomplish this goal, Winthrop Professor Zepf and Professor Kuhn worked closely together and visited each other's laboratories in the USA and Australia. A number of amino acid mixtures were piloted to deplete brain serotonin in adult mice, with results such as lower tryptophan in the brain and effects on serotonin turnover. The best approaches were selected and delivered to adolescent mice. Unfortunately, the mixtures that were effective in adults, were not effective in adolescents. Finally, a more extreme pharmacologic manipulation was used: the inhibition of tryptophan hydroxlase with para-chlorophenylalanine (PCPA). This process caused a dramatic decrease in serotonin in the brain of both adolescent and adult rats. This treatment was further tested on a well-characterised rodent test of anxiety, which was effective in adults, but ineffective in adolescents. These findings are concordant with recent meta-analyses demonstrating the limited efficacy of serotonin-specific reuptake inhibitors (SSRIs) in treating depression in children and suggest that alternative pharmacotherapies are much needed for the mental health care of children and adolescents.

OUTCOMES

Dissemination of Knowledge and Expertise

During this collaboration, Professor Kuhn gave numerous seminars in the USA about adolescent brain development and serotonin. The receipt of this award has allowed her to travel to Australia, where she presented two seminars to psychiatrists who care for children and adolescents, as well as youths and adults. Professor Kuhn spent an entire week with Winthrop Professor Zepf's staff providing education about adolescent brain development and especially the development of cranial serotonin systems. Similarly, Winthrop Professor Zepf visited Professor Kuhn's laboratory in the USA and interacted with her team of animal researchers regarding the clinical aspects of serotonin-related research during adolescence.

Collaboration

This award has allowed Professor Kuhn and Winthrop Professor Zepf to meet face-to-face to plan the next steps in their collaboration. Their findings indicate that it is critical to expand the research on tryptophan depletion to investigate novel targets; for example, the blockade of glutamate receptors with ketamine-like agents to treat psychiatric conditions in adolescents where the appropriate neural circuits to mediate SSRI effects are not yet mature.

Grants

Winthrop Professor Zepf has submitted a grant proposal to investigate serotonergic mechanisms in human adolescents.

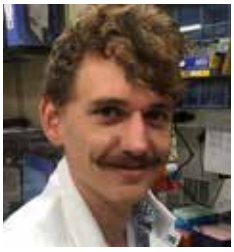
PRIZES

Raine Research Prize

The Raine Research Prize is awarded for the best scientific paper arising from research undertaken by an early-career medical research scientist in Western Australia. The Prize consists of a travel allowance to the value of $5,000 and a medallion.

In 2017, the Raine Research Prize was awarded to Dr Sam Taylor, to commence in 2018.

	2017 Recipient	Winning Publication	Journal
	Dr Ozren Bogdanovic Harry Perkins Institute of Medical Research	Active DNA demethylation at enhancers during the vertebrate phylotypic period	Nature Genetics

	2018 Recipient	Winning Publication	Journal
	Dr Samuel Taylor School of Pathology and Laboratory Medicine, The University of Western Australia	Preventing chemotherapy-induced myelosuppression by repurposing the FLT3 inhibitor quizartinib	Science Translational Medicine

2017 RAINE RESEARCH PRIZE

Dr Ozren Bogdanovic

The 2017 recipient of the Raine Research Prize was Dr Ozren Bogdanovic from the Harry Perkins Institute of Medical Research for his article "Active DNA demethylation at enhancers during the vertebrate phylotypic period" published in *Nature Genetics* (Bogdanovic *et al.*, *Nat Genet.* 2016; 48: 417-426).

This award made it possible for Dr Bogdanovic to attend a highly prestigious conference, *Gordon Research Conference Epigenetics* (2017; New Hampshire, USA), where his abstract was selected for an oral presentation entitled "Transphyletic conservation of developmental epigenome remodelling". As a grateful recipient, the award of $5,000 towards conference travel allowed him to present his latest cutting-edge research to a broad audience of genetics and epigenetics experts, as well as increasing Dr Bogdanovic's international visibility in the field.

This award also funded a visit to the Radboud Institute for Molecular Life Sciences, Radboud University (The Netherlands), where a number of his current collaborators are located, namely Professor Michiel Vermeulen, Professor Gert Jan Veenstra and Dr Simon van Heeringen. This visit resulted in the presentation of a seminar by Dr Bogdanovic entitled "Evolutionary conservation of developmental epigenome dynamics" and provided an excellent platform to discuss potential follow-ups of previously published collaborative work. During this visit, Dr Bogdanovic completed several final experiments, with analyses that were subsequently accepted for publication in *Genome Biology* (Elurbe *et al.*, *Genome Biol.* 2017; 18: 198), and developed new collaborations.

Since the award, Dr Ozren Bogdanovic has relocated to the Garvan Institute of Medical Research in Sydney, where he now leads the Developmental Epigenomics group.

2018 RAINE RESEARCH PRIZE

Dr Samuel Taylor

With six possible entrants in the running, the Research Committee members were overwhelmed by the quality of publications being considered. However, one research paper stood out as being of a high enough calibre to be awarded the 2018 Raine Research Prize. As such, it is with great pleasure that the Research Committee bestowed Dr Samuel Taylor of the School of Pathology and Laboratory Medicine, The University of Western Australia, with the honour of a $5,000 Travel Award for his article "Preventing chemotherapy-induced myelosuppression by repurposing the FLT3 inhibitor quizartinib", published in the prestigious journal *Science Translational Medicine* (Taylor *et al.*, *Sci Transl Med.* 2017; 9: eaam8060). As well as being the main author on a publication that discusses important work that could lead to a novel therapeutic approach for combatting acute myeloid leukaemia (AML), Dr Taylor wrote several accompanying editorials to provide additional perspectives on the results being presented in his article.

Ozren Bogdanovic (Row 2, 6th from the left)

Rigby Research Prize

Thanks to a generous donation from the Rigby family, an additional Prize entitled the Rigby Research Prize, providing a travel allowance of $5,000, was awarded.

In 2017, the Rigby Research Prize was awarded to Dr Edward Litton, to commence in 2018.

	2017 Recipient	Winning Publication	Journal
	Dr Tara Richman Harry Perkins Institute of Medical Research	Loss of the RNA-binding protein TACO1 causes late-onset mitochondrial dysfunction in mice	Nature Communications

	2018 Recipient	Winning Publication	Journal
	Dr Edward Litton Fiona Stanley Hospital and the School of Medicine and Pharmacology, The University of Western Australia	Intravenous iron or placebo for anaemia in intensive care: the IRONMAN multicentre randomized blinded trial: A randomized trial of IV iron in critical illness	Intensive Care Medicine

2018 RIGBY RESEARCH PRIZE

Dr Edward Litton

The Research Committee was unanimous in awarding the 2018 Rigby Research Prize to Dr Edward Litton for his article entitled “Intravenous iron or placebo for anaemia in intensive care: the IRONMAN multicentre randomized blinded trial: A randomized trial of IV iron in critical illness”. As a collaborative, multicentre-based paper involving multiple authors, including IRONMAN investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group, this article was published in the well-respected journal *Intensive Care Medicine* (Litton E *et al.*, *Intensive Care Med.* 2016; 42: 1715-1722). This study was the first to show the biological activity of intravenous iron in increasing the red blood cell count and reducing the requirement for red blood cell transfusion in critically ill patients with anaemia admitted to Intensive Care Units (ICUs). This is highly significant as more than 10,000 patients a year are treated in ICUs in WA alone, where they consume approximately 20% of the entire supply of red blood cells produced by the Australian Red Cross. Dr Litton is based at the Intensive Care Unit at Fiona Stanley Hospital and the School of Medicine and Pharmacology, The University of Western Australia, and was awarded a $5,000 Travel Award.

Strachan Memorial Prize

The Strachan Memorial Prize was established to honour the late Mary Strachan who bequeathed a sum of money to the Raine Medical Research Foundation for the purpose of funding medical research. The Prize is awarded to a Western Australian early-career clinician or clinical scientist for the most outstanding publication that may translate medical science into better health outcomes. The Prize consists of a travel allowance to the value of $5,000 and a medallion.

In 2017, there were two Prizes ongoing, including one from 2015 that was extended to accommodate travel plans. There was no Strachan Memorial Prize awarded in 2017 for commencement in 2018.

	2015 Recipient	Winning Publication	Journal
	Dr Tobias Strunk Centre for Neonatal Research and Education, The University of Western Australia	Infection-induced inflammation and cerebral injury in preterm infants	Lancet Infectious Diseases

	2017 Recipient	Winning Publication	Journal
	Dr Ashleigh Lin Centre for Child Health Research, Telethon Kids Institute	Outcomes of non-transitioned cases in a sample at ultra-high risk for psychosis: a medium to long-term follow-up study	American Journal of Psychiatry

2015 STRACHAN MEMORIAL PRIZE

Dr Tobias Strunk

In 2015, the winner of the Strachan Memorial Prize was Dr Tobias Strunk of the Centre for Neonatal Research and Education at The University of Western Australia. The Award was presented for his important article "Infection-induced inflammation and cerebral injury in preterm infants", which was published in the prestigious journal *Lancet Infectious Diseases* (Strunk *et al.*, *Lancet Infect Dis*, 2014; 14: 751-762).

The Strachan Memorial Prize allowed Dr Strunk to attend the largest and most prestigious annual paediatric conference, the *Pediatric Academic Societies (PAS)* meeting, which was held in San Francisco, USA, in 2017. As well as presenting data from a pilot open-label clinical trial directly related to the award-winning publication, Dr Strunk was able to meet with many North American and other international collaborators.

Back in Australia, the published article served as a critical backbone for a successful NHMRC project grant application, where the research team was awarded almost $3M to conduct a large international clinical trial entitled "*Can pentoxifylline improve long-term outcomes in preterm infants with late-onset sepsis or necrotizing enterocolitis? A pragmatic, randomised, controlled trial*". Dr Strunk is very grateful for the Strachan Memorial Prize, as it allowed him to meet with many key players and discuss this project in detail. Collectively, this facilitated the targeted recruitment of a total of 900 early preterm infants with late-onset sepsis and/or necrotising enterocolitis.

Prior to the large international clinical trial, the investigators conducted a pilot open-label study at King Edward Memorial Hospital to characterise the pharmacokinetics of pentoxifylline in extremely preterm infants. The results of this study were presented at a meeting hosted by PAS under the title *"Pharmacokinetics of intravenous pentoxifylline in preterm infants".* This presentation was very well received and initiated many fruitful discussions with collaborators from Canada, Australia, New Zealand, the UK and Ireland.

2017 STRACHAN MEMORIAL PRIZE

Dr Ashleigh Lin

The Strachan Memorial Prize for 2017 was awarded to Dr Ashleigh Lin at the Centre for Child Health Research, Telethon Kids Institute, for her exceptional publication in the *American Journal of Psychiatry* entitled "Outcomes of non-transitioned cases in a sample at ultra-high risk for psychosis: a medium to long-term follow-up study" (Lin *et al.*, *Am J Psychiatry*, 2015; 172: 249–258).

This Prize enabled Dr Lin to attend two national conferences and one workshop. In 2017, she attended the biennial meeting of the *Australian and New Zealand Professional Association of Transgender Health (ANZPATH)* to present her findings from *Trans Pathways* ("Trans Pathway: the mental health and care pathways of trans young people in Australia"), the largest study of the mental health and care pathways of transgender young people ever conducted in Australia. During her time on the east coast, specifically Melbourne, Dr Lin focussed on meeting with collaborators of three ongoing projects: (1) YoDA-F, a trial of fish oil for treating young people with depression; (ii) Altitudes East-West, an online platform for supporting carers of people with first episode psychosis; and (iii) COAST, a study of the overlap between psychosis and autism. Dr Lin was also invited to present her *Trans Pathways* findings at Orygen (The National Centre for Excellence in Youth Mental Health), as well as meet politicians and advocacy groups to translate the findings of the study into policy.

Subsequently, Dr Lin was invited to attend the *Australian Early Psychosis Research Network (AEPRN)* half-day meeting, where she presented on the status of early psychosis research in WA, as well as discussing potential collaborations with early psychosis networks around Australia.

Towards the end of 2017, Dr Lin attended the *Society for Mental Health Research (SMHR) Annual Meeting* in Canberra to present a talk entitled "Poorer developmental functioning in early childhood is associated with auditory hallucinatory experiences at ages 13 and 16" on psychotic experiences and early development from the Raine Study sample. While in Canberra, she took the opportunity to advocate for policy change in transgender mental health by meeting with various federal politicians, ACT government representatives and transgender advocacy groups.

In 2018, Dr Lin will be presenting an update of her work on "Translating Trans Pathways" at the Telethon Kids Institute Retreat.

Publications

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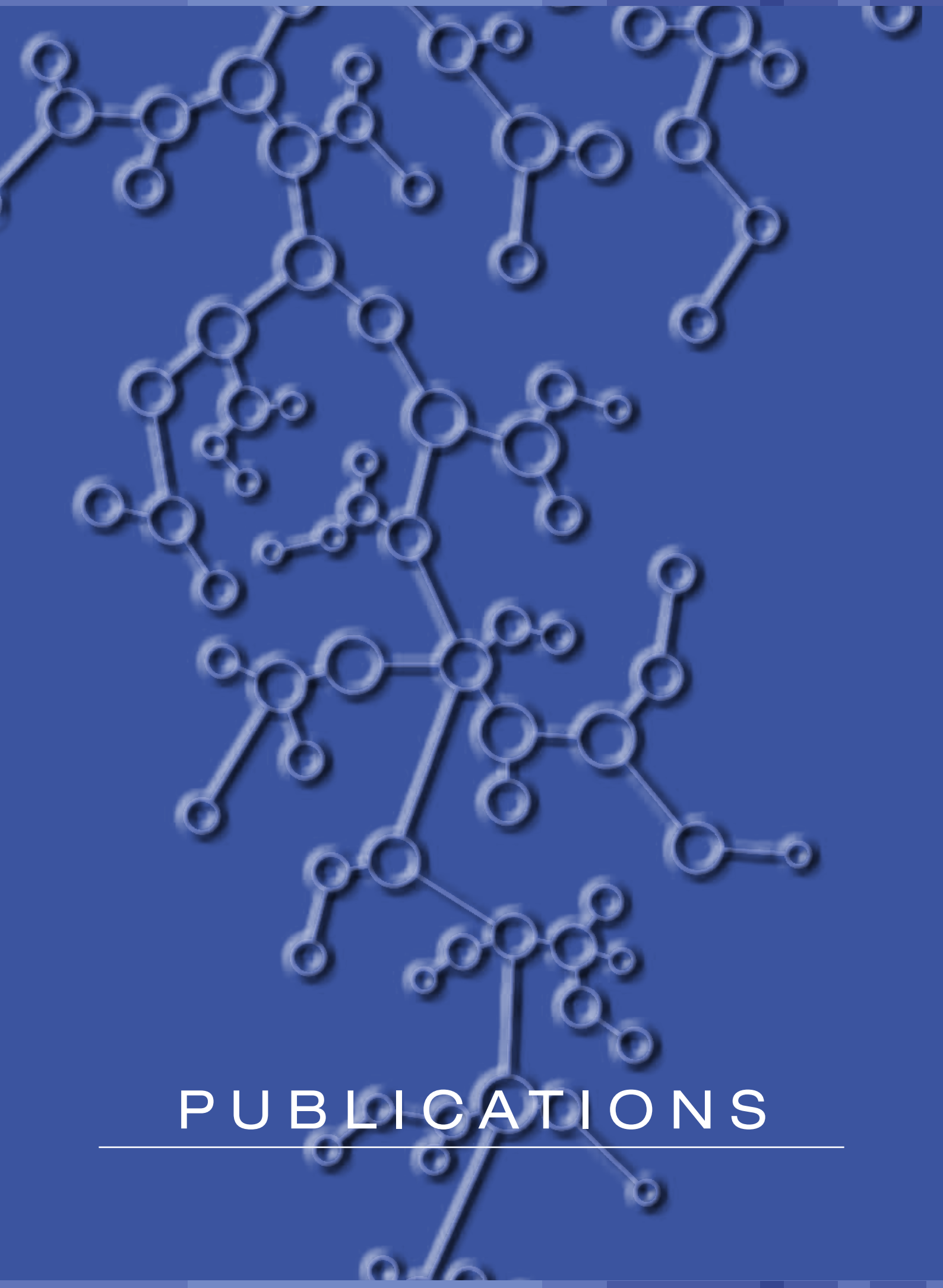

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73. Calisa V, Craig J, Howard K, Howell M, Alexander S, Chadban S, Clayton P, **Lim WH**, Kanellis J, Wyburn K, Johnson D, McDonald SP, Opdam H, Yang J, Chapman JR, Wong G. Survival and quality of life impact of a risk-based allocation algorithm for deceased donor kidney transplantation. *Transplantation.* 2018; In Press.

74. See E, Hawley C, Cho Y, Toussaint N, Agar J, Pascoe E, **Lim WH**, Francis R, Collins M, Johnson D. A comparison of graft and patient outcomes following kidney transplantation in extended hour and conventional haemodialysis patients. *Nephrology.* 2018; In Press.

75. **Lim WH**, Johnson D, Teixeira-Pinto A, Wong G. Association between duration of delayed graft function, acute rejection and allograft outcome after deceased donor kidney transplantation. *Transplantation.* 2018; In Press.

76. **Lim WH**, Wong G, McDonald SP, Chakera A, Luxton G, Isbel NM, Pilmore HL, Barbour T, Hughes P, Chadban SJ. Long-term outcomes of kidney transplant recipients with end-stage kidney disease attributed to presumed/advanced glomerulonephritis or unknown cause. *Scientific Reports.* 2018; In Press.

77. Blekkenhorst LC, Bondonno CP, Lewis JR, Woodman RJ, Devine A, Bondonno NP, **Lim WH**, Zhu K, Beilin LJ, Thompson PL, Prince RL, Hodgson JM. Cruciferous and total vegetable intakes are inversely associated with subclinical atherosclerosis in older adult women. *Journal of American Heart Association.* 2018; In Press.

78. Sharma A, Lewis JR, **Lim WH**, Palmer S, Strippoli G, Chapman JR, Alexander SI, Craig JC, Wong G. Graft and recipient outcomes associated with the development of de novo donor specific anti-human leukocyte antigen antibodies following kidney transplantation: a systematic review. *Nephrology Dialysis Transplantation.* 2018; In Press.

79. Lewis JR, Schousboe JT, **Lim WH**, Wong G, Wilson K, Zhu K, Thompson PL, Kiel DP, Prince RL. Long-term atherosclerotic vascular disease risk and prognosis in elderly women with abdominal aortic calcification on lateral spine images captured during bone density testing: A prospective study. *Journal of Bone and Mineral Research*. 2018; In Press.

Healy Research Collaboration Awards

1. Weizman OE, Adams NM, **Schuster IS**, Krishna C, Pritykin Y, Lau C, *et al*. ILC1 confer early host protection at initial sites of viral infection. *Cell.* 2017; 171: 795-808.

2. Sheppard S, **Schuster IS**, Andoniou CE, Cocita C, Adejumo T, Kung SKP, Sun J, Degli-Esposti MA, Guerra N. The murine natural cytotoxic receptor NKp46/NCR1 controls TRAIL protein expression in NK cells and ILC1. *Cell Reports*. 2018; In Press.

Cockell Research Collaboration Awards

1. Clément O, Hemming IA, Gladwyn-Ng IE, Qu Z, Li SS, Piper M, **Heng JI**. Rp58 and $p27^{kip1}$ coordinate cell cycle exit and neuronal migration within the embryonic mouse cerebral cortex. *Neural Development*. 2017; 12: 8.

2. Clément O, Hemming IA, Gladwyn-Ng IE, Qu Z, Li SS, Piper M, **Heng JI**. Correction to: Rp58 and $p27^{kip1}$ coordinate cell cycle exit and neuronal migration within the embryonic mouse cerebral cortex. *Neural Development*. 2018; 13: 1.

3. Harris L, Zalucki O, Clément O, Fraser J, Matuzelski E, Oishi S, Harvey TJ, Burne THJ, **Heng JI**, Gronostajski RM, Piper M. Neurogenic differentiation by hippocampal neural stem and progenitor cells is biased by NFIX expression. *Development*. 2018; 145: dev155689.

4. Stafford A, **Wood L**. Tackling health disparities for people who are homeless? Start with social determinants. *International Journal of Environmental Research and Public Health*. 2017; 14: 1535.

5. **Wood L**, Vallesi S, Flatau P. Harnessing the potential of linked administrative data for homelessness research. *Parity*. 2017; 30: 43.

Strachan Memorial Prize

1. **Lin A**. Working towards better understanding of neuropsychology in the ultra-high risk for psychosis group. *L'Encéphale*. 2017; 43: 281-282.

2. Berger G, Bartholomeusz C, Wood SJ, Ang A, Phillips LJ, Proffitt T, Brewer WJ, Smith D, Nelson B, **Lin A**, Borgwardt S, Velakoulis D, Yung AR, McGorry P, Pantelis C. Ventricular volumes in ultra high-risk for psychosis, first episode psychosis and chronic schizophrenia. *Australia and New Zealand Journal of Psychiatry*. 2017; 51: 1041-1051.

3. Mahfouda S, Moore J, Siafarikas A, Zepf F*, **Lin A*** (*joint last authors). Puberty suppression in transgender children and adolescents. *The Lancet Diabetes and Endocrinology*. 2017; 5: 816-826.

4. Armando M, **Lin A**, Pontillo M, Mazzone L, Vicari S. Prevalence and treatment of psychiatric disorders other than psychosis in children and adolescents with 22q11DS: examining associations with social and role functioning. *Psychiatry Research*. 2017; 254: 238-243.

5. Hancock KJ, Brennan-Jones CG, Vithiatharan R, Payne D, Runions K, **Lin A**, Eikelboom RH. Hearing problems and mental health disorders among 4–17 year olds: results from a nationally representative study. *Hearing, Balance and Communication*. 2017; 15: 145-155.

6. Ribolsi M*, **Lin A***, Wardenaar KJ, Pontillo M, Mazzone L, Vicari S, Armando M. (*joint first authors). Clinical presentation of Attenuated Psychosis Syndrome in children and adolescents: is there an age effect? *Psychiatry Research*. 2017; 252: 169-174.

7. Mechelli A, **Lin A**, Wood S, McGorry P, Amminger GP, Tognin S, McGuire P, Nelson B, Yung AR. Using clinical information to make individualized prognostic predictions in people at ultra-high risk for psychosis. *Schizophrenia Research*. 2017; 184: 32-38.

8. Cotter J, **Lin A**, Drake RJ, Thompson A, Nelson B, McGorry P, Wood SJ, Yung AR. Long-term employment among patients at ultra-high risk for psychosis. *Schizophrenia Research*. 2017; 184: 26-31.

9. Whitehouse AJO, Cooper MN, Beddington K, Alvares GA, **Lin A**, Wray J, Glasson E. Evidence of a reduction over time in the behavioral severity of community-based diagnoses of Autistic Disorder. *Autism Research*. 2017; 10: 179-187.

10. Cooper MN, **Lin A**, Alvares GA, de Klerk NH, Jones TW, Davis EA. Psychiatric disorders during early adulthood in those with childhood onset type 1 diabetes: rates and clinical risk factors over 20 years of follow-up. *Pediatric Diabetes*. 2017; 18: 599-606.

11. McHugh MJ, McGorry PD, Yuen HP, Yung AR, **Lin A**, Wood SJ, Hartman J, Nelson B. (2017). Cannabis-induced attenuated psychotic symptoms: Implications for prognosis in young people at ultra-high risk of psychosis. *Psychological Medicine*. 2017; 47: 616-626.

12. Reniers RLEP, **Lin A**, Yung AR, Koutsouleris N, Nelson B, Cropley V, Velakoulis D, McGorry PD, Pantelis C, Wood SJ. Neuroanatomical predictors of functional outcome in individuals at ultra-high risk for psychosis. *Schizophrenia Bulletin*. 2017; 43: 449-458.

13. **Lin A**, Di Prinzio P, Young D, Jacoby P, Whitehouse A, Waters F, *et al*. Academic performance in children of mothers with schizophrenia and other severe mental illness, and risk for subsequent development of psychosis: A population-based study. *Schizophrenia Bulletin*. 2017; 43: 205-213.

14. McHugh M, McGorry P, Yuen HP, Hickie I, Thompson A, De Haan L, Mossaheb N, Smesny S, **Lin A**, Markulev C, Schlögelhofer M, Wood SJ, Nieman D, Hartmann J, Nordetoft M, Schaefer M, Amminger GP, Yung AR, Nelson B. Defining trait and state risk for psychosis: Evidence to maintain the status quo. *Schizophrenia Research*. 2018; In Press.

15. Upthegrove R, Abu-Akel A, Chisholm K, **Lin A**, Zahid S, Pelton M, Apperly I, Hansen P, Wood SJ. Autism and Schizophrenia: clinical implications for depression and suicide. *Schizophrenia Research*. 2018; In Press.

16. Branch Smith C, Shaw T, **Lin A**, Runions K, Payne D, Hugo H, Cross D. Bullying and mental health amongst Australian children and young people with cystic fibrosis. *American Journal of Orthopsychiatry*. 2018; In Press.

17. Ratheesh A, Cotton SM, Davey C, **Lin A**, Wood S, McGorry PD, Yung A, Berk M, Nelson B. Pre-onset risk characteristics for mania among young people at clinical high risk for psychosis. Risk characteristics prior to onset of mania in a 5 to 13-year longitudinal study. *Schizophrenia Research*. 2018; In Press.

The Raine Study

2017 ACTIVITY SUMMARY REPORT FOR THE RAINE MEDICAL RESEARCH FOUNDATION

The Western Australian Pregnancy Cohort (Raine) Study

Professor Peter Eastwood (Raine Cohort Director)
Professor Leon Straker (Raine Cohort Associate Director)
Dr Manon Dontje (Raine Study Scientific Officer)
March 2018

HIGHLIGHTS OF 2017

Established in 1989 with support from the Raine Medical Research Foundation, the Raine Study is one of the largest, most successful prospective cohorts of pregnancy, childhood, adolescence and now adulthood to be carried out anywhere in the world. The Raine Study is now a multi-generational life-course study with participation of the original parents (Generation 1), along with their young adult children (Generation 2) and the children of the original children (Generation 3). The focus for 2017 was to update, revise and modernise the human and technical systems of the Raine Study, to create the basis for sustainable growth into the future.

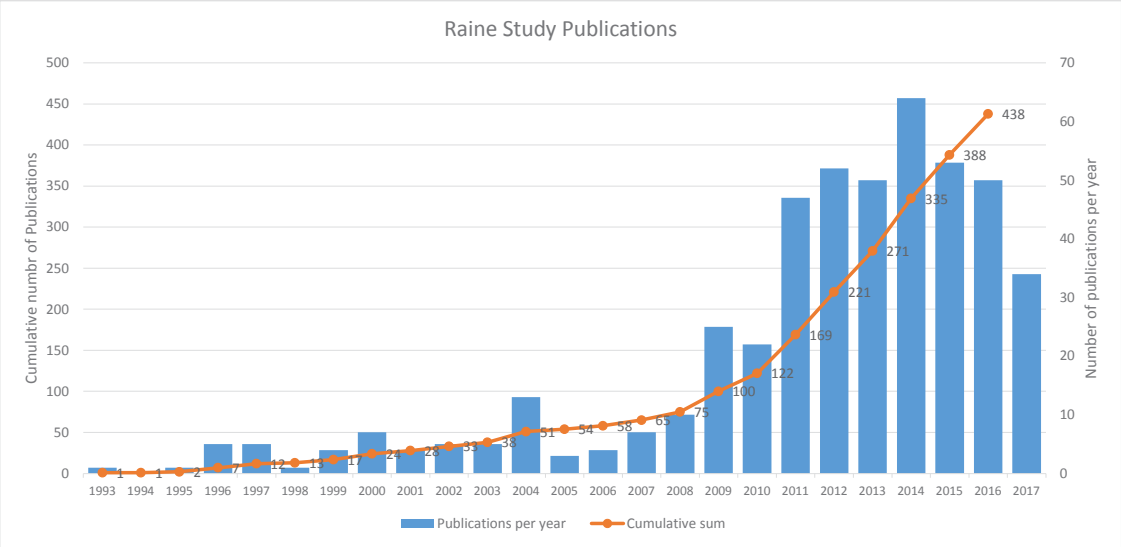
The highlights for the Raine Study in 2017 were:

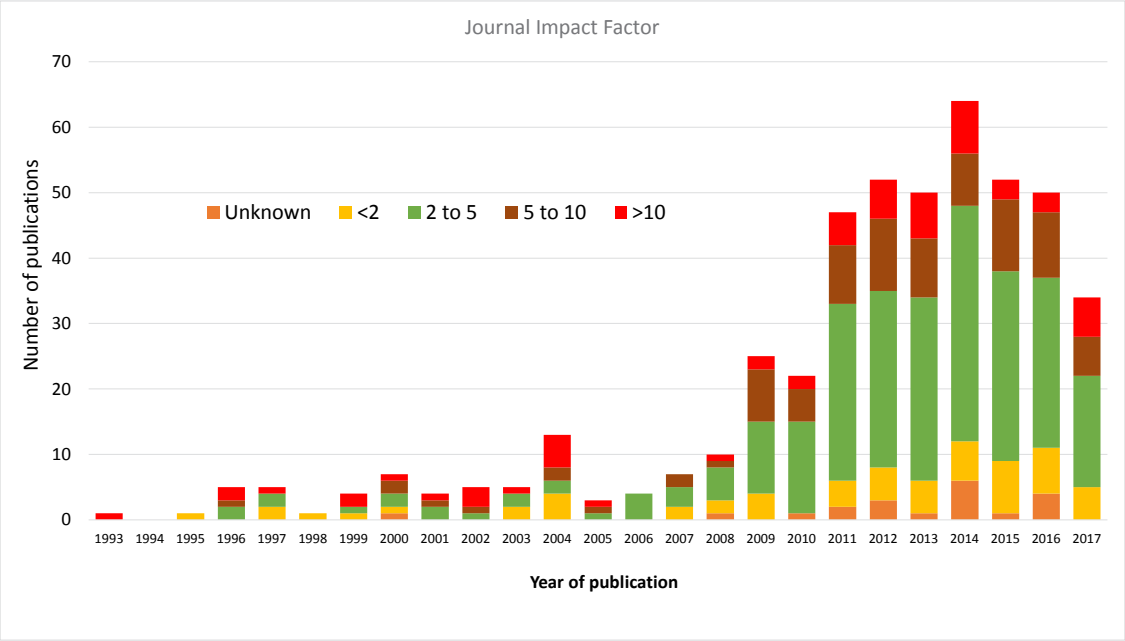
- Establishment of the Raine Study as a formal partnership between all the universities in Western Australia (University of Western Australia, Curtin University, Edith Cowan University, Murdoch University and University of Notre Dame) along with the Women and Infants Research Foundation and the Telethon Kids Institute. The Unincorporated Joint Venture structure provides strong governance and ownership of the Raine Study, a development that was supported by the Raine Medical Research Foundation.
- Implementation of a new organisational structure with clearer operational and scientific roles for staff, portfolios and committees, including explicit terms of reference and position descriptions.
- Appointment of new staff into senior leadership roles of Operations Manager, Communications Manager, Scientific Officer and Data Officers.
- Creation of a new Special Interest Group structure and appointment of early/mid-career and senior/mentor researchers as leaders for each group to provide capacity building opportunities and encourage maximisation of data resource use.
- Development of a new project management system to ensure more efficient management of Raine Study research and enable continued growth in activity (ROSS – Raine Online Submission System).
- Piloting of a secure analysis system that will enable greater data security (SHAPE – Secure Health data Analysis and Processing Environment).
- Creation of a strong participant involvement in all aspects of the new organisational structure including a specific participant committee, and participant representatives on the other substantial committees and the Unincorporated Joint Venture Board.
- Continuation of active data cleaning for Generation 1, with new data collection for Generation 2 on adiposity and economic areas, as well as new data collection for Generation 3 on broad development.

The following pages provide snapshots of publication numbers and impact, grant success, an Annual Scientific Meeting overview and new directions for 2018.

Publications

In 2017, 34 papers were published. The total number of publications by the end of 2017 was 472.





Grant applications 2016 (for 2017)

Thirteen grant applications totalling $11.4 million were prepared and submitted in 2016 for research projects to commence in 2017.

Three grant applications were successful:

- NHMRC APP1126494: D Green, L Beilin, L Straker, P Eastwood, T Mori, P Ainslie. Developmental origins of adult cardiovascular disease: Vascular health in the Raine cohort. 2017-2020; $1,087,427.
- NHMRC APP1121979: D Mackey, A Hewitt, S MacGregor, C Hammond. Young adult myopia: genetic and environmental associations. 2017-2020; $809,270.
- NHMRC CRE1116360. D Mackey, J Craig, A Hewitt, K Burdon, R Jamieson, J Grigg, S Macgregor, F Chen, M Otlowski, D Schofield. NHMRC Centres of Research Excellence (CRE) - From discovery to therapy in genetic eye diseases. $2,498,231.5. Please note that the Raine Study is part of this CRE.

Grant applications 2017 (for 2018)

Thirteen grant applications totalling $12.44 million were prepared and submitted in 2017 for research projects to commence in 2018, of which four were successful totalling $3.62 million:

- NHMRC APP1134894. K Steinbeck, R Skinner, L Sanci, D Schofield, F Brooks, A Dawson, R Ivers, L Perry, B Liu, P Collin, M Kang, A Third, J Mooney-Somers, L Straker, S Gibson, P Hazell, L Baur, S Eades, S Sawyer. A Centre of Research Excellence in Adolescent Health: Making health services work for adolescents in a digital age. 2018-2022; $2,496,294.50.
- Cancer Australia, NHMRC APP1147677. J Stone, C Saunders, D Sampson, M Hickey, L Lilge, G Cadby, J Shepherd, M Giorgi, M Cook. Measuring breast density in younger women to inform primary prevention and early detection of breast cancer. 2018-2020; $592,636.00.
- NHMRC APP1142858. RC Huang, R Foong, G Hall, A Lin. LIFECYCLE - Early life stressors and lifecycle health. 2017-2021; $453,810.60.
- Department of Health WA. A Smith. Lumbar pathology – irrelevant finding or treatment target for low back pain? 2018-2019; $75,000.00.

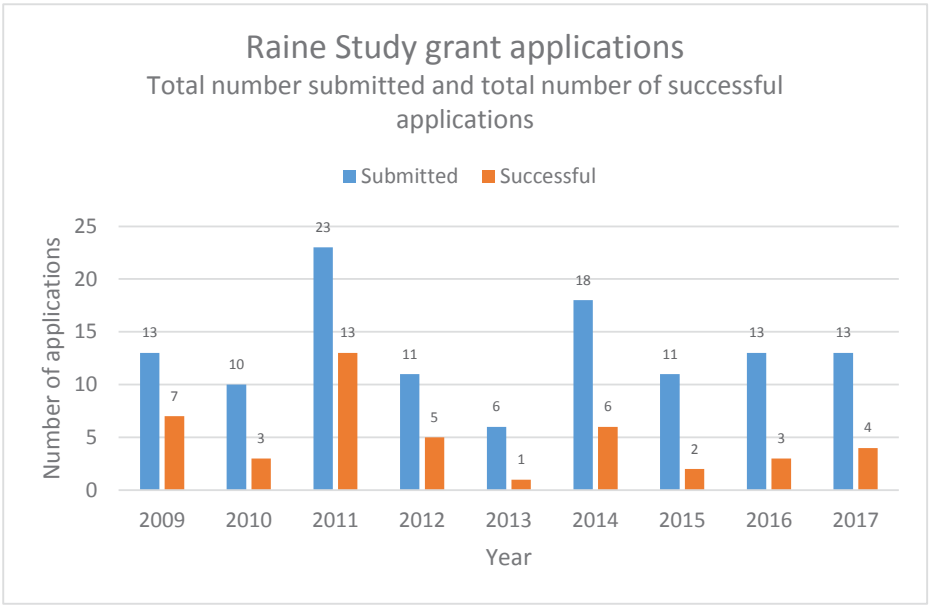


Figure 1 Raine Study grant applications. Total number submitted and total number of successful applications

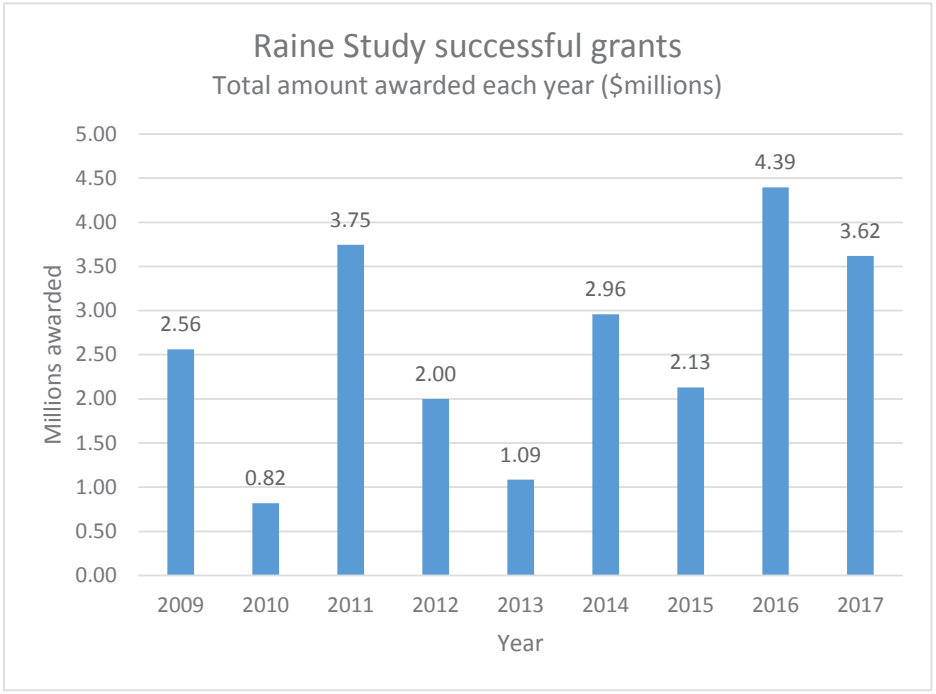


Figure 2 Raine Study successful grants. Total amount awarded each year ($millions)

Raine Study Annual Scientific Meeting

A very successful 10th Raine Study Annual Scientific Meeting was held on Friday 20 October 2017, at the University Club UWA. The meeting was formally opened by Her Excellency the Honourable Kerry Sanderson AC, Governor of Western Australia and patron of the Raine Study.

Four invited speakers did an excellent job presenting their research showing the multigenerational aspects of the Raine Study, followed by a live interview with a Raine Study family by Anne McKenzie of the Consumer and Community Health Research Network. Eleven more presentations were delivered over the course of the day that covered a wide variety of research areas. The Raine Medical Research Foundation Prizes for the two best presentations by early career researchers were presented by the Raine Study Director Professor Peter Eastwood to Anupama Bharadwaj for her talk on work design, personality and rationalising unethical behaviour, and Robert Waller for his talk on musculoskeletal pain and pressure and cold pain sensitivity.

Figure *3* Her Excellency the Governor, Professor Eastwood, and Professor Straker with Anne McKenzie and the Lim family.

Figure 4 Professor Peter Eastwood and Anupama Bharadwaj

Figure 5 Professor Peter Eastwood and Robert Waller

Activities planned for 2018

2018 will be the busiest year yet for data collection in the Raine Study, with the continued collection of Generation 3 and Generation 2 data, along with the start of four new Generation 2 data collections. We will also commence Generation 1 data collection and, for the first time, a Generation 0 (the grandparents) data collection will begin. In addition, the developmental focus for 2018 will be on continued capacity development, increasing community awareness and the exploration of sustainable funding opportunities.

In terms of creating system capacity, activities will include:

- Strengthening the Unincorporated Joint Venture;
- Strengthening new staff and committees;
- Developing Special Interest Group leaders to build active researcher capacity for projects and student supervision;
- Developing a strong positive research culture in researchers with a new involvement policy;
- Strengthen consumer engagement throughout all Raine Study activities;
- Shifting data to a new relational data base structure with a high level of quality control;
- Collaborative development of a five year strategic and implementation plan.

In terms of increasing community awareness, activities will include:

- Establishing a Translation Committee;
- Working with Unincorporated Joint Venture partners to increase traditional and new media coverage of the Raine Study.

In terms of exploration of sustainable funding opportunities, activities will include:

- Working with Unincorporated Joint Venture partners to develop funding opportunities.

Appendix 1. Publication list 2017

1. Armstrong RS, Scott JG, Whitehouse AJO, Copland DA, McMahon K L, Arnott W. Late talkers and later language outcomes: Predicting the different language trajectories. *International Journal of Speech Language Pathology*. 2017; 19: 237-250.

2. Armstrong RW, Whitehouse AJO, Scott JG, Copland DA, McMahon KL, Fleming S, Arnott WA. Relationship between early language skills and adult autistic-like traits: evidence from a longitudinal population-based study. *Journal of Autism and Developmental Disorders*. 2017; 47: 1478-1489.

3. Ayonrinde OTO, Oddy WH, Adams LA, Mori TA, Beilin LJ, de Klerk N, Olynyk JK. Infant nutrition and maternal obesity influence the risk of non-alcoholic fatty liver disease in adolescents. *Journal of Hepatology*. 2017. 67: 568-576.

4. Beales D, Kyaw-Myint S, Smith A, O'Sullivan P, Pransky G, Linton S, Job J, Straker L. Work productivity loss in young workers is substantial and is associated with spinal pain and mental ill-health conditions. *Journal of Occupational and Environmental Medicine*. 2017; 59: 237-245.

5. Bhat SK, Beilin LJ, Robinson M, Burrows S, Mori TA. Relationships between depression and anxiety symptoms scores and blood pressure in young adults. *Journal of Hypertension*. 2017; 35: 1983-1991.

6. Brennan-Jones CGE, Eikelboom RH, Jacques A, Swanepoel W, Atlas MD, Whitehouse AJ, Jamieson SE, Oddy WH. Protective benefit of predominant breastfeeding against otitis media may be limited to early childhood: results from a prospective birth cohort study. *Clinical Otolaryngology*. 2017; 42: 29-37.

7. Coenen PG, Gilson N, Healy GN, Dunstan DW, Straker LM. A qualitative review of existing national and international occupational safety and health policies relating to occupational sedentary behaviour. *Applied Ergonomics*. 2017; 60: 320-333.

8. Coenen PS, Smith A, Paananen M, Peter O'Sullivan P, Beales D, Straker L. Trajectories of low-back pain from adolescence to young adulthood. *Arthritis Care and Research*. 2017; 69: 403-412.

9. Foster ST, Trapp G, Hooper P, Oddy WH, Wood L, Knuiman M. Liquor landscapes: Does access to alcohol outlets influence alcohol consumption in young adults? *Health and Place*. 2017; 45: 17-23.

10. Goodwin RDR, Robinson M, Sly PD, Holt PG. Childhood atopy and mental health: a prospective, longitudinal investigation. *Psychological Medicine*. 2017; 47: 317-325.

11. Grace TO, Oddy W, Bulsara M, Hands B. Breastfeeding and motor development: A longitudinal cohort study. *Human Movement Science*. 2017; 51: 9-16.

12. Herbison CEA, Allen K, Robinson M, Newnham J, Pennell C. The impact of life stress on adult depression and anxiety is dependent on gender and timing of exposure. *Development and Psychopathology*. 2017; 29: 1443-1454.

13. Hinney AK, Kesselmeier M, Jall S, Volckmar AL, Focker M, Antel J, GCAN, WTCCC; Heid IM, Winkler TW; GIANT, SFA Grant, EGG, Guo Y, Bergen AW, Kaye W, Berrettini W, Hakonarson H; Price Foundation Collaborative Group, Children's Hospital of Philadelphia/Price Foundation, Herpertz-Dahlmann B, de Zwaan M, Herzog W, Ehrlich S, Zipfel S, Egberts KM, Adan R, Brandys M, van Elburg A, Boraska Perica V, Franklin CS, Tschöp MH, Zeggini E, Bulik CM, Collier D, Scherag A, Müller TD, Hebebrand J. Evidence for three genetic loci involved in both anorexia nervosa risk and variation of body mass index. *Molecular Psychiatry*. 2017; 22: 321-322.

14. Ing CH, Hegarty MK, Perkins JW, Whitehouse AJO, DiMaggio CJ, Sun M, Andrews H, Li G, Sun LS, von Ungern-Sternberg BS. Duration of general anaesthetic exposure in early childhood and long-term language and cognitive ability. *British Journal of Anaesthesia*. 2017; 119: 532-540.

15. Ing C, Wall MM, DiMaggio CJ, Whitehouse AJO, Hegarty MK, Sun M, von Ungern-Sternberg BS, Li G, Sun LS. Latent class analysis of neurodevelopmental deficit after exposure to anesthesia in early childhood. *Journal of Neurosurgical Anesthesiology*. 2017; 29: 264-273.

16. Kreiner E, Waage J, Standl M, Brix S, Pers TH, Couto Alves A, Warrington NM, Tiesler CMT, Fuertes E, Franke L, Hirschhorn JN, James A, Simpson A, Tung JY, Koppelman GH, Postma DS, Pennell CE, Jarvelin MR, Custovic A, Timpson N, Ferreira MA, Strachan DP, Henderson J, Hinds D, Bisgaard H, Bønnelykke K. Shared genetic variants suggest common pathways in allergy and autoimmune diseases. *Journal of Allergy and Clinical Immunology*. 2017; 140: 771-781.

17. Li J, Akaliyski P, Schafer J, Kendall G, Oddy WH, Stanley F, Strazdins L. Non-linear relationship between maternal work hours and child body weight: Evidence from the Western Australian Pregnancy Cohort (Raine) Study. *Social Science and Medicine*. 2017; 186: 52-60.

18. Mace A, Tuke MA, Deelen P, Kristiansson K, Mattsson H, Noukas M, Sapkota Y, Schick U, Porcu E, Rüeger S, *et al.* CNV-association meta-analysis in 191,161 European adults reveals new loci associated with anthropometric traits. *Nature Communications.* 2017; 8: 744.

19. Marouli E, Graff M, Medina-Gomez C, Lo KS, Wood AR, Kjaer TR, Fine RS, Lu Y, Schurmann C, Highland HM, *et al.* Rare and low-frequency coding variants alter human adult height. *Nature.* 2017; 542: 186-90.

20. Morris SL, O'Sullivan PB, Murray KJ, Bear N, Hands B, Smith AJ. Hypermobility and musculoskeletal pain in adolescents. *Journal of Pediatrics*. 2017; 181: 213-221.

21. Oddy WH. Breastfeeding, childhood asthma, and allergic disease. *Annals of Nutrition and Metabolism*. 2017; 70: 26-36.

22. O'Sullivan P, Smith A, Beales D, Straker L. Understanding adolescent low back pain from a multidimensional perspective: implications for management. *Journal of Orthopaedic and Sports Physical Therapy*. 2017; 47: 741-751.

23. Pena AS, Doherty DA, Atkinson HC, Hickey M, Norman RJ, Hart R. The majority of irregular menstrual cycles in adolescence are ovulatory: results of a prospective study. *Archives of Disease in Childhood*. 2018; 103: 235-239.

24. Rauschert S, Mori TA, Beilin LJ, Jacoby P, Uhl O, Koletzko B, Oddy WH, Hellmuth C. Early life factors, obesity risk, and the metabolome of young adults. *Obesity*. 2017; 25: 1549-1555.

25. Rauschert S, Uhl O, Koletzko B, Mori TA, Beilin LJ, Oddy WH, Hellmuth C. Sex differences in the association of phospholipids with components of the metabolic syndrome in young adults. *Biology of Sex Differences*. 2017; 8: 10.

26. Rzehak P, Oddy WH, Mearin ML, Grote V, Mori TA, Szajewska H, Shamir R, Koletzko S, Weber M, Beilin LJ, Huang RC, Koletzko B, WP10 working group of the Early Nutrition Project. Infant feeding and growth trajectory patterns in childhood and body composition in young adulthood. *American Journal of Clinical Nutrition*. 2017; 106: 568-580.

27. Skinner SR, Marino J, Rosenthal SL, Cannon J, Doherty DA, Hickey M. Prospective cohort study of childhood behaviour problems and adolescent sexual risk-taking: gender matters. *Sexual Health*. 2017; 14: 492-501.

28. Smith A, Beasles D, O'Sullivan P, Bear N, Straker L. Low back pain with impact at 17 years of age is predicted by early adolescent risk factors from multiple domains: analysis of the Western Australian Pregnancy Cohort (Raine) Study. *Journal of Orthopaedic and Sports Physical Therapy*. 2017; 47: 752-62.

29. Straker L, Mountain J, Jacques A, White S, Smith A, Landau L, Stanley F, Newnham J, Pennell C, Eastwood P. Cohort profile: The Western Australian pregnancy cohort (Raine) study - Generation 2. *International Journal of Epidemiology*. 2017; 46: 1384-1385.

30. Wain LV, Shrine N, Artigas MS, Erzurumluoglu AM, Noyvert B, Bossini-Castillo L, Obeidat M, Henry AP, Portelli MA, Hall RJ, *et al.* Genome-wide association analyses for lung function and chronic obstructive pulmonary disease identify new loci and potential druggable targets. *Nature Genetics*. 2017; 49: 416-425.

31. White EC, de Klerk N, Hantos Z, Priston M, Hollams EM, James A, Sly PD, Holt PG, Hall GL. Mannitol challenge testing for asthma in a community cohort of young adults. *Respirology*. 2017; 22: 678-683.

32. White SW, Eastwood PR, Straker LM, Adams LA, Newnham JP, Lye SJ, Pennell CE. The Raine study had no evidence of significant perinatal selection bias after two decades of follow up: a longitudinal pregnancy cohort study. *BMC Pregnancy and Childbirth*. 2017; 17: 207.

33. Zhu K, Allen K, Mountain J, Lye S, Pennell C, Walsh JP. Depressive symptoms, body composition and bone mass in young adults: a prospective cohort study. *International Journal of Obesity*. 2017; 41: 576-581.

34. Zhu K, Oddy WH, Holt P, Ping-Delfos WCS, Mountain J, Lye S, Pennell C, Hart PH, Walsh JP. Tracking of vitamin D status from childhood to early adulthood and its association with peak bone mass. *American Journal of Clinical Nutrition.* 2017; 106: 276-283.

AWARDS CEREMONY

Raine Annual Awards Ceremony

Dr Haibo Jiang, Professor Wally Langdon, Professor Jack Xu

Dr Rachel Foong, Dr Melissa O'Donnell, Dr Jonathan Chee, Dr Annette Reagan

Dr Koya Ayonrinde, Dr Andrew Martin, Dr Nathan Harvey

Dr Melanie McCoy, Dr Paul Cohen, Dr Yu Yu

BrightSpark Foundation: Mr Geoff Anderson, Professor Liz Davis, Mr Andrew Thompson, Mr Tony Barber, Mr Graham Dowland

2018 Grants, Fellowships, Awards and Prizes recipients

Clinical Professor John Burnett, Professor Hugh Barrett

Dr Melanie McCoy, Dr Sally Lansley

Professor Bruce Robinson, Mrs Caro Stewart, Mr Geoff Anderson

Charter Hall: Mr Tim Cash, Ms Anne Pesic, Ms Michelle Flanagan, Mr Patrick Hollingworth

Dr James Williamson, Dr Andrew Martin, Clinical Professor John Burnett

Financial Reports

Investment Performance

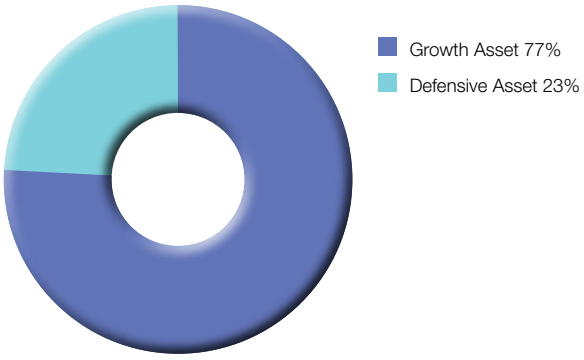
Overall The University's investment portfolio delivered a net return of +6.4% for the year (Dec 2016: +5.8%). The Long term pool (+11.3%) outperformed the budgeted return for the calendar year (+6.5%), while the Short term pool performed marginally behind the forecast return (+3.5%). The positive return for the year is primarily driven by growth from the global economy over the last quarter of the year.

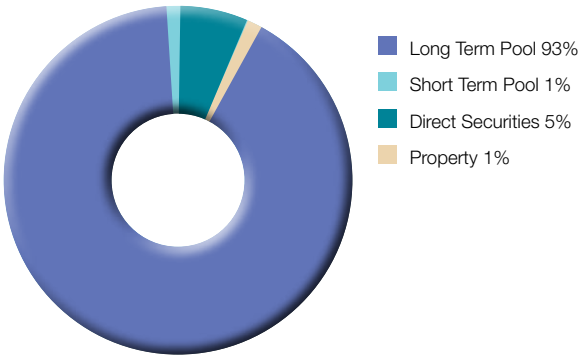
Investment Distributions

The Long Term Pool distributed 11.33% for the year and out-performed budget, largely due to positive performance driven by international equity funds. The Short Term Pool distributed 3.50% for the year which was in accordance with the original budget rate.

Investment Pool	Original Budget	Distribution Rate
LTP	5.56%	11.33%
STP	3.50%	3.50%

Raine Investment Exposure and Asset Allocations





Raine Financial Update

The total carrying value of the Foundation assets as at 31 December 2017 was $41.2M, of which 93% is invested in the Long Term Pool (LTP), 1% in the Short Term Pool (STP) and 5% in Direct Securities and 1% in Property.

In January 2017 the investment portfolio was rebalanced to 100 percent Long Term Pool and maintaining only sufficient funds in the Short term pool Raine Medical Research Operating Fund account for operating needs. The Fluctuation Capital Fund account was renamed to the 'Raine Research Committee Investment Fund'.

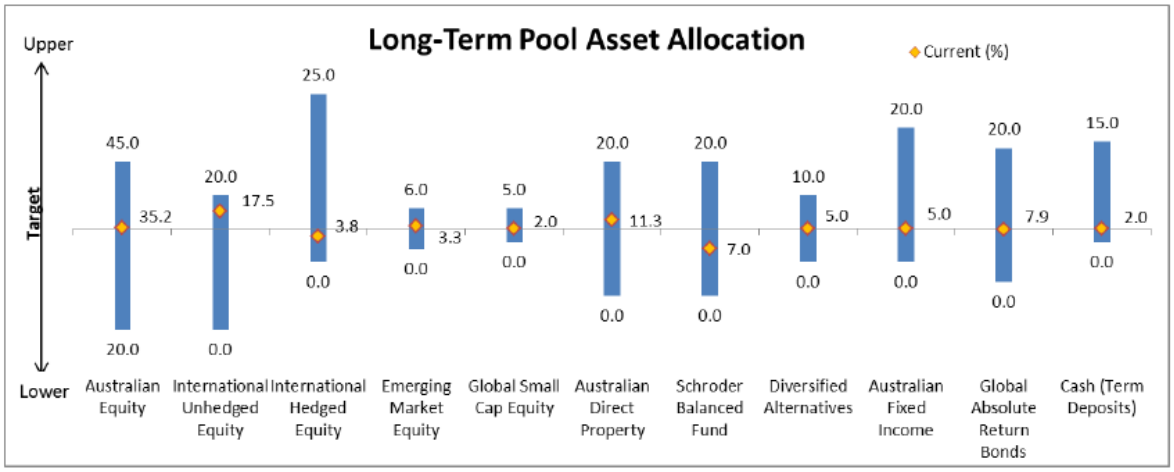
At December 2017 the Foundation transferred $1.46M from the Raine Medical Research Long term pool account to fund the annual Raine Medical Research Foundation (RMRF) operating costs. The residual balance [$297,535] at 31 December 2017 is to be considered for recapitalised to the Raine Medical Research Foundation long term pool operating account in 2018.

The Foundation at December allocated $1.52M in the RMRF Long term pool Operating account for 2018 spending. The funding is done through quarterly transfer from the RMRF Operating Fund Long term pool account.

The Foundation during the year received a $100 donation from Mrs Victoria Dodds to support research through the Raine Medical Research Foundation.

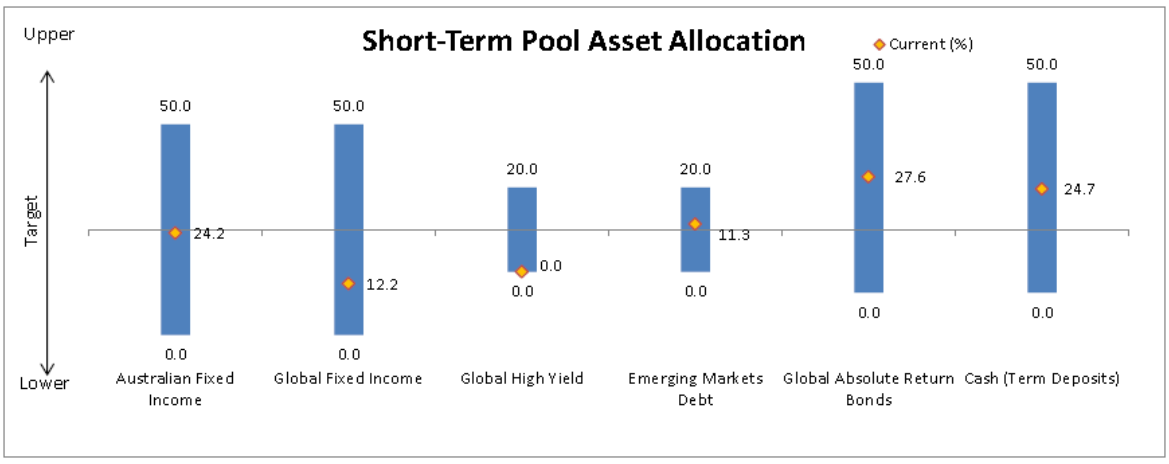
University Portfolio Asset Allocation
LONG TERM POOL (LTP) – STRATEGIC ASSET ALLOCATION

The LTP asset composition at 31 December 2017 is held within the strategic 80% growth and 20% defensive asset allocation. The primary Dynamic Asset Allocation strategy within the Long term pool is an overweight position in International Unhedged Equity with a corresponding underweight to International Hedged Equity. All the funds are invested within their permitted benchmark allocation ranges.



SHORT TERM POOL (STP) – STRATEGIC ASSET ALLOCATION BENCHMARK

The STP (comprises of 100% defensive asset) asset composition at 31 December 2017 is held in accordance to Mercer's dynamic asset allocation (DAA) positioning. The STP DAA includes an underweight position in Australian and Global Sovereign Bonds while overweight in Global Absolute Return Bonds and Cash. All funds are invested within their permissible ranges.



Raine Medical Research Foundation

Income and Expenditure for the year ended 31 December 2017

	Notes	2017 Actual $	2016 Actual $
INCOME			
Distribution from Raine Foundation			1,461,992
Transfer from Raine Medical Research Foundation Long term pool Operating Account		1,461,992	-
Other income:			
Funding retrieved from unspent grant		40,556	6,721
Management Fee (BrightSpark Raine Alliance)		25,375	25,000
General refund	1	14,205	-
Book Sale		840	-
Total Income		1,542,969	1,493,713
EXPENDITURE			
Specific Activities:			
Raine Visiting Professors		39,585	63,690
Honorariums		16,974	27,314
Raine Research Prize and Raine Study Travel Awards		2,858	11,500
Salary funding for Raine Study Scientific Directorship	2	65,000	65,000
Raine Priming Grants:			
Raine Priming Grants:			
2015 Grants		-	425,000
2016 Grants		350,535	221,000
2017 Grants		395,890	-
Other Expenses:			
Administration and Operating Expenses		49,310	68,936
Salary Expenses		325,280	275,654
TOTAL EXPENDITURE		**1,245,433**	**1,158,094**
NET OPERATING RESULT	3	**297,535**	**335,619**
Summary of Funds:			
Raine Medical Research (Long term pool) Account			
Opening Balance		3,174,889	-
Rebalancing Portfolio (Short term pool to Long term pool)	5	-	3,174,889
Long term pool Operating Funds Transferred to Short term pool Operating		(1,461,992)	-
Long term pool Interest		267,158	-
Closing Balance		1,980,055	3,174,889
Raine Medical Research Operating Fund (Short term pool) Account			
Opening Balance		-	2,839,270
Net Funds from Operating Activities		297,535	335,619
Rebalancing Portfolio (Short term pool to Long term pool)	5	-	(3,174,889)
Closing Balance		297,535	-
Raine Medical Research Operating Fund (Long term pool) Account			
Opening Balance		-	-
Investment Income Distribution	6	1,522,567	-
Closing Balance		1,522,567	-
Closing balance as at the end of the year		**3,800,157**	**3,174,889**

Notes:

1 Refund from the City of Nedlands for rates paid in the last five years.
2 Committee meeting minutes 01/05/2014 approved $65k for further five years until 2019.
3 The balance [$297,535] is to be considered for recapitalisation during 2018.
4 2017 distribution made available for future expenditure. Funds invested in long term pool transferred quarterly to the short term pool during 2018 to support operational expenditure incurred.
5 Previously invested in Short term pool.
6 Made available for future expenditure.

Raine Medical Research Foundation

Statement of Investments for the year ended 31 December 2017

	Notes	2017 Actual $	2016 Actual $
INVESTMENTS			
SHORT TERM POOL	1		
Raine Medical Research Operating Fund		297,535	-
Raine Medical Research Fund		-	3,174,889
Raine Research Committee Investment Fund		-	3,464,878
Raine Foundation Capital Account 2		-	3,877,140
Raine Medical Research Fund I&E Account 3	4	-	800,000
Clinical Research Fellowships	5	-	284,965
Strachan Bequest		-	16,900
KY Wong Memorial Prize		-	5,044
TOTAL SHORT-TERM POOL		297,535	11,623,816
LONG TERM POOL	1		
Raine Foundation Capital Fund		29,648,198	24,003,030
Raine Research Committee Investment Fund		4,748,088	-
Raine Medical Research Long term pool Account		1,980,056	-
Raine Medical Research Operating Funds		1,522,567	-
Strachan Bequest		85,508	76,806
Other Bequests		50,773	50,773
Clinical Research Fellowships		376,377	-
Strachan Bequest Income and Expenditure		18,814	-
KY Wong Memorial Prize		5,615	-
Donations		105	-
TOTAL LONG TERM POOL		38,436,100	24,130,609
TOTAL POOL INVESTMENTS		**38,733,635**	**35,754,425**
24/95 Monash Avenue (Hollywood) net carrying value		268,491	271,725
Dexus Property Securities	2	2,201,550	2,172,196
Dexus Imputation Credit (Accrual)		2,449	-
Total Other Investments		**2,472,490**	**2,443,921**
Total Investments at Carrying Value		**41,206,125**	**38,198,346**
Market Value – Other Investments			
24/95 Monash Avenue (Hollywood)	3	482,850	536,500
Dexus Property Securities	2	2,201,550	2,172,196
Dexus Imputation Credit (Accrual)		2,449	-
Total Other Investments – Market Value		**2,686,849**	**2,708,696**
Total Investments at Market Value		**41,420,485**	**38,463,121**

Notes:

1 2017 distribution rate net of fees: Long term pool at 11.33% and Short term pool at 3.50%

2 Investments and Dexus Securities are marked to market at the reporting date resulting in the carrying and market values being the same.

3 The reported market value for the property is based on the University's internal property valuation as at 31/12/2017. The decline in value is aligned with current property market pricing.

P B Healy Medical Research Bequest

Statement for year ended 31 December 2017

	Notes	2017 Actual $	2016 Actual $
Capital Fund			
Opening Balance		1,566,008	1,352,847
Long term pool Distributions	1	177,429	110,934
Rebalancing of asset to Long term pool		-	102,227
		1,743,437	1,566,008
Less:			
Senate Policy Distributions to I&E	2	-	-
Closing Balance		1,743,437	1,566,008
Income & Expenditure			
Opening Balance		104,563	239,500
Senate Policy Distributions from Capital	2	-	-
Short term pool Distributions		4,002	8,760
Unspent funds retrieved		10,413	-
Total Income		118,978	248,260
Less Transfers:			
Rebalancing of asset to Long term pool		-	102,227
Less Expenditure:			
Healy Travel Awards		19,014	18,400
Operating Expense		17,120	23,070
Closing Balance		82,844	104,563

Notes:
1 2017 distribution rates: Long term pool at 11.33%, Short term pool at 3.5%
2 2015 – Agreed with committee in meeting held on the 12th, November 2015 to suppress the 5% distribution from capital.

Raine Medical Research Foundation

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