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Financial Statement
Chair’s Address

It gives me great pleasure to present to you the Annual Report of the Raine Medical Research Foundation. 2015 was a year of increased scientific productivity as evident in some exciting results to emerge from projects in both the applied sciences and translational medicine. It was also a year when the Raine Foundation celebrated the importance of partnerships with the extension of the WA Department of Health Clinician Research Fellowship programme and the establishment of a new alliance with the BrightSpark Foundation.

Raine Priming Grants continued to be the principal focus of research activity. For more than 20 years, the Raine Foundation has been encouraging and supporting top young scientists to help build their research expertise and facilitate their transition into independent and successful Chief Investigators. Indeed, the Raine Foundation has launched the career of many of our State’s leading scientists who have made a major contribution to medical research - and the Foundation continues to maintain this excellent record. In 2015, there were 12 Raine Priming Grant projects in operation in various fields of applied research; five projects moved into their second year; five new grants were awarded in December, with two earlier projects finalising their project. The total funding allocation for these 12 grants was in excess of $1.8m.

2015 was also a year of outstanding clinical achievement as the excellent partnership between the Western Australia Department of Health and the Raine Medical Research Foundation entered Round 4 of the Clinician Research Fellowship programme. The translational studies pursued by this group of dedicated clinicians continued to deliver some ground-breaking results. An example of the significance and value of the Programme was captured by top Medical Journalist, Cathy O’Leary in The West Australian1 in her report in February 2016 on a project driven by Specialist Clinical Nurse, Dr Hugh Davies, entitled: The F.L.U.I.D. study (Forecasting Level of Ultrafiltration and Intensity of Dialysis). This project exemplifies the purpose, intent and translational achievements of the scheme, details of which can be found on page 56.

The award of a further four Clinician Research Fellowships now brings the total Fellowships in operation to 18, with funding in excess of $4.36m, as detailed on page 11.

In October, the Raine Foundation announced the establishment of a new strategic alliance with the BrightSpark Foundation in the field of child health research. As individual funding bodies, BrightSpark and Raine each has a long history of supporting medical research in WA; however, the combined new Alliance has the capacity to make a far greater difference in this important field of translational medicine. Together we will enhance leadership, strengthen and consolidate the overall funding base and offer more opportunities for child health researchers across WA. Ultimately, and most importantly, the Alliance will facilitate new discoveries and treatments in the battle against childhood illness and disease.

The Raine Visiting Professors’ Scheme, another of the Foundation’s major research commitments, continued to fill an important role for the scientific community. This Scheme is now a well-established resource for attracting top international scientists to Western Australia. Visiting scholars have made, and continue to make, a significant contribution to learning and discovery as they forge new networking partnerships, develop research collaborations, and enrich University life by their presence. The Raine Visiting Professor Lecture Series provides a forum for the wider academic community to hear and benefit from this group of top, international visitors during their time at the University. Nine distinguished scientists spent time at UWA during 2015 as detailed at page 18.

1 © WEST AUSTRALIAN NEWSPAPERS
The Raine Foundation was also pleased to consolidate its links to The Raine Study. This world-famous longitudinal study is well-known as one of the most successful prospective cohorts of pregnancy, childhood, adolescence, and now young adulthood. The remarkable achievements of The Raine Study, which now span 23 years, can be attributed to an excellent two-tiered partnership: outstanding scientific research and loyal family participants. It is through the allegiance of The Raine Study families, along with the vision of the four founding clinical professors that The Raine Study has developed into one of the most unique collections of biomedical data of human development. The Raine Foundation is proud to maintain a close association and continue its support for this outstanding longitudinal study that shares its name.

Turning to the Raine investment portfolio, I am pleased to report that, through careful long-term financial planning and the diligent efforts of a professional unit in the University Office of Investment and Treasury, the Raine Medical Research Foundation is in a sound financial position. I would like to thank the Financial Services Deputy Director, Mrs Victoria Wilmot and her team, including Ms Leona Marquand, Mr Michael Fitzgerald and Ms Rachel Wong for their excellent service throughout the year.

The success of any major organisation, however, depends largely on its management structure – and the Raine Foundation is no exception. We are very fortunate to have a group of professionals who provide leadership and guidance to the Raine Foundation in all its research endeavours and financial commitments. This group includes support from specialist clinicians and scientists who generously give their time as members of our Advisory Panels. I would like to extend my personal thanks and appreciation to all those involved in the successful management of the Raine Foundation and its research activities. I acknowledge the valuable role played by Mrs Lyn Ellis as Director of the Raine and Healy Foundations for a number of years. Lyn is a tireless worker behind the scenes and does a stellar job in promoting, managing and driving the Foundation activities and interaction with partner organisations. I would also like to take this opportunity to welcome to the Raine administrative team, Dr Amanda Cleaver. A former recipient of a Raine Priming Grant and, subsequently, a Faculty Research Development Adviser, Amanda brings with her direct research knowledge and University administrative experience that will benefit the Foundation in its operational commitments.

Finally, I wish to place on record my personal thanks to one Research Committee member – our Honorary Financial Consultant, Mr Peter Bird, who has served the Raine Foundation diligently for more than 16 years. Prior to the publication of this Report, I reluctantly accepted Peter’s resignation from the Committee. I know that I speak on behalf of all members when I say that Peter Bird’s commitment and contribution to the financial management of the Raine Foundation has been exceptional. His corporate knowledge, financial expertise and understanding of the investment market have proven invaluable. Peter leaves the Raine Foundation in a sound financial position with budget certainty that will ensure it can continue to play a major role in funding medical research in this State – and for this we remain extremely grateful.

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

The Raine Medical Research Foundation is governed by a Committee of Senate, constituted in accordance with the requirements of the Deed of Trust. The 2015 Research Committee consisted of the following members:

- **Professor Robyn Owens**  
  Deputy Vice-Chancellor (Research) Chair

- **Professor David Joyce**  
  Professor of Medicine

- **Professor Paul Norman**  
  Professor of Surgery

- **Professor Ryan Lister**  
  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 Science  
  Research Committee nominee

- **Mr Peter Bird**  
  Honorary Financial Consultant

- **Ms Lyn Ellis**  
  Director

- **Dr Amanda Cleaver**  
  Project Manager
Raine Priming Grants

Thirteen research projects were in progress in 2015 funded by the Raine Medical Research Foundation. These were represented by five, two-year grants awarded for 2014/2015 that completed their second year, together with six new two-year grants awarded for 2015/2016 that commenced in 2015. Two earlier Raine Priming Grant recipients finalised their research project in 2015.

The total value of funds allocated to the eleven projects awarded for 2014/2015 and 2015/2016 was $1.7m.

**2013 Raine Priming Grants**

Dr Senta Walton and Research Assistant Professor Caitlin Wyrwoll were each granted an extension to complete the final year of their research project in 2015.

<table>
<thead>
<tr>
<th>Chief investigator</th>
<th>Project title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Senta Walton</td>
<td>Characterisation of ( H. \text{ pylori} )-specific CD4T cell responses</td>
</tr>
<tr>
<td>Assistant Professor Caitlin Wyrwoll</td>
<td>Stress hormone excess in pregnancy impairs placental haemodynamics with novel implications for fetal cardiac function</td>
</tr>
</tbody>
</table>
### 2014 PRIMING GRANT RECIPIENTS (Second Year of award commenced in January 2015)

<table>
<thead>
<tr>
<th>Chief investigator</th>
<th>Project title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Melanie McCoy</td>
<td>Predicting response to neo-adjuvant chemo-radiotherapy in patients with rectal cancer</td>
</tr>
<tr>
<td>(The Raine Foundation/Alan Robson Fellow)</td>
<td>School of Medicine and Pharmacology, UWA</td>
</tr>
<tr>
<td><strong>Dr Kristyn Bates</strong></td>
<td><strong>Helping the brain to heal itself: controlling cell function to improve repair after injury</strong></td>
</tr>
<tr>
<td><strong>School of Animal Biology, UWA</strong></td>
<td><strong>The effects of IFN-α on T and B cell homeostasis in HIV patients on antiretroviral therapy</strong></td>
</tr>
<tr>
<td><strong>Dr Sonia Fernandez</strong></td>
<td><strong>Front to Back: Retinal Pigment Epithelium from Limbal Stem Cells</strong></td>
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<tr>
<td><strong>School of Pathology and Laboratory Medicine, UWA</strong></td>
<td><strong>The role of Bc12 S24P mutation in bone homeostasis</strong></td>
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<tr>
<td><strong>Dr Samuel McLenachan</strong></td>
<td><strong>Dr Jennifer Tickner</strong></td>
</tr>
<tr>
<td><strong>Centre for Ophthalmology and Visual Science, UWA</strong></td>
<td><strong>School of Pathology and Laboratory Medicine, UWA</strong></td>
</tr>
</tbody>
</table>
### 2015 Raine Priming Grants (First Year of award commenced in January 2015)

<table>
<thead>
<tr>
<th>Chief investigator</th>
<th>Project title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Holly Clifford</td>
<td>Environmental dust and the lung: impact in remote Aboriginal Australian communities</td>
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<tr>
<td>The Raine Foundation/Alan Robson Fellow</td>
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</tr>
<tr>
<td>Telethon Kids Institute</td>
<td></td>
</tr>
<tr>
<td>Dr Anja Stirnweiss</td>
<td>Protein signalling networks in NUT Midline Carcinoma (NMC)</td>
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<td>Dr Coral-Ann Almeida</td>
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<td>The effect of Fibroblast Growth Factor 9 on anti-tumour immunity in malignant mesothelioma</td>
</tr>
<tr>
<td>Centre for Asthma, Allergy and Respiratory, UWA</td>
<td></td>
</tr>
<tr>
<td>Harry Perkins Institute of Medical Research</td>
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</table>
### 2016 Raine Priming Grants recipients

Six new Priming Grants were awarded in December 2015 for 2016/2017 with a total funding allocation of approximately $950,000.

<table>
<thead>
<tr>
<th>Chief investigator</th>
<th>Project title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Annette Lim</td>
<td>Mechanisms that facilitate the metastatic potential in oral carcinomas</td>
</tr>
<tr>
<td>Raine/Robson Fellow</td>
<td>Medical Oncology, Sir Charles Gairdner Hospital</td>
</tr>
<tr>
<td>Dr Gemma Cadby</td>
<td>The association of sleep apnoea and long-term health outcomes in Western Australian adults</td>
</tr>
<tr>
<td>Centre for Genetic Origins of Health and Disease, UWA</td>
<td></td>
</tr>
<tr>
<td>Dr Tristan Clemons</td>
<td>Nanoparticle delivery for the treatment of scarring</td>
</tr>
<tr>
<td>School of Chemistry and Biochemistry, UWA</td>
<td></td>
</tr>
<tr>
<td>Dr Elin Gray</td>
<td>Genetic Analysis of Circulating Tumour Cells and Circulating Tumour DNA for Prognosis of Uveal Melanoma</td>
</tr>
<tr>
<td>School of Medical Sciences, Edith Cowan University</td>
<td></td>
</tr>
<tr>
<td>Dr Grand Roman Joldes</td>
<td>Towards translating the benefits of patient specific biomechanics into clinical practice</td>
</tr>
<tr>
<td>School of Mechanical and Chemical Engineering, UWA</td>
<td></td>
</tr>
<tr>
<td>Dr Alison McDonnell</td>
<td>Identifying immune biomarkers of response to chemotherapy in thoracic cancers</td>
</tr>
<tr>
<td>School of Medicine and Pharmacology, UWA</td>
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</table>
2015 marked Round 4 of the Clinician Research Fellowship programme. This outstanding initiative of the WA Department of Health was introduced in 2012 to encourage clinicians employed by WA Health in all areas of healthcare to become more involved in medical research whilst maintaining a level of clinical/healthcare duties. The Raine Medical Research Foundation readily acknowledged the value and importance of the Programme and was delighted to become a partner. Since that time, a total of 18 Clinician Research Fellowships have been awarded with funds in excess of $4.3m.

The research projects undertaken by these top clinicians cover a broad spectrum of translational medicine, ranging through from childhood illness and sickness, to chronic disease in adulthood. It is very pleasing to report that in the short time since the Programme was introduced there have been some remarkable research findings and major advances in clinical procedures with excellent outcomes for the general community. The West Australian Newspaper captured two excellent examples of the success of the Programme when it reported on the work undertaken by Dr Hugh Davies, Clinical Nurse in the Intensive Care Unit at Royal Perth Hospital, page 14; and Clinical Associate Professor Gareth Baynam, Clinical Geneticist, King Edward Memorial Hospital, page 13.

Details of the Clinician Research Fellowships currently in operation, which include two projects funded by the Nurses and Midwives Group, are provided overleaf.
## 2013 Clinician Research Fellowships (Round 1)

<table>
<thead>
<tr>
<th>Fellow</th>
<th>Project Title</th>
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</thead>
</table>
| Clinical Professor Tomas Corcoran | Project 1: REstrictive versus LiqEral Fluid therapy in major abdominal surgery (RELIEF study)  
Project 2: The influence of anaesthetic depth on patient outcome after major surgery (BALANCED study) |
| Dr André Schultz            | The airway surface liquid micro environment in children with cystic fibrosis |
| Dr Nicholas Gottardo        | Testing novel therapies using paediatric brain tumour models                  |
| Dr Nolan McDonnell          | Neuraxial magnesium and analgesia: animal and human studies                   |
### 2014 Clinician Research Fellowships (Round 2)

<table>
<thead>
<tr>
<th>Fellow</th>
<th>Project Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Associate Professor</td>
<td>1 in 12: Translational Research for Rare Diseases</td>
</tr>
<tr>
<td>Gareth Baynam</td>
<td></td>
</tr>
<tr>
<td>Dr Christopher Blyth</td>
<td>Preventing influenza morbidity and mortality in West Australian children through vaccination</td>
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<tr>
<td>Dr Aron Chakera</td>
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</table>
### Nurses and Midwifery Group

<table>
<thead>
<tr>
<th>Fellow</th>
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<tbody>
<tr>
<td>Dr Hugh Davies</td>
<td>The F.L.U.I.D. study (Forecasting Level of Ultrafiltration and Intensity of Dialysis)</td>
</tr>
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### 2015 Clinician Research Fellowships (Round 3)

<table>
<thead>
<tr>
<th>Fellow</th>
<th>Project Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Edward Fysh</td>
<td>Pleural effusions in intensive care patients: The physiological changes and clinical effects of drainage procedures</td>
</tr>
<tr>
<td>Clinical Associate Professor Kwok-ming Ho</td>
<td>Detailed assessment of risks and benefits of inferior vena cava filters on patients with complicated injuries (the da Vinci Trial)</td>
</tr>
<tr>
<td>Dr Thomas Snelling</td>
<td>Improving the West Australian Immunisation Program</td>
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### Nurses and Midwifery Group

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<td>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</td>
</tr>
</tbody>
</table>
### 2016 Clinician Research Fellowships (Round 4)

<table>
<thead>
<tr>
<th>Fellow</th>
<th>Project Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Rishi Sury Kotecha</td>
<td>Combinatorial therapeutics in high-risk infant acute lymphoblastic leukaemia</td>
</tr>
<tr>
<td>Dr Martin de Bock</td>
<td>Closed loop insulin delivery for patients with Type 1 Diabetes in free living conditions</td>
</tr>
<tr>
<td>Dr Annette Lim</td>
<td>Mechanisms that facilitate the metastatic potential of oral cancer</td>
</tr>
</tbody>
</table>
| Dr Edmond O’Loughlin | 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 |
The BrightSpark Raine Alliance

The BrightSpark Foundation has a long and distinguished history of commitment to the advancement of child health research in Western Australia, with an allocation of funds in excess of $7m.

For 40 years the BrightSpark Foundation has encouraged and supported many of the State’s brightest young scientists at an early stage of their career to help advance knowledge and find solutions to childhood illness and disease. The prestigious BrightSpark Fellowships have been the hallmark of the Foundation for many years. These Fellowships were well-known and highly sought after by young ‘rising stars’ working in the field of child health research.

The Raine Medical Research Foundation, the University’s largest private bequest for medical research has, similarly, been mindful of the importance of promoting and supporting scientific investigations into childhood illness. It has awarded numerous grants, awards, fellowships and prizes with total funds that exceed $6.5m.

It therefore became very clear in 2015 that the two largest Foundations in support of child health research in Western Australia would make perfect partners.

The BrightSpark Foundation joined forces with the Raine Medical Research Foundation in a strategic alliance in order to strengthen and advance childhood research and offer more opportunities for young scientists across Western Australia.

The BrightSpark/Raine Alliance is led by a group of top professionals who give their time willingly and generously in the interest of child health research.
The University of Western Australian was pleased to join with BrightSpark and Raine in October 2015 to celebrate the launch of the Strategic Alliance at a special event held in the Lawrence Wilson Art Gallery.
Magnus von Unge graduated as a medical doctor from the Karolinska Institute, Stockholm, Sweden. Professor von Unge specialises in Otorhinolaryngology, holding positions at Västerås Central Hospital and at Karolinska University Hospital. The focus of Professor von Unge’s research is on the regenerative properties of the human tympanic membrane for the purpose of tissue engineering and activation of repair processes.

We were delighted to welcome Professor von Unge to The University of Western Australia as a Raine Visiting Professor on two separate occasions in 2015 as guest of the Molecular and Cellular Otolaryngology Research Group at the School of Surgery Ear Sciences Centre. During his first visit to the Centre, Professor von Unge provided the research team with special expertise in eardrum biology and otology to complement and develop the team’s skills and interest in surgical repair of eardrum perforations.

Professor von Unge also participated in surgical device testing trials in the human teaching/research lab facility where his surgical experience and knowledge provided valuable insight to selecting materials and device construction methods for tympanic membrane repair. In addition, a joint project targeting growth of eardrum cells, keratinocytes, fibroblasts, vascular, nerve, muscosal cells has identified proliferative foci and their control in acute and chronic models. His understanding of stem cell therapies in the tympanic membrane also led to unique insights for one of the Honours students in identifying applications for adult stem cell therapies in ENT surgery.

On 27 November, Professor von Unge presented a Raine Lecture on a topic entitled: The tympanic membrane: Structure, damage and regeneration and he also presented the inaugural lecture of the Centre for Cell Therapy and Regenerative Medicine as part of the CCTRM 2015 seminar series.

The Raine Medical Research Foundation was delighted to welcome Anthony Levitt back to the University of WA as a Raine Visiting Professor. After graduating from UWA, Professor Levitt undertook his specialty training in Psychiatry at the University of Toronto, which he completed in 1989. In 1992 he was appointed Head of the Mood Disorders Programs, initially at the Centre for Addictions and Mental Health in Toronto, followed by McMaster University in Hamilton and subsequently, the Sunnybrook Health Sciences Centre in Toronto. In 2002 Professor Levitt took up the post of Chief of the Department of Psychiatry at Sunnybrook and at the Women’s College Hospital, and in 2014 became Chief of the Brain Sciences Program at Sunnybrook. Professor Levitt has published over 130 peer-reviewed manuscripts; served for four years as Chair of the Canadian Institutes for Health Research (formerly MRC) Randomized Controlled Trials Committee, and has participated in large-scale, multi-site clinical trials for the past two decades.

Professor Anthony Levitt’s clinical practice and research is focussed on the treatment of patients with resistant mood and anxiety disorders, with special expertise in the facilitation of patient and family access to care in complex mental health and addiction systems. As a result of his expertise in this area of clinical medicine, Professor Levitt was recently appointed Medical Director of the newly created Family Navigation Project – a non-profit program designed to provide expert navigation of the mental health and addictions service system for youth aged 13-26 with serious mental health and/or addiction problems.

On 5 March 2015 Professor Levitt presented to a packed audience of clinicians, scientists and former colleagues, a Raine Lecture entitled: Direct to brain treatments for psychiatric illness: the new wave or a new fad?
Professor Hiroshi Takayanagi is ranked in the top 1% of medical scientists in the world having made an outstanding contribution toward the development of osteoimmunology. In the first 10 years of his research career, Hiroshi Takayanagi published more than eight papers in Science, Nature and Cell. His contribution to osteoclast biology has been both empirical and conceptual. He has identified NFAT as a critical transcriptional factor for RANKL activation and has also developed several novel approaches to study molecular mechanism of bone resorption.

In the past five years, the Centre for Orthopaedic Research at The University of Western Australia has benefitted enormously from Professor Takayanagi with two postdoctoral fellowships provided for PhD graduates of UWA. Professor Takayanagi has also supported research in osteoclast biology through his influence in the international scientific societies and has provided excellent advice and guidance to the Centre on the quality of science.

Professor Takayanagi received his first Raine Visiting Professor award in 2010, and a Vice-Chancellor Visiting Professorship between 2011 and 2013. He is an Adjunct Professor of the School of Surgery at UWA and has published one Nature and three Nature Medicine articles under his UWA affiliation. Currently, the research team at the Centre of Orthopaedic Research is collaborating with Professor Takayanagi on H+-ATPase gene knock-out osteoclasts under support of an NHMRC grant.

On 16 December 2015, Professor Takayanagi presented a Raine Lecture entitled: Transcriptional Regulation of Self-antigens in the Thymus for Immune Tolerance.

The visit of Professor Dr Heiko Lickert to the University in April 2015 as a Raine Visiting Professor was part of a broader research exchange programme between researchers at HelmholtzZentrum (HMGU) in Munich and UWA. Supported by a Memorandum of Understanding between our two organisations, the Raine Visiting Professor award provided an ideal opportunity for Heiko Lickert to develop and advance his collaborative research ventures with his UWA research partners.

A graduate of the Albert-Ludwig University and Max-Planck Institute in Freiburg, Heiko Lickert conducted his Postdoctoral studies at the Mount Sinai Hospital, Toronto, Canada. He is an expert on organ development and tissue homeostasis with emphasis on endocrine lineage formation in the gut and pancreas, insulin-producing β-cell development, regeneration and replacement, as well as metabolic signalling and stem cell-based drug screening.

The work of Professor Lickert has been funded by the European Research Council (ERC), a prestigious Emmy-Noether Fellowship of the German Research Foundation (DFG), the Ministry of Education and Research (BMBF), the Alexander-von-Humboldt Foundation, the Helmholtz Association and the European Union.

On 9 April 2015, Professor Lickert presented a Raine Lecture entitled: Beta cell development and regeneration. The lecture was presented to a capacity audience in the McCusker Auditorium of the Harry Perkins Institute of Medical Research.
PROFESSOR HUI YAO LAN

In April 2015 the Foundation was delighted to welcome Professor Hui Yao Lan as a Raine Visiting Professor and guest of Professor Ming-hou Zheng, Director of the Centre of Orthopaedic Research. Professor Lan is an outstanding international scientist with a distinguished career. He holds the post of Chon-Ming Li Professor of Biomedical Sciences at the Department of Medicine and Therapeutics at Li Ka Shing Institute of Health Sciences; Associate Director of the Institute and Assistant Dean (Research) in the Faculty of Medicine. Professor Lan is also Director of Inflammatory Diseases Research at the Chinese University of Hong Kong. A graduate of Sun Yat-Sen University in Medicine in 1977, Professor Lan went on to complete a Master’s Degree in Pathology before proceeding to Monash University to undertake a PhD degree in Medicine, awarded in 1990.

Professor Lan’s major research focus is on TGF-β/Smad signaling in chronic kidney and cardiovascular diseases and, most recently, in cancer microenvironments. He has obtained more than 60 national and international research grants/programs and published in excess of 275 publications with over 11,000 citations. Professor Lan serves as an Editorial Board member/Associate Editor in many biomedical journals including Journal of American Society of Nephrology, International Journal of Biological Sciences, Frontiers in Renal and Epithelial Physiology, Chinese Journal of Integrative Medicine, Kidney Disease, and Associate Editor for Clinical experimental Pharmacology and Physiology.

On 8 April 2015, Professor Lan presented a Raine Lecture entitled: Treatment of Tissue Fibrosis by Targeting TGF-beta/Smad3 Signaling.

PROFESSOR GILES PLANT

In Australia, many victims of spinal cord injury are young men whose lives are changed in an instant, and Western Australia – with its love of cars, sport and the great outdoors – has twice as many cases as other Australian states.

Neuroscientist Professor Giles Plant, whose research on spinal cord regeneration at The University of Western Australia, led to him setting up a research centre at Stanford University. In April 2015 we were delighted to welcome Professor Plant back to UWA to share with fellow researchers the exciting developments being pursued at his US centre.

Director of the Stanford Partnership for Spinal Cord Injury and Repair, Professor Giles says that the challenge of establishing the Centre in 2010 was both an accolade for the work he had been doing at UWA, and an opportunity to join what is arguably the best neuroscience faculty in the US.

In an interview with UWA Communications Officer, Trea Wiltshire, Professor Plant explained that, while spinal cord regeneration remains elusive, there have been huge advances since he began his PhD research at UWA. One of the most exciting lines of research that his Centre is pursuing involves new techniques using adult stem cells. As explained by Professor Giles – At our centre we are using neural stem cells to improve functional movement and because there is the potential to use the patient’s own stem cells we avoid the ethical issues around embryonic stem cells. In our model we are able to get neurons transplanted into the spinal cord to synapse and form electrical connections with other neurons to achieve functional movement. We are able to see the stem cells integrating and providing regrowth, and we’re able to see functional benefits in movement in animals used in testing. We’ve never seen this before, so it is really promising – but we are at an early stage and it is slow, methodical work. What is promising is there are techniques now being studied that will allow us to get better outcomes for those with spinal injuries. At present this particular line of research is only being done in Stanford – that’s why I’ve come to Perth to tell my colleagues about it. I’m here to open a door and to ask, why not try this?

Trea Wiltshire
UWA Communications Officer
PROFESSOR WILLIAM COOKSON

Bill Cookson is Professor of Genomic Medicine at Imperial College London, Head of Respiratory Sciences for the College, and Head of the Asmarley Centre for Genomic Medicine at the National Heart and Lung Institute. In 2011 Professor Cookson won a Joint Wellcome Senior Investigator Award with Professor Miriam Moffatt and in 2013 he was elected to the College of National Institute for Health Research Senior Investigators.

After completing his studies at UWA, Professor Cookson initially trained as a respiratory physician before receiving a D.Phil. in human genetics at Oxford in 1994. He was Professor of Human Genetics at the University of Oxford between 1998 and 2004. Over the past 25 years Bill Cookson and Miriam Moffatt have developed a successful research group devoted to understanding the genetic causes of asthma.

The primary aim of Professor Cookson's visit to Perth was to increase collaborative activities and to enhance core facilities for Genomic Medicine at UWA, with an initial focus on lung diseases.

On 4 November 2015, Professor Cookson presented a Raine Lecture entitled: Asthma: Genes versus the microbiome at the airway barrier.

PROFESSOR JOSEPH PIVEN

Professor Joseph Piven is Director of the federally-funded University Center of Excellence in Developmental Disabilities (UCEDD) at the University of North Carolina and NICHD-funded Intellectual and Developmental Disabilities Research Center, while leading an NIH-funded T32 Post-Doctoral Research Training Program in Neurodevelopmental Disorders. He is also the Principal Investigator of an NIH-funded, multi-center Autism Center of Excellence (ACE), which examines early brain and behaviour development in infants at high familial risk for autism. Other NIH research projects include studies of brain and behavior development in children with Fragile X Syndrome, as well as examinations of late life manifestations and issues in elderly individuals with autism. Dr Piven is the Founding Editor-in-Chief of the new Journal of Neurodevelopmental Disorders (Springer 2009), the aim of which is to promote interdisciplinary research on the pathogenesis of a range of neurodevelopment disorders.

The Raine Visiting Professorship awarded to Professor Piven consolidated the strong research collaboration between UWA and the University of North Carolina. Professors Sergio Starkstein and Joseph Piven recently published a landmark study showing a high frequency of Parkinsonism in Autism, and they will continue to advance their studies on other behavioural and neurological aspects in adults with Autism Spectrum Disorder.

On 14 September 2015, Professor Piven presented a Raine Lecture entitled: Brain and Behavior Development in Autism: The First Two Years of Life.
The Raine Medical Research Foundation was delighted to welcome the return visit of Professor Stephen in 2015/16 as a Raine Visiting Professor.

Director of the Institute of Cell Signalling at Nottingham University and Head of the School of Biomedical Science, Professor Hill is an international scientist recognised for his research into the molecular pharmacology of G protein-coupled receptors and cross-talk between intracellular signaling cascades. Professor Hill returned to Western Australia in 2015/2016 to further advance his collaborative work with Associate Professor Kevin Pfleger, Head of Molecular Endocrinology and Pharmacology at Perkins Institute of Medical Research.

On 7 December Professor Hill presented a Raine Lecture entitled: Investigating GPCR dimerization and complex formation with fluorescent ligands. On 18 March 2016 Professor Hill will give a presentation at a Symposium on Molecular Medicine hosted by Perkins. Professor Hill's presentation is entitled: Use of fluorescent ligand approaches to study the kinetics of ligand-receptor interactions at GPCRs.

Professor Mingguang He is a clinician-scientist and rising star in ophthalmic epidemiology and genetics. In 2014 Professor He was appointed Professor of Ophthalmic Epidemiology at the University of Melbourne, having previously been Deputy Director of Zhongshan Ophthalmic Center at Sun-yat Sen University in Guangzhou, which is China’s Key National Laboratory in Ophthalmology. As Head of the Department of Preventive Ophthalmology, for many years Professor He was involved in Chinese studies on prevalence and prevention of myopia; the use of self-correction using adjustable lenses for the diagnosis of refractive error in children; and continues to lead a trial on the prevention of myopia based on increasing time outdoors in schools in Guangzhou. He is also extensively involved in the World Health Organization’s Refractive Error Study in Children looking at the prevalence of visual impairment from uncorrected refractive errors.

Professor He ran the first glaucoma survey and the largest twin registry in China and is leading several well-funded projects in China and Australia. Some of these studies have been running for more than 10 years and generated ample data. Although Professor He’s work is focussed on epidemiological and clinical trials in China, he is also involved in many international collaborations that contribute to a better understanding of the genetic and epidemiological influences on the structure and diseases of the eye.

On 29 September 2015 Professor He presented a Raine Lecture entitled: High myopia registry in Guangzhou.
Raine International Visiting Research Fellowships

Raine International Visiting Research Fellowships were introduced to encourage young postdoctoral scientists to visit the University to bring new knowledge and techniques in medical research; to facilitate the training of staff and students, and to initiate collaborative research.

In 2014 the Raine Foundation was delighted to join with the School of Women’s and Infants’ Health and award a Raine International Visiting Research Fellowship to Dr Brenda Kazemier from the Academic Medical Centre, Amsterdam, The Netherlands, to facilitate her visit to Perth in late 2015.

A graduate of the Wageningen University in 2007, Dr Kazemier proceeded to the University of Utrecht where she was awarded a Selective Utrecht Medical Master’s degree (MD and MSc Program) in 2011. In 2015 Dr Kazemier completed her doctoral studies in Obstetrics and Gynaecology, Academic Medical Centre Amsterdam.

Dr Kazemier’s strong research background in preterm birth research and, in particular, her direct involvement in the implementation of the Dutch nationwide preterm birth screening study, enabled her to participate in the Western Australian Preterm Birth Initiative Program. Although there were significant differences in the geographic spread of the two populations, Dr Kazemier’s knowledge of the infrastructure used in the Dutch preterm birth prevention programs was of substantial assistance in implementing components of the WA preterm birth prevention program.

During her visit to Perth Dr Kazemier conducted teaching sessions on cervical length screening and ultrasound techniques with the sonologists and sonographers of the King Edward Memorial Hospital Ultrasound Department. Ultrasound assessment of the pregnant cervix has been shown in clinical trials to be a powerful predictor of preterm birth risk. As this is a relatively new technique when used in population screening, it was of considerable importance to review the techniques and performance characteristics of this ultrasound screening modality with those who perform the testing. Dr Kazemier and Mrs Michelle Pedretti, PhD student in the School, collaborated on a review manuscript on universal cervical length screening in preterm birth prevention. This manuscript has now been submitted to the Australian and New Zealand Journal of Obstetrics and Gynaecology for publication.

Dr Kazemier also spent time with researchers at the School developing a draft population comparison initiative model for preterm birth characteristics of Netherlands, Chicago USA and Perth, Western Australia. This comparative research has the potential to identify common characteristics and differences between preterm birth risks in developed but culturally diverse areas.

The visit of Dr Kazemier as a Raine International Visiting Research Fellow was a resounding success. Strong links have been established between her academic centre in the Netherlands and staff of SWIH in Perth, Western Australia, with a view to advancing future research relationships. A planned future research innovation will compare the variation in preterm birth rates between the Netherlands and Perth and the influence of short cervical length on any observed variation.

In concluding this report, we are pleased to report that Dr Kazemier’s colleague, Professor Ben Mol from Adelaide South Australia, will continue the research relationship between the two academic centres from an Australian basis with proposals for clinical trials to be conducted in preterm birth prevention.
OBJECTIVES OF STUDY

The Gram-negative bacterium, Helicobacter pylori (H. pylori), infects over half of the world’s population and is the leading cause of gastric ulcers, and an important causative agent in gastric cancer. No vaccine against H. pylori exists so far and the only treatment is based on antibiotic therapy. Although major progress in understanding the mechanisms of H. pylori pathogenesis and persistence has been made in the last two decades, in vivo immune mechanisms at the site of infection, the gastric mucosa, are poorly described. It is known that H. pylori manipulate the host T cell response. In order to better understand this process and how H. pylori suppresses the host immune response leading to persistence, we are investigating H. pylori-specific CD4 T cells – the main immune effectors that control bacterial colonisation. More specifically we will focus on the identification of their priming site, migration patterns, expression of cell surface molecules involved in homing to the gastric mucosa, cytokine profiles and functionality. We will apply our new findings to investigate the basic requirements for the development of a successful anti-H. pylori vaccine. In this respect we intend to identify and characterise the prime CD4 T helper subset that protects the host from H. pylori challenge. Our study will help to develop new and improved H. pylori vaccines in the future.

HIGHLIGHTS

The focus of our project is to investigate the H. pylori -specific CD4 T cell response. H. pylori–specific CD4 T cells are very rare and hard to track. In order to circumvent this problem we proposed to augment the frequency of T cells recognising H. pylori by using newly generated H. pylori strains that express a well described CD4 T cell epitope derived from the Ovalbumin (OVA) protein in combination with adoptively transferring OVA-specific CD4 T cells specific for this OVA epitope. As we failed to stably transfer OVA-specific CD4 T cells over long period of times required to analyse CD4 T cell responses developing during chronic infections, we concentrated on the acute response developing during the first week of exposure. We were able to demonstrate that intraperitoneal injection with vaccine activated CD4 T cells, whereas live infection did not. We are currently investigating if this is due to the site of infection or differences in the state of the bacteria e.g. live infection versus lysate.

We also developed assays to identify H. pylori-specific CD4 T cells based on T cell restimulation, cytokine secretion assays and flow cytometry to visualise localisation of CD4 T cells infiltrating the stomach tissue by confocal microscopy. We are currently investigating the impact of different H. pylori strains and vaccination on the bacteria-specific CD4 T cell response.

PROJECT TITLE:
Characterisation of H. pylori–specific CD4 T cell responses

INVESTIGATOR
Dr Senta M Walton

SCHOOL/INSTITUTION/CENTRE
School of Pathology and Laboratory Medicine, The University of Western Australia
The objective of this study was to address how stress hormone excess in pregnancy alters placental blood flow and fetal heart function. A further facet involved the administration of a drug, pravastatin, to improve placental blood flow. This work has now been finalised and we have data that implies that poor development of placental vasculature has a direct effect on how the fetal heart functions. Furthermore, we have novel data that indicates that exposure of the placenta to stress hormones impairs placental blood vessel development and that this can be overcome by administering pravastatin.

In addition to this, my work imaging placental blood vessels as part of this research project has led to a collaboration with Dr Barry Doyle, School of Engineering, UWA. In 2015 we co-supervised an Honours student to assess whether computational fluid dynamics modeling (CFD) can be used to simulate blood flow. The preliminary study successfully optimised the parameters required to apply CFD to a more extensive network of placental blood vessels (see Figure). Furthermore, talks I have given based on work funded by the Raine Priming Grant has attracted Honours and PhD students to work with me.

The outcomes directly and indirectly arising from the Raine Priming Grant include:

**PUBLICATIONS**

Submitted

One publication currently under review by the journal *Proceedings of the National Academy of Sciences (PNAS)*.

In preparation

- The effects of glucocorticoids on placental blood vessel geometry
- Using CFD to model blood flow in a simplified placental vascular network

**GRANTS**

2015: NHMRC Project Grant submission (unsuccessful)
2016: ARC Discovery Grant submission (submitted)

**STUDENTS**

2014: Ms Eleanor Burrows (Honours)
2015: Mr Tim Crough (Honours)
2016: Mr Emily Chivers (Honours)
2016: Mr Nikhilesh Bappoo (Honours)
2016: Mr Yutthapong Tongpob (PhD)
2016: Ms Emma Panting (PhD) (will commence mid-year)

In all, the project has been extremely productive and has provided a launching pad for some unexpected and exciting collaborations.

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**PROJECT TITLE:**

Stress hormone excess in pregnancy impairs placental haemodynamics with novel implications for fetal cardiac function.

**INVESTIGATOR**

Dr Caitlin Wyrwol

**SCHOOL/INSTITUTION/CENTRE**

School of Anatomy, Physiology and Human Biology, The University of Western Australia.

The outcomes directly and indirectly arising from the Raine Priming Grant include:

**PUBLICATIONS**

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One publication currently under review by the journal *Proceedings of the National Academy of Sciences (PNAS)*.

In preparation

- The effects of glucocorticoids on placental blood vessel geometry
- Using CFD to model blood flow in a simplified placental vascular network

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In all, the project has been extremely productive and has provided a launching pad for some unexpected and exciting collaborations.
SUMMARY
Chemo-radiotherapy (CRT) prior to surgery (neo-adjuvant therapy) is currently standard treatment for patients with locally advanced rectal cancer. Approximately 20% of patients respond completely (i.e. have no residual tumour at the time of surgery) and have a significantly better long-term prognosis; However, not all patients benefit from neo-adjuvant therapy and it is difficult to predict who will respond. This project is investigating the role of the immune system in achieving a response to chemo-radiotherapy, with a particular focus on regulatory T cells (Treg), a subset of immune cells that suppress immune responses.

OVERALL AIM: To characterise the in situ and peripheral cellular immune response, before and after neo-adjuvant CRT, and identify immunological markers of treatment response.

KEY HYPOTHESES:
1. Treg inhibit the response of rectal carcinomas to neo-adjuvant CRT
2. Immunological markers will predict likely responders
3. Changes in peripheral blood T cell subsets after CRT reflect changes in the local tumour environment

This project is utilising samples from two cohorts of patients with locally advanced rectal cancer treated with neo-adjuvant CRT.

Cohort 1: A retrospective cohort of 131 patients from whom tissue samples are stored within the St John of God Pathology archive.

Cohort 2: A prospective cohort of 100 patients recruited from St John of God, Subiaco and Murdoch hospitals from whom pre- and post-CRT blood samples are also being collected.

WORK UNDERTAKEN AND RESEARCH RESULTS
Cohort 1 sample analysis
Surgical resection samples (post-CRT) from all cohort u.c. 1 patients were analysed for infiltration of T cell subsets, clinical information was collated, and the relationship between T cell subset densities and clinical outcome was evaluated. This work demonstrated a strong association between low Treg density and complete response to CRT. This is consistent with our first hypothesis that Treg inhibit the response of rectal cancers to neo-adjuvant CRT, and has resulted in two peer-reviewed publications and six conference abstracts (listed below).

In order to assess whether immunological markers could predict subsequent response to CRT (hypothesis #2), we then analysed pre-treatment biopsy tissue samples for T cell infiltration. Pre-CRT biopsy samples for 40% of Cohort 1 u.c. patients were available in the St John of God Pathology archive. In our initial research proposal, we anticipated increasing this figure to 80% through material from external pathology providers. We were in fact successful in obtaining pre-treatment material for 96% of patients in Cohort 1 u.c. These samples have now been analysed and evaluation of the data is underway. We anticipate submission of a third manuscript for publication in the coming months.

Cohort 2 sample analysis
The prospective collection of pre- and post-CRT blood samples has been ongoing in parallel. While the rate of recruitment was slower than anticipated, we have now reached our target of 100 patients, and analysis of peripheral blood T cell subsets is well underway. These data will be compared to T cell subset densities in pre and post-CRT tissue samples from the same patients (as performed for cohort 1 u.c.) in order to test our third hypothesis that changes in peripheral T cell subsets reflect those in the local tumour environment. We will also evaluate whether immune biomarkers in the blood are helpful in distinguishing likely responders from non-responders. This would have direct clinical impact by enabling selection of the most appropriate treatment strategy for individual patients with a minimally invasive test, and would also have important implications for the design of future clinical trials.

We anticipate completing remaining work on the project by mid-2017.
RELEVANT OUTCOMES

Publications in peer-reviewed journals


Conference abstracts


Figure 1. A. Treg (brown cells) infiltrating rectal cancer tissue. Bar indicates 50 μm. B. Proportion of complete responders with a low density of Treg compared to incomplete responders. Adapted from McCoy et al. Br J Cancer. 2015;113(12):1677-86. DOI: 10.1038/bjc.2015.427
Initial objectives of the study

1. To characterise the calcium signalling response within cultured astrocytes in response to different frequencies of pulsed magnetic fields (PMFs).
2. To determine whether PMFs influence astrocyte reactivity and alter the relative production of trophic versus neurotoxic substances in an in vitro injury model.

2015 HIGHLIGHTS

Brain injury studies

Following our results from 2014, we decided this year to focus on determining whether PMFs influenced astrocyte reactivity in an in vivo (i.e. whole animal) injury model. We chose a well-established model of brain injury, a cortical stab injury model (1). In this model, a small hole is drilled into the skull and a needle inserted into the brain for a period of 2 minutes. Over the course of 2 weeks, astrocyte and microglial cells become activated in response to the injury (2).

We applied focal PMFs for 14 days, and we determined whether the age and sex of the animal could influence the ability of PMFs to modulate glial scar formation. The spread and local response of reactive astrocytes and microglia, and intensity and area of proteoglycan expression were assessed. PMFs had age, sex, and frequency specific effects on the local response of glia and the expression of proteoglycans following injury. PMFs did not reduce reactive gliosis in young male mice and had contrasting effects on astrocyte and microglial density in young female mice. However, we observed the greatest effect in older female mice, characterised by a reduced astrocyte and microglial response combined with attenuated proteoglycan expression. The analysis of data from aged male mice is ongoing and has not yet been completed.

Cell morphology studies

We have also continued our in vitro experiments investigating whether the calcium response elicited by 1Hz PMF results in a change in astrocyte morphology. The analysis of these experiments is ongoing and has not yet been completed.

In 2015, Dr Bates was an invited speaker at two local events and gave an oral presentation at an international conference:

2. School of Animal Biology Research Seminar Series, 17th June, UWA.
3. Australasian Winter Conference on Brain Research, August Queenstown, New Zealand.

OVERALL SUMMARY

This study has provided evidence to suggest, for the first time, that astrocytes are responsive to PMFs in a frequency-specific manner. We have shown that:
- Astrocytes respond to 1Hz PMF through an increase in intracellular calcium. No other PMF frequency tested could elicit this response.
- PMFs can alter the glial scar response of astrocytes to brain injury in an age and sex specific manner, and maybe most effective for aged female mice.

These data are currently under preparation for publication. This study has laid the foundation for future studies to further investigate the effects of PMFs on astrocyte biology. Experiments are planned for 2016 to study the effect of PMF on human astrocytes grown in cell culture, and to complete analysis of the brain injury and cell morphology studies. The study has also provided good quality pilot data for future NHMRC project grant applications.

Publications

1. Bates KA, Drummond ES, Cozens GS and Harvey AR. Vascular insufficiency, not inflammation, contributes to chronic gliosis in a rat CNS transplantation model. Restorative Neurology and Neuroscience. Accepted 22/12/2015.
Publicity
In March of 2015, I published an article on The Conversation website on the science behind brain-to-brain interfaces. The article proved to be a popular read. It had over 410,000 reads and was one of the top 10 science and technology reads of 2015 https://theconversation.com/brain-to-brain-interfaces-the-science-of-telepathy-37926.

As a result of interest from The Conversation article, I was interviewed by three media outlets:

1. ABC Local Radio Queensland. Interviewed on the science of telepathy as part of the state-wide afternoon program.  
2. Radio 2Ser NSW. Interviewed on the science of telepathy as part of the breakfast program.  
3. The Age Newspaper. Interviewed for the story Mind control: EEG research closes in on thought-operated computers (28/10/2016).

Density of astrocytes and proteoglycan expression at the injury site. Representative images showing the density of cells (green, activated astrocytes) and proteoglycan expression (red, chondroitin sulfate proteoglycan) for the four different PMF frequencies tested (sham- no stimulation, 1Hz- above injury site, contra- 1Hz contralateral to injury site, BHFS- biomimetic high frequency stimulation above injury site, scale bar = 300µm). Cell density and proteoglycan expression is interpreted as having a negative impact on brain repair. Analysis of old male mice is ongoing, to be completed in the first half of 2016. The data are summarised below:

Young male mice, PMF increased cell density at the injury site.

Young female mice, PMF had frequency-specific effects on cell density.

Old female mice, PMF reduced cell density across all frequencies tested.

Literature cited

Homeostatic maintenance of these cell populations. Interleukin-21 (IL-21) mediated proliferation of B cells. These
interleukin-7 (IL-7) mediated proliferation of T cells and
α-interferon (IFN-α) inhibits the IL-7 mediated proliferation of CD4+ T cells. The support provided by the
Raine Foundation was utilised as salary to fund the CI,
Dr Sonia Fernandez, and to oversee these studies which
were designed to increase knowledge about how IFN-α
mediates immune activation in HIV patients with a long-term
aim of improving treatment outcomes.

The recruitment of a large cohort of HIV patients and
healthy age-matched controls was crucial to this project
and was carried out over the course of 2014 and early
2015. Cells, plasma and serum from 60 HIV patients and
20 healthy donors were frozen and stored for the study.
Work then proceeded to assess the effect of IFN-α on these components of the IL-7 signalling
pathway; the IL-7 receptor and STAT-5, however an effect
on two key components of the IL-7 signalling
pathway: the IL-7 receptor and STAT-5, however an effect
on these components was not evident. This work
might alter key pathways involved in their
homeostatic maintenance. The support provided by the
Raine Foundation was utilised as salary to fund the CI,
Dr Sonia Fernandez, and to oversee these studies which
were designed to increase knowledge about how IFN-α
mediates immune activation in HIV patients with a long-term
aim of improving treatment outcomes.

During late 2014 and 2015, we performed studies
examining the effects of IFN-α upon B cell differentiation,
assessing plasmablast induction and IgG antibody
subclass production following B cell stimulation with IL-21.
Our results suggest that while IFN-α does not affect the
induction of antibody producing plasmablasts from B cells,
it does exert an inhibitory effect on the production of IgG
antibodies, and may particularly inhibit the production of
downstream IgG2. Additional studies, again utilising the
novel imaging cytometry technique, suggest that this may
be linked to the effect of IFN-α on phosphorylation and
nuclear translocation of the key signalling molecule, STAT-
3. In addition, we were able to demonstrate for the first
time links between IFN-α activity and expansion of aging
and exhausted B cell populations. These data are being
prepared for publication.

In 2015 our focus was also on performing array studies to
characterise the IFN-α transcriptome in CD4+ T cell and
memory B cell subsets. This involved the flow cytometric
sorting of pure cell populations from which RNA and
subsequently cDNA was isolated. The final aspect of this
work (the arrays themselves) is currently in progress with
completion expected in the next two months.

Related presentations:
Interferon-α reduces isotype diversification of IgG without
inhibiting plasmablast induction. Australasian Cytometry
Society 37th Annual Conference, Workshop and AGM.
October 2014; Gold Coast, Australia. Oral presentation
selected from abstract.

Interferon-α reduces isotype diversification of IgG without
inhibiting plasmablast induction. 44th Australasian Society
for Immunology Annual Scientific Meeting.
December 2014; Wollongong, Australia. Oral presentation
selected from abstract.

Contrasting effects of IFNα on immune responses in HIV
infection. 2015 Australasian HIV and AIDS Conference.
September 2015; Brisbane, Australia. (Invited Presentation).

In addition, work pertaining to this grant was presented at
several local conferences during 2015, and related abstracts
have been submitted to two major conferences taking place
in 2016: 16th International Congress of Immunology; and
21st International AIDS Conference.
Related publications:

- Cha L, de Jong E, French MA, Fernandez S. IFN-α exerts opposing effects on activation-induced and IL-7-induced proliferation of T cells that may impair homeostatic maintenance of CD4+ T cell numbers in treated HIV infection. *J Immunol* 2014; 193: 2178-2186.


- Tanaskovic S, Fernandez S, Saraswati H, Yunihastuti E, Gani RA, Djauzi S, Price P. Naive and memory CD4+ T-cells are differentially affected in Indonesian HIV patients responding to ART. *Viral Immunology* 2016; accepted for publication.

Related grants:

2014 ($15,000) - Royal Perth Hospital Medical Research Foundation Project Grant. Awarded to Sonia Fernandez (Chief Investigator A). The effects of IFN-α on T cell homeostasis in HIV patients on ART.

2015 ($17,175) - Royal Perth Hospital Medical Research Foundation Project Grant. Awarded to Sonia Fernandez (Sole Chief Investigator). The effects of IFN-α on B cell activation and differentiation in HIV patients on ART.

Dr Sonia Fernandez at work in the laboratory.
**PROJECT TITLE**  
*Front To Back: Retinal Pigment Epithelium from Limbal Stem Cells*

**INVESTIGATORS**  
Dr Samuel McLenachan (Chief Investigator)  
Professor Fred Chen (Associate Investigator)

**SCHOOL/INSTITUTE/CENTRE**  
Centre for Ophthalmology and Visual Science  
The University of Western Australia

**SUMMARY**  
Macular degeneration is caused by the loss of retinal pigment epithelial (RPE) cells and can be cured by RPE transplantation into the retina. In this project, we aimed to test the therapeutic efficacy of RPE-like cells derived from human limbal stem cells in a rat model of retinal degeneration.

**RESEARCH OBJECTIVES, HIGHLIGHTS, RESULTS:**  
**Aim 1:** Characterise pigmented neurospheres in primary cultures derived from the human corneoscleral limbus.  
In Aim 1 we sought to examine the efficiency of human LiNS induction using our improved culture techniques and perform a detailed characterization of RPE cells present in pigmented spheres using RT-PCR and immunohistochemistry. We have successfully cultured pigmented LiNS and characterised them by RT-PCR, immunostaining and Western blot, demonstrating expression of optic cup progenitor genes such as PAX6, OTX2, MITF, CHX10 and SOX2.

**Aim 2:** Characterise limbal neurosphere derived pigment epithelial cells.  
In Aim 2, we aimed to further characterise the LiNS-RPE cell phenotype and identify culture conditions that enhance RPE cell differentiation and enable the propagation of LiNS-derived RPE cells as an epithelial sheet. We have characterised LiNS-RPE by immunostaining and microscopy, demonstrating the pigmented, polygonal phenotype of these cells as well as the expression of RPE cell markers. We have also performed functional assays to demonstrate photoreceptor uptake by LiNS-RPE. In addition, we have developed a novel method for production of a Bruch’s membrane-like extracellular matrix that promotes RPE differentiation. We have also developed a method for production of Bruch’s membrane-like extracellular matrix that promotes epithelial phenotype and promotes RPE differentiation in pluripotent and limbal stem cells and preserves pigmentation in primary human RPE cells. Finally, we have identified culture conditions that promote the expansion of pigmented LiNS cells. This development has enabled the production of large numbers of LiNS-RPE for gene expression analysis and transplantation.

**Aim 3:** Transplant pigmented limbal neurosphere cells into the Royal College of Surgeons rat retina.  
In Aim 3, we examined the therapeutic efficacy and functional phenotype of LiNS-RPE by transplantation into a common model of RPE dystrophy, the RCS rat. To date, we have performed injections in 28 rats and have demonstrated rescue of the photoreceptor layer in rats injected with human RPE, human LiNS and rat LiNS.

**OUTCOMES:**  
**ANTICIPATED PUBLICATIONS**  
- Subretinal Transplantation of Limbal Neuropheres Prevents Retinal Degeneration in the RCS Rat (manuscript in preparation)  
- Bioengineering of Bruch’s Membrane (manuscript in preparation)

**CONFERENCE PRESENTATIONS**  
- McLenachan S, Zhang D, Chen F. Production of Bruch’s-Like Extracellular Matrix Surfaces 5th Margaret River Region Forum, November 2014, Busselton, Western Australia (Talk)

**INVITED SEMINARS**  
- UHU Research Symposium (Perth, Australia) November 2015: Development of Autologous Stem Cell Therapies for Retinal Disorders  
- CBATEG (Barcelona, Spain) July 2014: Front to Back: Autologous Limbal Stem Cell Therapy for Macular Degeneration  
- CERA (Melbourne, Australia) May 2014: Front to Back: Autologous Limbal Stem Cell Therapy for Macular Degeneration  
- RANZCO Colloquia (Perth, Australia) Feb 2014: Front to Back: Autologous Limbal Stem Cell Therapy for Macular Degeneration
Stem cells from the human limbus (A) were cultured as neurospheres (LiNS) and produced pigmented RPE-like cells (B). These cells were injected into RCS rats (C). Rats receiving no or saline injections underwent retinal degeneration, while the outer retinal layer was preserved in rats receiving LiNS or human RPE cells (D).
The role of Bcl2 S24P mutation in bone homeostasis

INVESTIGATOR
Dr Jennifer Tickner (Chief Investigator)
Professor Jiakoe Xu (Associate Investigator)

SUMMARY
Pathological bone loss induced by excessive bone resorption, and/or reduced bone formation, is the major mechanism underlying many debilitating bone diseases, including osteoporosis. We have observed that mice carrying a mutation in the BH4 domain of the Bcl2 gene, which regulates apoptosis, exhibit bone loss. We hypothesise that the Bcl2 BH4 domain plays a critical role in bone homeostasis through regulating the survival of bone cells. To address this hypothesis we are investigating the differentiation, function and survival of bone cells derived from mutant mice.

During the past 12 months we have been focussing on the cellular defects in the cells isolated from mutant mice. We have found that there are variations in calcium regulation within the mature osteoclasts generated from mutant mice. Bcl2 has been shown to regulate calcium release from the endoplasmic reticulum through binding to the Inositol Triphosphate receptor (IP3R) and calcium regulation is critical to osteoclast function. This finding is in keeping with the changes that were observed by our collaborators in Belgium regarding the calcium flux in cells expressing the mutant protein. Failures to regulate calcium flux within the osteoclast impact on survival and bone resorption function. We have determined that survival of osteoclasts is not affected in the mutant osteoclasts, suggesting that the osteoporotic phenotype we see in the mice is likely due to a failure to respond to calcium signals regulating resorption. We are finalising our experiments on resorption to confirm this observation.

The phenotype of the mutant cells is very complex due to the multiple roles that Bcl2 plays in cells. We have previously observed that there is a missing population of B cells in the bone marrow of the mice and B cells are critical regulators of osteoclast formation. They produce cytokines that block osteoclast formation, the loss of B cells likely contributes to the reduced bone mass through loss of inhibitory osteoprotegerin (OPG) protein production in the missing B cells. OPG is critical for preventing excessive activation of the RANK receptor by the principle osteoclast differentiation factor RANK ligand.

Osteoblasts also support osteoclast formation and function. We have performed co-culture experiments to investigate the contribution of osteoblast derived factors to osteoclast formation in the mutant mouse. We observed that osteoblasts from the mutant mice were less capable of supporting osteoclast formation, and that bone marrow cells from mutant mice were less capable of forming osteoclasts in the presence of wild type osteoblasts. This suggests that osteoblastic support of osteoclast formation is altered by the Bcl2 mutation, and also points to an intrinsic defect in Bcl2 mutant osteoclasts.

To further our understanding of the role of Bcl2 in bone we have also investigated whether single nucleotide polymorphisms within the BCL2 gene in humans are associated with bone mineral density. We have found point mutations in 2 regulatory regions of the BCL2 gene that are associated with femoral and lumbar spine bone mineral density. In both instances the mutations are predicted to upregulate BCL2 gene transcription resulting in enhanced Bcl2 protein levels and this is associated with a reduction in BMD. This fascinating observation suggests that our mutation in osteoclasts may be a gain of function mutation, where enhanced Bcl2 function in bone specific processes drives osteoclast formation and function in vivo, whilst in vitro support of osteoclast formation is inhibited.

We also found that cells isolated from the bone marrow and stressed by freezing and storage in liquid nitrogen for a period of time failed to proliferate upon reanimation, whereas cells from wild type mice effectively proliferated and differentiated following the same stress process. We believe this is due to the interaction between autophagy and p53 controlled processes inducing cellular senescence in an environment inducing cellular stress. It will be of great interest in the future to investigate what happens in the bones of ageing mutant mice. It has been proposed that the bone loss that is observed during ageing is due to reduced capacity for cells to cope with stressors, a role for Bcl2 in regulating the cells ability to cope with environmental stress has not been previously identified.

The results from this project are currently being synthesised into a publication and parts of this project formed a component of the PhD thesis of Gaurav Jadhav, which was submitted for examination in late 2015 and passed in early 2016. A second PhD student is working on this project to finalise the resorption data prior to publication, and this project will form a significant component of their thesis. This project has been the subject of two poster presentations in one at the Combined Biological Sciences Meeting, 2015, and one at the Australian and New Zealand Bone and Mineral Society (ANZBMS) annual meeting in Hobart. The poster at the ANZBMS meeting was awarded a plenary poster presentation and was runner up for best poster prize at this meeting.
I’d like to sincerely thank the Raine Foundation for their generous support of this project over the past two years. It has been critical for my career progression by maintaining my position and giving me the opportunity to build my track record and maintain forward momentum. Thanks to this support I was part of a successful NHMRC project grant (CIC) in 2016, which will support my future development.

Tickner image 1_2015_WT: Wild type osteoclast stained for Bcl2 (FITC – Green), F-actin (Rhodamine Phalloidin – Red), and DNA (DAPI – blue).

Tickner image 2_2015_Mut: Bcl2 BH4 mutant osteoclast stained for Bcl2 (FITC – Green), F-actin (Rhodamine Phalloidin – Red), and DNA (DAPI – blue) demonstrating reduced bcl2 levels in the mutant cell.

Tickner image 3_2015_WT: Co-culture of osteoblast and osteoclast cells from WT mice. Purple stain indicates osteoclasts formed in co-culture.

Tickner image 4_2015_Mut: Co-culture of osteoblast and osteoclast cells from Bcl2 BH4 mutant mice. Reduced purple stain indicates impaired osteoclast formation in co-culture.
Summary
This study aimed to investigate the impact of inhaled environmental dust on the lungs of children growing up in remote Australia. We planned to address the health disparity commonly observed in Aboriginal children by examining the relationship between dust levels in the air in remote Aboriginal communities and the lung health of Aboriginal children. Our objectives included measuring inhalable dust exposure levels in the communities, characterising the dust, linking clinical respiratory data and dust levels and examining the mechanisms through which dust can make bacterial lung infections more common and severe.

In the past 12 months, we have concentrated mainly on the objective investigating the impact of dust on bacterial infections. Following training and optimisation, we have been able to carry out a number of assays addressing epithelial cell viability, bacterial attachment and invasion, and immune responses, following dust exposure. We initially concentrated on non-typeable Haemophilus influenzae (NTHi) – one of the most highly prevalent respiratory pathogens found in Aboriginal children, and in children and adults with chronic lung diseases such as bronchiectasis.

We found that dust exposure, depending on the source, can increase the attachment and invasion of NTHi, and affect the inflammatory immune responses against these bacteria. This supports our hypothesis that dust exposure may contribute to more common and severe bacterial infections.

This work has been undertaken primarily by a Research Assistant (Teck Hui) who was employed using Raine Priming Grant funds as outlined in the application budget. I was on maternity leave for the majority of 2015 (20th March 2015-1st February 2016) and Teck was supervised by my collaborators at UWA during this time. I did however stay in contact and was regularly updated on his progress, and will become a more primary supervisor now that I have returned. Teck will continue as a Research Assistant on this project in 2016.

The next stage includes completing the work on this objective including assessing the effects of dust exposure on the immune responses to other strains of NTHi, and to other bacteria such as Streptococcus pneumoniae, as well as assessing dust samples from other locations. Other objectives that include monitoring inhalable dust exposure levels in the communities and obtaining the community-specific clinical data will be given priority in 2016.

This project has produced two publications in 2015 (see below), and another paper is in preparation. The project also led to a new collaboration with researchers at UWA (Dr Janessa Pickering, Dr Ruth Thornton and Dr Lea-Ann Kirkham). The data collected in 2015 will be presented at two international conferences in 2016.


SUMMARY
NUT midline carcinoma (NMC) is an extremely aggressive cancer that has no cure and a survival time of only a few months from diagnosis. The molecular hallmark of the disease is a specific chromosomal translocation that fuses together two genes to create an abnormal chimeric BRD4-NUT protein that halts normal development and drives cells to proliferate out of control. The proposed research project aims to understand how the protein-signalling networks in the NMC cells give rise to such an aggressive phenotype. This information will assist in the identification of novel drug-targets for this fatal disease, which in turn will help in the development of novel treatments for patients. We will also assess the efficacy of promising drugs that we have identified previously in an expanded panel of NMC cell lines.

PROGRESS
Over the last 12 months, we have validated the efficacy of 25 short-listed drugs in twelve NMC and eight non-NMC cell lines. The drug screen analysis showed that the efficacy of aurora kinase and bromodomain inhibitors varies considerably between the NMC cell lines. This was unexpected, given that they specifically target functions/interaction partners of the BRD4-NUT fusion protein. Moreover, the data suggests that NMC cells that express a BRD4-NUT (ex11:ex2) fusion subtype are particularly susceptible to iBET treatment. Since iBETs are currently in phase I clinical trials for NMC and other solid cancers, it is essential to understand why some of the NMC cell lines didn’t respond to the iBET treatment. To address this, we analysed the transcription profile of 12 NMC cell lines and four non-NMC carcinoma lines with, and without, iBET treatment. A comparison of iBET resistant versus sensitive NMC cell lines identified iBET induced transcriptional changes of genes within the p53, STAT3 and PTEN and the NFκB pathway that were specific to the resistant NMC cell lines. We are currently utilising immunochemistry approaches to correlate those transcriptional changes with changes in protein signalling pathways. Next, we will target key hubs of those pathways to further validate their role in iBET resistance.

PUBLICATIONS

A further manuscript is currently under preparation.

PRESENTATIONS
Findings from this work have been presented at the EMBL conference in Personalised Health in Heidelberg (Germany), at the Lorne Genome Conference in Lorne (Victoria, Australia) as well as at eight local conferences and seminars.

SUCCESSFUL FUNDING APPLICATIONS
Children’s Leukaemia and Cancer Research Foundation Project Grant: Novel therapies for patients with drug resistant NUT midline carcinoma (Stirnweiss A, $104,981 for 2016).
Objective 3 has been successfully completed. We have performed a genome-wide association study for all detected CNV with a minor allele frequency ≥1% for association with spine, femoral neck and total hip BMD using SNPTEST v2.3.0. Using a Bonferroni-corrected significance threshold of $2.16 \times 10^{-5}$, we failed to identify any CNV associated with any of the phenotypes.

Objective 4 is currently underway. We have generated genome-wide marker array genotype data using the Illumina OmniExpress 700K BeadChip for a replication population of 1,046 individuals. Genome-wide detection of CNV in this dataset will be performed using the Illumina GenomeStudio v2011.1 software package in conjunction with the cnvPartition v3.2.0 plugin. Statistical analysis in this population will be performed using the Genome-wide Efficient Mixed-Model Analysis (GEMMA) software.

Additional work completed

We have recently completed a genome-wide association study for osteoporosis phenotypes in two family-based study populations (combined n=6,696) using deeply imputed genotype data. We observed a single variant, rs2566752, associated with spine BMD at the genome-wide significance level ($P=3.36 \times 10^{-9}$). This is an intronic variant located in the wntless Wnt ligand secretion mediator (WLS) gene (1p31.3), a known BMD locus which encodes an integral component of the Wnt ligand secretion pathway.

Gene-wide association testing using the VERSatile Gene-based Association Study 2 (VEGAS2) software revealed associations between the coiled-coil domain containing 170 (CCDC170) gene and BMD at the spine, femoral neck and total hip sites ($P=1.0 \times 10^{-6}$, $2.0 \times 10^{-6}$ and $2.0 \times 10^{-6}$ respectively). The manuscript describing the results from this study is currently under review at BMC Genomics.

We are also currently conducting a genome-wide association study meta-analysis for quantitative ultrasound measures of bone structure using a combination of whole-genome sequencing and deeply imputed genotype data in three study populations (combined n=16,419). We have completed the analysis in each population and are in the process of meta-analysing the results. Preliminary results from this study were presented at the Australian Society for Medical Research (ASMR) WA Scientific Symposium and the presentation was awarded the St John of God Health Care Award.
Publications

Presentations
Although current anti-retroviral regimens have reduced the morbidity and mortality associated with HIV-1 infection, suppression of viral replication requires adherence to lifelong therapy which 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. CD8 T cells have been identified as an important component of the immune response against HIV-1, where control of the virus is attributed to the quality of the CD8 T cell response while progression to AIDS is associated with the loss of viral-specific memory CD8 T cells. Therefore, 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 that 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. During 2015, we investigated the ability of HIV-specific CD8 T cells to recognise and respond to allo-HLA antigens. These CD8 T cells were isolated from individuals enrolled in the Western Australian HIV Cohort Study and recognised peptides derived from the Gag protein of HIV-1. The cells were identified using HLA-tetrameric complexes, cloned using single-cell sorting and the T cell receptor (TCR) expression characterised by flow cytometry and next generation sequencing (NGS). The NGS sequencing was performed by our collaborators at the Institute for Immunology and Infectious Diseases, Murdoch University. The allo-reactivity of these HIV-specific CD8 T cells was then investigated by co-culturing the clones with cell lines that expressed a single HLA-antigen. Allo-recognition resulted in CD8 T cell effector functions including cytokine secretion and cytotoxicity that were simultaneously detected in a novel assay developed in our laboratory.

The next stage of the project is to determine whether HIV-specific CD8 T cells can be directly expanded from a pool of peripheral blood mononuclear cells without the need for single cell sorting. These investigations will be performed on cells isolated from HIV-infected individuals and healthy controls that carry the HLA-allele of interest. Additionally, we have established collaborations with Dr Nicole Mifsud from Monash University to identify the peptide presented by the allo-HLA molecules that stimulate HIV-specific T cells. Both stages of the project are currently underway.

The results investigating the allo-reactivity of HIV-specific CD8 T cells are currently being prepared for publication purposes and have been presented at the following conferences:

- “Allo-HLA reactivity by HIV-specific T cells: A potential adjunct to HIV vaccine design?” – 29th European Immunogenetics and Histocompatibility Conference, April 2015, Geneva, Switzerland
- “A novel assay for the detection of allo-HLA crossreactivity by virus-specific memory T cells” - 29th European Immunogenetics and Histocompatibility Conference, April 2015, Geneva, Switzerland
- “Allo-HLA reactivity by HIV-specific T cells: Important implications for solid organ transplantation in HIV seropositive patients” – The Transplantation Society of Australia and New Zealand, June 2015, Canberra, Australia
- “Allo-HLA reactivity by HIV-specific T cells: A potential adjunct to HIV vaccine design?” – 38th Annual Scientific Meeting of the Australasian Cytometry Society, October 2015, Perth, Australia
Figure 1: Flow cytometric detection of cross-reactivity
Single antigen lines (SALs) were cultured overnight with HIV-specific CD8+ T cell clones. Recognition of the allo-HLA molecule on the SALs by the CD8 T cells resulted in activation of the T cells (up-regulation of CD137, A) and lysis of the SALs (7AAD expression, C). In comparison, figures B and D demonstrate examples of allo-HLA molecules that did not activate HIV-specific CD8 T cells.

Figure 2: Cross-recognition of allo-HLA molecules results in activation of CD8+ T cells
Recognition of the allo-HLA molecule HLA-A*33:03 by HLA-B*07:02/GL9 HIV-specific CD8 T cells was detected by increased expression of the activation molecule CD137.

Figure 3: Cross-recognition of allo-HLA molecules causes lysis
Recognition of the allo-HLA molecule HLA-A*33:03 by HLA-B*07:02/GL9 HIV-specific CD8 T cells results in lysis of the single antigen line (SAL) expressing the allo-HLA molecule.

Figure 4: Cross-recognition of allo-HLA molecules results in IFN-γ production
Recognition of the allo-HLA molecule HLA-A*33:03 by HLA-B*07:02/GL9 HIV-specific CD8 T cells was detected by measuring the cytokine IFN-γ.
SUMMARY
Manipulating the immune system to treat cancer is currently becoming a viable option for many patients that fail conventional therapies. Due to their ability to target a wide range of different cancers, natural killer (NK) cells are ideal candidates for immunotherapy. We have characterised several subsets of NK cells that expand in the context of Cytomegalovirus (CMV) infection. These NK cells display a mature phenotype, have increased functional capabilities, increased potential to mediate antibody dependent responses, increased survival capacity and the potential to be long lived. Clinically, CMV infection has been associated with reduced risk of leukemic relapse and improved overall survival in transplant recipients. The overall aim of this project is to determine if CMV expanded NK cell subsets have enhanced anti-tumour potential. To achieve this, the project is divided into two main aims:

Aim 1: To determine which subset(s) of NK cells has the capacity to eliminate tumours in vitro.

Aim 2: To evaluate if CMV infection drives anti-tumour responses in vivo and determine the efficacy of transferring CMV expanded NK cell subsets in a preclinical model.

Progress To Date: This project officially began in May 2015. Progress has been made towards completion of both Aim 1 and Aim 2.

Aim 1: During 2015, healthy donors were recruited from the Red Cross Blood Bank (27 CMV+, 23 CMV- collected by the end of 2015). PBMC was stored and NK cell subsets characterised by flow cytometry. We did not observe any differences in the phenotypes of these cells compared to previously published work (1, 2). Cell line panels have been selected from patient derived tumour cells (10 acute lymphoblastic leukaemia (ALL) and 15 melanoma). Multiparametric flow cytometry panels have been designed and optimised to detect NK cell activity (cytotoxicity and cytokine production) against the tumour cell panel. Our preliminary evidence has demonstrated that NK cells from CMV seropositive donors have increased capacity against B cell ALL but not T cell ALL. Additionally, NK cells from CMV seropositive donors increased capacity to eliminate 7/7 of the melanoma cell lines tested so far. These results need to be confirmed against all tumour cell lines as well as all PBMC donors.

Aim 2: Two preclinical models (melanoma and B cell ALL) are being utilised to determine if and how CMV drives anti-tumour responses in vivo. Preliminary experiments have identified that active CMV infection is required to increase survival in mice with either aggressive melanoma or leukaemia. Experiments are currently being performed to confirm these findings. During 2015 we encountered some difficulties with our leukaemia model that delayed our experiments. Even though this model was established by our collaborators, we had difficulty replicating it in our laboratory. This model involves transducing bone marrow cells with BCR-Abl to drive B cell ALL and transplanting these cells into naive mice. This model did not reliably develop leukaemia and the timing to develop disease was extremely varied. Recently we have begun to culture B ALL cells from a mouse that developed leukaemia. These cells grow well in vitro and robustly develop leukaemia with similar kinetics in 100% of mice. This is the model that we have used to demonstrate increased survival with active CMV infection and will continue to use this model for all future experiments.

Current and Future Work:
- Complete identification of NK cell subset(s) with enhanced capacity to eliminate leukaemia and melanoma.
- Identify the receptor/ligand pair that is involved in enhanced anti-tumour activity.
- Investigate additional ways to boost NK cell mediated anti-tumour activity (e.g. monoclonal antibodies directed at tumour antigens).
- Complete in vivo experiments to determine if CMV drives anti-tumour responses.
- Perform NK cell depletion experiments to identify the role of NK cells in this response.
- Determine the efficacy of adoptive transfer of CMV expanded NK cell subsets.

Additional Outcomes:
- Preliminary findings have been presented at two conferences in 2015 – Australasian Cytometry Society Annual Meeting and the Kirkbride Melanoma Symposium.
- Results from this project are expected to be presented at conferences in 2016
- No publications have arisen from this work to date
References
Mesothelioma is an aggressive cancer, resistant to current treatments, with poor survival rates. We discovered that a factor produced by the tumour, known as FGF9, interferes with the body’s natural anti-tumour immune response (immunosuppressive). We found that reducing tumour FGF-9 levels resulted in reduced tumour growth. This study aims to examine the mechanisms through which FGF9 affects the immune system and tumour growth and to inform future development of targeted mesothelioma treatments.

**Aims of the study**
1. To identify and characterise the immune cells affected by FGF-9.
2. To assess the mechanism/s by which FGF-9 exerts its immunosuppressive effect.
3. Enhance the anti-tumour effect of anti-FGF-9 strategies using targeted immunotherapy.

To address these aims we investigated the effect/s of FGF-9 on CD8+ and CD4+ T cell responses in vitro as we know from our preliminary immune depletion experiments that both CD8+ and CD4+ T cells play a role in the anti-tumour response against mesothelioma. We hypothesised that one of the ways the FGF9 produced by mesothelioma tumours affects T cells is via suppression of CD8+ and CD4+ T cell activation to inhibit the anti-tumour immune response. We suggest this is due in part to an increase in regulatory (inhibitory) T cells (Tregs). T cells obtained from naïve mouse spleens were activated using CD3/CD28 in the presence of FGF9 (100ng/mL). FACS analyses demonstrated that, in the presence of FGF9, the percentage of Tregs increased compared to untreated controls and the percentage of activated CD8+ and CD4+ T cells decreased which confirms that FGF9 has a direct inhibitory effect on CD8+ and CD4+ T cell activity.

In order to determine whether the effect of FGF9 requires binding of FGF9 receptors on T cells, we used a receptor antagonist (BGJ398) in vivo to block FGF9 binding to T cells and assessed whether this rescued the anti-tumour response. Flow cytometric analyses were performed for markers of CD4+ and CD8+ T cell activation (ICOS), inactivation (CTLA-4) and exhaustion (PD-1) and the presence of regulatory T cells (Tregs) in tumour, draining and non-draining lymph nodes. BGJ398 significantly reduced tumour burden in mice treated with the FGFR inhibitor (p<0.0001). We saw a striking decrease in the percentage of inactivated CD4+ and CD8+ T cells in the tumour microenvironment of BGJ398 treated mice compared to controls and a decrease in the percentage of exhausted CD8+ but not CD4+ T cells. The proportion of Tregs was also halved in BGJ398 treated tumours compared to controls. These results demonstrate that FGF9 blockade restores anti-tumour immunity which leads to significant tumour regression.

Other mechanisms of immune suppression that prevent effective anti-tumour immunity such as negative immunologic regulators (checkpoints; CTLA-4 and PD-1) are being targeted in several cancers. We therefore aimed to determine whether we could enhance the therapeutic efficacy of anti-FGF9 therapy by combining the FGFR inhibitor with antibodies against these molecules. We trialed an anti-PD-1 antibody alone and in combination with BGJ398 in the subcutaneous model of mesothelioma and found that anti-PD-1 did not enhance or perform as well as BGJ398 treatment alone.
In the next stage of work we will further characterise the immune cells and their response to FGF9 in vitro and in vivo and explore other possible mechanisms of action. We will also test the efficacy of BGJ398 in our pleural mesothelioma mouse model and trial additional checkpoint blockade therapies in combination with the FGFR inhibitor.

**Invited Oral Presentations**


**Collaborations**

We have entered into an industry partnership with a pharmaceutical company to determine the efficacy of a new FGF receptor inhibitor and combination therapy with immune checkpoint blockade.

**Grants**

2015-2016: SCGH Research Advisory Council Grant (consumables; $43,185); The effect of Fibroblast Growth Factor 9 on anti-tumour immunity in malignant mesothelioma.
Clinician Research Fellowships

PROJECT TITLE 1
Restrictive versus Liberal Fluid Therapy in Major Abdominal Surgery [RELIEF study]

PROJECT TITLE 2 The influence of anaesthetic depth on patient outcome after major surgery [BALANCED study]

CLINICIAN RESEARCH FELLOW
Clinical Professor Tomas Corcoran

Project Aims
These two trials are multicentre, randomised controlled trials to examine the influence of two major anaesthesia interventions on patient outcomes.

The RELIEF study will examine the influence of total amount of fluid that patients receive during their surgical period, on the long term outcomes after anaesthesia and surgery.

The BALANCED study will examine the influence of the depth of anaesthesia, and total dose of anaesthetic agents, on long term patient outcomes following surgery and anaesthesia.

Report Progress
Both trials are currently actively recruiting in over 50 sites in Australia, New Zealand, Hong Kong, the USA and the UK. The BALANCE study has recruited over 3300 patients, and is almost at the half-way stage. The RELIEF study is currently within four months of completion (2100 patients) of recruitment, approximately one year ahead of schedule.

There have been benefits both in terms of my research career advancement, and in terms of building profile and capacity for research in WA Health. As a consequence of the time afforded to me by my Clinician Research Fellowship, there have been a considerable number of achievements that have accrued. I was the ANZCA ASM 2015 invited speaker in Adelaide; and an invited speaker for the International Collaborative Clinical Trials in Anaesthesia Conference, Prato, Italy, 2015. I was also successful in securing a $4.6m NHMRC grant funding for the PADDI trial as the CIA (the largest NHMRC grant awarded in 2014). This project has now started recruitment and is expected to be commencing in WA sites within the next three months.

Importantly, the PADDI trial funding has permitted me to employ a Research Manager with a WA Trial office (in Royal Perth Hospital). This office will be co-ordinating sites both domestically and internationally, hence advancing the profile of WA as a State in which high quality multicentre international research is being led.

I am the lead Investigator in two sub-studies of the RELIEF trial - a BNP sub-study (adverse cardiac outcomes) and an economic sub-study. Both of these sub-studies have attracted grant funding (Medical Research Foundation, RPH, and the Australia and New Zealand College of Anaesthetists (ANZCA)). I am also a Chief Investigator on a genomic/epigenetic sub-study of the RELIEF trial, which has secured funding of over $100,000 from ANZCA.

Finally, I am a Chief Investigator on an application to the NHMRC 2016-2017 (C-CAFÉ Trial) which will examine perioperative patient blood management for colorectal cancer. None of these would have been possible without the Clinician Research Fellowship.

SUMMARY
As a consequence of the time afforded through this Fellowship, I am bringing to fruition a large, high-profile international clinical trial (PADDI Trial). I have been in a position to advance into the field of perioperative genomics (RELIEF- genomics sub-study), and have developed a number of lines of investigation into health economic outcomes (RELIEF- Economics sub-study). I have also been in a position to participate in a large number of new initiatives, many of which are directly or indirectly related to the trials that I am currently pursuing. Many of these trials are clinical effectiveness trials or pragmatic research which will involve the introduction of models of care or management that will be at the forefront of current medical knowledge and care.

The resultant papers (from both the main trials and the sub-studies) will be published in leading international medical journals. They will, in all likelihood, change aspects of the practice of anaesthesia care, globally. The output from these initiatives will take some time, but through these initiatives, I have helped my research network to position Australia in general, and WA in particular, at the forefront of anaesthesia and perioperative medicine research. The extension into perioperative genomics is a truly exciting development that has come about through my Fellowship and will be an ongoing line of investigation in WA. This will be facilitated through collaboration with the very strong genetics capacity in WA.
SUMMARY
Cystic fibrosis is a life-shortening, lethal genetic disease that affects over 70,000 people worldwide. It commences in early infancy, usually before patients develop symptoms. An existing, world leading surveillance program for children with cystic fibrosis from birth was the platform that we used to investigate the early lung micro-environment using novel methodologies including: combining fibre-optic and luminescent technology to perform accurate measurements of the lung surface, developing new methods to sample the lower airway in young children, the analysis of metabolic markers, sensitive measures of bacterial and viral infection and biochemistry. The results of these analyses will be used to develop simple tests to monitor lung disease in babies and pre-school children. This age group currently require regular anaesthetics to perform the current gold-standard measurements of lung disease.

PROGRESS REPORT
The Clinician Research Fellowship provided by the WA Department of Health and the Raine Medical Research Foundation allowed me to study a number of important research questions with potential to help children with cystic fibrosis. I specifically focused on studying cystic fibrosis in young children because if we can prevent the disease from progressing early on, then we can keep people with cystic fibrosis healthy.

The first research question that I answered with the help of a dedicated team was about airway surface acidity (pH). A highly contentious and topical issue is whether the pH of the airway surface liquid is reduced in cystic fibrosis. Reduced airway surface liquid pH has implications for potential therapies and has been demonstrated in animal models of cystic fibrosis. Until now accurate measurements of the ultrathin airway surface liquid layer in the lungs has not been possible in humans. Through international collaboration between medical doctors, physiologists, and biochemical engineers we developed technology to accurately measure airway surface liquid pH in the lungs of children with, and without, cystic fibrosis. We have demonstrated conclusively that the airway surface liquid pH is not affected by the genetic mutation that causes cystic fibrosis. So, scientists can now focus their efforts on other potential targets for intervention.

The second area that I focused on was using novel ways to sample the ultra-thin layer of airway surface liquid that covers the lower airways in order to find improved ways to measure lung disease. Accurate measurement of lung disease is important to keep track of disease progression (young children can look healthy from the outside while their lungs may be less healthy), and also to measure the effect of treatments in clinical practice and in clinical research trials. The current best way to measure lung disease in children with cystic fibrosis is through CT-scanning. CT-scanning is reasonably safe but we are trying to develop ways to measure lung disease without the use of ionising radiation.

I demonstrated that a new way of lower airway sampling can be used to get better samples than traditional sampling methods can provide. With a team we identified substances in the airway surface liquid that can help detect and measure lung disease. We will now determine if we can detect these substances in exhaled breath. If successful, then we may be able to use our findings to develop a method where we can simply capture and analyse the exhaled breath from young children in order to measure their lung health.

PUBLICATIONS

INTERNATIONAL SCIENTIFIC CONFERENCE PRESENTATIONS

Acknowledgement

I am deeply grateful to the WA Department of Health and the Raine Medical Research Foundation for helping to make the above research, and a number of other research projects, possible. Being both a clinician and a scientist can be challenging. The Fellowship has not only facilitated the above projects, but also allowed me to develop a number of new research projects in collaboration with top experts in their fields nationally, and internationally. Results are expected to improve the lives of children with cystic fibrosis, chronic suppurative lung disease, and childhood interstitial lung disease.
SUMMARY

Brain tumours are the second most common childhood cancer, with 200 children affected in Australia each year. Many children with brain tumours continue to die of their disease, whilst survivors are often left with devastating life long side effects. Our goals are to harness the power of innovative model systems of childhood brain tumours, in order to test the effectiveness of new treatments for these devastating diseases, so that the most promising therapies can be taken through to the clinic.

PROGRESS REPORT

Few new drugs have entered clinical trial for medulloblastoma, pineoblastoma and ependymoma. Potential new chemotherapies frequently fail in the clinic because until recently, accurate laboratory models of these diseases did not exist and new therapies could not be appropriately tested in the lab. The work funded here is significant for several reasons. This grant, along with previous and current funding, has led to the development of multiple in vivo models of medulloblastoma, pineoblastoma and ependymoma that can now be used to evaluate new therapies, such that only those with the best potential to be effective are put forward for paediatric cancer clinical trials. Although our assessments of dacomitinib and CDDO-Im revealed that they are not more effective than the existing clinical protocols, our results have prevented the evaluation of these drugs in clinical trial. Therefore, patients will not be subjected to inactive therapies, and will hopefully be enrolled on trials where there is a better chance they will benefit from new treatments.

These assessments have become the framework for a large-scale drug-screening pipeline to evaluate the efficacy of novel compounds against medulloblastoma, pineoblastoma and ependymoma. Our aim moving forward is to rigorously evaluate new therapies using our robust mouse models that only test drug combinations that yield synergistic results in vitro.

PUBLICATIONS


SUMMARY
Cumulatively rare diseases affect approximately 1 in 12 individuals, which equates to 1.5 million Australians including over 400,000 children. This project provides a framework for the coordination of Western Australian Rare Diseases (RD) research and clinical care that integrates with global initiatives. It develops resources that: 1). Define RD impact; 2). Generate new functionality of existing RD registries; 3). Facilitate modular generation of novel RD registries; 4). Provide new objective tools, including 3D facial analysis, for RD diagnosis, description and treatment monitoring; 5). Facilitate access to resources for individuals living with RD; and 6). Synergistically contribute towards international RD efforts.

This Clinician Research Fellowship is providing a unique and unparalleled opportunity and flexibility to develop translational research skills from the coal face of the health system. In doing so, it has supported the implementation of new diagnostic initiatives for genetic and rare diseases (genomic and phenomic) including the clinical genomic diagnostic pipeline, 3D facial analysis and the Undiagnosed Diseases Program. Simultaneously it has facilitated the improved ascertainment and analysis of globally unique rare diseases data, and relatedly congenital anomalies (birth defects) and cerebral palsy, for health system planning through transformational public health policy. It has also enabled local, national and international partnerships for capacity building in Western Australia and beyond; enhanced health in WA, particularly through improved diagnosis of genetic and rare diseases; and has simultaneously contributed to the Western Australian knowledge economy.

Research Translation and Diffusion
The two overlapping initiatives in this Fellowship have been implemented and further embedded into clinical care are summarised below:

1. Rare and Undiagnosed Diseases Diagnostic Service – This service has trebled the rate of confirmed genetic diagnosis in clinical service.

2. The Undiagnosed Diseases Program, part of the Undiagnosed Diseases Network International (GB a founding member of the International Board of Directors) – This is being initiated at PMH as a novel and internationally coordinated approach for those with extraordinary clinical (diagnostic) need.

3. Rare Diseases Data from WARDA – This is providing world first population level information on the impact of congenital rare diseases for health system planning for improved health care.

4. Patient Archive and the Orphanet Knowledge Management System – Building clinical interfaces and knowledge management tools for the clinical genomics and for curation of congenital anomalies and cerebral palsy.

5. Clinical implementation of 3D facial analysis for genetic and rare diseases - first stage implementation of 3D facial analysis in the clinical work flow for genetic and rare diseases.

Advancing Knowledge
International Oral Conference Presentations
Rare Diseases in Australia: People, Policy and Partnerships First Vietnamese Rare Diseases Multi-stakeholder Forum.

The Rare and Undiagnosed Diseases Diagnostic Service Asia-Pacific Congress of Human Genetics.

The Rare and Undiagnosed Diseases Diagnostic Service Human Genetics Society of Australasia.

An Aboriginal family with a novel familial genetic condition Human Genetics Society of Australasia.

Phenotyping
First Australasian Undiagnosed Diseases Program Workshop.


Chair of the Local Organising Committee for International Conferences
Human Genetics Society of Australasia, August 2015

First Australasian Undiagnosed Diseases Program Workshop

International Session Chairs or Panels
First Vietnamese Rare Diseases Multi-stakeholder Forum

Science on the Swan Originator and co-convenor the the Science on the Swan initiative “Faces of WA”. A multi-sector initiative to build on unique WA strengths in 3D facial information for health, arts and education.
National/ Interstate Oral Presentations or Panels
CliniFace – CRC for spatial information conference
Health Panel – CRC for spatial information conference
Garvan Institute – DiagKNOWsis across the Nullarbor

Committees and Boards
- Member of the Scientific and Medical Advisory Board, Rare Voices Australia
- Member of the Board of the Genetic and Rare Diseases Network (GaRDN), WA
- Member of the Diagnostics Scientific Committee of the International Rare Diseases Research Consortium (IRDiRC)

New position
- A/ Head of the Western Australian Register of Developmental Anomalies.

Published Papers


X-exome sequencing of 405 unresolved families identifies seven novel intellectual disability genes, Molecular Psychiatry, 2016 Jan;21(1):133-48

Media coverage/publicity
Print
- The Australian
  1. Article on the discovery of a novel familial genetic condition in an Aboriginal family.
  2. Article on the first Australasian undiagnosed diseases program workshop.

Television
- Hanoi, Vietnam, Nightly News – Rare Diseases partnerships in the Asia-Pacific.
- WA health department video – The Undiagnosed Diseases Program.

Youtube
- Facing 175 Million Invisible Children https://www.youtube.com/watch?v=ffK5CIvqXCK

Capacity Building
New Grants
Targeted Call for Translation of Clinical Genomics. NHMRC. Cl. $25m.

Improved models of care for Aboriginal genetic health care delivery. Lowitja Institute. Cl. approx. $400,000

Improved Models of care for Aboriginal genetic health care delivery. NHMRC partnership grant. Cl. approx $400,000

3D facial alliance of WA $72,000. PI.

CliniFace – delivering 3D facial analysis for the clinic – CRC-SI $ 150,000. PI

Goldfields Foundation. 3D facial analysis for Aboriginal Health $50,000. PI

Media Report
- The West Australian – 19 September 2015

Yin and Yang – rare diseases, with Lesley Murphy, Director of Rare Voices Australia

An article covered by Weekend West’ on 19th September 2015 documented a friendship that developed between Lesley Murphy and Professor Baynam. Lesley, the mother of a child born with Duchenne Muscular Dystrophy, lovingly cared for her son until his passing in 2015 at age 25 years from this rare degenerative neuromuscular disease. Lesley met Gareth in 2011 when she was part of a committee helping to start an awareness and advocacy group.

Although their approach to the impact of Rare Diseases is from different perspectives, Lesley and Gareth are working together to bring about change and improve our knowledge and understanding. In 2012 Lesley co-founded Rare Voices Australia, the national advocacy organisation to provide a collective voice for people living with rare diseases.
Gareth Baynam and Leslie Murphy

Photo provided by courtesy of The West Australian Newspapers
Hundreds of children in Western Australia (WA) are admitted to hospital each year with influenza. Preschool children and children with specific underlying conditions are at greatest risk of severe infection and death. WA is the only state with a publically-funded influenza vaccination program for all pre-school children. Following vaccine-associated adverse events in 2010, the uptake of childhood influenza vaccine has been poor.

The research undertaken with this WA Department of Health/Raine Clinician Research Fellowship will determine the effectiveness of influenza vaccine in West Australian children; explore the uptake in children with specific underlying conditions; and describe patient and parental factors that influence acceptance of this important public health intervention.

**Aims of the Project**

**Primary aim:**

1) Determine the effectiveness of inactivated trivalent influenza vaccination in West Australian children.

**Secondary aims:**

2) Investigate the uptake and effectiveness in children with predisposing medical conditions placing them at greatest risk of severe influenza infection.

3) Identify patient and parental factors which influence uptake and acceptance of influenza vaccination.

**Advancing Knowledge**

**Publications (Accepted and ‘in press’)**


**Acknowledgement**

The salary support provided by the WA Department of Health and the Raine Medical Research Foundation in the form of a Clinician Research Fellowship has enabled me to undertake research evaluating a key public health program in WA. This evaluation has been instrumental in the decision to continue and potentially expand the program, thereby impacting on the lives of many young children.

The Fellowship and the research made possible by this support has also been instrumental in seeking and further funding by NHMRC support to continue research into influenza.
SUMMARY

One of the major causes of morbidity and mortality in transplant recipients is infectious diseases and CMV is the commonest viral infection. Even subclinical reactivation of CMV is associated with adverse outcomes, caused by direct viral cytopathic effects as well as immune modulation induced by the virus. In healthy individuals a balance exists, keeping the virus in the latent phase, with the expansion of virus specific immune cells central to this control. In the setting of transplantation, two factors can occur to upset this balance:

i) new strains of CMV can be acquired through the donor tissue; and

ii) the recipient is immunosuppressed. This project is advancing our understanding of the host responses to CMV and how immunosuppression and the presence of new viral strains affect the usual status quo.

Using registry data we have demonstrated an association between CMV and increased cancer risk, that appears specific to recipients of well-matched organs and in the laboratory are starting to define the mechanisms by which CMV infection and immunosuppression alter the host immune response. Collectively this work is helping us to better understand the impact of immunosuppression and may drive changes in the way we manage our transplant recipients.

(a) Research Translation and Diffusion

Data from our preliminary work has demonstrated the limitation of serological testing for CMV, which has been part of our donor and recipient work-up process. Currently the laboratory assay used to determine prior CMV exposure is based on the detection of antibody, reactive against a laboratory strain of CMV-AD169. As CMV becomes attenuated through growth in cell lines and this can result in loss of genetic material, not all antibody epitopes that are present in wild-type viruses are displayed by the AD169 strain, and this can result in false negative results. We have demonstrated that up to 15% of patients may have false negative results (serologically negative but evidence of CMV specific T cells and/or increased frequencies of NKG2C+ NK cells-a marker of prior CMV exposure). As a result, we have changed our post-transplant management such that all patients now receive CMV prophylaxis for a minimum of three months.

(b) Advancing Knowledge

Cancer is one of the major causes of mortality and morbidity in kidney transplant recipients. Although there is now considerable evidence from observational studies demonstrating a substantial increase in the overall risk of viral-related cancers in transplant recipients compared to age and gender matched general population, the role of CMV in cancer development remains uncertain. A few observational studies have reported a higher incidence of cancer, particularly colorectal, lung and skin cancers among CMV exposed compared to CMV-naïve kidney transplant recipients, whilst others did not find a significant association between CMV and cancer risk in transplant recipients.
We undertook a retrospective study using data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry to assess the association between CMV viral serological status of the recipient and the risk of cancer development after kidney transplantation. The donor and recipient CMV viral serological status were divided into four groups: CMV donor seropositive/recipient seropositive (D+/R+), CMV donor seropositive/recipient seronegative (D+/R-), CMV donor seronegative/recipient seropositive (D-/R+), and CMV donor seronegative/recipient seronegative (D-/R-). We identified 8,140 deceased donor kidney transplant recipients during the study period. Of which, 895 recipients developed their first incident cancers during a follow-up time of 51,555 person-years.

Overall, the association between CMV viral serological status and cancer was modified by human leukocyte antigen (HLA) matching (p-value of interaction = 0.03). For recipients with 0-2 HLA ABDR mismatches, compared with the reference of CMV D+/R+, the adjusted hazard ratios (HR) for cancer incidence among those with CMV D-/R-, CMV D-/R+ and CMV D+/R- were 0.47 (95%CI: 0.24 – 0.91), 1.42 (95%CI: 0.97- 2.07) and 1.02 (95%CI: 0.67 - 1.57), respectively. In contrast, for those with > 2 HLA ABDR mismatches, there was no significant association between CMV donor/recipient viral status and cancer incidence after adjusting for the effects of age, gender, time on dialysis, the use of induction therapy, the presence and number of acute rejection episodes, and baseline immunosupression use.

Our study findings suggested that overall cancer incidence in CMV naïve kidney transplant recipients who had received well matched kidneys from CMV seronegative donors (CMV D-/R-) was significantly reduced compared to those who had previously been exposed to CMV and received kidneys from CMV seropositive donors (CMV D+/R+). Recipients with negative donor and recipient CMV serological (CMV D-/R-) status experienced at least a 9% reduction in the overall risk of cancer compared to recipients with prior CMV exposure (i.e. CMV D+ or R+). This is the largest cohort to date to explore the association between CMV status, immunological factors (HLA matching) and the risk of malignancy following transplantation. Mechanistic explanations for this finding are being sought and further validation in other cohorts is planned.

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(c) Capacity Building
Data generated from work undertaken for the WA Department of Health/Raine Clinician Research Fellowship has been of invaluable assistance in developing my research career. It has enabled me to combine my clinical practice with my research interests, has led to my appointments as a Laboratory Head with the Perkins Institute and as the Director of Research at Sir Charles Gairdner and Osborne Park Health Care Group. In addition, it has allowed me to develop new collaborations with interstate and overseas researchers and to continue to submit research grants in this field.

**Publications**


**Acknowledgement**

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SUMMARY
Critically ill patients sometimes require dialysis to replace kidney function as part of their treatment in the Intensive Care Unit (ICU). The ability to deliver the prescribed dose or amount of dialysis depends on minimising the number of delays which can interrupt treatment delivery. Adequacy of dose delivered to the patient also incorporates fluid balance control. This project will investigate if patients requiring dialysis receive the prescribed dose compared with the dose delivered. Factors impacting on the continuity of treatment, reduction in dose delivery and fluid balance control will be measured during the study. The project may assist in improving the quality of dialysis through better dose ordering and delivery to the critically ill patient. In support of the project a systematic review of the literature will be conducted on the reliability of daily fluid balance measurements compared with body weight changes in patients who require intravenous fluid and liquid nutrition as part of their treatment in ICU.

Progress Report
A risk for patients with severe acute kidney injury (AKI) is fluid overload when the effects of fluid therapy are not managed carefully. The study involved a review of observations of patients who received continuous renal replacement therapy (CRRT) – a form of dialysis used in ICU to treat AKI. Fluid overload is a condition where body water normally present is increased and when distributed in the wrong places can be harmful for the whole body. A problem highlighted by reviewing observations of fluid balance control during CRRT was that in this study daily fluid removal targets were not always achieved.

Some interruptions to treatment delivery observed in the retrospective study were unavoidable but awareness of the importance of meeting daily fluid removal targets has the potential to improve patient outcomes. The prospect of improving fluid balance control is now under investigation by prospective observations of fluid balance control following changes made to clinical practice. It includes the implementation of a system that uses green, orange and red flags to indicate the degree of success in achieving daily fluid removal targets. The importance of improving fluid balance control has also focused on the practice of fluid balance charting and in the monitoring of body weight changes.

Acknowledgement
The experience I have gained as a recipient of the 2013 WA Department of Health/Raine Clinician Research Fellowship has been invaluable. My profile as a researcher has profited from being awarded the Fellowship. I have increased the number of research papers published as primary author and the opportunity to attend conferences has enabled me to interact with other researchers in the same field of medicine who have faced similar challenges in the course of their work. It has also highlighted the importance of investigating routine nursing activities like fluid balance charting that when clinical practice is reviewed, has the potential to improve patient outcomes.


It was particularly rewarding that the top Medical Reporter for The West Australian, Ms Cathy O’Leary, covered the importance of this work in an article published on 5 February 2015.

Warning on fluid overload

WA hospitals are being urged to use a traffic light warning system to prevent dangerous fluid overload in critically ill patients. A Royal Perth Hospital study found that some patients meeting criteria for acute kidney failure were not having their fluid levels managed properly, putting them at risk of organ damage.

They were often given inappropriate antibiotics, liquid nutrition and fluids to treat low blood pressure and dehydration.

Clinical nurse Hugh Davies said that overload put them at increased risk of further medical complications and death. His study, funded by a Clinician Research Fellowship grant, analysed information from patients given continuous renal replacement therapy, a form of dialysis used to treat acute kidney failure.

“It found daily fluid targets were not being met more than a quarter of the time,” Dr Davies said.

He recommended that hospital intensive care units adopt a traffic light system to show the patient’s total fluid load, also taking into account changes in their weight.

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PROJECT TITLE
Does exercise training improve muscle strength and function after burn injury?

CLINICIAN RESEARCH FELLOW
Dr Dale Edgar

SUMMARY
The functional outcomes after burn trauma remain a long-term burden to patients, families and the health service. Muscle strength loss occurs due to the skin repair process, irrespective of burn size. Strength loss causes loss of function. Patients are hindered in returning to work and normal life.

The aim of this study is to determine if adding resistance exercise training to routine practice reduces loss of strength and function. The study could feasibly benefit burn survivors around the world through justification of simple exercise training regimes which could apply in any environment after acute burn.

Progress Report
This study is well on the way to unpacking the mysteries of prescribing exercise therapy for acute burn patients. To date, the reportable progress has been realised in related research in parallel and within the main resistance exercise study, which is ongoing.

Mr Gittings, in fulfilment of his PhD study program, and Associate Professor Edgar have confirmed the reliability and validity of a number of outcome measurement tools which are being used in the CRF-supported study. Quantifying burn patient activity is aided by our novel understanding of the parameters to accurate performance of the ActivePAL remote monitoring devices and methodology. In addition, the applicability of the survey tool to measure functional outcomes in patients with lower limb burns, the Lower Limb Functional Index (LLFI), was confirmed through our work. Once published, the outcomes of these studies will be applicable in burn units around the world, particularly the LLFI as it is cost free and has multiple language translations.
SUMMARY
Lumbar discectomy is considered a safe, efficacious and cost-effective treatment for selected cases of patients with leg pain associated with the presence of a disc protrusion (sciatica), but despite technically successful surgery, 30% of patients complain of persistent pain on long-term follow up. Identification of possible predictors for a negative outcome is important in the search for appropriate pre- and/or post-operative care and prevention of persistent disability.

Nerve root compression and inflammation can cause damage to both myelinated (large A, small A fibres) and small unmyelinated sensory fibres (C-fibres). Some nerve fibre populations may be more affected than others and this is important to identify as the extent of sensory fibre loss may account for poorer outcomes. Enhanced sensitivity of specific neuronal populations (central sensitisation) is associated with the development and maintenance of persistent pain. However, the role of altered nerve fibre function in sciatic pain and the association with poorer outcomes after lumbar discectomy has not yet been explored.

Overall aim
The overall aim of this project is to determine the predictive value of QST parameters in patients with lumbar radiculopathy/radicular pain, for predicting patients’ clinical outcome after lumbar discectomy.

Hypotheses:
1. There will be sub-groups of participants with differing somatosensory profiles before surgery.
2. There will be a difference in QST profiles between patients with and without persistent pain after surgery.
3. Sensory profiles showing enhanced pain sensitivity will be associated with pain persistency and functional status at 3 and 12 months follow-up after surgery.

We proposed to recruit 50 patients with radiculopathy/radicular pain from the elective surgery waitlist at Sir Charles Gairdner Hospital (SCGH) over a period of 18 months. All patients will undergo lumbar discectomy performed by one neurosurgeon. A standardised QST protocol comprising all of the somatosensory sub-modalities that are mediated by different primary afferents (C-, A -, A β-) will be performed prior to surgery. QST will be conducted in the patients’ main pain area and contralateral side, in the affected dermatome and at a remote control site. The presence of other predictor variables (medical/psychological/cognitive behavioural factors) will be captured by questionnaires. Follow-up at three months will include QST and measurements of pain intensity, pain descriptors, functional status, health related quality of life, return to work and health care utilisation. A further one-year follow-up will include the same measurements except QST.
Progress and results to date
Patient recruitment is on target; the 18 months recruitment phase ended in March 2016. Seventy-nine patients had been recruited and gave verbal consent to participate in the study. Of those, 47 patients did participate and further seven patients are scheduled to undergo surgery in April 2016. Twenty-five patients did not participate. Three months outcome data have been obtained for 41 patients; so far no participant has been lost to follow-up at the three months time point. Twelve months outcome data have been obtained for nine patients.

Preliminary baseline group data on 47 patients indicate a significant loss of function in all nerve fibre populations in the symptomatic leg compared to the asymptomatic leg. However, at an individual level we observe that some patients demonstrate a loss of function in only small fibres (hyposensitivity to thermal stimulation) or only large fibres (hyposensitivity to mechanical stimulation) as well as various combinations of loss and gain of function when comparing the symptomatic and asymptomatic side. These observations support our hypothesis that there are sub-groups of participants with differing type of nerve fibre dysfunction as a result of nerve root compression caused by a disc protrusion. The sensory testing in our study seems to add diagnostic value for the assessment of nerve fibre dysfunction in people with sciatica as we observed small nerve fibre dysfunction which can not be diagnosed by conventional nerve conduction studies.

Next stage
Three and 12 months outcome data will be obtained in the next 14 months. In order to validate our observations and to explore if specific sensory profiles are associated with pain persistency, lower limb QST reference data have to be obtained from age and gender matched healthy control subjects for each body region assessed in our patient cohort. This is even more important for the evaluation of sensory abnormalities in patients who demonstrate bilateral sensory alterations as a side to side comparison may not be valid. We anticipated that the lower leg would be nominated as main pain area, however other lower limb regions have also been nominated, hence we will have to recruit more healthy controls than originally planned.

RELATED PUBLICATIONS

OTHER PUBLICATIONS


CONFERENCE ABSTRACTS
Tampin B., Royle J, Olsen L, Bharat C, Goucke R. Psychological factors can contribute to a false classification of neuropathic pain on the painDETECT questionnaire. Australian Pain Society 36th Annual Scientific Meeting, Perth, Australia 2016. (Rapid Communication Session, Poster)


Accepted conference abstracts


RESEARCH SUPPORT AWARDED
2015 Grant in Aid Arthritis Australia

This grant supports a concurrent study at the Neurosurgery Spinal Clinic, Sir Charles Gairdner Hospital, which is conducted in collaboration with my associate investigators Professor Christopher Lind and Associate Professor Helen Slater. The study investigates sensory nerve dysfunction in patients with unilateral sciatica with or without nerve root compression who do not meet criteria for surgery. Similar to the Fellowship project, the study explores the associations between QST findings and persistent pain and functional outcomes at 3 and 12 months.

INVITED SPEAKER
2015 Australian Pain Society 35th Annual Scientific Meeting, Brisbane

Topical session: “The value of quantitative sensory testing (QST) in the assessment of pain disorders: Developments and perspectives”. Invited Session Coordinator, Chair and Presenter
SUMMARY
Venous thromboembolism (VTE) including pulmonary embolism (PE) is a major morbidity after major trauma. Currently, the best way to prevent fatal PE in patients who are at risk of bleeding after major trauma is uncertain. A filter placed inside the major vein inside the abdomen has been widely used as a mechanical means to prevent PE for patients who cannot tolerate other means to prevent venous thromboembolism. This study will compare 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.

PROGRESS REPORT
The study is still in its early phase and this has not changed existing policies. The initiation of the trial has, however, increased the awareness of risk of venous thromboembolism in trauma patients and all severely trauma patients now screened for contraindication to anticoagulation on admission and this has increased the early initiation of pharmacological venous thromboembolism prophylaxis both in patients screened for the trial and recruited in the trial.

Effect of the Fellowship supported research work on clinical practice
The study is still in its early phase and this has not changed existing policies. The initiation of the trial has, however, increased the awareness of risk of venous thromboembolism in trauma patients and all severely trauma patients are now screened for contraindication to anticoagulation on admission and this has increased the early initiation of pharmacological venous thromboembolism prophylaxis both in patients screened for the trial and recruited in the trial.

Conference presentations
2015 Sept: Australian Society of Anaesthetists and New Zealand Society of Anaesthetists Combined Scientific Congress (Free paper oral presentation: Determinants of urinary output response to intravenous furosemide)

2015 Aug: Malaysian Intensive Care Society Annual Scientific Meeting, Kuala Lumpur (Three invited talks: Diuretics in acute kidney injury, Pitfalls in haemodynamic monitoring, Predicting outcomes of critically ill)

2015 May: Royal Australasian College of Surgeons Annual Scientific Congress, Perth (One invited talk: Trauma prevention program)

Publications


PROJECT
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


Grants obtained in 2015:

1. Medical Research Foundation (MRF) Project Grant, Royal Perth Hospital: “Predicting venous thromboembolism using advanced laboratory tests” (CIA $20,000 over 1 year).

2. Jackson Rees Research Award, Australian Society of Anaesthetists: “Effects of resveratrol on risk of acute kidney injury and coagulation parameters in a haemorrhagic shock model” (CIA $25,000 over 1 year).

3. Translational Research Project Grant, State Health Research Advisory Council (SHRAC): “Use of Melatonin to prevent delirium” (CID: $264,000 over 2 years).

4. Translational Research Project Grant, SHRAC: “Cranial reconstruction using Mesenchymal Stromal Cells (MSC) and a bioceramic scaffold, a Phase II study” (AI1: $$260,444 over 2 years).

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Prizes, new appointments and academic progression:

1. 2015 Feb–date: Adjunct Associate Professor, Murdoch University.


3. My h-index and i10 index have been increased to 28 and 85 to date, respectively.

The specific research project supported by the WA Department of Health/Raine Clinician Research Fellowship is what trauma researchers have been talking about for years but have never been able to accomplish. There is no doubt that I would not be able to initiate this study with many other likeminded trauma clinicians and researchers if not because of this people-support grant. To be able to be the Chief Investigator on what will surely be a landmark study is extremely fulfilling. In addition, the WA Department of Health/Raine Clinician Research Fellowship has made an enormous difference on my overall research productivity, well beyond the specific project supported by this people-support grant.
Aims of the Project
1. To determine the reliability of clinical assessment of dry weight in comparison to IVCUS.
2. To determine the incidence of intradialytic adverse events that are related to ultrafiltration.
3. To determine whether the additional use of IVC-US in determination of haemodialysis patients' volume status is able to reduce the incidence of ultrafiltration related adverse events.

Progress Report
The WA Department of Health/Raine Fellowship has allowed me to investigate the fluid status of haemodialysis patients while they are on their clinical treatment. Patients with chronic Renal Failure need haemodialysis treatment to survive. Fluid removal during haemodialysis can have significant side effects such as circulatory collapse and loss of consciousness which is undesirable. With the use of ultrasound nurses have the opportunity to understand the fluid status of their patients better and to adjust the fluid removal of an individual, so that negative consequences from the treatment itself can be avoided. It also offers a visual impression of the direct impact of a medical treatment on the health of a patient.

These findings can lead to a novel approach in the assessment of a patient’s fluid status by renal nurses which, in return, could deliver a better and safer treatment to haemodialysis patients. The addition of ultrasound measurement could potentially improve the health outcomes for haemodialysis patients. This may include a direct positive impact on their quality of life.

This Fellowship also enabled me to significantly progress my academic pathway to a PhD in Nursing. It allowed me to perform research relevant tasks while at the same time I was able to advance my scholarly skills. It empowered me to attend a broad variety of scientific seminars and to gain more experience in the field of clinical research. Additionally, I was able to refine my clinical skills in performing ultrasound and it will allow me to train other nurses in this specific expertise. I also feel deeply grateful and thrilled by having this fantastic opportunity to further my clinical career and to network and collaborate with like-minded scientists.
Raine Priming Grants

1. Bates KA, Drummond ES, Cozens GS and Harvey AR. Vascular insufficiency, not inflammation, contributes to chronic gliosis in a rat CNS transplantation model. Restorative Neurology and Neuroscience. Accepted 22/12/2015.


7. Tanaskovic S, Fernandez S, Sarasewati H, Yunihastuti E, Gani RA, Djauzi S, Price P. Naive and memory CD4+ T-cells are differentially affected in Indonesian HIV patients responding to ART. Viral Immunology 2016; accepted for publication.


Clinician Research Fellowships


The Raine Study

Professor Peter Eastwood
(Raine Foundation Scientific Director)
Professor Leon Straker
(Raine Foundation Associate Scientific Director)
Jenny Mountain (Raine Study Manager)

The Raine Medical Research Foundation has generously supported the Western Australian Pregnancy Cohort (Raine) Study since the cohort’s inception over 26 years ago.

The Raine Study cohort is one of the largest successful cohorts of pregnancy, childhood, adolescence and now adulthood to be carried out anywhere in the world. The participants, now at an average age of 27, have been assessed 12 times since their mothers were recruited at 16 to 18 weeks of pregnancy. There is frequent contact between enrolled families and study organizers and there is enthusiasm amongst participants to provide high quality information. Consequently, the Study has high retention rates, with over 2000 (70%) of the original cohort participants still involved in study activities. The Raine Medical Research Foundation provides funding to support the position of the Raine Study Scientific Director(s).

In January 2015 The Raine Study moved from the Telethon Kids Institute to the University of Western Australia and was incorporated into the School of Population Health. The new location has increased capacity for office space and assessment rooms.

2015 was a busy and productive year for The Raine Study. There were six successful grant applications, NHMRC project grants were awarded to Peter Eastwood et al, to examine the prevalence, phenotype and genotype of common sleep disorders in The Raine Study parents, and Pat Holt et al, to examine the waxing and waning of asthma during transition from teens to adulthood. Sharon Parker et al received an ARC grant to examine work design and the interplay of work and person factors. This study will examine how personality and demographics shape or constrain an individuals’ work. A National Breast Cancer Foundation Grant was awarded to Jennifer Stone et al, to pilot a new method of measuring breast density. Two grants were awarded by the WA Department of Health. Peter Eastwood et al received a WA Future Health grant to enhance existing Raine Study resources and capabilities and to contribute new data to the Study. Sarah Foster et al received a WA Targeted Research fund grant to examine alcohol outlets and the implications for alcohol consumption patterns and mental health in adolescents and young adults.

At the end of 2015 two NHMRC project grants for 2016 were awarded, one to Trevor Mori et al, to assess the early life predictors of ectopic (internal) fat and its association with cardiometabolic health and disease in the Raine Study age 27 follow up (2016), and the other to Peter Eastwood et al, to examine previously collected sleep study data and the relationship between obstructive sleep apnoea and craniofacial features.

Raine Study researchers published 58 new scientific papers in 2015, with another six accepted for publication.

The parents of Raine Study participants who completed a sleep study were invited to attend an overnight sleep study at the UWA Centre for Sleep Science and participate in other assessments including eyesight measurements, a DXA scan, lung function testing, blood pressure, anthropometric testing, accelerometry and to provide a blood sample. Disturbed sleep is common in the Australian community and the objectives of the study are to establish the prevalence, phenotype and genetic basis of sleep disorders, particularly obstructive sleep apnoea, insomnia, restless legs syndrome and periodic leg movement syndrome in middle aged people. Together, the parent and children datasets will define any associations between parent and child sleep disorders and lead to the discovery of genetic variants associated with common sleep disorders. In 2015 nearly 300 parents completed the overnight sleep study and assessment. Data collection will continue throughout 2016.

In January 2015 the Raine Study Executive Committee awarded two Raine Study PhD top-up scholarships to Sunil Bhat and Anahita Hamidi.

The eighth Raine Study Annual Scientific Meeting was held on Friday 18 September 2015 at the University Club, UWA. The meeting was formally opened by the Governor of Western Australia, Raine Study Patron and Raine Study parent, Her Excellency the Honourable Kerry Sanderson AO. A highlight of the day were talks by Judith and Michael about their experiences as Raine Study parents and as participants in The Raine Study parent sleep study. Two $750 prizes, kindly donated by the Raine Medical Research Foundation for best presentations, were awarded by Professor Paul Norman to Anya Jones and Tegan Grace.

The Raine Study is made possible through the dedication and commitment of the Raine Study participants and their families, and the ongoing support of the Raine Medical Research Foundation and other funding institutions.

Raine Study publications 2015


3. Appannah G, Pot GK, Huang RC, Oddy WH, Bellin LJ, Mori TA, Jebb SA, Ambrosini GL. Identification of a...


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.

In 2015 nine Awards were allocated with a total funding allocation of $106,300.

These Awards provide an excellent opportunity for all scientists working in the field of mental illness to develop national and international research collaborations. They also 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 essence, these Awards support the establishment of national and international partnerships that seek a better understanding of the cause and treatment of mental illness.

In May 2015, a Cockell Research Collaboration Award was allocated to the five successful candidates listed below, with total funds amounting to $62,700.

<table>
<thead>
<tr>
<th>Scientist</th>
<th>Project Title</th>
<th>Collaborating Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor David Bruce</td>
<td>Neuroinflammation in Type 2 diabetes: A PET study using the novel radioligand, (18F)- FEEPPA</td>
<td>University of Toronto</td>
</tr>
<tr>
<td>School of Medicine and Pharmacology, UWA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associate Professor Julian Lk-Tsen Heng</td>
<td>Understanding how genetic mutations to gene regulatory proteins cause childhood brain disorder</td>
<td>University of Queensland</td>
</tr>
<tr>
<td>Centre for Medical Research, UWA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Jenny Rodger</td>
<td>Preclinical optimisation of repetitive transcranial magnetic stimulation for youth with treatment-refractory depression</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>School of Animal Biology, UWA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professor Sergio Starkstein</td>
<td>Autism Spectrum Disorder in middle to late adulthood: Phenomenology, behavioural correlates and societal costs</td>
<td>University of North Carolina</td>
</tr>
<tr>
<td>School of Psychiatry and Clinical Neurosciences, UWA</td>
<td></td>
<td>University of Cambridge</td>
</tr>
<tr>
<td>Professor Florian Zepf</td>
<td>Studying the role of serotonin in anxiety in adolescence – An Iterative translational research approach</td>
<td>Duke University</td>
</tr>
<tr>
<td>School of Psychiatry and Clinical Neurosciences, UWA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In December 2015, a further four Cockell Research Collaboration Awards were allocated with total funds amounting to $46,300.

<table>
<thead>
<tr>
<th>Scientist</th>
<th>Project Title</th>
<th>Collaborating Institution</th>
</tr>
</thead>
</table>
| Dr Wayne Davies  
School of Animal Biology, UWA | Light therapy in the treatment of Bipolar Disorder | University of Oxford |
| Dr Kevin Runions  
Centre for Child Health Research, UWA | Social Reward and Impulsivity in Disruptive Behaviour Problems: The Roles of Oxytocin and Serotonin | University of Sydney |
| Assistant Professor Anna Waterreus  
School of Psychiatry and Clinical Neurosciences, UWA | Simple Physical Activity Questionnaire (SIMPAQ) and international validation study | University of New South Wales  
Universidade Federal do Rio Grande do Sul, Brazil and  
University of Leuven, Belgium |
| Professor Andrew Whitehouse  
Centre for Child Health Research, UWA | Very early intervention in infants at risk of autism: Bringing a novel therapy to Australia | University of Manchester and  
La Trobe University |
Raine Research Prize

The Raine Research Prize is available each year to Western Australian researchers in the field of medical/health science and is awarded to the candidate with the best scientific paper published within six years’ of award of their doctoral degree or professional qualification. It consists of a Travel Grant to the value of $5,000, a Medallion and a Certificate of Distinction.

2015 Raine Research Prizewinner

Research Committee members were unanimous in their view that there was one publication that was outstanding in the 2015 round, with the author a particularly worthy recipient of the award. It was with great pleasure that the Research Committee awarded the Raine Research Prize for 2015 to Dr Helena Viola for her article entitled: Impaired functional communication between the L-type calcium channel and mitochondria contributes to metabolic inhibition in the mdx heart, Proceedings of the National Academy of Sciences (PNAS) 2014; vol. 111 no.28, published online June 26, 2014 doi: 10.1073/pnas.1402544111.

2014 Raine Research Prizewinner

The 2014 recipient, Dr Iona Schuster, extended her thanks to the Raine Medical Research Foundation for the Raine Research Prize and was pleased to report that the Prize had enabled her to attend three important meetings, namely, the 4th Network of Immunology Frontiers (NIF) Winter School on Advanced Immunology in Singapore; the Keystone Symposia meeting on Autoimmunity and Tolerance in Colorado; and the Australasian Cytometry Society Annual Meeting in Perth. Dr Schuster reported on the benefit of international networking and new ideas gained from attending these meetings, as summarised below.

Dr Schuster first attended the Winter School on Advanced Immunology in Singapore in January 2015 where she presented her research in the form of a short talk and in a Poster Session where she was awarded a Travel Scholarship. A meeting with Professor Frank Carbone from the University of Melbourne resulted in an invitation for her to present at the Seminar Series of the Peter Doherty Institute for Infection and Immunity in Melbourne.

The second conference on Autoimmunity and Tolerance – one of the most significant meetings on autoimmunity world-wide – was held in the Keystone Resort in Colorado in February. Dr Schuster was again invited to present her research in a short talk and a Poster Session.

The third meeting was the Australasian Cytometry Society Annual Meeting held in Perth in October. Dr Schuster was pleased to report that she managed to obtain a place in two highly sought after Master Classes on cytometric analysis techniques held by pioneers in their respective field of cytometry. These Master Classes were of particular value, as her experimental approaches often include flow cytometric analysis of cell phenotypes.

In thanking the Raine Medical Research Foundation for the 2015 Raine Research Prize, Dr Schuster was pleased to report that these three major meetings, not only deepened her understanding of immunological processes, but also allowed her to extend her scientific international network.
The Strachan Memorial Prize

The Strachan Memorial Prize was established in 2008 from a generous bequest to the Raine Medical Research Foundation by the late Mary Bickford Strachan. The Prize, which consists of a Travel Grant valued at $5,000 and Certificate of Distinction, is awarded to a clinician or clinical scientist in Western Australia in the field of medical/health science for the best scientific paper published within five years’ of award of their doctoral degree or professional qualification.

2016 Strachan Memorial Prizewinner
The 2016 Strachan Memorial Prize was awarded to Dr Rishi Kotecha from the School of Paediatrics and Child Health Research, UWA for his outstanding publication entitled: Meningiomas in children and adolescents: a meta-analysis of individual patient data.

2015 Strachan Memorial Prizewinner
The 2015 winner of the Strachan Memorial Prize, Dr Tobias Strunk from the Centre for Neonatal Research and Education, School of Paediatrics and Child Health, UWA will attend the Pediatric Academic Societies’ Meeting in Baltimore in May 2016.

The Pediatric Academic Societies Annual Meeting is the largest international meeting focused on research in child health. It brings together thousands of paediatricians and other health care providers united by a common mission: to improve the health and well-being of children worldwide. This international gathering includes researchers, academics, as well as clinical care providers and community practitioners. It is particularly pleasing that the Strachan Memorial Prize will enable Dr Strunk to attend this important meeting.

*The American Pediatric Society. Inc [US] website*
Raine Annual Awards Ceremony

George Yeoh, Peter Bird, Marjorie Bird

Alison McDonnell, Elin Gray; Annette Lim, Tristan Clemons Grand Joldes

Jodie Hegarty, Hugh Davies, Joshua Lewis, Benjamin Mullin

Norman Palmer, Babu Simon and George Yeoh

Meg Sangster and Adele Sangster

Paul Johnson, Jo Agnew, Alan Robson

Ed O’Loughlin, Annette Lim, Rishi Kotecha and Martin de Bock
Market Commentary
The University’s investment portfolio delivered positive returns during 2015 despite ongoing market volatility throughout the year. However, market growth in 2016 remains uncertain, with post quarter-end volatility evident as markets continue to assess the prospect of possible adjustments in monetary policy and commodities markets continuing to experience weakness.

Income Summary
The source of the income for the Foundation is derived from the Long Term Pool, Short Term Pool and the unit trust investment with the Dexus Property Group.

The Fluctuation Capital Fund increased from $4.1m to $4.2m as a result of STP income earned on the Fluctuation Fund balance. The Committee agreed at its November, 2015 meeting to preserve the 10% portion of the 5% Capital Distribution from the Long Term Pool and retain this within the Long Term Pool Capital Fund, with a review undertaken annually on a ‘need to transfer basis’.

At reporting period end, the Fluctuation Capital Fund balance was 12% of the carrying value of the investment portfolio held by the Raine Foundation.

The carrying value of the Foundation’s total investments for year ended 31 December 2015 was $36.3m compared to $35.5m in 2014, with the principle contributor to the increase being the LTP return.

Investment Strategy
Pursuant to the University Investment Strategy Review approved in 2015, Financial Services will continue to assist the Foundation in the review of their investments, to ensure it aligns with the Foundation’s objectives to preserve and grow capital, whilst maximising the income available for awards.
Raine Medical Research Foundation

Income and Expenditure for the year ended 31 December 2015

<table>
<thead>
<tr>
<th>Notes</th>
<th>2015 Actual $</th>
<th>2014 Actual $</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INCOME</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distribution from Raine Foundation</td>
<td>1,416,088</td>
<td>1,280,984</td>
</tr>
<tr>
<td>Other income:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding retrieved from unspent grant</td>
<td>50,177</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total Income</strong></td>
<td>1,466,265</td>
<td>1,280,984</td>
</tr>
</tbody>
</table>

**EXPENDITURE**

Specific Activities:

<table>
<thead>
<tr>
<th></th>
<th>2015 Actual $</th>
<th>2014 Actual $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raine Visiting Professors</td>
<td>49,233</td>
<td>60,124</td>
</tr>
<tr>
<td>Honorariums</td>
<td>21,598</td>
<td>16,290</td>
</tr>
<tr>
<td>Raine Research Prize and Travel Awards</td>
<td>6,500</td>
<td>6,000</td>
</tr>
<tr>
<td>Salary funding for Scientific Directorship</td>
<td>65,000</td>
<td>50,000</td>
</tr>
</tbody>
</table>

Raine Priming Grants:

<table>
<thead>
<tr>
<th></th>
<th>2015 Actual $</th>
<th>2014 Actual $</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013 Grants</td>
<td>310,500</td>
<td></td>
</tr>
<tr>
<td>2014 Grants</td>
<td>428,222</td>
<td>412,892</td>
</tr>
<tr>
<td>2015 Grants</td>
<td>425,000</td>
<td></td>
</tr>
</tbody>
</table>

Other Expenses:

<table>
<thead>
<tr>
<th></th>
<th>2015 Actual $</th>
<th>2014 Actual $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration and Operating Expenses</td>
<td>23,780</td>
<td>33,738</td>
</tr>
<tr>
<td>Salary Expenses</td>
<td>193,624</td>
<td>134,876</td>
</tr>
<tr>
<td><strong>TOTAL EXPENDITURE</strong></td>
<td>1,212,957</td>
<td>1,024,421</td>
</tr>
</tbody>
</table>

**NET OPERATING RESULT**

<table>
<thead>
<tr>
<th></th>
<th>2015 Actual $</th>
<th>2014 Actual $</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>253,308</td>
<td>256,563</td>
</tr>
</tbody>
</table>

**Raine Medical Operating Funds:**

<table>
<thead>
<tr>
<th></th>
<th>2015 Actual $</th>
<th>2014 Actual $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening Balance</td>
<td>2,585,962</td>
<td>2,329,399</td>
</tr>
<tr>
<td>Net Funds from Operating Activities</td>
<td>253,308</td>
<td>256,563</td>
</tr>
<tr>
<td><strong>Closing balance as at the end of the year</strong></td>
<td>2,839,270</td>
<td>2,585,962</td>
</tr>
</tbody>
</table>

Notes

1 Committee meeting minutes 01/05/2014 approved $65k for further five year until 2019.
### Statement of Investments for the year ended 31 December 2015

<table>
<thead>
<tr>
<th>Investments</th>
<th>Notes</th>
<th>2015 Actual $</th>
<th>2014 Actual $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Term Investment Pool</td>
<td>1</td>
<td>4,264,877</td>
<td>4,072,079</td>
</tr>
<tr>
<td>Raine Foundation Fluctuation Capital Fund</td>
<td></td>
<td>2,839,270</td>
<td>2,585,963</td>
</tr>
<tr>
<td>Raine Medical Research</td>
<td></td>
<td>229,162</td>
<td>-</td>
</tr>
<tr>
<td>Clinical Research Fellowships</td>
<td></td>
<td>17,568</td>
<td>18,017</td>
</tr>
<tr>
<td>Strachan Bequest</td>
<td></td>
<td>7,250,877</td>
<td>6,678,069</td>
</tr>
<tr>
<td><strong>Total Pool Investments</strong></td>
<td></td>
<td><strong>34,364,372</strong></td>
<td><strong>33,685,332</strong></td>
</tr>
<tr>
<td>Long Term Investment Pool</td>
<td>1</td>
<td>26,888,298</td>
<td>26,893,687</td>
</tr>
<tr>
<td>Raine Foundation</td>
<td></td>
<td>74,424</td>
<td>74,813</td>
</tr>
<tr>
<td>Strachan Bequest</td>
<td></td>
<td>50,773</td>
<td>40,773</td>
</tr>
<tr>
<td>Other Bequests</td>
<td></td>
<td>27,013,496</td>
<td>27,009,273</td>
</tr>
<tr>
<td><strong>Total Pool Investments</strong></td>
<td></td>
<td><strong>34,364,372</strong></td>
<td><strong>33,685,332</strong></td>
</tr>
<tr>
<td>24/95 Monash Avenue (Hollywood) net carrying value</td>
<td>2</td>
<td>275,026</td>
<td>278,377</td>
</tr>
<tr>
<td>Dexus Property Securities</td>
<td></td>
<td>1,693,500</td>
<td>1,573,826</td>
</tr>
<tr>
<td><strong>Total Other Investments</strong></td>
<td></td>
<td><strong>1,968,526</strong></td>
<td><strong>1,852,203</strong></td>
</tr>
<tr>
<td><strong>Total Investments at Carrying Value</strong></td>
<td></td>
<td><strong>36,332,899</strong></td>
<td><strong>35,537,535</strong></td>
</tr>
<tr>
<td><strong>Market Value - Other Investments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24/95 Monash Avenue (Hollywood)</td>
<td>3</td>
<td>580,000</td>
<td>580,000</td>
</tr>
<tr>
<td>Dexus Property Securities</td>
<td>2</td>
<td>1,693,500</td>
<td>1,573,826</td>
</tr>
<tr>
<td><strong>Artwork</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Other Investments - Market Value</strong></td>
<td></td>
<td><strong>2,273,500</strong></td>
<td><strong>2,153,826</strong></td>
</tr>
<tr>
<td><strong>Total Investments at Market Value</strong></td>
<td></td>
<td><strong>36,637,872</strong></td>
<td><strong>35,839,158</strong></td>
</tr>
</tbody>
</table>

Notes:

1. 2015 distribution rate: LTP at 4.48% and STP at 4.60%
2. University Investment Pool 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 31/12/2015.