RAINE
MEDICAL RESEARCH FOUNDATION

Raine Medical Research Foundation

annual report
2016

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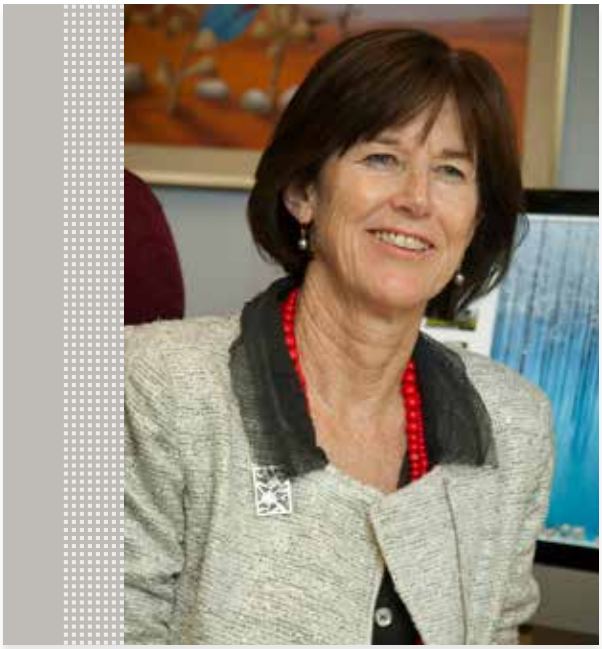
Chair's Address



As Chair of the Research Committee, it gives me great pleasure to report that 2016 was another highly successful and productive year for the Raine Medical Research Foundation.

The Foundation continued to fulfil its principal goal of supporting the brightest and best young medical research minds in Western Australia with overall funding in excess of $2 million. Congratulations go to the 27 recipients who were awarded a Project Grant, a Clinician Research Fellowship, a Collaboration Award, or Publication Prize. This excellent result was achieved in association with our partners, the WA Department of Health and the BrightSpark Foundation, who share the philosophy of the Raine Foundation and are similarly committed to encouraging and nurturing the career of young medical research scientists. It is further rewarding to know that this level of research and funding promises to provide the wider community with improved clinical practices and better health outcomes.

The development of the Clinical Research Fellowship Program, initiated in 2012 by the Department of Health, continues to be a resounding success. Since its establishment, twenty-one Fellowships have been awarded in support of top clinical research projects with combined funding of $5.3m. And now, four years since those first four Fellowships were awarded, we are able to see how the determination and commitment of these young clinicians is making a real impact on the development of health policy and planning, along with changes to clinical practice. The Reports commencing on page 40 demonstrate how these innovative programs are improving the lives of those suffering ill health.

Similarly, the excellent partnership between BrightSpark and Raine is now firmly consolidated into one outstanding Alliance as it works diligently to support young rising stars who, in turn, are breaking barriers in their quest to find answers to childhood disease and improve the lives of sick children. I am also delighted to report that the Jon and Caro Stewart Family Foundation has made a generous donation over two years in support of the top Raine Priming Grant project in child health research. The Grant was awarded to an outstanding young scientist, Dr Melissa O'Donnell, which carries the name *Stewart/BrightSpark/Raine Grant* for her project entitled: *Alcohol-related harm in young people: Developing a longitudinal evidence base*.

The Raine Foundation is mindful that the development of collaborative partnerships for our young scientists is now more important than ever, not only for the dissemination and sharing of knowledge, but also for the advancement of science to improve the well-being of everyday life of those suffering illness and disease. The Raine Foundation manages two successful Research Collaboration Award programs: the first funded by the Edith E Cockell Bequest is directed toward research into mental health illness, and the second, funded by the BrightSpark Foundation, is in support of research into childhood illness. Since 2015, a total of 12 Research Collaboration Awards have been allocated with total funds in excess of $130,000. These Awards give scientists the opportunity to develop links with their national and international counterparts, advance their research strengths and facilitate visits to academic institutions that, hopefully, will lead to long-term partnerships. The ultimate goal, however, is to advance medical knowledge into the cause and treatment of illness and disease.

Distinguished scientists visiting WA universities continue to enrich and advance our medical research knowledge and expand our collaborative global network under the Raine Visiting Professorship scheme. We were privileged to welcome six outstanding scientists from some of the top international Universities, including Nanjing, Kobe, the Erasmus University Medical Center and the Israel Institute of Technology. These Visiting Professors, each a leader in their field of expertise, were generous with their knowledge and time, and were excited to develop new collaborative networks with our WA scientists. It was particularly pleasing to note that the Raine Lectures were well attended, attracting a wide-ranging audience that included scientists from cross-disciplinary fields and often from various academic and research institutions. It is clear that the Raine Visiting Professorship scheme is a major and valued resource among the local research community and one that the Raine Foundation is pleased to endorse. Full details of the 2016 Raine Visiting Professors is on page 67.

Professor Robert McLaughlin

The importance that Raine places on seeding money and the power of innovative research to translate into clinical outcomes was recently displayed in the outstanding success of one of our earlier Priming Grant recipients, Professor Robert McLaughlin. In 2007 Raine was pleased to award one of its largest Priming Grants to Dr McLaughlin to facilitate his return to WA from Oxford University where he had spent three years as a researcher. The Raine Foundation funded his research project entitled: *Bringing Optical Imaging into clinical practice for breast cancer and breathing disorders*.

Professor McLaughlin now heads the Bioengineering Group at The University of Adelaide and is also Managing Director of the medical device start-up company, Miniprobes. We were therefore particularly proud to read in the University February News Bulletin that the award winning invention, a miniaturised optical imaging probe known as the microscope in a needle, had been licensed to Miniprobes Pty Ltd so that it may be developed and commercialised for use by surgeons.

These are the kind of clinical outcomes that the Raine Foundation works tirelessly to support; however, the Research Committee is also mindful that the success of the Raine investment portfolio is the 'financial compass' that determines the level of funding capacity available. There is an excellent team looking after our financial interests in the office of Treasury and Investment and I extend my personal thanks to Michael Fitzgerald, Leona Marquand, and Rachel Wong for their hard work and guidance during the year.

It also gives me great pleasure to welcome Mr Garry Prendiville to the Raine Board as our Financial Consultant. A UWA graduate in Engineering and Commerce, Mr Prendiville brings to Raine and Healy a wealth of corporate knowledge and financial expertise from his many years as a successful businessman and former President of the Motor Trade Association of Western Australia. Mr Prendiville is also centrally involved in a diverse group of successful family companies operating in wine, petroleum, hospitality and tourism industries.

Mr Garry Prendiville

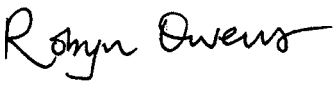
Notwithstanding our achievements in 2016, the Raine Foundation is acutely aware that there remains a lot more to do if we are to meet rising research costs and retain our young investigators in Western Australia. Universities and research institutes across WA are mindful of the shortfall in research funds coming to WA, due partly to the drop in national competitive medical research grants, and partly due to the ongoing increase in salaries and research costs. The Raine Management Office plans to become more proactive in 2017 and has in train plans to establish an outreach program whereby it can engage with the wider community and share its vision for the future of medical research and better health outcomes. Driven by its long-term philosophy of funding only scientific excellence and aligned to international assessment standards, the Raine Management Office is preparing to formalise and expand its portfolio as Venture Managers. We are mindful that scientific endeavour has become wide-ranging and multi-disciplinary and we also plan to work closely with our stakeholders to establish a fund-raising campaign to achieve the best overall outcome.

Finally, I would like to extend my personal thanks to members of the Research Committee who give their time willingly and generously in the interest of medical research. This professional group, comprised of scientists, clinicians and financial consultant, provide expert leadership and guidance to ensure the Foundation retains its proud reputation and remains a major source of research funding in WA. This important work is further supported by five Advisory Panels whose members provide specialist advice in the research and operational activities of the Foundation. Their involvement is particularly appreciated and highly valued.

Professor Paul Norman

I would, however, like to take this opportunity to place on record my thanks and appreciation for the outstanding contributions made by our retiring Professorial Surgeon, Paul Norman. Paul has served the Raine and Healy Foundations diligently over the past nine years, willingly taking on additional Advisory Panel roles while carrying a heavy clinical and administrative workload. It is because of the expertise and generosity of its honorary members that the Raine Foundation is acknowledged as a leader among medical research providers in WA.

As we move into 2017, the growth and advancement of the Foundation is further complemented by the Raine Management Office – the cornerstone of the Foundation. Under the guidance of the two senior dedicated staff, Lyn Ellis and Amanda Cleaver, Raine is poised to move forward. We now have in place a new integrated online grants system, a revised governance structure, and there are ambitious plans to broaden research horizons, including development of new partnerships. I extend congratulations to Lyn and Amanda on their hard work and commitment.



Robyn Owens
UWA 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 2016 Research Committee consisted of the following members:

Professor Robyn Owens
UWA 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 Garry Prendiville
Honorary Financial Consultant

Ms Lyn Ellis
Director

Dr Amanda Cleaver
Project Manager

BrightSpark/Raine Alliance Committee

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

The 2016 BrightSpark/Raine Alliance Committee consisted of the following members:

Mr Graham Dowland, Chair

Dr Elizabeth Davis

Mr Geoff Anderson

Mr Peter Smith

Dr Richard Choong

Mr Andrew Thompson

Mr Tony Barber

Ms Lyn Ellis

Mr Garry Prendiville

Dr Amanda Cleaver

GRANTS

Raine Priming Grants

Eleven research projects were in progress in 2016 funded by the Raine Medical Research Foundation. These were represented by six, 2-year grants awarded for 2015/2016, together with five new 2-year grants awarded for 2016/2017 to commence in 2016.

The total value of funds allocated to the eleven projects awarded for 2015/2016 and 2016/2017 was $1.58m.

2015 Raine Priming Grants
(Second Year of award commenced in January 2016)

	Chief investigator	Project title
	Dr Holly Clifford Raine/Robson Fellow Telethon Kids Institute	Environmental dust and the lung: Impact in remote Aboriginal Australian communities
	Dr Anja Stirnweiss Telethon Kids Institute	Protein signalling networks in NUT Midline Carcinoma (NMC)
	Dr Benjamin Mullin School of Medicine and Pharmacology The University of Western Australia	Role of genetic copy number variation in osteoporosis
	Dr Coral-Ann Almeida School of Pathology and Laboratory Medicine The University of Western Australia	Stimulation of HIV-specific cytolytic effector function using allogeneic cell immunotherapy

	Dr Bree Foley Telethon Kids Institute	Enhancing NK cell mediated anti-tumour responses
	Dr Sally Lansley School of Medicine and Pharmacology The University of Western Australia Institute for Respiratory Health	The effect of Fibroblast Growth Factor 9 on anti-tumour immunity in malignant mesothelioma

2016 Raine Priming Grants recipients (First Year of award commenced in January 2016)

Dr Annette Lim was awarded the title of 'Honorary Raine/Robson Fellow'.

	Chief investigator	Project title
	Dr Gemma Cadby Centre for Genetic Origins of Health and Disease The University of Western Australia	The association of sleep apnoea and long-term health outcomes in Western Australian adults
	Dr Tristan Clemons School of Chemistry and Biochemistry The University of Western Australia	Nanoparticle delivery for the treatment of scarring
	Dr Elin Gray School of Medical Sciences Edith Cowan University	Genetic Analysis of Circulating Tumour Cells and Circulating Tumour DNA for Prognosis of Uveal Melanoma

	Dr Grand Roman Joldes School of Mechanical and Chemical Engineering The University of Western Australia	Towards translating the benefits of patient specific biomechanics into clinical practice
	Dr Alison McDonnell School of Medicine and Pharmacology The University of Western Australia	Identifying immune biomarkers of response to chemotherapy in thoracic cancers

2017 Raine Priming Grant recipients

Five new Priming Grants were awarded in December 2016 for 2017/2018 with a total funding allocation of $797,128. Dr Yit Heng Chooi was awarded the title of 'Honorary Raine/Robson Fellow'.

A generous donation by the Jon and Caro Stewart Family Foundation, in partnership with the BrightSpark Foundation and the Raine Medical Research Foundation, made possible a Raine Priming Grant to be awarded to the top research in child health. Dr Laurens Manning was awarded the title of 'Honorary Stewart/BrightSpark/Raine Fellow' and Dr Melissa O'Donnell was awarded the 'Stewart/BrightSpark/Raine Project'.

	Chief investigator	Project title
	Dr Melissa O'Donnell Stewart/BrightSpark/Raine Project The University of Western Australia Telethon Kids Institute	Alcohol-related harm in young people: developing a longitudinal evidence base
	Dr Ashleigh Lin School of Anatomy, Physiology and Human Biology The University of Western Australia	GENTLE: The GENder identiTy Longitudinal Experience Project

	Dr Helena Viola School of Anatomy, Physiology and Human Biology The University of Western Australia	A novel approach for the prevention of hypertrophic cardiomyopathy
	Dr Katrina Ellis School of Medicine and Pharmacology The University of Western Australia	Novel Aspects of the Role of Lipoprotein(a) in Premature Heart Disease
	Dr Mark Agostino School of Biomedical Sciences Curtin University	Structural characterisation of the Wnt signalling pathway

2016 Annual Research Reports
Raine Priming Grants

PROJECT TITLE
Environmental dust and the lung: Impact in remote Aboriginal Australian communities

INVESTIGATOR
Dr Holly Clifford (Chief Investigator)

SCHOOL/INSTITUTE/CENTRE
Telethon Kids Institute

SUMMARY OF AIMS AND RESULTS
This study aimed to investigate the impact of inhaled environmental dust on the lungs of children growing up in remote communities in 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, linking clinical infectious disease data and dust levels and examining the mechanisms through which dust can make bacterial lung infections more common and severe.

During the period of this grant, we have had extensive engagement and discussions with the Bidyadanga Aboriginal Community in the Kimberley, WA. Community leaders and members have expressed that dust is a problem in their community and have lent their support to our study. Dust monitoring at several sites within the community, including the school, clinic and general store (see Figure 1), have indicated that dust exposure levels are extremely high; average readings at the school entrance were more than 16 times greater than the recommended national air quality standards. With a view to collecting more comprehensive monitoring data over at least a year-long period, through both wet and dry seasons, we have recently obtained two Dust Monitors that will be installed in Bidyadanga in early 2017. We have also gained the support of the Kimberley Aboriginal Medical Services Council over 2016 and will be able to collect clinical infectious disease data this year from the Bidyadanga clinic. We have also embarked on a new collaboration with the Nirrumbuk Environmental Health and Services organisation based in Broome.

In collaboration with researchers at Princess Margaret Hospital for Children and the School of Paediatrics and Child Health at UWA, we have also been able to show that dust can make the human airway more susceptible to bacterial infection with 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 have been able to perform a number of assays addressing epithelial cell viability, bacterial attachment and invasion, and immune responses, following dust exposure. We have found that dust exposure, depending on the source, can increase the attachment and invasion of NTHi, and affect the inflammatory immune responses against this bacteria.

This supports our hypothesis that dust exposure may contribute to more common and severe bacterial infections. Our experiments have also revealed that one dust sample was more inflammatory than others and further investigation revealed the presence of *Bacillus licheniformis*, an environmental spore-forming pathogen. This has led us to begin exploring the "dust microbiome", with a new collaboration with the School of Earth and Environment at UWA and a successful grant application to the Wesfarmers Centre of Vaccines and Infectious Diseases for 2017.

Over the past year, results from this study have led to two successful grants for 2017 and have been presented at local, national and international conferences. One conference abstract has been published and a manuscript will be submitted in March 2017.

ONGOING RESEARCH
In addition to exploring the dust microbiome and effects of dust on other respiratory infections, the next stages of work will primarily involve a translational initiative in the Bidyadanga Aboriginal Community. The results we have acquired with the support of the Raine Foundation Priming Grant has provided the evidence base required for the community to advocate for dust suppression strategies in their community. Our next step will be to assess the effectiveness of dust suppression interventions, in order to advocate for large-scale dust control and a change in policy and practice – both of which will lead to tangible improvements in the health and well-being of Aboriginal Australian children and their families.

Figure 1: Sites within Bidyadanga that highlight the community's considerable dust problem. From left: The main road into the community with a dust plume caused by a car, the school front entrance gates, and the dust covered road outside the general store and common gathering areas (photos from our site visits, 2013-2016).

OUTCOMES

Grants

- Wesfarmers Centre of Vaccines and Infectious Diseases Seed Funding (2017-2018) $22,920 *"The dust microbiome: how does it affect susceptibility to bacterial lung infections in Aboriginal Australian children?"* **In the top two of ranked applications.
- Institute for Respiratory Health Alan King Westcare Grant (2017) $50,000 *"Environmental dust exposure and bacterial lung infections: Impact in remote Aboriginal Australian communities"*.

Conference Presentations

- April 2016 (*oral presentation*) Japanese Respiratory Society (JRS) conference, Kyoto, Japan.
- Aug 2016 (*poster presentation*) Combined Biological Sciences Meeting (CBSM), Perth, WA.
- Sept 2016 (*poster presentation*) European Respiratory Society (ERS) Congress, London, UK.
- Mar 2017 (*oral presentation*) Thoracic Society of Australia and New Zealand and Australian and New Zealand Society of Respiratory Science (TSANZSRS) ASM, Canberra, ACT.

PROJECT TITLE
Protein signalling networks in NUT Midline Carcinoma (NMC)

INVESTIGATORS
Dr Anja Stirnweiss (Chief Investigator)
Associate Professor Alex Beesley (Associate Investigator)
Professor Ursula Kees (Associate Investigator)

SCHOOL/INSTITUTE/CENTRE
Telethon Kids Institute

SUMMARY OF AIMS AND RESULTS
Rare cancers represent approximately 20% of all human cancers and are associated with worse survival than other so-called frequent tumours. Patients often experience delays to accurate diagnosis, inadequate treatments, and fewer opportunities to participate in clinical trials. NUT midline carcinoma is a rare form of cancer, with only 200 people affected worldwide. Patients range from newborns to the elderly, but the disease is most often diagnosed in children and adolescents. In NUT midline carcinoma, the patient's genetic material is incorrectly repaired, resulting in the joining of two genes (called BRD4 and NUT) and creating a new hybrid gene that causes cancer. To date, there are no survivors, and better treatments for this devastating disease are desperately needed. Drugs that are specifically designed to block the function of BRD4, called bromodomain inhibitors, have been recently developed. However we, and others, have evidence suggesting that the therapeutic benefit of those inhibitors will be curbed through the acquisition of resistance. The major focus of our research is to find other effective therapies to improve the fatal outcome for NUT midline carcinoma patients.

In 2015, we 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 NUT midline carcinoma cell lines. This was unexpected, given that the bromodomain inhibitors specifically target functions/interaction partners of the BRD4-NUT fusion protein. Moreover, the data suggests that NUT midline carcinoma cells that express a BRD4-NUT (ex11:ex2) fusion subtype are particularly susceptible to bromodomain inhibitor treatment.

Multiple research groups have published the observation of a strong association between acquired bromodomain inhibitor resistance and enhanced WNT/β-catenin signaling in leukaemia and pancreatic cancer. As a result these cells undergo epithelial to mesenchymal transition, which maintains overexpression of the master oncogene MYC in a BRD4 independent manner. A comparative analysis of our bromodomain inhibitor sensitive and resistant NUT midline carcinoma cell lines showed no differential regulation of protein pathways associated with WNT/β-catenin signaling and MYC. However, expression of another oncogene, called FOS, was stabilised in the resistant NUT midline carcinoma cells as a result of bromodomain inhibitor treatment. When we used our unique collection of cells to identify drug-induced changes in gene expression, FOS was also identified to be a central node of the gene network that is associated with drug resistance.

Given that the gene expression and protein analysis experiments highlighted FOS to be strongly associated with bromodomain resistance, we decided to further investigate the role of FOS in bromodomain resistance. Removal of the gene from the resistant NUT midline carcinoma cells showed that FOS is not a driver of resistance, but an ideal marker to predict if the cancer cells will respond to iBET treatment. Ultimately, assessment of FOS could be used in the clinic to predict which patients will benefit from iBET treatment. This has important clinical ramifications, given that iBETs are currently assessed worldwide in 21 clinical trials for cancers such as leukaemia, brain tumours, aggressive breast cancers and NUT midline carcinoma.

PROJECT TITLE
Role of genetic copy number variation in osteoporosis

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

SCHOOL/INSTITUTE/CENTRE
School of Medicine and Pharmacology, The University of Western Australia

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

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

Objective 2: Test common CNV in 56 loci with a known association with bone phenotypes for association with intermediate and clinical endpoints for osteoporosis.
We identified 1,533 CNV regions located within 1.2Mb of 56 known bone loci with a MAF ≥1%. Analysis of these CNV for association with spine, femoral neck and total hip bone mineral density (BMD) was completed using PLINK 1.07. None of the CNV were found to be significantly associated with BMD after correction for multiple testing (Bonferroni). However, we identified interesting suggestive associations between a series of CNV located within the locus 12p11.22 and BMD at the lumbar spine, femoral neck and total hip sites (*P=0.01*, *0.01* and *0.007* respectively). This CNV region spans the last two exons of the *SMCO2* gene (Figure 1) – knockout of this gene in mice has been shown to have effects on body mass and may therefore be relevant to skeletal biology.

Objective 3: Perform a genome-wide association study of common CNVs and phenotype data for intermediate and clinical endpoints for osteoporosis.
We have performed a genome-wide association study for all detected CNV with a MAF ≥1% for association with spine, femoral neck and total hip BMD using PLINK 1.07. Using a Bonferroni-corrected significance threshold of 1.66×10^{-6}, we failed to identify any CNV associated with BMD phenotypes at the genome-wide level, possibly due to the statistical power of the study.

Objective 4: Replicate provisional associations from the discovery studies in an independent cohort comprised of 1,040 individuals genotyped using a commercial SNP array.
We have generated genome-wide marker array genotype data using the Illumina OmniExpress 700K BeadChip for a replication population of 1,046 individuals with BMD data. Genome-wide detection of CNV in this dataset has been performed using the Illumina GenomeStudio v2011.1 software package in conjunction with the cnvPartition v3.2.0 plugin, which is able to detect both duplication and deletion CNV. We detected 18,828 CNV genome-wide with a MAF ≥1%. Statistical analysis is currently underway in this population and will utilise the PLINK 1.07 software.

Additional Research
We 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 ($P=3.4\times10^{-9}$). This variant was also found to be associated with fracture rate (*P=0.017*). This is an intronic variant located in the WLS gene (1p31.3), a known BMD locus which encodes an integral component of the Wnt ligand secretion pathway. Gene-based association testing using the VErsatile Gene-based Association Study 2 (VEGAS2) software revealed associations between the *CCDC170* gene and BMD at the spine, femoral neck and total hip sites ($P=1.0\times10^{-6}$, 2.0×10^{-6} and 2.0×10^{-6} respectively). A manuscript describing these findings has been published in BMC Genomics.

We have also recently completed a genome-wide association study meta-analysis for quantitative ultrasound (QUS) parameters of bone in three study populations (combined n=16,627) using a combination

of whole-genome sequence and deeply imputed genotype data. We identified 8 genetic loci associated with QUS parameters at the genome-wide level, including three novel loci located at 8p23.1 (*PPP1R3B*), 11q23.1 (*LOC387810*) and 22q11.21 (*SEPT5*) ($P=2.4\times10^{-8}$–1.6×10^{-9}). Gene-based association using VEGAS2 identified a novel locus at 8p23.1 (*FAM167A*) ($P=1.4\times10^{-6}$) and gender-specific analyses yielded an additional novel locus at 8p23.1 (*DEFB103B*) in the male subgroup ($P=1.8\times10^{-6}$). Fracture analysis revealed significant associations between variation at the *WNT16* and *RSPO3* loci and fracture risk ($P=0.004$ and 4.0×10^{-4} respectively). A manuscript describing these results is currently under review at Human Molecular Genetics.

OUTCOMES

Publications

- **Mullin BH**, Walsh JP, Zheng HF, Brown SJ, Surdulescu GL, Curtis C, et al. Genome-wide association study using family-based cohorts identifies the WLS and CCDC170/ESR1 loci as associated with bone mineral density. BMC Genomics. 2016;17(1):136. Epub 2016/02/26.

Presentations

- Mullin BH. Genome-wide association study meta-analysis identifies five novel genetic loci associated with quantitative ultrasound parameters of bone. Sir Charles Gairdner Hospital New Investigator Awards – 19th October 2016.

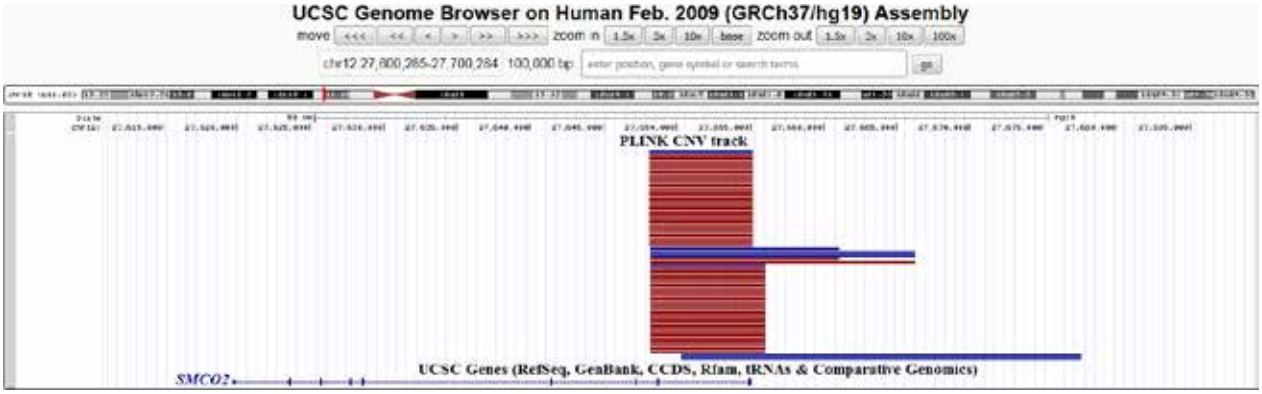


Figure 1. Image taken from the UCSC Genome Browser depicting the location of a series of CNV on chromosome 12p11.22 spanning part of the SMCO2 gene that were found to be suggestively associated with BMD at the lumbar spine, femoral neck and total hip sites in our discovery study. Each horizontal bar represents an individual study subject from the cohort for whom a CNV was detected (blue for deletion, red for insertion), with the length of the bar representing the extent of the genetic variant.

PROJECT TITLE

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

INVESTIGATORS

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

SCHOOL/INSTITUTE/CENTRE

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

SUMMARY OF AIMS AND RESULTS

Although current anti-retroviral regimens have reduced the morbidity and mortality associated with HIV-1 infection, suppression of viral replication requires adherence to life-long therapy 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.

Although viral-specific responses are peptide specific and restricted to recognising self-HLA molecules, recent investigations have shown that many virus-specific T cells break the law of HLA restriction and directly cross-react with foreign or allo-HLA molecules. This cross-reactivity has been demonstrated for Epstein-Barr virus (EBV), cytomegalovirus (CMV), Varicella Zoster virus (VZV), Influenza A virus and more recently for HIV-specific T cells. However, the ability of viral-specific CD8 T cells to mediate a drug-induced allo-reactive response has never been demonstrated. As part of the investigation into allo-specific CD8 T cell responses, we also investigated whether exposure to the anti-retroviral drug, abacavir, could induce allo-recognition of HLA-B*57:01 in HIV-infected individuals. Carriage of HLA-B*57:01 has previously been associated with the abacavir hypersensitivity reaction, a potentially life-threatening syndrome mediated by CD8 T cells. Our results suggest that drug exposure could induce de novo HLA-specific allo-recogntion, which has important clinical implications in the context of HLA-mismatched solid organ transplants.

Peripheral blood mononuclear cells were isolated from individuals enrolled in the Western Australian HIV Cohort Study. These cells recognised peptides derived from the Gag protein of HIV-1 and were identified using HLA-tetrameric complexes and cloned using single cell sorting. Allo-HLA responses were determined by co-culturing HIV-specific CD8 T cells with a panel of cell lines expressing a single HLA molecule (SAL) in the presence or absence of abacavir. Abacavir-induced allo-recognition was determined by cytokine production, activation of the HIV-specific CD8 T cells and killing of the SAL target cells.

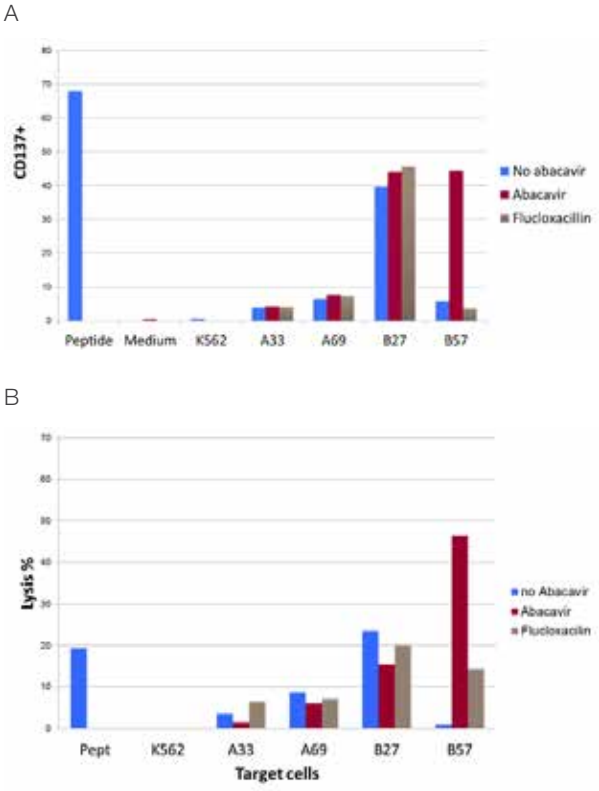


Figure 1: Allo-recognition of HLA-B*57:01 in the presence of abacavir. The HIV Gag RK9/HLA-A3 CD8 T cell clone demonstrated cross-reactivity with allo-HLA-B*27:05. This clone cross-reacted with the HLA-B*57:01 SAL only in the presence of abacavir as seen by up-regulation of CD137 expression (A) and lysis of HLA-B*57:01 target cells (B). Medium alone and flucloxacillin was used as a negative control.

Our results support the hypothesis that pre-existing abacavir-reactive memory CD8 T cells are primed by earlier exposure to foreign pathogens, and that these T cells cross-react with an abacavir/HLA-B*57:01 peptide ligand complex. Investigations are continuing to identify the cognate peptide presented by the allo-HLA molecules that stimulates HIV-specific T cells both in the presence and absence of abacavir. These assays are being performed by our collaborator Dr Nicole Mifsud from Monash University.

OUTCOMES

Conference Presentations

The results investigating the allo-reactivity of HIV-specific CD8 T cells and the allo-recognition of HLA-B*57:01 in the presence of abacavir are currently being prepared for publication and have been presented at the following conferences in 2016:

- "Abacavir induced self-reactivity by HIV-specific CD8 memory T cells" – 40th Conference of the Asia-Pacific Histocompatibility and Immunogenetics Association, September 2016, Perth, Australia.
- "Drug induced alloreactivity: A new paradigm for allorecognition" – 40th Conference of the Asia-Pacific Histocompatibility and Immunogenetics Association, September 2016, Perth, Australia.

PROJECT TITLE
Enhancing NK Cell Mediated Anti-Tumour Immunity

INVESTIGATORS
Dr Bree Foley (Chief Investigator)
Dr Jason Waithman (Associate Investigator)
Dr Jerome Coudert (Associate Investigator)

SCHOOL/INSTITUTE/CENTRE
Telethon Kids Institute

SUMMARY OF AIMS AND RESULTS
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. For successful NK cell therapy and other immune based therapies it is essential to have an understanding of not only how NK cells interact with the tumour but also how to enhance their anti-tumour potential. We have recently characterised several subsets of NK cells that expand in the context of CMV infection. These NK cells display a mature phenotype, have increased functional capabilities, increased potential to mediate antibody dependent responses, increased survival capacity and the potential to be long lived. Clinically, CMV infection has been associated with reduced risk of leukemic relapse and improved overall survival in transplant recipients. This project will aim to determine if these subsets of NK cells have enhanced anti-tumour properties and to determine their potential use as a novel immunotherapy.

This project has focused on both leukaemia and melanoma. Whilst we did detect differences in NK cell activity against melanoma, our findings were most profound for leukaemia. As such, this will be the focus of this report.

Aim 1: To determine which subset(s) of NK cells has the capacity to eliminate tumours in vitro.
We sought to determine if NK cells from CMV positive donors have enhanced capacity to eliminate leukaemia and thus, would be a preferable donor to use for adoptive transfer. Healthy donors were divided into two groups and tested for their anti-tumour activity (both cytotoxicity and cytokine production) against a panel of patient-derived B or T cell acute lymphoblastic leukaemia (ALL) *in vitro* (Figure 1).

While there was no significant difference between CMV$^+$ and CMV$^-$ donors in the capacity of NK cells to express CD107a, CMV$^+$ donors produced significantly more TNFα against several of the ALL cells. For an optimal NK cell anti-tumour response it is critical to not only have enhanced cytotoxicity potential, but also the potential to secrete potent proinflammatory cytokines. Increased secretion of cytokines allows the activation of other immune cells and pathways to strengthen the immune response against the cancer.

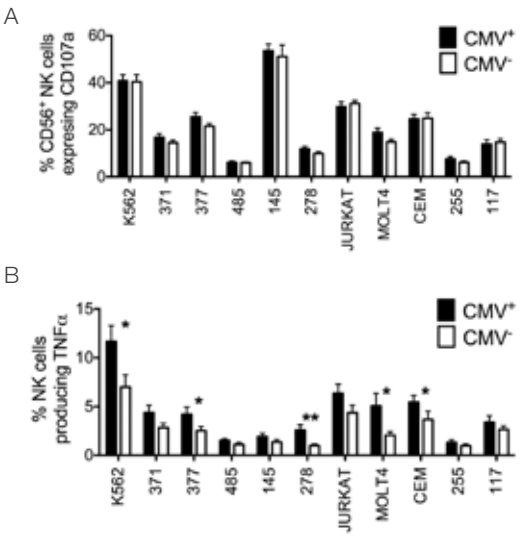


Figure 1: Enhanced effector function of resting NK cells against a panel of patient-derived B- and T-ALL cells. PBMC were incubated with either B- or T-ALL cells for 5 hours. CD107a expression (A) or TNFα production was measured on CD56$^+$ NK cells by flow cytometry. CMV$^+$ and CMV$^-$ donors were compared using student's t test, *p<0.05, **p<0.01.

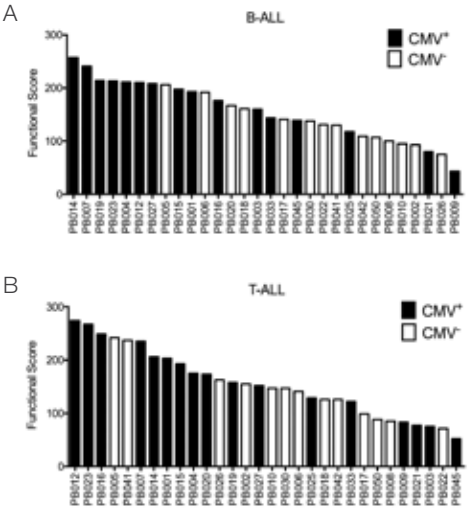


Figure 2: CMV$^+$ donors have enhanced functional capacity against both B and T-ALL. PBMC were ranked based on the percentage of CD56$^+$ NK cells expressing CD107a and TNFα following incubation with each of the ALL cell lines. Ranks were combined for B-ALL (A) and T-ALL (B).

Therefore, to further investigate whether CMV+ donors would make more preferable donors than CMV- donors, we ranked each donor by their functional potential against the combined B or T-ALL panel (Figure 2).

While the top ten donors were not all CMV+, CMV+ donors trended to have a higher functional capacity against both B and T-ALL. Due to these preliminary findings we would predict that adoptive transfer of NK cells from a CMV+ donors will have enhanced efficacy against both B and T-ALL. Next we sought to determine which NK cell subset(s) had the greatest effector function against leukaemia. The most striking differences were observed between NKG2C+ and NKG2C- NK cells and their capacity to produce TNFα (Figure 3).

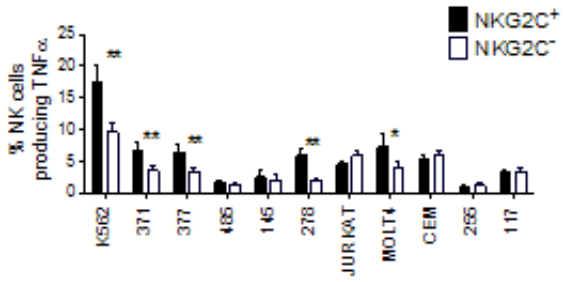


Figure 3. NKG2C+ NK cells produce significantly more TNFα. PBMC from CMV+ donors were incubated with either B- or T-ALL cells for 5 hours. TNFα production was measured on NKG2C+ and NKG2C- NK cells by flow cytometry. NKG2C+ and NKG2C- NK cells were compared using the paired student's t test, *p<0.05, **p<0.01.

NKG2C+ NK cells produced significantly more TNFα than NKG2C- NK cells. Since NKG2C+ Therefore, we we were interested in determining what NK cell activating receptors were involved in recognising the leukaemic cells target. Using antibodies to block NKG2D and DNAM-1, two of the main activating receptors expressed on NK cells, we identified that NKG2D is the predominant receptor involved in recognition of both B- and T-ALL (Figure 4).

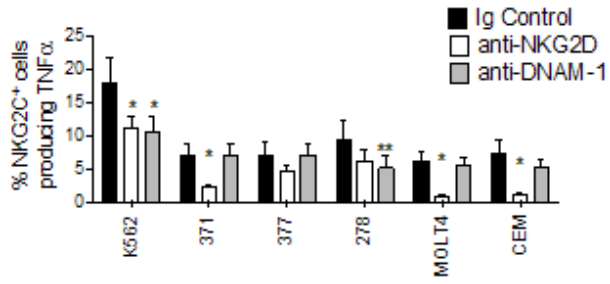


Figure 4. NKG2D is the predominant activating receptor involved in the recognition of ALL. PBMC from CMV+ donors were incubated with isotype control, anti-NKG2D or anti-DNAM-1 followed by incubation with either B- or T-ALL cells for 5 hours. TNFα production was measured on NKG2C+ NK cells by flow cytometry. Isotype control and anti-NKG2D or anti-DNAM-1 were compared using the student's t test, *p<0.05, **p<0.01.

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.

During the past year we have focused on developing a robust model of B-ALL to investigate the effect of CMV infection on the progression of leukaemia. We have developed a model of BCR-ABL+ B-ALL in C57BL/6 mice that reproducibly develop leukaemia and succumb from their disease in approximately 16 days. This model of B-ALL was developed by transducing bone marrow cells with an expression vector containing the p185 BCR-ABL fusion protein linked to the fluorescent protein mCherry. This fusion protein is known to preferentially induce B cell leukaemia. Transduced cells were injected into lethally irradiated recipients and following the development of leukaemia, bone marrow cells were harvested and cultured *in vitro* generating a BCR-Abl+ B ALL cell line (BM A82 P185+). Using this model we tested whether CMV infection delayed progression of leukaemia in this model. Percentage of leukaemic cells detected in the blood at D12 post leukaemia transfer was lower in latently MCMV infected mice (2.4±1%) compared with naïve mice (14.5±5%). Both naïve and latently infected mice who were infected with MCMV on Day 3 post leukaemic transfer also had lower leukaemic cells detected in the blood (4.5±2%, 3.1±1%). However while there was a decrease in leukaemic burden and a slight delay in disease progression CMV infection did not significantly delay disease progression. Our current experiments are focused on determining if NK cells from CMV+ donors can be used to treat mice with leukaemia. Using this model we hope to demonstrate that these NK cells do have enhanced effector function in vivo.

OUTCOMES

Grants

To enhance NK cell immunotherapy we have been focused on identifying additional ways to further equip NK cells to eliminate leukaemia. Our current approach involves redirecting NK cells towards the leukaemic cells by using a CD19 chimeric antigen receptor (CAR). Last year based on the results from this study, we were awarded seeding funding (Telethon Kids Institute RFA Seeding Grant) to investigate the potential of CD19 CAR+ NK cells. Data obtained from both this Raine grant and the seeding grant forms the basis of our current application to the Cancer Council WA for 2018.

Conference Presentations

- 15th Meeting of the Society for Natural Immunity October 2016, Sicily, Italy.
- 2016 Cure Cancer Australia Researcher Symposium March 2016, Sydney, Australia.
- 2015 Kirkbride Melanoma Symposium November 2015, Perth, Australia.
- 38th Annual Meeting of the Australasian Cytometry Society. October 2015, Perth, Australia.
- 2015 Cure Cancer Australia Researcher Symposium March 2015, Sydney, Australia.

PROJECT TITLE

The effect of Fibroblast Growth Factor 9 on anti-tumour immunity in malignant mesothelioma

INVESTIGATORS

Dr Sally Lansley (Chief Investigator)
Professor Gary Lee (Associate Investigator)

SCHOOL/INSTITUTE/CENTRE

School of Medicine and Pharmacology, The University of Western Australia
Institute for Respiratory Health

SUMMARY OF AIMS AND RESULTS

Mesothelioma is an aggressive cancer with poor survival that is resistant to current treatments. 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 FGF9 levels resulted in reduced tumour growth. This study aimed 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 firstly investigated the effect 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 showed that this is due, in part, to an increase in regulatory (inhibitory) T cells (Tregs). We showed 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 confirmed that FGF9 has a direct inhibitory effect on CD8+ and CD4+ T cell activity. Therefore, we have shown that removal of FGF9 has potential for therapy in mesothelioma, which is now being tested in a clinical trial led by our group.

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. We assessed expression of 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 responses also appear to predominate within the tumour itself as no differences were observed in the lymph nodes of treated versus untreated mice. These results demonstrated that FGF9 blockade restores anti-tumour immunity within the tumour microenvironment 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 final stage of our work however, we further characterised the immune cells and their response to FGF9 *in vivo* and have identified new targets with the potential to enhance anti-FGF9 therapy.

In the next stage of our work we will be trialing a novel immune checkpoint blockade drug being developed for clinical trial of combination therapy with anti-FGF9 therapy (based on our results). We will also be utilising patient samples obtained from a current clinical trial targeting FGF9 receptors led by our group to examine changes in immune and other cells in response to therapy which may guide further therapeutic approaches.

OUTCOMES

Grants

- 2017: Cancer Council WA Research Project Grant (consumables); $81,581); The effect of fibroblast growth factor 9 on the body's natural immune response to mesothelioma.
- 2015-2016: SCGH Research Advisory Council Grant (consumables; $43,185); The effect of Fibroblast Growth Factor 9 on anti-tumour immunity in malignant mesothelioma.

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 a novel immune checkpoint blockade drug. This work is ongoing.

PROJECT TITLE

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

INVESTIGATORS

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

SCHOOL/INSTITUTE/CENTRE

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

SUMMARY OF AIMS AND RESULTS

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

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

This study focuses on the investigation of obstructive sleep apnoea (OSA) and its association with common health outcomes, such as cardiovascular diseases (e.g. myocardial infarction, stroke, and heart failure), cancers (e.g. breast, prostate, and lung), diabetes, motor vehicle accidents, and mental health disorders. In particular, we are investigating whether OSA severity is an independent risk factor for these outcomes, with and without treatment, after adjusting for known risk factors, such as obesity and blood lipids.

The aim of this study is to establish if the presence and severity of OSA, and its treatment, are independent risk factors for incident or recurrent health outcomes in a large consecutive cohort of patients (n=27,000) who were referred for overnight sleep studies at a Western Australian sleep clinic from 1988 to 2014. These health outcomes will include all-cause mortality, cancer, cardiovascular events, diabetes, mental health disorders, and motor vehicle accidents.

We will investigate the associations between OSA and these health outcomes by linking this cohort to the Western Australian Data Linkage System, which connects all available health and related information for the Western Australian population. As part of this project, we will link individuals from the sleep clinic with the following data collections: Hospital Morbidity System, Death Registrations, Western Australian Cancer Registry, Mental Health Information System, and the Insurance Commission of Western Australia.

In the three months that the grant has been running, all ethics and project approvals have been attained from the WA Department of Health, and ethics approval from UWA. We are now awaiting linkage of our cohort (27,000 patients) to health records, and anticipate receiving this data by April 2017.

PROJECT TITLE

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

INVESTIGATORS

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

SCHOOL/INSTITUTE/CENTRE

School of Chemistry and Biochemistry, The University of Western Australia

SUMMARY OF AIMS AND RESULTS

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

In this project we will generate nanoparticle-based delivery vehicles to deliver potent LOX inhibitor molecules topically, with the surface chemistry of the nanoparticles being specifically chosen to provide optimum dermal delivery characteristics. The nanoparticles will then act as a reservoir for delayed release of the therapeutic, resulting in major benefits with regard to long-term drug release at the site of action, and minimised off-site drug toxicity, circumventing a major clinical issue experienced by previous therapeutic agents in this field.

Aim 1 – Generate polymeric multimodal nanoparticle delivery vehicles for the delivery of therapeutic LOX inhibitors to scar tissue

Through collaboration with Pharmaxis Pty. Ltd., we have tested a range of inhibitors of lysyl oxidase activity (iLOX) in our *in vitro* models of scarring. The iLOX are effective *in vitro* at being able to reduce the amount of collagen production as well as return the coherency of the deposited collagen fibers to a random basketweave structure as is evident in controls (Figure 1). We are currently assessing biodistribution of the lead iLOX candidate *in vivo* in mice.

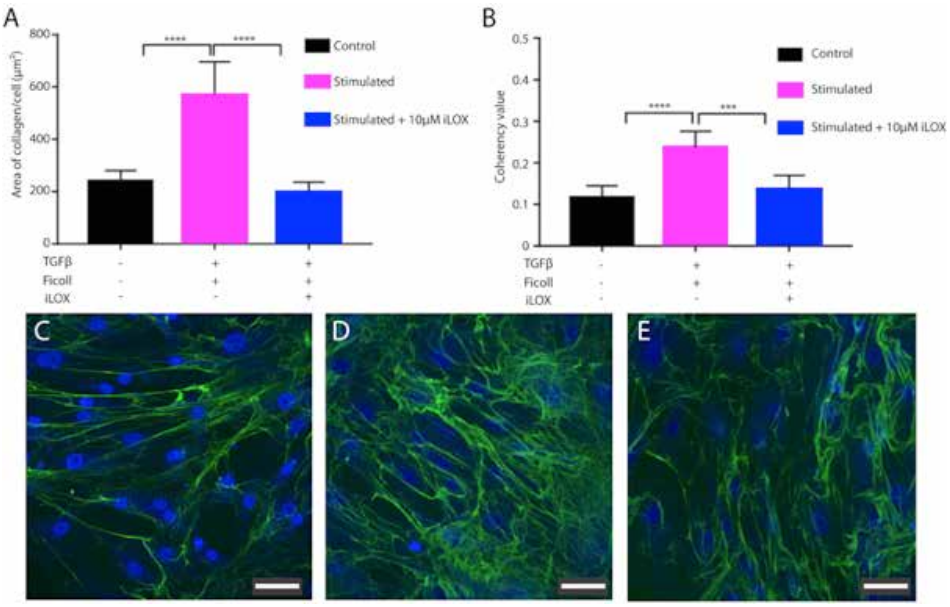


Figure 1. Scar in a jar assessment of iLOX inhibitors in primary human fibroblasts. A – Area of collagen per cell and B – coherency of collagen deposition. Representative images of C-control, D-stimulated and E-stimulated + 10μM iLOX by confocal microscopy. Scale bars are 50 μm.

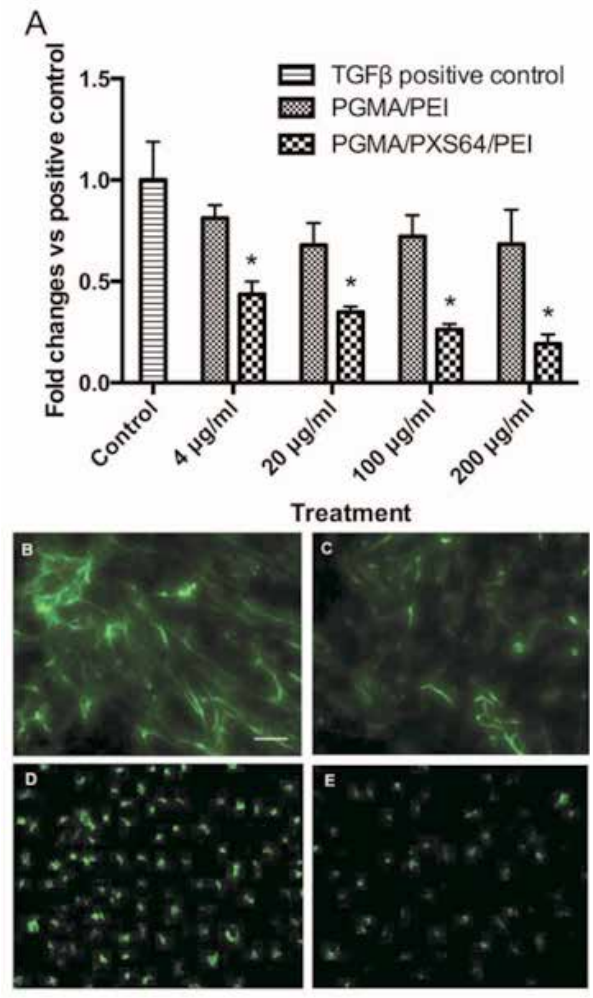


Figure 2. Collagen deposition analysis and morphology observation from scar-in-a-Jar *in vitro* study. A. Collagen deposition per cell (area deposited) treated with different concentrations of PGMA/PXS64/PEI or PGMA/PEI NPs (no drug). Fluorescence microscopy images of the deposited collagen morphology for B. control (no treatment) C. PGMA/PEI NPs (200 µg/ml), no drug, D. PGMA/PXS64/PEI NPs (200 µg/ml), E. PXS64 alone (10 µM). Data displayed as mean ± standard deviation, significance assessed with an ANOVA followed by a Bonferroni post-hoc test with $p<0.05$. Scale bar: 100 µm.

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

Skin penetration studies of the nanoparticle formulations will commence in the latter part of this year. It is anticipated that surface modifications to the nanoparticles will be required to optimise the uptake and localisation of these particles in the scar. Furthermore, testing in the porcine model will progress once *in vivo* bio-distribution studies in mice have confirmed no cytotoxicity or adverse effects.

Skin penetration studies of the nanoparticle formulations will commence in the latter part of this year. It is anticipated that surface modifications to the nanoparticles will be required to optimise the uptake and localisation of these particles in the scar.

Aim 2 – Assess efficacy of the therapeutic LOX inhibitor delivery from within the nanoparticle platform in a clinically relevant porcine model.
Testing in the porcine model will progress once in vivo bio-distribution studies in mice have confirmed no cytotoxicity or adverse effects.

OUTCOMES

Publications

B. Li, **T. Clemons**, V. Agarwal, J. Kretzmann, M. Bradshaw, P. Toshniwal, N. Smith, S. Li, M. Fear, F. Wood, S. Iyer. *Regulation of collagen expression using nanoparticle mediated inhibition of TGF-β activation. New J. Chem*. **2016**, *40*, 1091-1095.

Conference Presentations

- Amine Oxidase Conference, 2016. University of Birmingham, UK. Presented by PhD student Priyanka Toshniwal.
- 252nd ACS National meeting and exposition in Philadelphia, PA. 21st August to 25th August, 2016. Presented by PhD student Priyanka Toshniwal.
- Invited presentation – Curtin University Chemistry Seminar Series. Friday 22nd April, 2016. Presented by Dr Tristan Clemons.
- Emerging Therapuetics Summit, 2016. Mercure Hotel, Melbourne, Australia. Friday 25th November 2016. Presented by Dr Tristan Clemons.

Publicity and Engagement

- The Fiona Wood Foundation outreach program – presentation of work at a number of Perth schools.
- Scitech 'Beyond the Beaker Program' – presentation of work, reaching over 10,000 school students from all over Western Australia.
- Involved in the development of a nanotechnology guide (in collaboration with educational experts from the SPICE secondary enrichment group at UWA), addressing the national chemistry curriculum for Year 11, which now includes nanotechnology in the syllabus.

PROJECT TITLE

Genetic Analysis of Circulating Tumour Cells and Circulating Tumour DNA for Prognosis of Uveal Melanoma

INVESTIGATORS

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

SCHOOL/INSTITUTE/CENTRE

School of Medical and Health Sciences, Edith Cowan University

SUMMARY OF AIMS AND RESULTS

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

Aim 1: To determine the frequency of CTC detection in UM patients at diagnosis.

We have quantified circulating tumour cells (CTCs) in 23 patients with primary localised UM, at the time of radiation plaque insertion. CTCs were enriched by targeting the melanoma associated chondroitin sulphate proteoglycan (MCSP). Of 23 cases tested, 15 had CTCs (70%) ranging from 1 to 37 CTCs per 8 mL of blood.

We evaluated the expression of a panel of melanoma markers in UM using a Tissue Microarray and 5 UM cell lines. UM tumours and cell lines exhibited a high heterogeneity of marker expression. Commonly used CTC markers such as MCSP, MCAM or surface gp100 were not expressed homogenously, while 5HT2B and ABCB5 were more highly expressed in the tumours than in the cell lines. Our results demonstrate that capture of CTCs with a single marker is not sufficient given the high heterogeneity of patients, and a multi-marker approach could provide more efficient capture and identification of UM CTCs.

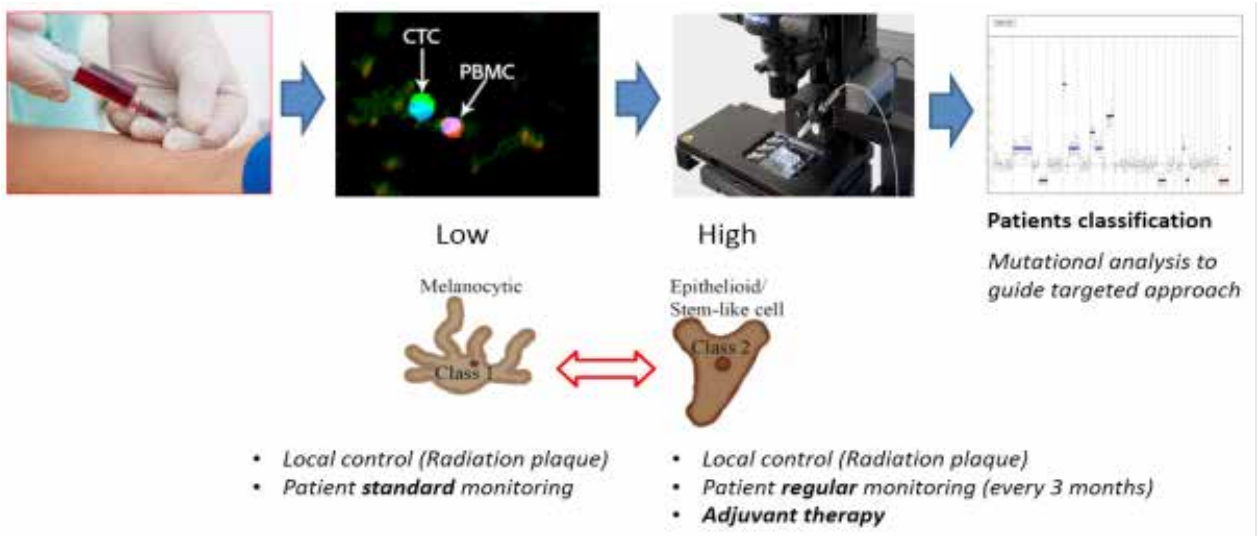


Figure 1: Proposed analysis pipeline.

We evaluated a multi-marker approach to capture UM cells spiked into healthy controls blood. We observed a recovery rate of 60-80% for the markers alone or in combination. In August 2016, we implemented this method to process new UM blood samples. We will further compare the number of CTC recovered using this multiimarker approach to our previous rate using only MCSP to enriched CTCs.

Aim 2: To develop methodologies to identify metastatic UM by genetic analysis of CTCs.
We compared two different commercial whole genome amplification (WGA) kits (PicoPlex WGA Kit (Rubicon Genomics) and Repli-G Single Cell Kit (Qiagen)) to determine their ability to provide accurate copy number information. The PicoPlex Kit, but not the Repli-G kit, was able to WGA cells after fixation. WGA-DNA from single cells amplified using PicoPlex provided accurate genomic profiles concordant with the parental cell lines. Cytogenetic features of prognostic value such as loss of Chr3 and gain in 8q was clearly distinguishable in all the samples analysed.

We implemented the multi-marker method described in Aim 1 and the single cell WGA/low-pass sequencing to identify chromosomal aberrations associated with the metastatic risk, in three UM patients so far. Where available, these will be compared to the genetic profile of matching tumour biopsies.

Aim 3: To evaluate whether ctDNA analysis can be used to identify markers of metastatic UM.
We detected ctDNA in five of the 27 primary UM patients tested (19%, range 2-28.5), two cases had a GNAQ Q209L mutation and three had the GNA11 Q209L variant. All five cases with detectable ctDNA also had CTCs. The ctDNA levels were associated with tumour size. Given the low tumour burden in this patient population, it is likely that ctDNA will be detected in a low proportion of cases. Continued follow up of these patients will reveal whether ctDNA detection is prognostic of metastatic disease.

OUTCOMES

Collaborations
Collaborations with oncologists and ophthalmologist from the Kinghorn Cancer Centre, Chatswood Grove Eye Clinic and Save Sight Institute have been established. We are currently preparing a human ethics application to expand our sample collection to these sites. We have also visited Dr William Harbour's laboratory at the Bascom Palmer Eye Institute, Miami University and established a collaboration to expand our study. We are currently evaluating the feasibility of our methodology using frozen peripheral blood mononuclear cells, so we can analysed archive samples from their clinical site.

Conference Presentations
- Beasley A. Poster presentation at Lorne Cancer, 11-13th February 2016, Lorne, VIC.
- Gray E.S. Invited speaker at the 3rd Thomas Ashworth CTC Symposium, 21st September 2016, Sydney, NSW.
- Beasley A. Poster presentation at the 3rd Thomas Ashworth CTC Symposium, 21st September 2016, Sydney, NSW.

PROJECT TITLE

Towards translating the benefits of patient specific biomechanics into clinical practice

INVESTIGATORS

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

SCHOOL/INSTITUTE/CENTRE

School of Mechanical Engineering, The University of Western Australia

SUMMARY OF AIMS AND RESULTS

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

This study aims to develop algorithms allowing generation of computational models from medical images, as well as robust, fast and accurate solution methods. Specifically, we will create a quick and robust method of generating patient-specific computational grids from diagnostic medical images, develop robust and accurate solution methods, create a fast updating procedure for high resolution 3D images and reduce computation cost of the developed algorithms through efficient parallel implementation on Graphics Processing Units (GPU).

This study has resulted in the development of several algorithms for improving the accuracy and robustness of meshless solution methods. These include accurate numerical integration methods using adaptive quadrature, a new method for imposing essential boundary conditions, and a new, more robust approximation method. All of these algorithms have been combined with meshless solution methods that we have previously developed, to form a new framework for computing soft tissue deformation.

We have also made progress in the use of computational biomechanics for the study of abdominal aortic aneurysms (AAA). We conducted an investigation of the relationship between AAA wall thickness and wall stress, including development of a software package for the evaluation of AAA rupture risk. This software extracts AAA geometry from medical images (CT/MRI), generates a model, evaluates the stress in the wall and computes a rupture potential index. We have also been involved in the development of a new method for evaluating fluid flows for irregular geometries, suited for the evaluation of blood flow in AAA.

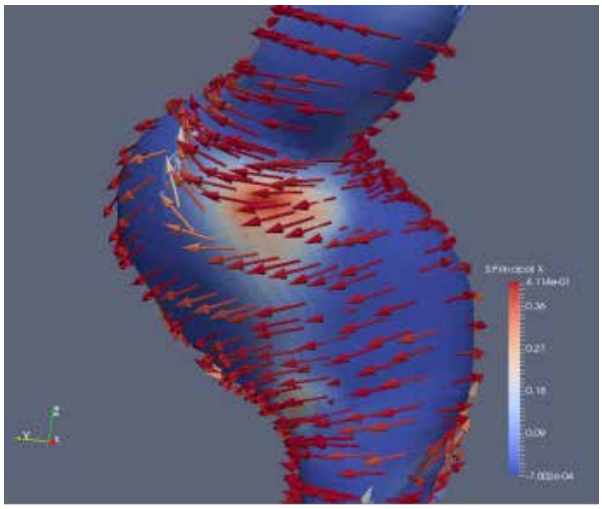


Figure 1. The size and direction of the maximum principal stress computed for an abdominal aortic aneurysm (AAA). The arrows indicate that the maximum principal stress is tangential to the AAA wall. The image gives an indication of the possible location (maximum stress) and direction (perpendicular to the stress direction) of an AAA rupture.

A new algorithm for warping 3D images has also been developed and implemented during this study. This algorithm transforms a deformation field defined at scattered points into a uniform B-Spline transform, using the multi-level B-Spline approximation algorithm (MBA). The new algorithm reduces the image warping computation time from hours to seconds. The algorithm is available for download as an extension, for visualisation and medical image computing 3D Slicer software.

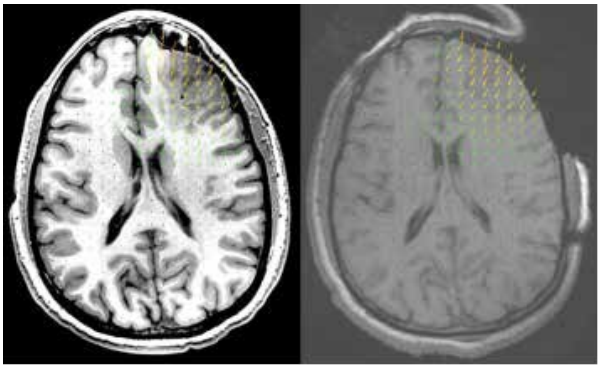


Figure 2. Brain registration using a biomechanical model. The warped high-quality pre-operative MRI image (left) is compared to the intra-operative MRI image (right). Arrows show the size and direction of deformation. Warping was performed using the ScatteredTransform extension I developed for 3D Slicer. Only one slice from each of the two 3D images is presented.

OUTCOMES

Collaborations

Collaborations have been formed with Professor Stanislav Polzer (Brno University of Technology, Czech Republic), Professors Zeike Taylor and Christopher Noble (University of Sheffield) to develop and evaluate a method of incorporating the effects of residual stress in the abdominal aortic aneurysm (AAA) wall stress estimation. Professor Polzer will be providing AAA cases for evaluation of methods developed in this study.

Grants

- Mr Tey Wah Yen, **Dr Grand Joldes**, *Element Free Galerkin Method for Ray Propulsion Mechanism*, UCSI University, Pioneer Scientist Incentive Fund 2016, $7,000.

Publications

- Chowdhury HA, Wittek A, Miller K, **Joldes GR**. An Element Free Galerkin Method Based on the Modified Moving Least Squares Approximation. Journal of Scientific Computing. 2016:1-15.
- Bourantas GC, Loukopoulos VC, Chowdhury HA, **Joldes GR**, Miller K, Bordas SPA. An implicit potential method along with a meshless technique for incompressible fluid flows for regular and irregular geometries in 2D and 3D. Eng Anal Bound Elem. 2017: 77:97-111.
- **Joldes GR**, Teakle P, Wittek A, Miller K. Computation of Accurate Solutions when using Element-Free Galerkin Methods for Solving Structural Problems. Engineering Computations. 2017; 34(3). Accepted.
- Chowdhury H, **Joldes GR**, Wittek A, Miller K. An element free Galerkin framework for computing soft tissue deformation. International Conference on Computational and Mathematical Biomedical Engineering; April 10-12, 2017; Pittsburgh, PA, United States 2017. Accepted.

PROJECT TITLE

Identifying immune biomarkers of response to chemotherapy in thoracic cancers

INVESTIGATORS

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

SCHOOL/INSTITUTE/CENTRE

School of Medicine and Pharmacology, The University of Western Australia

SUMMARY OF AIMS AND RESULTS

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

Patient recruitment: The study population consists of patients with malignant mesothelioma and advanced non-small cell lung cancer with recurrent pleural effusion, undergoing standard care chemotherapy. Matched peripheral blood (PB) and pleural effusion (PE) samples will be collected from 35 patients across 4 time points (pre-treatment and 3 in-treatment time points). While patient recruitment is currently ongoing, to date, matched PB and PE samples from 21 patients (15x mesothelioma and 6x lung cancer) have been stored. However, serial samples from all of these patients has not been possible. This has largely been due to teething problems with the sample collection protocols, however some samples have been missed for clinical reasons outside of our control. Thus far, serial samples from 5 patients in the study have been collected.

Aim 1: Characterise the phenotype and activation status of $CD8^+$ T cells at the tumour site (PE and systemically (PB)

In preparation for these experiments, two 13-parameter flow cytometry panels have been designed and optimised to look at the T cell subsets. Current work has progressed towards the optimisation of a 16 parameter panel.

Using multi-parameter flow cytometry, the phenotype of PE T cells has been compared with those in matched PB samples from 13 patients. Preliminary analysis shows that when compared with PB T cells, PE T cells (1) show increased expression of the inhibitory T cell receptors PD-1, Tim-3, LAG-3 and TIGIT, and (2) display a predominantly memory T cell phenotype with reduced expression of the effector molecule, granzyme B. This preliminary data suggests that the T cells located near the tumour microenvironment (PE) display a more dysfunctional phenotype than those circulating within the blood.

Aim 2: Investigate and compare the TCR repertoire of lymphocytes within matched PE and PB samples

This work is underway in collaboration Associate Professor Mark Watson at the Institute for Immunology and Infectious Diseases (IIID) at Murdoch University. We have performed bulk T cell receptor (TCR) sequencing of matched PB and PE from one patient at one time point and are moving forward with single cell techniques to look at the T cells in more detail. Preliminary results have shown (1) no clear bias in the distribution of T cell clones between the two compartments (PB and PE), and (2) a highly discordant distribution of TCR clones in the antigen experienced ($PD\text{-}1^+$) population between the PB and PE sample, suggesting an enrichment of antigen specific clones.

Aim 3: Determine whether immunological changes in the pleural effusion following treatment correlate with clinical outcome

This aim will be assessed at the end of the study.

FELLOWSHIPS

WA Department of Health/Raine Clinician Research Fellowships

The Clinician Research Fellowship program is now well-established and acknowledged as an outstanding opportunity for talented young clinicians employed by WA Health to become more involved in clinical research. These Fellowships represent the hallmark of clinical excellence, offered only to clinicians of high research standing through an assessment process that is rigorous, transparent and equitable.

2016 marked Round 5 of the program which was initiated in 2012 by the WA Department of Health and enthusiastically supported by the Raine Medical Research Foundation. We are proud to report that a total of twenty-one Clinician Research Fellowships have now been awarded with a funding commitment in excess of $5.3m. These clinicians effectively work at the "coal face" of clinical medicine. Every day they see patients suffering chronic pain, severe illness, debilitating disease and other medical conditions; and it is these young doctors who have the dedication, the commitment and the generosity to spend personal time pursuing answers to challenging questions that often confound the medical fraternity. International collaboration has become an imperative tool in the sharing of new ideas and techniques; and it is particularly pleasing to observe how our young physicians have maximised the opportunity to engage with their international counterparts in developing a global network of clinical and translational links.

As the early Fellowship projects near completion, some exciting results are beginning to emerge – results with the potential to be translated into improved clinical practice and better health care delivery. The CRF Annual Reports documenting the progress of each research study are available commencing page 40.

The WA Department of Health is to be congratulated for this.

Details of the Clinician Research Fellowships awarded from Round 1 to Round 5 are provided below. These include two projects funded by the Nurses and Midwives group.

2013 Clinician Research Fellowships (Round 1)

	Fellow	Project Title
	Clinical Professor Tomas Corcoran	Project 1: REstrictive versus LIbEral 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)

	Fellow	Project Title
	Clinical Associate Professor Gareth Baynam	1 in 12: Translational Research for Rare Diseases
	Dr Christopher Blyth	Preventing influenza morbidity and mortality in West Australian children through vaccination
	Dr Aron Chakera	The influence of multi-strain cytomegalovirus infections on the immune repertoire: Implications for organ transplantation
	Dr Dale Edgar	Does exercise training improve muscle strength and function after burn injury?

	Dr Brigitte Tampin	The role of sensory parameters in predicting clinical outcome after lumbar discectomy

Nurses and Midwifery Group

	Fellow	Project Title
	Dr Hugh Davies	The F.L.U.I.D. study (Forecasting Level of Ultrafiltration and Intensity of Dialysis)

2015 Clinician Research Fellowships (Round 3)

	Fellow	Project Title
	Dr Edward Fysh	Pleural effusions in intensive care patients: The physiological changes and clinical effects of drainage procedures
	Clinical Associate Professor Kwok-ming Ho	Detailed assessment of risks and benefits of inferior vena cava filters on patients with complicated injuries (the *da Vinci* Trial)
	Dr Thomas Snelling	Improving the West Australian Immunisation Program

Nurses and Midwifery Group

	Fellow	Project Title
	Dr Ulrich Steinwandel	Do ultrasound measurements of the inferior vena cava (IVC-US) by nursing staff improve assessment of intravascular volume status in the satellite haemodialysis clinic settings

2016 Clinician Research Fellowships (Round 4)

	Fellow	Project Title
	Dr Rishi Sury Kotecha	Combinatorial therapeutics in high-risk infant acute lymphoblastic leukaemia
	Dr Martin de Bock	Closed loop insulin delivery for patients with Type 1 Diabetes in free living conditions
	Dr Annette Lim	Mechanisms that facilitate the metastatic potential of oral cancer
	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

2017 Clinician Research Fellowship Awards (Round 5)

	Fellow	Project Title
	Dr Dimitri Azmanov	Diagnostic genomics applications for short stature
	Dr Wai Lim	Improving health outcomes of kidney transplant recipients
	Dr Tobias Strunk	Pentoxifylline to protect the preterm brain

Clinician Research Fellowships

PROJECT TITLE
1 in 12: Translational Research for Rare Diseases

CLINICIAN RESEARCH FELLOW
Clinical Associate Professor Gareth Baynam

PROJECT OVERVIEW
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.

ONGOING CLINICAL DEVELOPMENTS
Research Translation and Diffusion

The overlapping initiatives in this Fellowship have been implemented and further embedded into clinical care as summarised below:

- Rare and Undiagnosed Diseases Diagnostic Service (RUDDS) – this service has trebled the rate of confirmed genetic diagnosis in clinical service. The RUDDS has continued from initiation and implementation under this Fellowship and was a finalist for the WA Health Excellence Awards, 2016.
- The Undiagnosed Diseases Program http://www.kemh.health.wa.gov.au/services/genetics/#udp-wa – This was implemented at Princess Margaret Hospital in March 2016 as a novel and globally coordinated approach (The Undiagnosed Diseases Network International http://www.udninternational.org/) for those with extraordinary clinical (diagnostic) need. To date it has achieved a definitive diagnosis for two-thirds of the children seen. It involves multiple National Institutes of Health and their equivalents (e.g. US, Japan, Italy, Korea and others) ;
- Rare Diseases Data from WARDA.
- http://www.kemh.health.wa.gov.au/services/register_developmental_anomalies/ This has continued to provide world first population level information on the impact of rare diseases for health system planning and improved health care. This includes involvement in the RUDDS and the UDP (Undiagnosed Diseases Program); and also obtaining baseline state-wide microcephaly data, covering the last 30 years, as preparation for Zikka virus and an expanding range of rare genetic microcephalies.
- Cliniface http://www.crcsi.com.au/research/4-4-health/completed-projects/4-406-cliniface/ – implementation of new 3D facial analysis tools in clinical practice.

FELLOWSHIP OUTCOMES
Oral Conference Presentations

- *Function-all*, Athel Hockey Symposium, Perth 2016.
- *Facial Diagknowsis*, Royal Australasian College of Pathologists Annual Conference, Melbourne, 2016.
- *You can't do it without me phenotyping*, The European Conference on Rare Diseases & Orphan Products, Edinburgh, 2016.
- *Mysteries, Shadows and Light*, Western Australian Dental Study Group Annual Meeting, Perth.
- *Rare and everywhere; ancient wisdom and innovative solutions*, Indigenous Business, Enterprise and Corporations Conference – Perth 2016.
- *The Western Australian Register of Developmental Anomalies and Australian Aboriginal Genomics and Phenomics*, Rare Diseases X – The First African Rare Diseases Conference, South Africa, 2016.
- *Undiagnosed Diseases Program-WA*. 4th International Meeting on Undiagnosed Diseases, Tokyo, Japan 2016.
- *Undiagnosed Diseases Program*, 3rd International Meeting on Undiagnosed Diseases, Vienna, Austria, 2016.
- *Red flags in the Red Sand*, First Australian Annual Genomics Update, Sydney, NSW 2016
- *Indigenous Reference Data – a local and global need*, Board Meeting of the Aboriginal Health Council of WA, 2016.

Session Chairs

- *Newborn Screening*, Rare Diseases X – The First African Rare Diseases Conference, South Africa, 2016
- *Translating Clinical Genomic*, First Australian Annual Genomics Update, Sydney, NSW 2016.

Workshop Lead

- *Research and Research Funding*, The First African Rare Diseases Conference, South Africa, 2016.

Published Papers

[1-10]

1. **Baynam G.** 2016. Facial diagknowsis. *Pathology* **48 Suppl 1**: S32.
2. **Baynam G, et al.** 2016. African Challenges and Opportunities for Rare Diseases Research. *Rare Diseases and Orphan Drugs*.
3. **Baynam G, Pachter N, McKenzie F, Townshend S, et al.** 2016. The rare and undiagnosed diseases diagnostic service - application of massively parallel sequencing in a state-wide clinical service. *Orphanet journal of rare diseases* **11**: 77.
4. **Baynam GS, Pearson G, Blackwell J.** 2016. Translating Aboriginal genomics – four letters Closing the Gap. *The Medical Journal of Australia* **205**: 379.
5. **Bogershausen N, Gatinois V, Riehmer V, Kayserili H, et al.** 2016. Mutation Update for Kabuki Syndrome Genes KMT2D and KDM6A and Further Delineation of X-Linked Kabuki Syndrome Subtype 2. *Human mutation* **37**: 847-64.
6. **Hu H, Haas SA, Chelly J, Van Esch H, et al.** 2016. X-exome sequencing of 405 unresolved families identifies seven novel intellectual disability genes. *Molecular psychiatry* **21**: 133-48.
7. **Kohler S, Vasilevsky NA, Engelstad M, Foster E, et al.** 2016. The Human Phenotype Ontology in 2017. *Nucleic acids research*.
8. **Lochmuller H, Le Cam Y, Jonker AH, Lau LP, et al.** 2016. 'IRDiRC Recognised Resources': a new mechanism to support scientists to conduct efficient, high-quality research for rare diseases. *European journal of human genetics*: EJHG.
9. **Simeoni I, Stephens JC, Hu F, Deevi SV, et al.** 2016. A high-throughput sequencing test for diagnosing inherited bleeding, thrombotic, and platelet disorders. *Blood* **127**: 2791-803.
10. **Walker CE, Mahede T, Davis G, Miller LJ, et al.** 2016. The collective impact of rare diseases in Western Australia: an estimate using a population-based cohort. *Genetics in medicine: official journal of the American College of Medical Genetics*.

New Board Positions

International Advisory Board, Atlas of Human Malformations in Diverse Populations – An international group of clinical geneticists, dysmorphologists, and other medical specialist have come together to create an atlas of human malformation syndromes in diverse populations. https://research.nhgri.nih.gov/atlas/

International Advisory Board, Minerva and Me – facial diagnostics for rare diseases, including crowdsourcing https://www.minervaandme.com/

New Committee Roles

Vice-Chair (in-coming Chair), Diagnostics Scientific Committee of the International Rare Diseases Research Consortium. IRDiRC is a consortium of research funding agencies and interested parties acting to accelerate research through collaborations. http://www.irdirc.org/

Media coverage/publicity

Multiple articles in written print in state and national media, TV interviews and news broadcasted across channels 7,9,10 and ABC.

Some examples:

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

Capacity Building

New Grants

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

New research team members

2 postdoc positions in 3D facial analysis funded for 2 years.

0.5 FTE RA position funding for 5 years for 3D facial analysis.

Additional personal role

Head, WA Register of Developmental Anomalies

ACKNOWLEDGEMENT

This fellowship provided a unique and unparalleled opportunity and flexibility to develop transformational research skills from the clinical interface. In doing so, it has supported the implementation of new diagnostic initiatives for genetic and rare diseases (genomic and phenomic), including the Rare and Undiagnosed Diseases Diagnostic Service; 3D facial analysis platforms, including CliniFace; and the Undiagnosed Diseases Program. 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 public health policy. Furthermore it has been critical to the development of clinical genetic and rare diseases initiatives for equitable health, notably through providing the foundation for success for multiple Aboriginal health grants.

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.

Quite simply, a clinician could not have asked for a better opportunity to deliver against the four pillars of WA Health:

1. Caring for individuals and the community
2. Caring for those who need it most
3. Making best use of funds and resources
4. Supporting our team.

PROJECT TITLE
Preventing influenza morbidity and mortality in West Australian children through vaccination

CLINICIAN RESEARCH FELLOW
Dr Christopher Blyth

PROJECT OVERVIEW AND AIMS
Influenza virus infections remain a major contributor to the global burden of acute respiratory disease. Young children, the elderly and others with underlying medical conditions are at greatest risk of hospitalisation, morbidity and death. The direct and indirect costs associated with influenza are substantial.

Influenza vaccination has been recommended since 2008 for all children aged six to 59 months in Western Australia (WA). In addition, influenza vaccination is recommended in older children with risk factors for severe disease. The primary aim of this fellowship was to determine the effectiveness of inactivated trivalent influenza vaccine in West Australian children. In addition, research was undertaken to: a) investigate the effectiveness of TIV in children with predisposing conditions placing them at increased risk of severe influenza infection, b) investigate vaccine coverage in children with and without risk factors for severe influenza infection and c) identify patient and parental factors which influence coverage and acceptance of influenza vaccination.

Research presented demonstrates the effectiveness of TIV in young children with and without risk factors was similar to that observed in older children and adults. TIV coverage remains poor in children in Western Australia following adverse events in 2010. As a result, the full benefits of influenza vaccination are not being realised. Parental attitudes towards vaccine safety and efficacy appear to be the most important factor influencing coverage. These data have been highly influential in informing WA's ongoing influenza vaccination program and the national influenza vaccination policy and education campaign.

Primary aim:
- Determine the effectiveness of inactivated trivalent influenza vaccination in West Australian children.

Secondary aims:
- Investigate the uptake and effectiveness in children with predisposing medical conditions placing them at greatest risk of severe influenza infection.
- Identify patient and parental factors which influence uptake and acceptance of influenza vaccination.

The proposed aims were addressed by the following studies:
- A prospective incidence density case-control study enrolling children with influenza-like illness, comparing influenza vaccination coverage in those with and without laboratory provide influenza.
- A retrospective case-control study using test negative design comparing the vaccination status of children undergoing virological testing with and without laboratory-proven influenza.
- A retrospective population-based cohort study using de-identified, individually linked records.

ONGOING CLINICAL DEVELOPMENTS
Research Translation and Diffusion

Knowledge gained from these projects has resulted in real changes in public policy. Based on the effectiveness data demonstrated, WA Health has continued to support and fund the preschool influenza vaccination program in WA. In addition, these data have been instrumental in the decision nationally to fund influenza vaccine for preschool Indigenous children and renewed interest in a national universal preschool program.

In addition, data generated from these projects were used with data from other centres to inform vaccine strain choice for the annual influenza vaccine. Collated through the Global Influenza Vaccine Effectiveness (GIVE) collaboration, data from observational studies assessing vaccine effectiveness against PCR-confirmed influenza infection in both the ambulatory care and hospital setting were presented at the WHO Consultation and Information Meeting on the Composition of Influenza Virus Vaccines: Northern and/or Southern Hemisphere. Data collected by paediatric programs in Australia (including studies previously described) were included in the GIVE report to assist with Southern Hemisphere vaccine strain choices.

Based on the data and feedback from parents, WA Health and Princess Margaret Hospital has incorporated paediatric vaccine effectiveness and safety data in its annual influenza-vaccination education campaign. In addition, programs providing general practitioners and vaccination clinics with the key findings from the project (online videos; electronic and paper mail-outs; formal presentations at annual updates) have facilitated a more informed and accurate discussions about the merits of vaccination. These data have also been incorporated into presentations held at community fora with parents.

FELLOWSHIP OUTCOMES
Capacity Building

This fellowship has enabled me to be successful with a 2016 NHMRC Career Development Fellowship application (2016-2019)[1]. This will fund ongoing salary support thereby allowing me to focus further on influenza, pneumococcus

and pneumonia in Australia and the region. The outputs from this new fellowship will continue to influence public policy, particularly Australian and PNG vaccine policy.

Through ongoing relationships with research partners (FluCAN and the Paediatric Active Enhanced Diseases Surveillance [PAEDS] network), ongoing influenza vaccine effectiveness assessments will be undertaken and provided to national and international committees. These proposed research programs have been successfully awarded an NHMRC Partnership Grant[2] and will assess paediatric influenza vaccination in five Australian paediatric tertiary hospitals.

The publications arising from this fellowship form a major part of my PhD (Awarded May 2016). Having a higher degree enables me to supervise higher degree students, thereby contributing to research capacity building in the future. We have employed medical students and nurses on all projects, thereby providing research training to the next generational of clinical researchers.

Grants

[1]**Blyth CC.** Evaluation and optimisation of paediatric vaccination programs in Australia and the region, *NHMRC Career Development Fellowship Level 1* (APP1111596): 2015, A$293,428.00.

[2]Macartney K, **Blyth C**, Marshall H, Leask J, McIntyre P, Elliot E, Snelling T, Clark J, Buttery J, Wood N. Reducing vaccine preventable diseases in children: using national active hospital-based surveillance to evaluate and improve immunisation program performance. *National Health and Medical Research Council Partnership Grants 2016* (APP1113851), A$1,049,915.76.

Publications

Building on the original publication early in 2014 (Blyth et al, Pediatrics 2014 133(5); e1218-25), four further publications have been published during this fellowship:

Blyth CC, Richmond PC, Jacoby P, Thornton P, Regan A, Robins C, et al, The Impact of Pandemic A(H1N1pdm09 Influenza and Vaccine-Associated Adverse Events on Parental Attitudes and Influenza Vaccine Uptake in Young Children. *Vaccine 2014 Jul 7;32(32):4075-81. doi: 10.1016/j.vaccine.2014.05.055*.

Blyth CC, Cheng AC, Finucane C, Jacoby P, Effler PV, Smith DW et al. The effectiveness of influenza vaccination in preventing hospitalisation in children in Western Australia, *Vaccine. 2015 Dec 16;33(51):7239-44. doi: 10.1016/j.vaccine.2015.10.122.*

Blyth CC, Macartney KK, Hewagama S, Senenayake S, Friedman ND, Simpson G et al. Influenza epidemiology, vaccine coverage and vaccine effectiveness in children admitted to sentinel Australian hospitals in 2014: the Influenza Complications Alert Network (FluCAN), *Eurosurveillance 2016*, 28;21(30). doi: 10.2807/1560-7917.ES.2016.21.30.30301.

Blyth CC, Jacoby P, Effler PV, Kelly H, Smith DW, Borland ML, et al. Influenza vaccine effectiveness and uptake in children at risk of severe disease, *Pediatr Infect Dis J. 2016 Mar;35(3):309-15. doi: 10.1097/INF.0000000000000999.*

In addition to the publications presented, data collected during this fellowship has been incorporated into the following publications:

Cheng AC, Maccartney KK, Kotsimbox T, Kelly P, **Blyth CC**, FluCAN Investigators. (2017) Serial vaccination does not appear to impact on influenza vaccine effectiveness against hospitalisation with confirmed influenza. *Clinical Infectious Diseases 2017, in press.*

Li-Kim-Moy J, Yin, JK, **Blyth CC**, et al, Influenza hospitalisations in Australian Children. *Epidemiology and Infection* 2017 Feb 6:1-10. doi: 10.1017/S0950268816003381.

Cheng AC, Holmes M, Dwyer DE, et al. Influenza epidemiology in patients admitted to sentinel Australian hospitals in 2015: the Influenza Complications Alert Network (FluCAN). *Commun Dis Intell Q Rep. 2016 Dec 24;40(4):E521-E526*.

Cheng AC, Holmes M, Senenayake S, et al, Influenza epidemiology in adults admitted to sentinel Australian hospitals in 2014: the Influenza Complications Alert Network (FluCAN). *Commun Dis Intell Q Rep. 2015 Sep 30;39(3):E355-60*.

Jelly L, Levy A, Deng YM, et al. Influenza C infections in Western Australia and Victoria from 2008-14. I*nfluenza and other Respiratory Viruses, Influenza and other Respiratory Viruses*, 2016 Jul 4. doi: 10.1111/irv.12402.

Conference Presentations

Li-Kim-Moy J, **Blyth C**, Kesson A, et al K. High burden and low vaccination rates in children hospitalised with influenza. *National Immunisation Conference, Brisbane '16*.

West R, Willis GA, Finucane CM, … **Blyth C**. Verifying influenza vaccines in children: How accurate is ACIR? *National Immunisation Conference, Brisbane '16*.

Willis G, Richmond P, Jacoby P … **Blyth C** The impact of Influenza on young children in metropolitan Western Australia. *National Immunisation Conference, Brisbane 2016*.

Robins C, Richmond PC, Jacoby P … **Blyth CC**. Effectiveness of Trivalent Influenza Vaccine in Healthy Children. *National Immunisation Conference, Melbourne '14*.

Blyth CC, Richmond PC, Thornton P, et al The Impact of Adverse Events on Parental Attitudes and Influenza Vaccine Uptake in Young Children. *National Immunisation Conference, Melbourne 2014*.

PROJECT TITLE

The influence of multistrain cytomegalovirus infections on the immune repertoire: Implications for organ transplantation

CLINICIAN RESEARCH FELLOW

Dr Aron Chakera

PROJECT OVERVIEW

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.

ONGOING CLINICAL DEVELOPMENTS

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.

Research Translation and Diffusion

Cytomegalovirus (CMV) establishes a lifelong infection that is efficiently controlled by the immune system; however infection can be reactivated in cases of immunosuppression such as following solid organ transplantation. CMV viraemia is associated with CMV disease, as well as increased mortality and allograft failure. Recently new assays have been introduced in WA Health to measure levels of CMV in the blood, and these are significantly more sensitive than older assays, raising questions of the significance of positive results. We reviewed patient and graft outcomes from all adult (18 years and over) Western Australian renal transplant recipients transplanted between 1 January 2007 and 31 December 2012 and assessed the factors associated with CMV reactivation, and the impact of CMV reactivation on outcomes. We demonstrated that kidney transplant recipients aged 65 years and over, receiving a graft from a deceased donor, receiving a graft from a donor aged 60 years and over, and/or receiving anti-T lymphocyte antibody post-transplant increased the risk of CMV viraemia only when viral loads are ≥600 copies/ml (significantly above the cut-off of the new assays at 20 copies/mL). CMV viraemia with viral loads ≥4590 copies/ml was a risk factor for death following renal transplantation, as was receiving a transplant from a deceased donor, being aged 65 years and above at transplant, being Aboriginal and having vascular disease. Importantly 50% of the episodes of CMV viraemia with viral loads ≥4590 copies/ml occurred while the patients were expected to be on CMV prophylaxis. This work has confirmed the clinical threshold for interpretation of CMV viral titres post-renal transplantation and confirmed the need for greater vigilance in monitoring CMV levels if antiviral prophylaxis is stopped prematurely or poor patient compliance is suspected.

FELLOWSHIP OUTCOMES

Advancing Knowledge

The data on CMV assays and interpretation has been presented locally at the Western Australian Kidney Transplant meeting and has been submitted to *BMC Nephrology*. Cytomegalovirus viraemia and mortality in renal transplant recipients in the era of antiviral prophylaxis. Lessons from the Western Australian experience. Linda Anne Selvey; Wai H Lim; Peter Boan; Ramyasuda Swaminathan; Claudia Slimings; Amy E Harrison; Aron Chakera.

The work on post-transplant CMV and the potential link to cancer has now been published. This study reviewed 8140 adult deceased donor kidney transplant recipients between 1990 and 2012. A total of 895 (11%) recipients developed incident cancers during a follow-up time of 51,555 person-years. Although there was no statistically significant association between CMV serological status and cancer risk, the human leukocyte antigen (HLA) mismatches were an effect modifier between CMV serological status and cancer ($p = 0.03$ for interaction). In recipients who have received 0-2 HLA-ABDR mismatched kidneys, 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 compared with the reference of CMV D+/R+. A similar association was not observed in those with >2 HLA-ABDR mismatches.

This data suggests that CMV D-/R- status is associated with a reduced risk of cancer in kidney transplant recipients who have received well-matched renal allografts, implicating HLA-matching in cancer development.

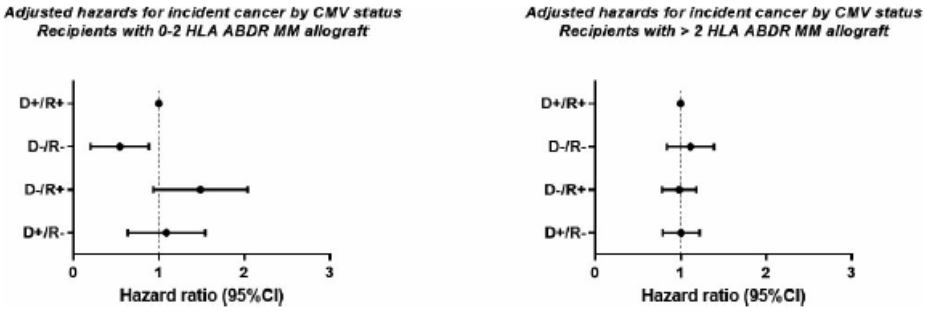


Figure 1. Hazard ratios for incident cancer according to CMV status and HLA Matching.

Figure 2. Combined surface and DNA staining using the ImageStreamX Imaging Flow Cytometer.

Wong G, **Chakera A**, Chapman JR, Chadban SC, Pilmore H, Craig JC, Lim WH. Cytomegalovirus and cancer after kidney transplantation: Role of the human leukocyte antigen system? *Transpl Infect Dis*. 2016 Nov 12. doi: 10.1111/tid.12631.

Further studies to prospectively assess how different cell subsets may influence this risk are planned using samples collected into the Renal Biobank. A further spin-off project from this Fellowship, to look at combining cell surface staining and fluorescent in situ hybridisation has also now been published.

Fuller KA, Bennett S, Hui H, **Chakera A**, Erber WN. Development of a robust immuno-S-FISH protocol using imaging flow cytometry. *Cytometry A*. 2016 May 3.

Capacity Building

Work from the registry has also been linked to additional outcomes for transplant recipients, in particular the risk of developing diabetes post-kidney transplant, which is also associated with CMV. This work has been published:

Rosettenstein K, Viecelli A, Yong K, Do Nguyen H, **Chakera A**, Chan D, Dogra G, Lim E-M, Wong G, Lim W. Diagnostic Accuracies of Glycated Haemoglobin, Fructosamine and Homeostasis Model Assessment of Insulin Resistance In Predicting Impaired Fasting Glucose, Impaired Glucose Tolerance or New Onset Diabetes Following Kidney Transplantation. *Transplantation*, 2016 Jul;100(7):1571-9. doi: 10.1097/TP.0000000000000949.

Funding has also been obtained from the Diabetes Foundation of Western Australia to look at a new clinical pathway to reduce the risk of post-transplant diabetes, and this work is ongoing.

The analysis of cell subsets from transplant patients has led to stronger collaboration with the Centre for Microscopy and Cellular Analysis (at UWA), and in particular the head of the flow cytometry suite Dr Andrea Holmes. Dr Homes is a co-author on a manuscript currently in preparation and additional grants to continue this work are in preparation.

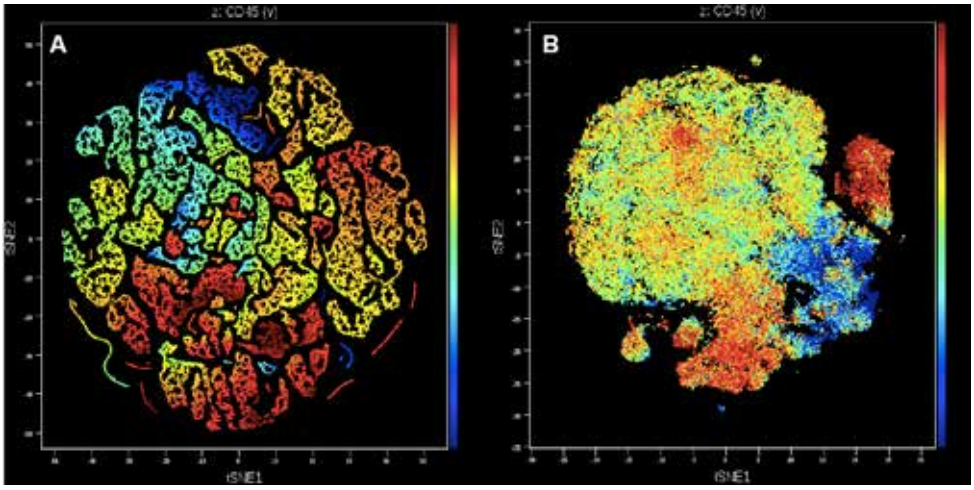


Figure 3. Thymic leukocyte profiles in mice in the absence (A) or presence (B) of CMV infection.

Publications

Wong G, **Chakera A**, Chapman JR, Chadban SC, Pilmore H, Craig JC, Lim WH. Cytomegalovirus and cancer after kidney transplantation: Role of the human leukocyte antigen system? Transpl Infect Dis. 2016 Nov 12. doi: 10.1111/tid.12631

Mitchell T, **Chakera A**, Jeffrey GP, Adams LA, Garas G, Jones T, MacQuillan G. Reversal of end-stage renal failure using direct-acting antiviral agents for chronic hepatitis C. Med J Aust. 2016 Sep 5;205(5):205-6.

Fuller KA, Bennett S, Hui H, **Chakera A**, Erber WN. Development of a robust immuno-S-FISH protocol using imaging flow cytometry. Cytometry A. 2016 May 3

Jiwa M, **Chakera A**, Dadich A, Meng X, Kanjo E. The profile of patients with chronic kidney disease who regularly present at an Australian general practice. Curr Med Res Opin. 2016 Jan;32(1):183-9.

Rosettenstein K, Viecelli A, Yong K, Do Nguyen H, **Chakera A**, Chan D, Dogra G, Lim E-M, Wong G, Lim W. Diagnostic Accuracies of Glycated Haemoglobin, Fructosamine and Homeostasis Model Assessment of Insulin Resistance In Predicting Impaired Fasting Glucose, Impaired Glucose Tolerance or New Onset Diabetes Following Kidney Transplantation. *Transplantation*. 2016 Jul;100(7):1571-9. doi: 10.1097/TP.0000000000000949.

Chakera A, MacEwen C, Bellur SS, Chompuk LO, Lunn D, Roberts IS. Prognostic value of endocapillary hypercellularity in IgA nephropathy patients with no immunosuppression. *J Nephrol*. 2016 Jun;29(3):367-75. doi: 10.1007/s40620-015-0227-8.

ACKNOWLEDGEMENT

The WA Department of Health/Raine Clinician Research Fellowship has been pivotal to my ability to continue with research along with my clinical practice and has enabled me to develop a series of research projects aimed at improving outcomes for patients with kidney diseases. These projects have spanned the spectrum from discovery science (host-pathogen interactions at a cellular level) through to clinical applications and the epidemiology of infections (CMV outcomes post-transplantation), and have led to new techniques to study disease (FISH-IS) and clinical pathways (post-transplant diabetes and CMV prophylaxis in D-/R- recipients). A direct result of this work has also been an appreciation for the limitations within our current system to support research and my involvement in a number of initiatives to support research within WA Health.

Through the support of this Fellowship, my research group has expanded to include 2 PhD students, 2 post-doctoral researchers as well as 2 research nurses. I have been able to submit applications for a number of grants and established new collaborations with researchers and clinicians locally, nationally and internationally. I have also been invited to join research committees representing Sir Charles Gairdner Hospital and the North Metropolitan Health Service as well as the Australia and New Zealand Society of Nephrology and Australian Kidney Trials Network. With the foundation for my research endeavours now established through the WA Department of Health/Raine Foundation Fellowship I look forward to building upon this in the years to come and thank the Department of Health and the Raine Foundation for their support.

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 OVERVIEW AND AIMS
The RELIEF study was a multicentre, pragmatic, randomised controlled trial which was designed to examine the influence of total amount of fluid that patients receive during their surgical period, on the long term outcomes after anaesthesia and surgery in moderate to high risk patients undergoing major abdominal surgery. Patients were randomised to either a "Liberal" or "Restrictive" group, and were followed up for one year postoperatively. The primary outcome was Disability Free Survival at one year.

The BALANCED STUDY was designed to examine the influence of the depth of anaesthesia, and total dose of anaesthetic agents, on long term patient outcomes following surgery and anaesthesia.

ONGOING CLINICAL DEVELOPMENTS
Research Translation and Diffusion

Although the RELIEF study planned to recruit 2800 patients, a decision was made in mid-2016 by the Steering Committee to expand recruitment to 3000 patients. Recruitment has been completed and the 30 day data collection for the primary outcome data has passed for all trial patients.

The data is currently undergoing final cleaning, prior to analysis by the trial statisticians. The preliminary results will be presented at the Collaborative Clinical Trials in Anaesthesia meeting in Prato, Florence, June 2017.

The impact of these trials on the WA health system cannot as yet be ascertained; however, any results will be translated by means of presentation at the ASA and ANZCA WA meetings to reach as wide an audience as possible.

FELLOWSHIP OUTCOMES
Capacity Building

WA is the lead site for the BNP and Economic sub-studies of the RELIEF main trial. The BNP sub-study has a total of 516 patients recruited and will provide important information regarding cardiac stress relating to fluid administered. The Economic sub-study will provide information relating to the economic benefits to be derived from the entire cohort of patients, if a clinical benefit is shown once the main trial has been analysed. These two trials have facilitated collaboration with other groups in Australia, Europe and Hong Kong and we have now established a group that is performing studies into perioperative epigenetics. This is in collaboration with:

- Dr Chris Bain
  Specialist Anaesthetist and Lecturer,
  Department of Anaesthesia and Perioperative Medicine,
  Alfred Hospital and Monash University.
- Dr Kiymet Bozaoglu BSc (Hons), PhD
  Head, Genomics and Systems Biology laboratory,
  The Baker IDI Heart and Diabetes Institute
- Dr Matthew Chan, MBBS, HKAM, FANZCA
  Specialist Anaesthetist, Department of Anaesthesia and Intensive Care, Prince of Wales Hospital
  Professor, Department of Anaesthesia and Intensive Care, Chinese University of Hong Kong.
- Dr Jan Dieleman, Utrecht University Medical Centre,
  The Netherlands.

We have two successful grant applications for the epigenetic sub-studies of the RELIEF trial and also for the NHMRC funded PADDI trial.

As a further consequence of these trials and the successful PADDI trial (NHMRC 2014), we have now been in a position to run multicentre trials from the ANZCA Clinical trials network at:

- Royal Perth Hospital
- Fremantle Hospital
- Fiona Stanley Hospital
- Rockingham Hospital
- St John of God Hospital, Subiaco
- Sir Charles Gairdner Hospital (to commence in 2017)

Publications

Myles P, Bellomo R, **Corcoran T**, Forbes A, Wallace S, Peyton P, Christophi C, Story D, Leslie K, Serpell J, McGuinness S, Parke R, Australian, New Zealand College of Anaesthetists Clinical Trials N, the A, New Zealand Intensive Care Society Clinical Trials G. Restrictive versus liberal fluid therapy in major abdominal surgery (RELIEF): rationale and design for a multicentre randomised trial. BMJ open 2017;7:e015358.

PROJECT TITLE
The F.L.U.I.D. study (Forecasting Level of Ultrafiltration and Intensity of Dialysis)

CLINICIAN RESEARCH FELLOW
Dr Hugh Davies

PROJECT OVERVIEW AND AIMS

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.

The aim of this study was to (1) identify factors which can affect the ability of continuous renal replacement therapy (CRRT) to deliver a prescribed dose of dialysis including fluid balance control and (2) evaluate changes in clinical practice designed to improve how fluid balance control can be monitored more effectively during CRRT.

The two aims of the project were achieved by dividing the study into two phases.

Phase One of FLUID (Forecasting Level of Ultrafiltration and Intensity of Dialysis) included conducting retrospective observations of events that interrupted or delayed treatment delivery in patients who received continuous veno-venous haemodiafiltration (CVVHDF). Findings from the retrospective study found almost a quarter of treatment days did not meet the prescribed fluid removal target. Shortfalls in meeting fluid removal targets suggested changes in clinical practice could improve treatment delivery.

Phase Two of FLUID investigated ways changes in clinical practice could improve treatment delivery in terms of fluid balance control. A system of using green, orange and red "flags" was developed to see whether this would improve the identification of shortfalls in meeting daily fluid removal targets in patients receiving CVVHDf. The "traffic light" approach was evaluated as a case study and findings suggested it was a useful tool in drawing attention to shortfalls in meeting the previous day's fluid removal target that unless corrected the next day placed the patient at increased risk of fluid overload. Although this approach was successful as a single case study, the use of a paper-based method for charting fluid balance made its wider application at the study site difficult to implement.

Another change in clinical practice included changing the frequency and timing of when patients receiving CRRT were weighed. Over short length of stays changes in body weight are almost entirely the result of alterations in body fluid and so in the first week of critical illness body weight measurements can provide a more reliable estimate of total body water. One of the limitations of Phase One was body weight measurements were recorded on alternate days and measured at different times of the day. In implementing Phase Two a change in clinical practice allowed prospective observations of daily body weight changes. These measurements were measured at midnight and compared with fluid balance totals calculated at the same time to determine if they corresponded to a similar change in body weight.

The benefit of the FLUID study to the WA health system has been to highlight the importance of achieving fluid balance control in patients with severe AKI who are at increased risk of fluid overload. Specifically the importance of meeting daily fluid removal targets in patients receiving CRRT. Observational studies have shown that the effect of fluid overload is associated with increased patient mortality.[1] This study also demonstrated the difficulties of maintaining an accurate fluid balance chart and the importance of consistency in obtaining consecutive daily changes in body weight as two methods most commonly used in ICU to estimate body fluid status.

ONGOING CLINICAL DEVELOPMENTS

Research Translation and Diffusion

Since the implementation of Phase One of FLUID awareness of the possibility that fluid removal targets may not always be achieved during CRRT has increased. This has been identified as an issue of concern by other researchers investigating fluid balance control in patients at risk of fluid overload.[2] The paper has been cited by other researchers working in this area.[3]

The two methods most commonly used in ICU to estimate and monitor body fluid status is by the charting of daily fluid balance and measurement of body weight changes. The usefulness of fluid balance in estimating body fluid

1 Zhang L, Chen Z, Diao, Y. Yang, Y. Fu, P. Associations of fluid overload with mortality and kidney recovery in patients with acute kidney injury: A systematic review and meta-analysis. Journal of Critical Care. 2015; 30: 860e7-860e13.

2 Corden D, Bone, A Elderkin T. Oral Presentation "Achievement of fluid balance prescription while on continuous renal replacement therapy" 41st ANZICS/ACCCN Intensive Care ASM and the 22nd Annual Paediatric and Neonatal Intensive Care Conference. 20-22 October 2016 Perth, Western Australia.

3 Murugan R, Hoste E, Mehta RL, Samoni S, Ding X, Rosner MH, Kellum, JA, Ronco C on behalf of the Acute Disease Quality Initiative (ADQI) Consensus Group. Precision Fluid Management in Continuous Renal Replacement Therapy. Blood Purification. 2016;42:266-278.

status has not been evaluated in terms of its impact on patient outcomes and medical interventions. A number of studies have shown fluid balance charting is prone to errors and overtime can become an increasingly inaccurate estimation of body fluid status.[4,5] The alternative approach of weighing patients daily can be effective in monitoring changes in body weight over an average ICU length of stay due entirely to the result of fluid alterations. With the widespread introduction of ICU beds with built-in scales in WA, the feasibility of obtaining daily measurements is now possible and avoids the time consuming and risky activity of using hoists and slings. Despite this advantage the use of bed scales in clinical practice has not been entirely successful in increasing the frequency of when patients are weighed. The value of monitoring daily trends is diminished when not measured at the same time and omission of body weight measurements occurs over several days. It is hoped that by undertaking a systematic review on the effectiveness of daily fluid balance charting in comparison to the measurement of body weight will create awareness that highlight the difficulties that both approaches pose to the nurse and medical staff when used to estimate body fluid status in critically ill adult patients.

Implementation of the "traffic light" approach to improving fluid balance control in patients receiving CRRT would likely be more successful if the approach was incorporated into an electronic spreadsheet of an existing clinical information system. It may possible to trial the "traffic light" approach in the ICU at FSH following the installation of MetaVision clinical information system (iMDsoft®, Red Hill, QLD).

Overall the compliance to weigh patients at midnight during Phase Two of FLUID was successful during the study period but has lapsed following completion of the study. This was a change in clinical practice that was difficult to sustain without constant reminders, ongoing education and quality control activities.

FELLOWSHIP OUTCOMES

Systematic Review

My Clinician Research Fellowship included a proposal to conduct a systematic review on the effectiveness of fluid balance charting in comparison to the measurement of body weight when used in guiding fluid therapy for critically ill adult patients. The ability to achieve fluid balance control relies primarily on the non-invasive methods of charting daily fluid balance totals and monitoring of changes in body weight measurements. The Joanna Briggs Institute (JBI) methodology was used to evaluate the quality and level of evidence from studies that have investigated both methods. The project involved developing a systematic review protocol and this was accepted for publication by JBI.[6]

A search of the literature found seventeen studies met the systematic review inclusion criteria. Fourteen papers were prospective observational studies and three were retrospective observational studies. No randomised controlled trials involving critically ill adult patients were found comparing fluid balance charting with measurement of body weight. Studies were grouped into three areas of interest: (1) effectiveness of charting fluid balance, (2) effectiveness of monitoring changes in body weight and (3) agreement between fluid balance and body weight.

The review found that paper-based charting of fluid balance is susceptible to mistakes in mathematical calculation. This is complicated by mistakes in documentation that can also occur in electronic spread sheets where volumes are either missed or charted incorrectly. The recoding of daily fluid balance totals is further confounded by output that is not measureable. Fluid that is lost through breathing as water vapour is difficult to predict and relies on a calculated value rather than one that is measured.

The other approach of estimating body fluid status by monitoring changes in body weight can provide a more accurate estimation of how fluid is distributed though out the body. This is of particular importance when fluid has left the intravascular space into the interstitial spaces. Nevertheless, measuring body weight changes is not without its own set of issues. Discipline amongst operators of weighing equipment is required to ensure procedures for obtaining accurate body weight measurements are followed. The finding that compliance in achieving consecutive daily body weight measurements is not always possible, means changes in body weight alone is not always robust enough to replace daily charting of fluid balance.

The final area of review looked at the relationship between fluid balance and body weight. Over short length of stays in hospital changes in body weight can almost entirely be the result of alterations in body water. Studies investigating the relationship between fluid balance and body weight found it to be unreliable and a loss or gain in fluid was not always reflected by a similar change in body weight.

Some of the key recommendations based on this review include:

- Maintaining a fluid balance chart provides a quantitative record of fluid volume gained and lost over a given time period. The chart also provides a qualitative record of the type of fluid gained and lost over the same time period. But to maintain a daily fluid balance chart that accurately reflects inputs and outputs is challenging and time-consuming.
- Weighing the patient daily offers a better option for determining the distribution of body water in patients who are suspected of being fluid overloaded, and removes the difficulty of accounting for IWL when output

4 Perren A, Markmann M, Merlani G, Marone C, Merlani P. Fluid balance in critically ill patients: Should we really rely on it? Minerva Anestesiol. 2011;77(8):802-11.

5 Diacon A, Bell J. Investigating the recording and accuracy of fluid balance monitoring in critically ill patients. Southern African Journal of Critical Care. 2014 doi: 10.7196/SAJCC.193;30(2):55-7.

6 Davies H, Leslie G, Morgan D. "Effectiveness of daily fluid balance charting in comparison to the measurement of body weight when used in guiding fluid therapy for critically ill adult patients: a systematic review protocol" *JBI Database of Systematic Reviews & Implementation Reports*. 2015; 13(3):111-123 doi:10.11124/jbisrir-2015-2010.

is measured by changes in body weight rather than a calculated value.
- Fluid balance charting and measurement of body weight combined with physical assessment is recommended for estimation of body fluid status and to guide fluid therapy in the management of critically ill patients with severe AKI.
- Sole reliance on a daily record of inputs and outputs should not be used for the purposes of estimating body fluid status and for guiding fluid therapy in patients who are suspected of being under volumed or at risk of fluid overload without other assessments being performed.

Capacity Building

The benefit of securing a Clinician Research Fellowship has been to maintain the presence of nursing research within ICU at Royal Perth Hospital. As a result, I have been able to:

- demonstrate the capacity to develop a research proposal;
- successfully apply for research funding to implement the project and see it through to its completion; and
- analyse the data collected and interpret findings.

I have then been able to conclude the project by presenting my findings at a national conference and manuscript submission for publication in a peered reviewed journal.

The topic under investigation covered an area of practical interest to nursing staff. The project was seen as being relevant to what nurses do every day in the management of patients receiving CRRT. The research activity I undertook was also seen by my colleagues as playing an important role in improving patient care by focusing attention on fluid balance control in patients at risk of fluid overload. My presence on the floor sometimes involved working alongside nurses who were caring for patients participating in the study. This involved face-to-face education and individual follow-up that established my profile and presence in the unit. At times this led to discussions on other areas of nursing practice that are worthy of closer scrutiny. My intention here was to be a catalyst for other nurses to consider undertaking a research project that has the potential to improve patient outcomes.

Conference Presentations

Oral presentation "A Journey to better fluid balance control in CRRT" to the 12th Congress of the World Federation of Critical Care Nurses, Brisbane Convention & Exhibition Centre, QLD, 21-23 April 2016.

Poster presentation "A Traffic Light Approach to Fluid Balance Control During CRRT" at the 40th Australian and New Zealand meeting on Intensive Care, Skycity Convention Centre, Auckland, New Zealand, 29-31 October 2015. Presentation won "Best Poster" prize.

Oral presentation "A retrospective review of fluid balance control in CRRT" was presented at the 39th Australian and New Zealand meeting on Intensive Care, Melbourne Convention and Exhibition Centre, 9-11 October 2014.

Publications

Davies H, Leslie G, Morgan D. A retrospective review of fluid balance control in CRRT. *Australian Critical Care* (2016). http://dx.doi.org/10.1016/j.aucc.2016.05.004.

Davies H, Leslie G. A "Traffic Light" approach to fluid balance control during CRRT. *Australian Critical Care*. 2016, 29(2)120-121. http://dx.doi.org/10.1016/j.aucc.2015.12.028.

Davies H, Leslie G, Morgan D. "Effectiveness of daily fluid balance charting in comparison to the measurement of body weight when used in guiding fluid therapy for critically ill adult patients: a systematic review protocol" *JBI Database of Systematic Reviews & Implementation Reports. 2015*; 13(3):111-123 doi:10.11124/jbisrir-2015-2010.

Summary

My profile as a researcher has profited from being awarded the Clinician Research Fellowship. Details about the findings of Phase One of FLUID were published by the *West Australian* newspaper (Friday 5th February 2016). I have increased the number of research papers published as primary author and the number of invites I receive to present on the topic of AKI. My work has over 400 reads and I have 63 citations. My Research Gate score is 19.78 (see https://www.researchgate.net/profile/Hugh_Davies9).

The opportunity to attend conferences has enabled me to interact with other researchers who have the same interests and have faced similar challenges in the course of their work. This has increased my self-confidence and continued passion for the topic under investigation. It also highlights the importance of investigating routine nursing activities like fluid balance charting that when clinical practice is reviewed, has the potential to improve patient outcomes. The opportunity to present my findings to an audience who have expertise in my area of interest has also helped me to improve how I present my work. Changes in the way I articulate information has helped me to respond more effectively when challenged on aspects of my investigation. Similarly, this has helped me to be more critical and to ask questions of work undertaken by other researchers.

ACKNOWLEDGEMENT

I would like to acknowledge the support I have received from Professor Gavin Leslie, Curtin University and Intensive Care Specialist Dr David Morgan, Fiona Stanley Hospital. Both have given their time freely in making themselves available to offer advice and mentorship in support of my Clinician Research Fellowship.

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

CLINICIAN RESEARCH FELLOW
Dr Dale Edgar

PROJECT OVERVIEW AND AIMS
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 was to determine if adding resistance exercise training to routine practice reduced 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.

ONGOING CLINICAL DEVELOPMENTS
Research Translation and Diffusion
The preliminary findings of the study have been promoted during hospital team in-services (burns MDT education); physiotherapist professional development and training sessions (plastics, burns and orthopaedics); along with Service 4 Physiotherapy group and Allied Health group information update sessions. The anecdotal and observed diffusion of outcomes is that burn patients who have not been eligible or willing to join the study are receiving more objective assessments using the study methodology and equipment (Nicholas Muscle Meter and Grip Strength).
In addition, the regular use of bioimpedance as an assessment tool in this study has promulgated its use in new research projects which have been established, including three studies underway (D Edwick, PhD program). These are:

- Does electrical stimulation therapy improve healing in small area acute burns as measured by localised bioimpedance monitoring?
- Validation of alternate electrode positioning for the *measurement of hand volume* using BIS in uninjured subjects.
- Validation of measurement of *hand volume* using BIS in a burns population.

We have also developed a new plan which is a precursor step to other burn service centres engaging in the high, level complex exercise therapy as proposed in this study.

Lastly, as noted above, Mr Gittings completed the statistical analyses for all outcomes to ameliorate the risk to the proposed milestones and outputs. A number of issues were discussed with his supervisory team and Mr Gittings will endeavour to recruit to the new sample size targets. The study population is, however, quite specific and a suitable patient shall have suffered a burn trauma to be eligible to join the study.

Advancing Knowledge
The study has successfully demonstrated that resistance exercise training significantly improves muscle strength outcomes by ~30% out to 6 weeks post-burn. This is a promising result (with small patient numbers) and we hope to corroborate this outcome with further results using the other outcome measures embedded in the study.
Mr Gittings has been making good progress in development of publications, in line with his PhD project which envelope this study.

FELLOWSHIP OUTCOMES
Capacity Building
This project has added value to the Fiona Wood Foundation Clinical Research Programme in the Fiona Stanley Hospital (FSH) Burn Unit. Dr Tiffany Grisbrook, Pippa Kenworthy and Dale Edwick have established their own postdoctoral and PhD programmes in synergy with Mr Gittings. I am pleased to report that this group has become a team of clinical researchers who support each other in their research study completion and also in the general community of research in the FSH Burn Unit environment. Mr Gittings and Associate Professor Edgar further added value by increasing capacity to complete this study in multiple centres around Australia and New Zealand. This is the first time that a consensus battery of rehabilitation (burn recovery) outcomes will be established in the world; and the first step necessary to return to an intervention trial as planned.

Conference Presentations

- ISBI Congress, Miami, Florida, August 2016 – **Preliminary results of a randomised trial of resistance exercise training in acute burn patients**. Abstract presented by Paul Gittings.
- ISBI Congress, Miami, Florida, August 2016 – **Rehabilitation Symposium** – Exercise training in burn care, moderated by Associate Professor Dale Edgar.
- University of Notre Dame Australia, November 2016 – **Institute of Health Research Symposium** – Resistance training in acute burn injury. Presented by Paul Gittings.

ACKNOWLEDGEMENT

I thank the Department of Health and the Raine Medical Research Foundation for award of the Clinician Research Fellowship and trust that the major challenges and successful achievements of this research programme will be recognised. To put some context around the degree of difficulty of the study, this project, led by Paul Gittings, requires patients with >5% TBSA acute burn wound to engage immediately in a resistance training programme for 4 weeks or more, while accommodating acute skin reconstruction surgery and the pain of wounds and donor sites. When completed, the preliminary results suggest that this study will revolutionise the application of exercise therapy in acute burn patients around the world.

PROJECT TITLE

Pleural Effusions in Intensive Care Patients: The Physiological Changes and Clinical Effects of Drainage Procedures

CLINICIAN RESEARCH FELLOW

Dr Edward Fysh

PROJECT OVERVIEW AND AIMS

Pleural effusions are common in intensive care – affecting 60% of patients, i.e. 68,000 patients per annum. While some small studies have shown improved oxygen levels after fluid drainage, they are not consistent. The Study will review the effectiveness of pleural drainage in Intensive Care Unit (ICU) patients, and the clinical benefits that may be achieved. Drainage procedures may incur risk, especially in ICU patients on life support, increasing the risks of lung damage and potentially even death. Evidence is needed to inform clinicians which patients are likely to benefit without complications.

This project will prospectively evaluate the physiological and clinical effects, as well as complication rates of pleural effusion drainage in patients in four Australian ICUs. It will find predictors to select the best patients for drainage.

ONGOING CLINICAL DEVELOPMENTS

Research Translation and Diffusion

Although it is too early to fully interpret the findings, an initial analysis of the data has shown that oxygenation (P:F ratio) does improve significantly in patients selected for drainage procedures and not in medically managed patients (Fig. 1). No life-threatening adverse events have occurred to date. An abstract reporting these findings has been accepted for presentation at the ANZICS/Singapore intensive care society meeting in Singapore in April 2017 (see below).

The pilot data that was used to inform the design of this study has been published in one of the top respiratory and critical care journals in the World – *Pleural effusions in intensive care*. Fysh ETH et al. Chest. 2016;150(6):1419-1420.

FELLOWSHIP OUTCOMES

Capacity Building

Capacity to care for ICU patients has been increased through this study. The investigator performs additional ultrasound-scans of patients with potential pleural effusions. Through this extra scanning, previously unrecognised diagnoses have been made, one of which (pericardial tamponade), resulted in improved patient care through enabling a life-saving procedure that otherwise may not have been performed. In further instances the Principal Investigator (PI) has been able to help guide treatment in emergencies. The PI is currently preparing an application for funding from the NHMRC (an Early Career Fellowship) to continue the research beyond the Clinician Research Fellowship.

The PI has also given multiple training talks and ultrasound practical sessions, upskilling the trainees and specialists in the three tertiary ICUs. Every unit in Perth now has at least one Consultant and one Registrar at all times who are skilled in pleural procedures and ultrasound.

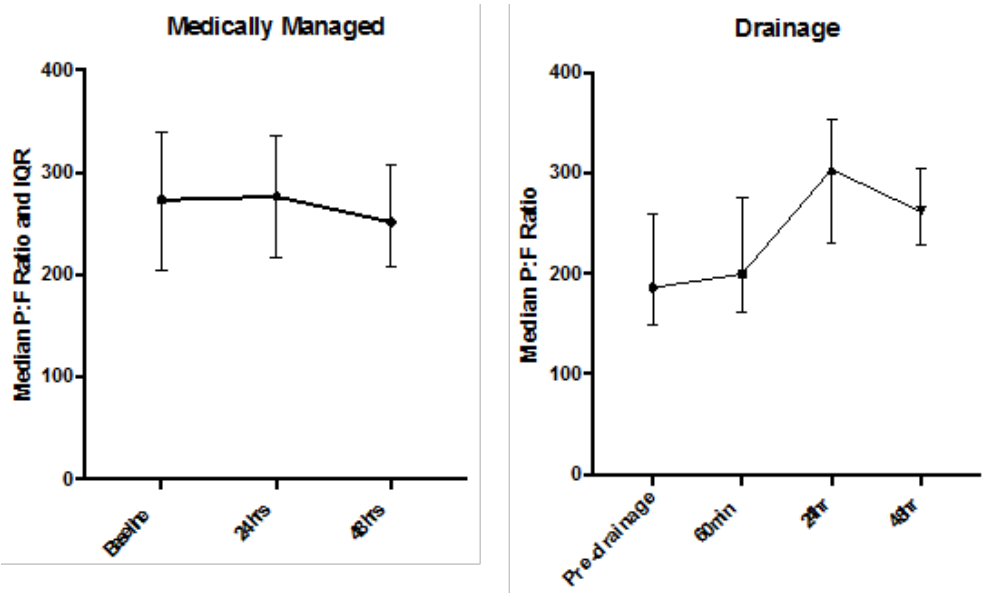


Fig 1. Oxygenation (P:F ratio) significantly improved at 24 and 48hrs after drainage ($p<0.01$).

The PI has also put together a team of five junior doctors interested in research from across all three major teaching hospitals to introduce them to clinical research. Their contribution and efforts have been recognised through authorship of the Abstract at the Conference mentioned below. One of the doctors (Dr Smallbone) plans to visit Singapore to experience the process of preparing and presenting research at an international conference for the first time, as she is currently pursuing a career in academic medicine.

Conference Presentations

It is anticipated that the planned interim analysis of the project will be presented at the combined Australian, New Zealand and Singaporean Intensive Care Societies Conference in Singapore in April 2017. Further manuscripts on ultrasound use and treatment decisions are in the data collection and analysis phase.

ACKNOWLEDGEMENT

The progress of this Study could not have been achieved without the award of the Clinician Research Fellowship from the WA Department of Health and the Raine Medical Research Foundation.

PROJECT TITLE

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

CLINICIAN RESEARCH FELLOW

Clinical Associate Professor Kwok-ming Ho

PROJECT OVERVIEW AND AIMS

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 randomised to receive the filter soon after their injury compared to those who do not receive the filters.

FELLOWSHIP OUTCOMES

The study is still actively recruiting patients and therefore the final results of the study remain unknown; consequently, the study 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 severe trauma patients are now screened for contraindications to anticoagulation on admission to the study centres. This has increased the early initiation of pharmacological venous thromboembolism prophylaxis both in patients screened for the trial and recruited into the trial.

Conference presentations:

- 2016 Aug: World Congress in Anaesthesiology in Hong Kong (two invited oral presentations: *(a) Diuretics and acute kidney injury, (b) Predicting outcomes of the critically ill; two e-posters oral presentations: (a) Predicting long-term outcome after severe traumatic brain injury requiring decompressive craniectomy, (b) Prognostic significance of strong ion gap in the critically ill*).
- 2016 Sep: Australian Society of Anaesthetists National Scientific Congress in Melbourne (invited oral presentation: Management of Major Haemorrhage).
- 2016 Oct: Asian-Pacific Congress in Thrombosis and Haemostasis in Taipei, Taiwan (one oral free-paper presentation: *Use of viscoelastic testing to predicting clinical thrombotic events in the critically ill*).
- 2016 Oct: Australian and New Zealand Intensive Care Society Annual Scientific Meeting in Perth (two invited oral presentations: *(a) Preventing thromboembolism in the critically ill, (b) What the Editor wants; one oral free-paper presentation: Use of Quick Sequential Organ Failure Score (qSOFA) to predict outcomes of septic and non-septic patients*).

Publications

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Cuadros L, Ismail H, **Ho K.** Evaluation of Reliability of MYZONE MZ-3 Heart Rate Monitor: A Study for the Future of Telephysiotherapy for Preoperative Prehabilitation in Cancer Patients. *Telemed J E Health* 2016 (published on-line on August 18).

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Grants obtained in 2016
Medical Research Foundation (MRF) at Fremantle Hospital *(Supercooled storage for extended preservation of hearts: a rodent model, CIC $100,000 over 2 years).*

MRF Project Grant at Royal Perth Hospital
(Effect of intravenous gelatine solution of renal biomarkers and acute kidney injury, CIB $ 19,463 over 1 year).

Prizes, new appointments and academic progression
First Prize in Neuroscience e-Poster in the World Congress of Anaesthesiology 2016.

Global DVT Advisory Board Member (Medtronic®).

My h-index and i10 index have increased to 31 and 96, respectively.

ACKNOWLEDGEMENT

The specific research project supported by the Department of Health and the Raine Foundation 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 multicentre study with many other likeminded trauma clinicians and researchers in Australia without this Fellowship support. To be able to be the Chief Investigator on what will surely be a landmark study – likely to complete enrolment within the next 12 months – is extremely fulfilling. In addition, the Department of Health/Raine Clinician Research Fellowship has made an enormous difference to my overall research productivity, well beyond the specific project supported by this people-support grant.

PROJECT TITLE
Mechanisms that facilitate the metastatic potential of oral cancer

CLINICIAN RESEARCH FELLOW
Dr Annette Lim

PROJECT OVERVIEW AND AIMS
Head and neck cancer (HNC) is the 6th most common cancer worldwide, affecting non-smokers and smokers alike. Despite treatment, 50% of patients will die within five years of diagnosis. The incidence of oral cavity carcinomas is increasing consisting predominantly of young patients (<45 years) who develop tongue cancers without known risk factors.

The WA Department of Health and Raine Medical Research Foundation Clinician Research Fellowship enables me to work with a dedicated multidisciplinary head and neck cancer team to conduct laboratory based research and clinical trials that aim to improve the diagnosis, management and outcome for patients with head and neck cancers and other cancers.

PROGRESS
The first project of the Fellowship investigates the clinical use of a liquid biopsy technique that detects cancer fragments in blood. These cancer fragments are known as “tumour-derived exosomes” or “TEX” (Figure 1).

The study focuses on patients who are diagnosed with oral cavity cancers and tongue cancers. From blood tests we are able to isolate cancer fragments and perform gene mutation analyses. Using this liquid biopsy, we hope to identify a way that could lead to an earlier cancer diagnosis. We will also assess whether the presence of more cancer fragments in the blood stream identifies high-risk disease requiring an escalation of treatment. Similarly, if cancer fragments are detectable in the blood after treatment, this may help us detect residual microscopic cancer. The ability to perform gene analyses on tumour obtained from blood tests will enhance the opportunity for novel precision medicine treatments throughout the cancer journey, and minimise the need for invasive biopsies.

Highlights from the first year of this project include the partnership of patients and head and neck cancer specialists to participate in this research, and we have met one half of the recruitment target so far. We have developed new collaborations with different healthcare and university institutions to extend the application of this technology. The team now also includes two post-graduate honours students and Cancer Council WA summer vacation students keen to develop skills and experience in cancer-specific research. Our team and research has also benefited greatly from the involvement of a consumer volunteer.

The second laboratory based project will investigate in oral cancers whether the nature of the immune response impacts on patient survival. This research is important given the efficacy of immunotherapy to treat HNC. This research aims to identify features of the immune response that could predict whether an escalation of treatment is required. We have successfully assembled a cohort of 100 specimens with comprehensive clinical information captured, in which detailed laboratory analyses of the immune response have commenced in collaboration with the PathWest team.

FELLOWSHIP OUTCOMES
Capacity Building

An additional key aim of the fellowship is to provide greater access to clinical trials for all cancer patients, to improve the opportunity for people to receive new and cutting-edge treatments. With the support of this fellowship I have been able to provide access to a number of unique therapeutic clinical trials including immunotherapy trials, as part of an international effort to improve outcomes for head and neck cancer patients and all cancer patients.

ACKNOWLEDGEMENT
I am deeply grateful for the support of this fellowship as it represents a recognition of the importance of partnership in research to improve outcomes for patients.

PROJECT TITLE
The airway surface liquid micro environment in children with cystic fibrosis

CLINICIAN RESEARCH FELLOW
Dr André Schultz

PROJECT OVERVIEW AND AIMS
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.

ONGOING CLINICAL DEVELOPMENTS
Research Translation and Diffusion
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 has been whether the pH of the airway surface liquid is reduced in cystic fibrosis. The challenge was to measure pH in the ultrathin fluid layer that covers the airways in the lungs of young children. We 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 focussed on 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. I demonstrated that a new way of lower airway sampling can be used to get better samples than traditional sampling methods can provide. Specialised analysis of the samples allowed us to gain knowledge of the lungs of young children with cystic fibrosis that will guide treatment in the future. We identified substances in the airway surface liquid that can help detect and measure lung disease. We are aiming to use the knowledge to develop non-invasive tests to measure lung disease in young children.

Our findings are critically important for the understanding of cystic fibrosis lung disease and the development of treatment. Our manuscript describing the work has just been accepted pending minor revisions by *Nature Communications*.

During my time as a Clinician Research Fellow I also developed novel bronchoscopic microsampling techniques to study early cystic fibrosis lung disease. The focus was on young children as cystic fibrosis lung disease trajectories are determined in the early years of life.

FELLOWSHIP OUTCOMES
Capacity Building
The Clinician Research Fellowship has given me the opportunity to develop and establish a career as a clinician scientist, as illustrated by grant funding obtained in the last year. My research is embedded in my clinical practice as I research clinically relevant questions when I treat patients.

I have established strong research collaborations with specialist scientists working on cystic fibrosis at the University of North Carolina in Chapel Hill, USA. I have also established research collaborations with scientists from the Australian Phenome Centre.

Grant Funding
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D'Sylva, P., Caudri, D., Shaw, N., Turkovic, L., Douglas, T., Bew, J., Keil, A.D., Stick, S., **Schultz, A**. Induced sputum to detect lung pathogens in young children with cystic fibrosis. *Pediatric Pulmonology*. 2017 Feb;52(2):182-189.

André Schultz, Ramaa Puvvadi, Sergey M Borisov, Nicole C Shaw, Ingo Klimant, Luke J Berry, Samuel T Montgomery, Thien Nguyen, Silvia M Kreda, Anthony Kicic, Peter B Noble, Brian Button, Stephen M Stick. Airway surface liquid pH is not acidic in children with cystic fibrosis, *Nature Communications*, Accepted, minor revisions.

ACKNOWLEDGEMENT

I am deeply grateful to the WA Department of Health and the Raine Medical Research Foundation for helping to make possible the above research, along with a number of other research projects. Being both a clinician and a scientist at the same time can be challenging. The Fellowship has 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 suppuratives lung disease, and childhood interstitial lung disease.

PROJECT TITLE

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

CLINICIAN RESEARCH FELLOW

Dr Ulrich Steinwandel

PROJECT OVERVIEW AND AIMS

The initial objectives of this project were:

1. To determine the incidence of intradialytic adverse events that are related to ultrafiltration
2. To determine if a renal nurse can perform IVC-US and reliably assess the obtained scans on intravascular volume status, classifying a patient in either hypo-, eu- or hypervolemic status.
3. To determine whether the additional use of IVC-US in determination of haemodialysis patients' volume status can reduce the incidence of ultrafiltration related adverse events.

A total of 2357 haemodialysis sessions in 64 patients were investigated on the prevalence of clinical events of symptomatic and asymptomatic hypotension over a retrospective 3-month period. It was found that symptomatic intradialytic hypotension was the most common adverse event during 221 (9.4%) of all sessions, while hypervolemia was found after 103 (4.4%) treatments. Asymptomatic hypotension occurred during 88 (3.7%) of all sessions. Indigenous Australians, females and diabetics had the highest prevalence of hypotensive episodes. Combining asymptomatic and symptomatic hypotension resulted in a prevalence of 13.1% and underscores the need for more preventative strategies and/or more objective parameters for volume assessment.

Upskilling of the renal nurse in the use of ultrasound was provided by an expert Sonologist from Emergency Department Sir Charles Gairdner Hospital. After receiving substantial training, the renal nurse performed 100 preliminary scans of the IVC on a variety of patients to refine the technique and to comprehend the relationship between clinical findings. After receiving appropriate feedback on these scans the nurse then performed 60 scans on 10 patients, assessed them and categorised these into the appropriate fluid status according to the 'Guidelines for the Echocardiographic Assessment of the Right Heart in Adults, American Society of Echocardiography'. Two blinded expert reviewers found a good interrater agreement between the nurse and any of the experts.

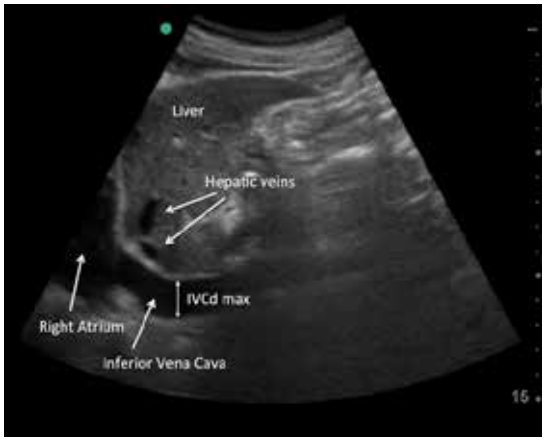


Figure 1. IVC longitudinal view – maximal diameter (IVCd max) at expiration.

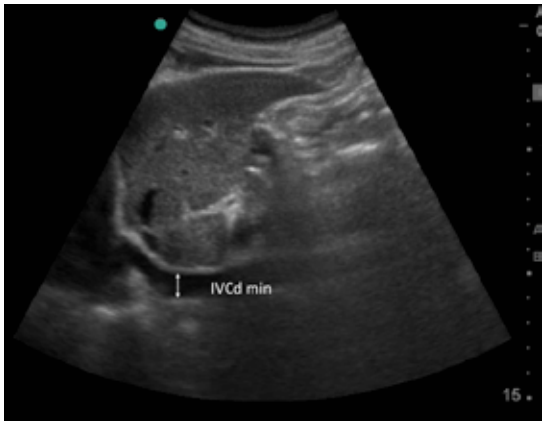


Figure 2. IVC longitudinal view – minimal diameter (IVCd min) at inspiration.

In the current and final stage of this project the renal nurse investigates 30 randomly selected patients and their trend in the IVC diameter over the course of a treatment session, compared to an initial bioimpedance measurement, while observing for clinical symptoms. Data collection is now almost completed and preliminary data analysis from the first 10 patients demonstrated that only 2 out of 10 were classified hypervolemic upon treatment initiation while 8 were euvolemic. This information could have been beneficial for the nurse when initially deciding for an ultrafiltration goal.

SUMMARY

We have found that IVC-US can add valuable information when assessing for intravascular volume status. Additionally, we are confident to state, that it is potentially possible to train an ultrasound naïve health professional in the skill of performing an ultrasound on the inferior vena cava, which is a big step forward in advancing renal care. It has good potential to have an impact on the fluid assessment routine for haemodialysis patients and may be reflected in clinical guidelines, once approved by the relevant institutions as an additional valid non-invasive method. When applied on a broader scale with more patients and nurses, it has potential to result in beneficial health outcomes for the patients we treat.

Publications

U Steinwandel, N Gibson, J Rippey, A Towell, J Rosman, "Use of ultrasound by registered nurses – A systematic literature review", Journal of Renal Care, 2017.

Grants

Winner of the Barry Marshall Travel Grant 2017, Spinnaker Health Research Foundation.

ACKNOWLEDGEMENT

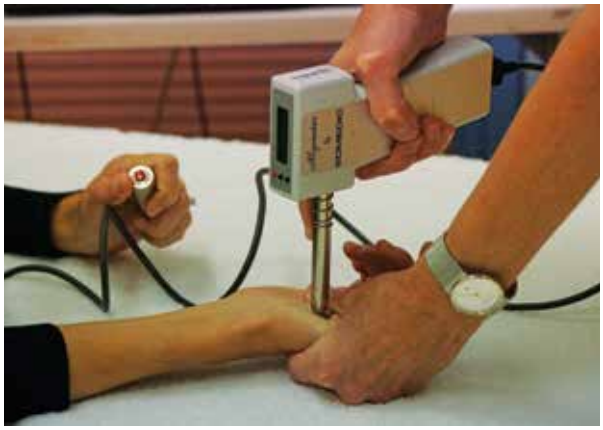
The financial support during the Fellowship allowed me to spend significant time with data collection at the bedside, statistical analysis and interpretation of data and finally creating publishable information on the findings. I am very grateful that I had this opportunity to contribute to the body of knowledge and advance the renal nursing care. As we renal nurses spend a significant amount of time with patients, I see the absolute necessity for us to gain a better understanding of a patient's condition and tailoring individual treatment concepts to deliver improved health outcomes.

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

CLINICIAN RESEARCH FELLOW
Dr Brigitte Tampin

PROJECT OVERVIEW AND AIMS
Some people report persistent pain after back surgery. Whilst several risk factors have been identified (e.g. psychological factors), the role of sensory parameters is unknown. Research suggests that certain people who demonstrate hypersensitivity to sensory stimuli such as thermal and mechanical stimulation may be more vulnerable to develop ongoing pain; however this has not yet been explored in people with back and leg pain. This study has been investigating if responses to various sensory stimuli (to heat and cold, to light touch and pressure, to pin-prick and vibration) may play a role in predicting poor outcome after back surgery. The overall aim of the study has been to determine the predictive value of quantitative sensory testing (QST) parameters in patients with lumbar radiculopathy/radicular pain for predicting clinical outcome(s) after lumbar discectomy.

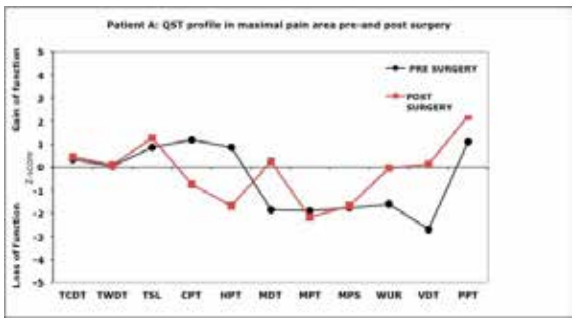
Specific aims:
1. To establish the QST somatosensory profile of participants with lumbar radiculopathy/radicular pain before and after surgery;
2. To investigate if there is an association between pre-surgical QST parameters and clinical outcome (functional status, pain intensity,health-related quality of life, return to work, health care utilisation, global perceived impression of change, 'bothersomeness') after lumbar microdiscectomy.



ONGOING CLINICAL DEVELOPMENTS
Research Translation and Diffusion

Patient recruitment was completed in 2016. Of the 78 patients who gave verbal consent to participate, 53 patients participated in the study. Three months outcome data have been obtained for all patients; so far twelve months outcome data have been obtained for 36 patients.

At baseline, our patient cohort was characterised by a significant loss of function in all sensory fibre populations in the symptomatic leg compared to the asymptomatic leg in the main pain area and dermatome. The loss of sensory nerve fibre function as well as clinical outcomes measures (e.g. functional status, pain intensity, pain descriptors) improved significantly after surgery. Seven individuals reported little improvement at three months post-surgery. Results have been submitted for presentation at the 6th International Conference on Neuropathic Pain, 15-18 June 2017, Gothenburg, Sweden.



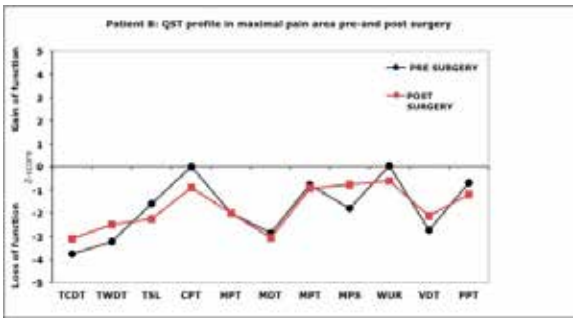


Fig. 1 and 2. Sensory profiling. The z-score sensory profiles are shown of two patients with S1 radiculopathy in their main pain area (foot) pre-and post surgery. Healthy control data are represented by a z-score of "zero". Patient A demonstrated a loss of function in mechanical detection, vibration detection thresholds and mechanical pain thresholds plus cold hypersensitivity pre-surgery. Cold hypersensitivity, mechanical and vibration detection thresholds improved post-surgery. Patient B demonstrated a loss of function in thermal, mechanical and vibration detection thresholds and heat sensitivity which did not improve much post-surgery. CDT, cold detection threshold; WDT, warm detection threshold; TSL,thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; MDT,mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, windup ratio; VDT, vibration detection threshold; PPT, pressure pain threshold.

Next stage:

- Complete 12 months follow up data collection;
- Continuous collection of lower limb QST reference data from age and gender matched healthy control subjects for validation of abnormal patient data and for exploration if specific sensory profiles are associated with pain persistency;
- Publication of results.

FELLOWSHIP OUTCOMES

Capacity Building

The fellowship has allowed me to enhance my research collaborations nationally and internationally. It also placed me in a stronger position to be successful in research grant applications. The grant obtained in 2016 allows us to extend the current 'normative' database for QST and to build research and clinical capacity at Sir Charles Gairdner Hospital for characterising larger clinical cohorts with nerve-related leg pain. The assessment of patients' QST somatosensory profile assists in the diagnostic work-up and will give valuable information on nerve fibre dysfunction and associated underlying pain mechanisms possibly contributing to the persistency of pain. Using the obtained normative data can help to inform appropriate targeting of pain management, such as specific pharmaceutical intervention for the treatment of neuropathic pain or surgical intervention in case of nerve root compromise. Early and targeted treatment is known to affect better clinical outcomes and may prevent the transition to persistent pain and associated poorer health outcomes and greater health economic burden.

Publications

Tampin, B. (2016). Untersuchung des peripheren Nervensystems. In: Frans van den Berg (Ed): Physiotherapie für alle Körpersysteme- Evidenzbasierte Tests und Therapie. Thieme Verlag, Stuttgart, Germany.

Tampin, B. (2016). Behandlung neurogener Störungen In: Frans van den Berg (Ed): Physiotherapie für alle Körpersysteme- Evidenzbasierte Tests und Therapie. Thieme Verlag, Stuttgart, Germany.

Grant awarded

Study: *Investigation of altered sensory nerve fibre function in patients with lumbar radicular leg pain* – 2016 Research Advisory Committee Grant, Sir Charles Gairdner and Osborne Park Health.

Awards / New Appointments

- Contribution as an Emergent Researcher; Australian Physiotherapy Association.
- Professorship in Physiotherapy (part-time), Faculty Business Management and Social Sciences, Hochschule Osnabrück, Germany.

ACKNOWLEDGEMENT

I would like to acknowledge the WA Department of Health and the Raine Medical Research Foundation as well as the School of Physiotherapy and Exercise Science at Curtin University for financial support of the study. I sincerely thank my Associate Investigators, Professor Christopher Lind (Department of Neurosurgery, SCGH) and Associate Professor Helen Slater (School of Physiotherapy and Exercise at Curtin University) for their invaluable contribution and collaboration. I also thank the staff at the Physiotherapy Department, Pain Management Department and Neurosurgery Department at Sir Charles Gairdner Hospital for their support in recruitment of research participants and organisational and administrative tasks. And I would like to thank staff at the Department of Research, Sir Charles Gairdner Hospital for their assistance in all research related matters.

AWARDS

Raine Visiting Professor Awards

PROFESSOR RAFFAELE DELLACÀ

In August 2016, the Raine Foundation was delighted to welcome Raffaele Dellacà from Milan Politecnico, Milan, to the The University of Western Australia (UWA) as a Raine Visiting Professor and guest of Professor Jane Pillow, School of Anatomy, Physiology and Human Biology.

Professor Dellacà has an outstanding research career in biomedical engineering. He is internationally recognised for his research in respiratory physiology, particularly respiratory mechanics, linear and non-linear modelling of respiratory system mechanical properties and the development of new technologies for the analysis of respiration, mechanical ventilation and anaesthesia.

After obtaining his PhD degree from the Politecnico di Milano on the assessment of respiratory mechanics by opto-electronic plethysmography and forced oscillations, Professor Dellacà proceeded with postdoctoral studies at the Biomedical Engineering Department, Boston University and the University of Liverpool.

Professor Dellacà spent three months at UWA where he made a major contribution to the scientific community in both teaching and research. Raffael became directly involved in the day-to-day Preclinical Intensive Care Research Unit preterm lamb research studies with his colleague and host, Professor Jane Pillow. This involvement led to meetings with individual scientists in affiliated research, spanning biomedical engineering, respiratory medicine, anaesthesiology and physiotherapy. Professor Dellacà also presented a number of seminars and collaborative scientific workshops. The Dean of Engineering invited him to help shape the development of a new specialisation in Biomedical Engineering which will form the basis of a future Master's course on Biomedical Engineering at UWA.

Overall, the visit of Professor Raffaele Dellacà was an outstanding success – and even more rewarding in that

Raine Visiting Professors Dr Gijs van Soest and Professor Raffaele Dellacà.

his visit coincided with another outstanding Raine Visiting Professor, Gijs van Soest, Head of the Thorax Centre at Erasmus University Medical Centre in Rotterdam. These two top international scientists, both involved in bioengineering and translational medicine, met up and were able to share their advances in medical science.

On 2 August 2016 Professor Dellacà presented a Raine Lecture to a packed audience of scientific researchers from a range of disciplines involved in translational medicine. The title of his Raine Lecture was: *Contemporary Measurements of Lung Mechanics – What are they? What do they tell us?*

Professor Dellacà collaborates widely with leading international researchers around the globe, and his research is sponsored by public agencies, foundations and industry. He is co-founder of Restech, a spin-off company that develops innovative devices for lung function testing in adults and children.

Professor Jane Pillow and Professor Raffaele Dellacà.

PROFESSOR GAO XIANG

Professor Gao Xiang is the Founder and Director of the Model Animal Research Centre (MARC) of Nanjing University, the largest transgenic core facility in Asia. Professor Gao also established the Nanjing University Biomedical Research Institute 10 years ago, which comprises more than 20 principal investigators with a strong focus on the study of molecular mechanism of diseases in animal models. He is recognised globally for his pioneer work in the field of genetic manipulation and recently hit the headlines in the scientific publication, Nature.

The visit of Professor Gao in December 2016 was part of a broader collaborative partnership that resulted from the Joint Biomedical Symposium in Nanjing in September, attended by delegates of The University of Western Australia. The Raine Visiting Professor Award provided an ideal opportunity to extend an invitation to Professor Gao to attend and participate in the Joint 6th Margaret River Region Forum and 9th ASSCR Annual Scientific Meeting in December 2016.

During his visit to UWA, Professor Gao met with senior scientists from Harry Perkins Institute of Medical Research and extended his collaborative research program with leading scientists in the School of Surgery and the School of Pathology and Laboratory Medicine. These included Professor Mnghao Zheng, Professor Jiake Xu and Associate Professor Tak Cheng.

PROFESSOR STEPHEN HILL

The Raine Medical Research Foundation was delighted to welcome the return visit of Professor Stephen Hill as a Raine Visiting Professor. Professor Hill returned to Western Australia to further advance his collaborative work with Associate Professor Kevin Pfleger, Head of Molecular Endocrinology and Pharmacology at Harry Perkins Institute of Medical Research.

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. Work in his laboratory, using fluorescent receptor agonists and antagonists, has provided novel insights into regulation by orthosteric and allosteric ligands, as well as receptor dimerisation in single living cells. This work has demonstrated negative cooperativity between different ligand-binding conformations. Professor Hill's lab has also used a fluorescent antagonist to study the binding characteristics of antagonist-occupied receptor conformations (R) in membrane microdomains of single cells. In addition his lab has developed novel ligand binding assays using cell surface receptors tagged with a novel N terminal luciferase (NanoLuc; Promega) and bioluminescence resonance energy transfer (BRET) to a fluorescent ligand.

On 7 December 2016 Professor Hill presented to a packed audience a Raine Lecture entitled: *Investigating GPCR dimerisation and complex formation with fluorescent ligands*.

PROFESSOR SHULAMIT LEVENBERG

In 2014 Professor Shulamit Levenberg was listed in the 10 top Israeli women in science and technology by the Israel Ministry of Education and in 2013 the daily Israeli newspaper, Maariv, included her in a list of 10 Israeli scientists. In the same year, Professor Levenberg received the Woman of the Year Award from the Emuna Foundation.

In December 2016, the University of WA was delighted to welcome Professor Levenberg from the Israel Institute of Technology as a Raine Visiting Professor and guest of Professor Geoff Laurent, Director of the Centre for Celll Therapy and Regenerative Medicine. Professor Levenberg also attended the Joint 6th Margaret River Region Forum and 9th ASSCR Annual Scientific Meeting, December, 2016 where she presented a talk on her research entitled: Stem Cells and Tissue Engineering.

Professor Levenberg's research is focussed on stem cells and vascular tissue engineering. She was awarded her PhD in cell adhesion by the Weizmann Institute followed by postgraduate research at MIT on stem cell tissue engineering with Professor Robert Langer, a world leader in biomaterials, drug delivery and tissue engineering.

Professor Levenberg has delivered more than 80 talks as invited or keynote speaker to international conferences, including; Third Annual Cambridge Stem Cell Institute International Sympoisum, Cambridge, UK (2013); International Symposium on Engineering Complex Tissues, Drexel University, USA (2015); Fourth TERMIS World Congress, Boston, USA (2015).

PROFESSOR RO OSAWA

As one of the first scientists to discover bacteria in the Koala gut that enables it to break down gum leaves for food, Professor Ro Osawa's distinguished career in Bacteriology involves the study of a wide range of bacteria from pathogenic species to probiotic bacteria, including lactobacilli and bifidobacteria – a corresponding range of hosts from koala to human. Director of the Research Centre for Food Safety and Security, Graduate School of Agricultural Science, Kobe University, Professor Osawa also holds Professorships in the Departments of Microbiology and Immunology, and Bioresource Science, along with a Professorship in the Division of Bacteriology, Graduate School of Medicine at Kobe University.

Professor Osawa's research also involves the development of technologies to ensure "traceability" of pathogenic bacteria endangering safety of foods and agricultural products "from stable to table"; along with the development of safe and effective probiotics to promote health of both human and animals.

In October 2016 the Raine Foundation was delighted to welcome Professor Osawa from Kobe University, Japan, guest of Professor Kevin Croft and key speaker at the Microbiome Symposium held at Technology Park Function Centre, Bentley. Professor Osawa presented to the Symposium audience his Raine Lecture entitled: Evaluation of functionality and safety of food components by human intestinal models: Kobe University's approach.

Professor Osawa is currently a Unit leader for Innovative BioProduction KOBE supported by Special Coordination Funds for Promoting Science and Technology, MEXT, Japan, developing a human intestinal model for the most practical evaluation of functionality and safety of food components. He is also a collaborative researcher for The US-Japan Cooperative Medical Sciences Program.

PROFESSOR GIJS VAN SOEST

In his research Professor Gijs van Soest is unique. He has expertise in optical, photoacoustic, and ultrasonic imaging of atherosclerosis in the coronary and carotid arteries. His research integrates a fundamental understanding of the physics and engineering principles of the respective diagnostic modalities, with well-rounded insights in their clinical application. This translational success reflects his early research training at the University of Amsterdam where he worked at the interface between clinical, basic science and engineering disciplines.

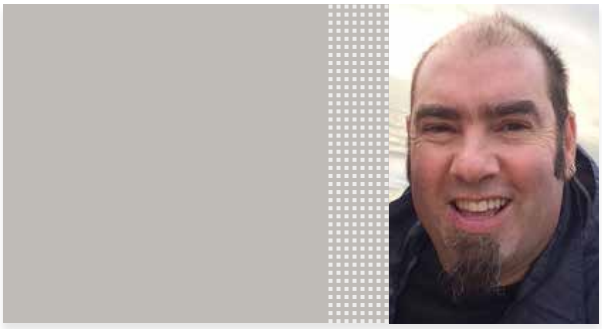
As Head of the Thorax Centre of the Department of Biomedical Engineering at the Erasmus University Medical Centre in Rotterdam, Professor van Soest's work has led to impressive technological achievements in catheter-based imaging. He and his team pushed the technology from concept-phase, through in vitro and in vivo tests, and into clinical evaluation.

Professor Gijs van Soest with Professor Raffaele Dellaca from Milan Politecnico.

Professor Gijs van Soest with Professor Paul Johnson.

The Raine Medical Research Foundation was delighted to attract Professor van Soest to Western Australia with a 2016 Raine Visiting Professor Award where he worked closely with the Head of the School of Electrical, Electronics and Computer Engineering, Professor David Sampson. On 13 October 2016, Professor van Soest presented his Raine Lecture to a wide-ranging audience where he discussed the topic: Imaging of atherosclerosis with light and sound.

One of the major strengths of the RVP program is its capacity to link top international scientists with colleagues at local Universities and medical research institutes to advance their collaborative research programs. It was even more pleasing therefore to see that the visit of two outstanding international scientists did not only coincide during their time at UWA as Raine Visiting Professors, but they were able to connect with each other and discuss their respective scientific advances in the field of biomedical engineering – a fantastic outcome that demonstrates the power and scope of the Raine Visiting Professor program.



PROFESSOR JOSÉ LUIS GÓMEZ-SKARMETA

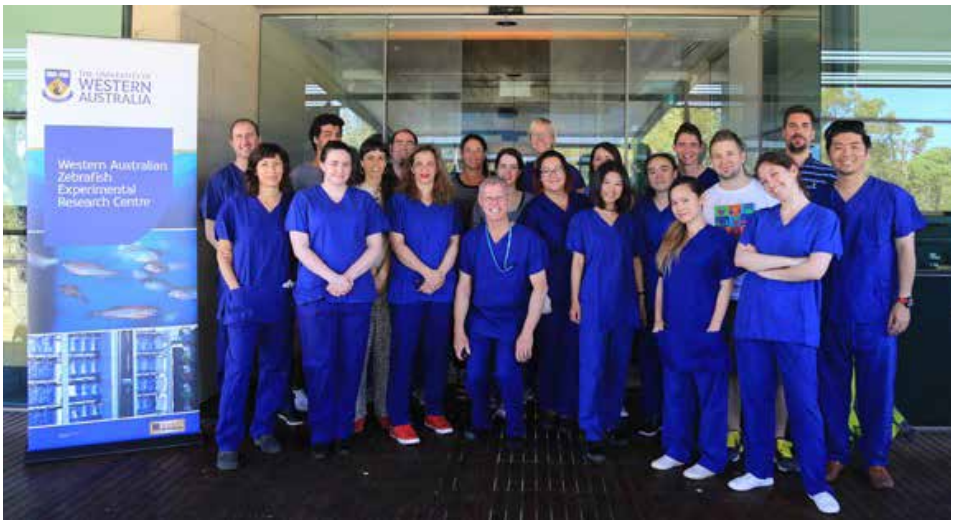
In October 2016 the Raine Medical Research Foundation was delighted to welcome Professor José Luis Gómez-Skarmeta from the Andalusian Center for Developmental Biology (Centro Andaluz de Biologia del Desarrollo) in Spain, to visit the The University of Western Australia as guest of Professor Ryan Lister at the Centre for Medical Research, Harry Perkins Institute of Medical Research.

A founding member of the CADB in 2003, the research team of Professor Gómez-Skarmeta is focused on combining epigenomics, chromosome capture assays, transgenic enhancer experiments and mutagenic studies. Their goal is to determine how cis-regulatory elements and chromatin structure contribute to development and evolution, and how alteration in this non-coding part of the genome affects human health.

One of the most outstanding studies of Professor Gómez-Skarmeta during his early years at the CABD was the identification of a large and complex regulatory process for genes of the vertebrate IrxB complex, constituting pioneering work in this field. The laboratory of Professor Gómez-Skarmeta also pioneered the introduction of various new genomic techniques to identify cis-regulatory elements globally. The combination of these techniques with functional assays in zebrafish, has allowed his group to identify genetic mechanisms and regulatory elements that play an essential role in the construction of the vertebrate body plan and its variations during evolution.

Recently, in collaboration with Professor Ryan Lister, they have identified an evolutionarily conserved mechanism in which deeply conserved enhancers are demethylated during vertebrate body plan formation, as published in *Nature Genetics*, 2016.

The visit of Professor Gómez-Skarmeta to the University in 2016 was highly successful. It enabled him to use the new Western Australia Zebrafish Facility and to transfer to his UWA collaborators his extensive knowledge and expertise in zebrafish development, genomics and 3D chromatin structure. It also strengthened and advanced the collaboration with Professor Lister with new applications for national and international competitive grant schemes.



Participants of the 'UWA-Raine Zebrafish Practical Course: Introduction to genetic manipulation of zebrafish' held in November 2016.

BrightSpark Research Collaboration Awards

The BrightSpark/Raine Alliance has resulted in the establishment of the BrightSpark Research Collaboration Awards which were offered for the first time in 2016, to commence in 2017. These Awards encourage early-career researchers in Western Australia to establish and develop research collaborations, both nationally and internationally, to seek a better understanding of the cause and treatment of childhood disease and illness.

In 2016, two Awards were allocated with a total funding allocation of $18,856.

2016 BrightSpark Research Collaboration Awards

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

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 2017, three Awards were allocated with a total funding allocation of $41,594.

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.

2015 Cockell Research Collaboration Awards

	Chief Investigator	Project Title	Collaborating Institution
	Professor David Bruce School of Medicine and Pharmacology, The University of Western Australia	Neuroinflammation in Type 2 diabetes: A PET study using the novel radioligand, (18F]p FEEPPA	University of Toronto, Canada
	Associate Professor Julian Lk-Tsen Heng Harry Perkins Institute of Medical Research	Understanding how genetic mutations to gene regulatory proteins cause childhood brain disorder	University of Queensland
	Dr Jenny Rodger School of Animal Biology, The University of Western Australia	Preclinical optimisation of repetitive transcranial magnetic stimulation for youth with treatment refractory depression	Mayo Clinic, USA
	Professor Sergio Starkstein School of Psychiatry and Clinical Neurosciences, The University of Western Australia	Autism Spectrum Disorder in middle to late adulthood: Phenomenology, behavioural correlates and societal costs	University of North Carolina, USA University of Cambridge, UK

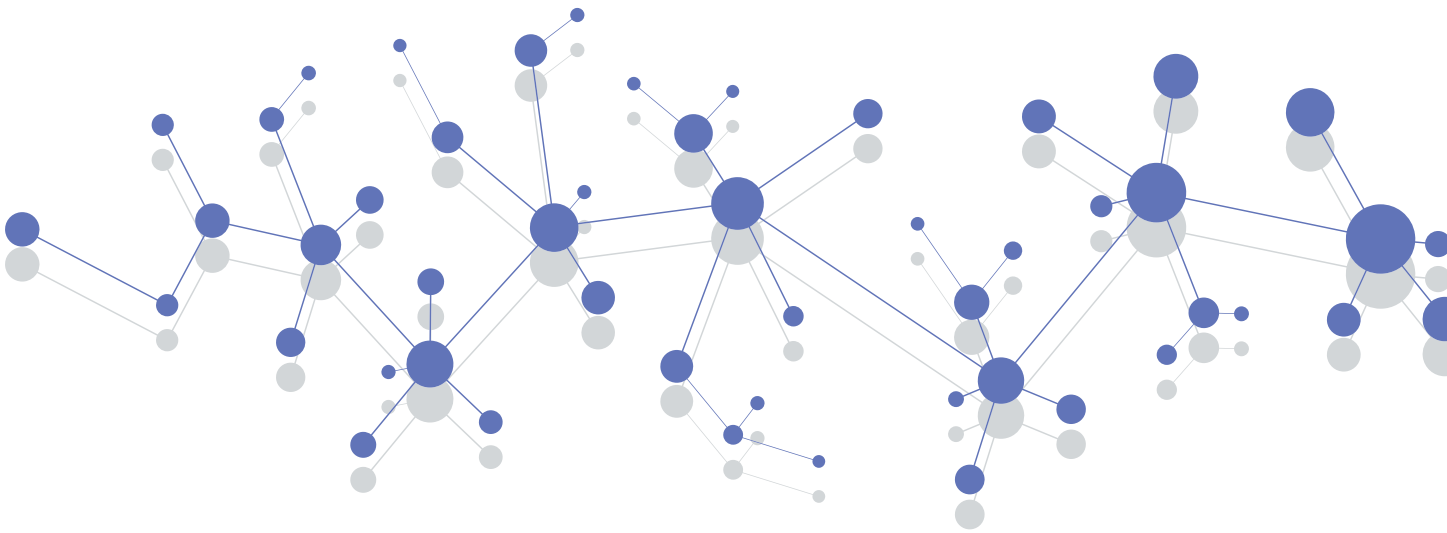
	Professor Florian Zepf School of Psychiatry and Clinical Neurosciences, The University of Western Australia	Studying the role of serotonin in anxiety in adolescence – An iterative translational research approach	Duke University, USA

2016 Cockell Research Collaboration Awards

	Chief Investigator	Project Title	Collaborating Institution
	Dr Wayne Davies School of Animal Biology, The University of Western Australia	Light therapy in the treatment of Bipolar Disorder	University of Oxford
	Dr Kevin Runions Telethon Kids Institute	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, The University of Western Australia	Simple Physical Activity Questionnaire (SIMPAQ)L and international validation study	University of New South Wales Universidade Federal do Rio Grande do Sul, Brazil University of Leuven, Belgium
	Professor Andrew Whitehouse Telethon Kids Institute	Very early intervention in infants at risk of autism: Bringing a novel therapy to Australia	University of Manchester La Trobe University

2017 Cockell Research Collaboration Awards

	Chief Investigator	Project Title	Collaborating Institution
	A/Prof Lisa Wood School of Population Heath, The University of Western Australia	Prevalence of Mental Illness and Treatment Pathways among people who are homeless in Perth, Western Australia	Institute Social Inclusion, Royal Perth Hospital Pathway UK
	Dr Benjamain Milbourn School of Occupational Therapy and Social Work, Curtin University	Mental health outcomes of adolescents with ASD as they transition to adulthood	Vanderbilt Kennedy Centre at Vanderbilt University, Nashville, USA
	Dr Ben Grafton School of Psychology, The University of Western Australia	Enhancing the treatment of depression through the delivery of attentional bias modification procedures	University of Exeter, UK



Cockell Research Collaboration Awards

PROJECT TITLE

Neuroinflammation in type 2 diabetes: A PET study using the novel radioligand, [18F]-FEPPA

INVESTIGATORS

Professor David Bruce (Chief Investigator)
Associate Professor Romina Mizrahi (Collaborating Partner)

SCHOOL/INSTITUTE/CENTRE

School of Medicine and Pharmacology and School of Psychiatry and Clinical Neuroscience, The University of Western Australia
Mental Health Research Institute, University of Toronto (Collaborating Institution)

SUMMARY

Type 2 diabetes is highly prevalent, strongly age-related and accounts for a significant burden of illness in the Australian community. In addition to typical complications, type 2 diabetes is associated with an increased risk of cognitive impairment and dementia in older patients. The cause of these disorders remains unclear and both cerebral microvascular disease and neurodegenerative processes (i.e. Alzheimer's disease) have a role. This study will help determine the role of neuroinflammation in diabetic brain disorders and guide a planned longitudinal study.

OUTCOMES

Dissemination of knowledge and expertise

The Award funded two visits by senior research staff (Ms Simone Brockman, Fremantle Hospital Neuroimaging laboratory and Ms Simone Culleton, Senior Nuclear Medicine technologist, PET Centre, SCGH) to the Research Imaging Centre at the Centre for Addiction and Mental Health (CAMH) and the University of Toronto, Canada. CAMH is Canada's largest mental health and addiction teaching hospital and an international research centre in the areas of addiction and mental health. Over the past 20 years, their work in positron emission tomography (PET) has had a major global impact on the understanding of brain chemistry and functioning, and they have been responsible for the development of half of all the radiotracers commonly used in PET imaging around the world today.

Our research staff received training and gained valuable experience specifically with [^{18}F]-FEPPA PET imaging under the guidance of the scientists responsible for developing and validating the technique, Drs P. Rusjan and R. Mizrahi. We are now ready to conduct a pilot study, scheduled to commence in early 2017, to support an NHMRC grant application in 2017. This study will investigate the role neuro-inflammation may have in patients with dementia and diabetes. The acquisition of pilot data will significantly strengthen our application to state and nationally competitive funding bodies.

PROJECT TITLE

Preclinical optimisation of repetitive transcranial magnetic stimulation for youth with treatment-refractory depression

INVESTIGATORS

Dr Jennifer Rodger (Chief Investigator)
Dr Paul Croarkin (Collaborating Partner)
Dr Doo-Sup Choi (Collaborating Partner)

SCHOOL/INSTITUTE/CENTRE

School of Animal Biology, The University of Western Australia
Mayo Clinic, USA (Collaborating Institution)

SUMMARY

Adolescent depression is one of the most prevalent and costly medical conditions worldwide. Afflicted youth have a chronic course and often fail to respond to standard treatments. Repetitive transcranial magnetic stimulation (rTMS) is FDA-approved for treating depression with response rates of up to 40% in drug-resistant patients. My lab has pioneered rTMS coils in preclinical (animal) depression models. This Award has allowed us to establish a collaboration with researchers at Mayo Clinic (USA), who are spearheading large trials of rTMS in adolescents. Our combined human and animal approach will identify clinically relevant biomarkers to enhance rTMS research protocols for depressed patients.

OUTCOMES

Dissemination of knowledge and expertise

Dr Paul Croarkin and his PhD student Mr Daniel Lindberg visited our lab in March 2016. They were hosted by my PhD student Alesha Heath and myself. We discussed biophysical aspects and clinical considerations of designing medical devices to deliver stimulation to the human and animal brain. Dr Croarkin and Mr Lindberg took one of our custom-built stimulation devices back to the US in order to perform parallel experiments between our two groups.

I visited Dr Croarkin and Mr Lindberg at the Mayo Clinic in Rochester Minnesota in May 2016. I met with clinicians actively engaged in treating adolescents with anxiety disorder and depression and gained insight into the challenges involved in clinical application of brain stimulation.

Collaboration

A researcher at the Mayo Clinic who works in the field of addiction, Dr Doo-Sup Choi, became involved in our project as he and Dr Croarkin obtained additional funding to perform extensive analysis of metabolic changes in our animal model of depression.

Dr Croarkin had also invited Dr Zhi Deng from Duke University (USA) to the Mayo Clinic at the same time as my visit. Dr Deng is the world expert on brain stimulation coil design and modelling. I was extremely privileged to meet Dr Deng and have since published a paper with him as a co-author.

Conference travel

My PhD student, Ms Alesha Heath, attended an international conference (Annual Meeting of the American College of Neuro-Psychopharmacology) in December 2016 and presented a poster. She met leading researchers in her field and gained valuable insight into the clinical and preclinical aspects of her research.

Presentations

- Dr Croarkin gave a research seminar to the Telethon Kids Institute, and in the same session, Mr Lindberg participated in an Early Career Researchers presentation.
- Dr Croarkin gave an informal research presentation to the Experimental and Regenerative Neurosciences group at UWA.
- I delivered a research seminar to Dr Choi's lab on my animal studies.
- I participated in a mentoring session for early career clinician researchers in Dr Croarkin's group and discussed aspects of career progression, gender equity and work/life balance.
- Abstract presented by Ms Alesha Heath at the American College of Neuropsychopharmacology: Repetitive Transcranial Magnetic Stimulation in the Olfactory Bulbectomy Mouse Model of Depression. Alesha Heath, Avalon Young, Sofia Rinaldi, Kalina Makowiecki, Jennifer Rodger. Poster T118.

Grants

- Preclinical Optimisation of Repetitive Transcranial Magnetic Stimulation for Adolescent Depression. CCaTS Team Science Pilot Award (Mayo Clinic). Croarkin, Choi (US$75,000).

Photos from Dr Croarkin and Mr Lindberg's visit to Perth in 2016.

PROJECT TITLE

Autism Spectrum Disorder in middle to late adulthood: Phenomenology, behavioural correlates and societal costs

INVESTIGATORS

Professor Sergio Starkstein (Chief Investigator)
Emeritus Professor German Berrios (Collaborating Partner)
Professor Joseph Piven (Collaborating Partner)

SCHOOL/INSTITUTE/CENTRE

School of Psychiatry and Clinical Neurosciences, The University of Western Australia
University of Cambridge, UK (Collaborating Institution)
University of North Carolina, USA (Collaborating Institution)

SUMMARY

Based on current estimates of the prevalence of Autism Spectrum Disorder (ASD), it is expected that older adults with ASD will impose a tremendous burden on the health care system and society at large. Currently, very little is known about the main clinical problems in this population. Our overall aims are firstly 1) to examine the following characteristics in a clinic sample of adults older than 40 years with ASD in comparison to age-, gender- and IQ-matched controls (a) rates and patterns of behavioural, medical and neuropsychiatric disorders; (b) frequency and nature of health care contacts; (c) degree of financial and social support; (d) level of function; and (e) quality of life; and secondly, 2) to calculate and compare direct and indirect costs of care for both groups.

OUTCOMES

Dissemination of knowledge and expertise

The project involved two simultaneous collaborations: finalising data analysis on a study of behavioural problems in adults with Autism Spectrum Disorder (ASD), and writing a book on the concepts of anxiety from a historiographic and epistemological perspective. During my visit to the University of Cambridge, I gained experience in writing grants for the National Institutes of Mental Health, as well as conducting conceptual research in psychiatry with a world leader in the field. The experience I acquired at the University of Cambridge will allow me to write more extensively on conceptual issues in psychiatry.

PROJECT TITLE

Simple Physical Activity Questionnaire (SIMPAQ): an international validation study

INVESTIGATORS

Assistant Professor Anna Waterreus (Chief Investigator)
Associate Professor Philip B. Ward (Collaborating Partner)
Dr Simon Rosenbaum (Collaborating Partner)
Marcelo Pio de Almeida Fleck (Collaborating Partner)
Dr Davy Vancampfort (Collaborating Partner)

SCHOOL/INSTITUTE/CENTRE

School of Psychiatry and Clinical Neurosciences, The University of Western Australia
University of New South Wales (Collaborating Institution)
Universidade Federal do Rio Grande do Sul, Brazil (Collaborating Institution)
University Leuven, Belgium (Collaborating Institution)

SUMMARY

The inclusion of physical activity programs into mental health services can improve the health outcomes of people with mental illness, but physical activity is difficult to measure. Existing questionnaires are limited in their ability to measure sedentary behaviour. As part of an International Working Group, we have developed a new interview-based physical activity questionnaire (SIMPAQ) which assesses sedentary and low intensity behaviours in people with mental illness. It now requires validation. Accelerometers are movement monitors that capture intensity of physical activity. They are considered a gold standard measure and have been used in this study to validate the SIMPAQ.

SIMPAQ was translated into many languages (Portuguese, French, Czech, Danish, Dutch (Flemish), Finnish, German, Greek, Chinese, Malayalam, Farsi, Italian, Japanese, Dhivehi, Igbo, Norwegian, Punjabi, Spanish, Swedish, Mandarin) and in 2016 a validation study, comparing the data obtained via SIMPAQ to objective accelerometer-based measurements, was undertaken. Initially 1000 people, over 10 sites, in developed and developing countries, were to be involved, but due to the strong interest from across the world, currently 25 countries and 38 sites are involved (Figure 1), with 745 people participating in this study. With more sites than expected wanting to participate, recruitment has been extended from December 2016 to 30th June 2017. Ongoing International Working Group meetings are planned for the near future to disseminate results and discuss future directions of the group.

This Award has enabled participation in the international validation study. We purchased six accelerometers, and over a period of three months successfully recruited 40 participants. I was able to attend a meeting of collaborators in Sydney, and will be attending another meeting in March 2017 in the USA.

Figure 1: Countries current participating in the SIMPAQ validation study.

OUTCOMES

Dissemination of knowledge and expertise

I have gained considerable knowledge and expertise from my involvement with this International group of researchers and clinicians specifically in the use of accelerometers and assessing physical activity. I have ongoing communication with national and international SIMPAQ collaborators and have been able to disseminate information and my expertise to them. I have also discussed the benefits of including SIMPAQ as an assessment tool in a proposed randomised controlled trial of lifestyle intervention to enhance maternal mental health and fetal outcomes for women with serious mental illness and was invited to join this study group.

Meeting travel

- International SIMPAQ meeting of collaborators – Sydney, 2016
- International SIMPAQ meeting of collaborators – USA, March 2017

Presentation

Poster presentation at the 6th International Congress on Physical Activity and Public Health in Bangkok, Thailand in November 2016: 'Assessing physical activity among people experiencing mental illness: feasibility and validity of the Simple Physical Activity Questionnaire (SIMPAQ).' Authors: J Richards, S Rosenbaum, A Bauman, A Carraro, F Gaughran, M Gerber, F Schuch, B Stubbs, D Vancampfort, **A Waterreus** and P Ward.

PRIZES

Raine Research Prize

The Raine Research Prize is available each year to early career Western Australian researchers in the field of medical/health science and is awarded to the candidate with the best published scientific paper. It consists of a Travel Grant to the value of $5,000, a Medallion and a Certificate of Distinction.

2017 Raine Research Prize

Research Committee members were unanimous in their view that there was one publication that was outstanding in the 2017 round, with the author a particularly worthy recipient of the Prize. It was with great pleasure that the Research Committee awarded the Raine Research Prize for 2017 to Dr Ozren Bogdanović from the Harry Perkins Institute of Medical Research, for his article: Active DNA demethylation at enhancers during the vertebrate phylotypic period; *Nature Genetics*. 2016; vol. 48: 417 – 426.

2016 Raine Research Prize

The 2016 recipient of the Raine Research Prize, Dr Helena Viola from the School of Anatomy, Physiology and Human Biology, The University of Western Australia, extended her thanks to the Raine Medical Research Foundation for the Raine Research Prize. She was pleased to report that the Prize had enabled her to attend and present at the Australasian Section Meeting of the International Society for Heart Research (ISHR) (Adelaide SA), as well as the World Congress of the ISHR (Buenos Aires, Argentina). Additionally, as an early career researcher (ECR) representative for the ISHR, travelling to the *Australasian Section Meeting* enabled her to implement the first ever Australasian Section ECR Panel Discussion and Symposium. The panel discussion was aimed at providing an opportunity for ECRs and senior investigators from both basic science and clinical backgrounds to discuss an interesting and potentially controversial topic "Are stem cells the future of cardiovascular research?".

Travelling to the *ISHR World Congress* enabled Dr Viola to present her work as a finalist for the prestigious Richard J Bing Young Investigator Award. She was one of four finalists selected from a total of 38 submitted abstracts, and was winner of second place. She was also winner of the ISHR World Congress Poster competition.

In thanking the Raine Medical Research Foundation for the 2016 Raine Research Prize, Dr Viola was pleased to report that attending these conferences provided a fantastic opportunity to share her work, network with other researchers in the field, and continue her leadership role promoting ECR career progression on both a national and international level.

Left: Professor David Eisner (ISHR International Council Member and Editor in Chief, JMCC). Centre: Dr Helena Viola (UWA) and fellow ISHR World Congress Richard J Bing Young Investigator Award finalists.

The ISHR World Congress (Buenos Aires, Argentina). L-R: Dr Kim Mellor (University of Auckland), Professor Livia Hool (UWA), Dr Helena Viola (UWA).

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 or professional qualification.

2017 Strachan Memorial Prize

The 2017 Strachan Memorial Prize was awarded to Dr Ashleigh Lin from the Telethon Kids Institute for her outstanding publication: Outcomes of non-transitioned cases in a sample at ultra-high risk for psychosis: a medium to long-term follow-up study; *The American Journal of Psychiatry*. 2015; vol. 172 (3): 249 – 258.

Dr Ashleigh Lin, winner of the 2017 Strachan Memorial Prize.

2016 Strachan Memorial Prize

The 2016 winner of the Strachan Memorial Prize, Dr Rishi Kotecha from the School of Paediatrics and Child Health Research, The University of Western Australia used his Prize to attend three major international conferences to advance his knowledge of childhood leukaemia. Dr Kotecha was invited to attend the 27th International BFM Study Group meeting in Athens, Greece by virtue of his position within the international INTERFANT committee. This committee is responsible for the design, implementation and reporting of clinical trials for babies less than one year of age with acute lymphoblastic leukaemia. He also attended the joint meeting of the 10th Biennial Childhood Leukemia Symposium. Attendance at these Conferences enabled further discussions in regard to development of international trials for this group of patients, and importantly allowed for invaluable networking and collaboration amongst global experts in the field of childhood leukaemia.

Dr Kotecha's research group was also selected to make two presentations at the 58th American Society of Haematology Annual Meeting and Exposition in San Diego, USA. The abstracts of these presentations have both been published as conference proceedings in the journal Blood, Volume 128, Issue 22.

Dr Rishi Kotecha at the 27th Annual Meeting of the International BFM Study Group in Athens, Greece and the 58th American Society of Hematology Annual Meeting.

PUBLICATIONS

Raine Priming Grants

1. B. Li, **T. Clemons**, V. Agarwal, J. Kretzmann, M. Bradshaw, P. Toshniwal, N. Smith, S. Li, M. Fear, F. Wood, S. Iyer. Regulation of collagen expression using nanoparticle mediated inhibition of TGF-β activation. *New J. Chem.* 2016, *40*, 1091-1095.

2. Chowdhury HA, Wittek A, Miller K, **Joldes GR**. An Element Free Galerkin Method Based on the Modified Moving Least Squares Approximation. *Journal of Scientific Computing.* 2016:1-15.

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Strachan Memorial Prize

1. Sutton R, Law T, Venn NC, Wadham C, Mould EVA, Norris MD, **Kotecha RS**, Marschalek R, Meyer C, Dalla-Pozza L, Marshall GM, Lock RB, Trahair TN. Comparison of MRD Levels and Gene Expression Patterns in MLL-R Versus Non-MLL Infant ALL. *Blood*. 2016. Volume 128, Issue 22 (Conference Abstract).

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The Raine Study

2016 ACTIVITY SUMMARY REPORT FOR THE RAINE MEDICAL RESEARCH FOUNDATION

The Western Australian Pregnancy Cohort (Raine) Study

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

HIGHLIGHTS OF 2016

Established in 1989 with support from the Raine Medical Research Foundation, the Raine Study is one of the largest, most successful prospective cohorts of pregnancy, childhood, adolescence and now adulthood to be carried out anywhere in the world. Over 2,000 of the now young adult participants (Generation 2) remain active, and participated in assessments of work and obesity in 2016. In addition, the original parents (Generation 1) participated in assessments of sleep, obesity and activity this year.

The highlights for the Raine Study in 2016 were:

- The University of Western Australia, Curtin University, Edith Cowan University, Murdoch University, Notre Dame University, Women and Infants Research Foundation and Telethon Kids Institute agreed to become core partners in a new Raine Study Unincorporated Joint Venture;
- The Raine Study led the WA Cohorts Network component of the WAHTN application for AHTRC recognition;
- Over 150 researchers were engaged in Raine Study research and over 50 new research projects within Raine were approved;
- Peer-reviewed publication output remained high in terms of quantity and quality. In 2016 50 peer-reviewed papers were published, with 78% of these in journals with impact factors of 2 or greater (Figure 1). High impact publications included Nature (IF=38), Nature Communications (IF=11.3), and Journal of Allergy and Clinical Immunology (IF=12);
- Raine Study research activity was funded by 6 NHMRC project grants, 1 ARC discovery grant, a Cooperative Research Centre for Living with Autism (Autism CRC) grant and other grants from the WA Department of Health and the National Breast Cancer Foundation. Two further NHMRC project grants (to start in 2017) and one NHRMC CRE grant (to start in 2017) applied for in 2016 were successful;
- A very successful 9th Raine Study Annual Scientific meeting was held on Friday 30 September 2016.

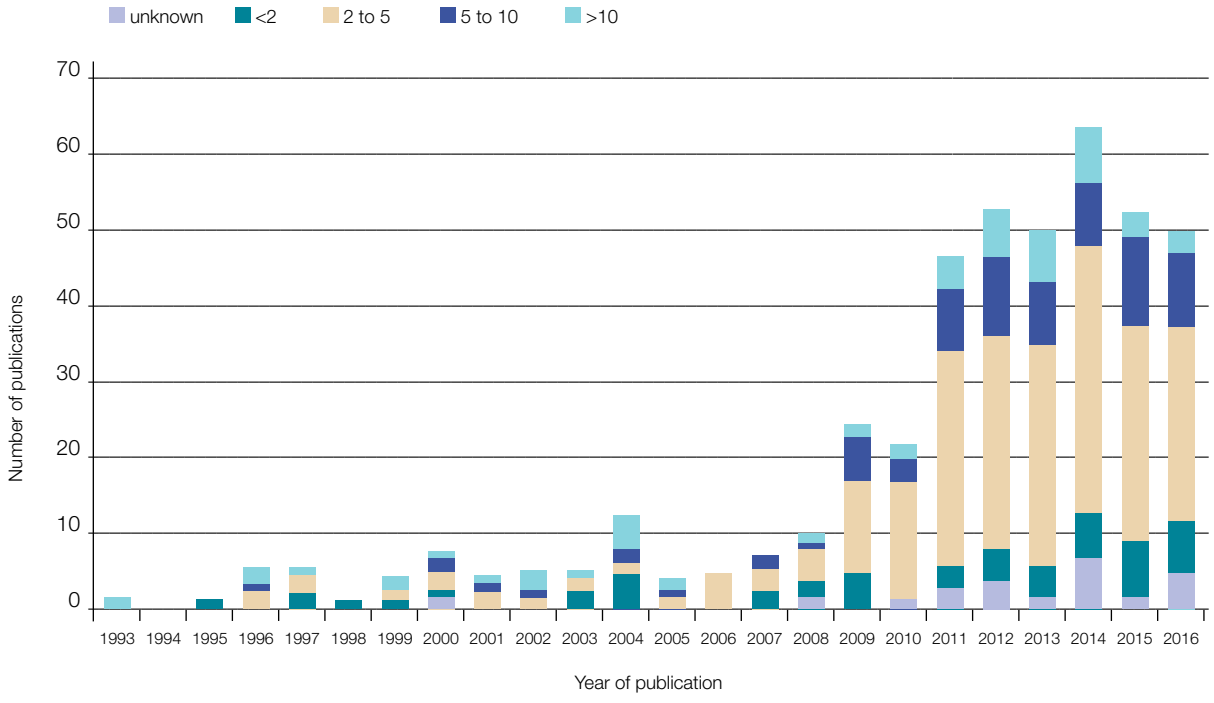

Figure 1: Number of Raine Study publications by year and impact factors.

GRANT APPLICATIONS 2015 (FOR 2016)

Eleven project grant applications totalling $8.4 million were prepared and submitted in 2015 for research projects to commence in 2016. Seven grants proposed the collection of new data (i.e. a new cohort assessment), and four grants proposed utilising previously collected Raine Study data.

Two grant applications were successful:

- NHMRC 1102106, 2016-2020, T Mori, L Beilin, E Moses, G Watts, L Adams, Genetic and early life predictors of ectopic fat and their association with cardiometabolic health and disease, $1,706,136.
- NHMRC 1109057, 2016-2018, P Eastwood, A Mian, N McArdle, D Hillman, Predicting obstructive sleep apnoea using 3D craniofacial photography, $424,715.

The Raine Study also became involved in the Autism Cooperative Research Centre via a grant awarded to Professor Andrew Whitehouse and colleagues: The creation of the Australian Autism Biobank. Autism Cooperative Research Centre (1.002RC), with a total amount of $130,000 contributing to Raine Study related activities.

GRANT APPLICATIONS 2016 (FOR 2017)

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

Three grant applications were successful:

- NHMRC 1126494, 2017-2020, D Green, L Beilin, L Straker, P Eastwood, T Mori, P Ainslie, Developmental origins of adult cardiovascular disease: Vascular health in the Raine cohort, $1,087,427.
- NHMRC 1121979, 2017-2020, D Mackey, A Hewitt, S MacGregor, C Hammond, Young adult myopia: genetic and environmental associations, $809,270.
- NHMRC CRE1116360, D Mackey, J Craig, A Hewitt, K Burdon, R Jamieson, J Grigg, S Macgregor, F Chen, M Otlowski, D Schofield, NHMRC Centres of Research Excellence – From discovery to therapy in genetic eye diseases (Raine Study is part of this CRE), $2,498,231.5.

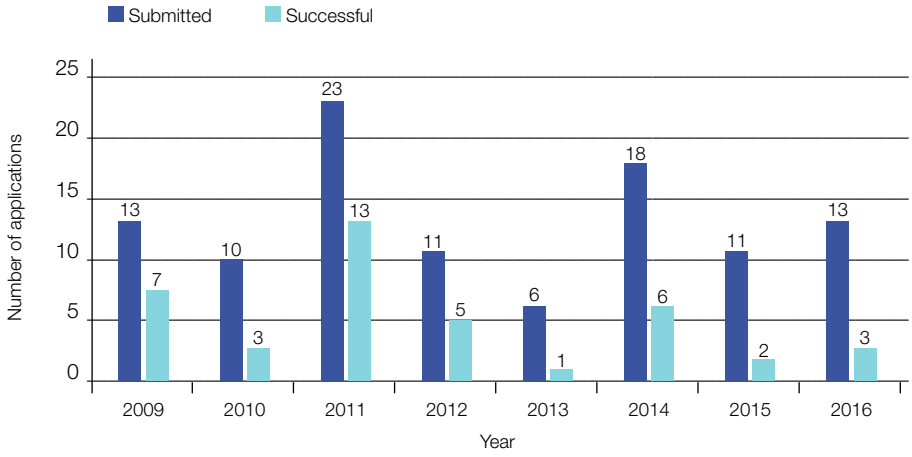

Figure 2: Raine Study grant applications. Total number submitted and total number of successful applications.

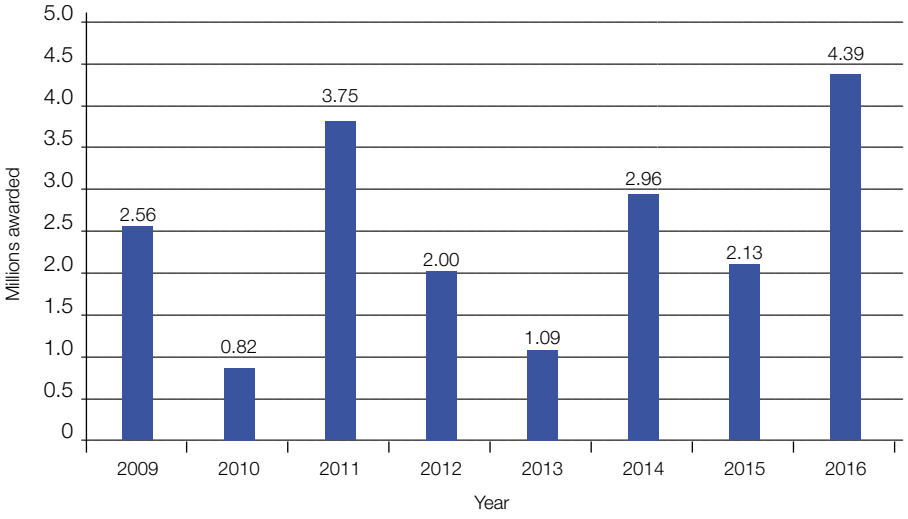

Figure 3: Raine Study successful grants. Total amount awarded each year ($millions).

RAINE STUDY ANNUAL SCIENTIFIC MEETING

A very successful 9th Raine Study Annual Scientific meeting was held on Friday 30 September 2016, at the University Club UWA. The meeting was formally opened by Her Excellency the Honourable Kerry Sanderson AC, Governor of Western Australia and patron of the Raine Study. Professor John Newnham gave an excellent and entertaining talk about Mary Raine, and presented Her Excellency with a biography on Mary Raine, signed by the author, Meg Sangster.

Sixteen presentations were delivered over the course of the day that covered a wide variety of research areas. The Raine Medical Research Foundation prizes for the two best presentations by early career researchers were present by Emeritus Professor Lou Landau to Niamh Troy for her talk on predicting causes of gene expression changes in T-helper memory responses in asthma, and to Karen Richards for her presentation on the association of neck posture and neck pain in adolescents.

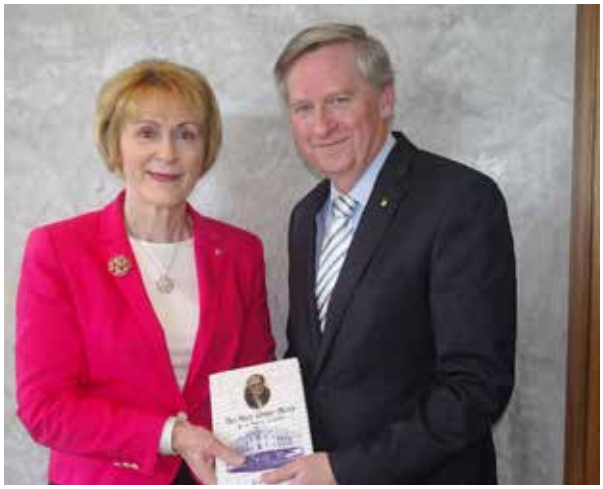

Figure 4: Her Excellency the Governor and John Newnham.

Figure 5: Lou Landau with Karen Richards and Niamh Troy.

ACTIVITIES PLANNED FOR 2017

Activities planned for 2017 represent the next major change in the Raine Study and its operations, the last major change being the appointment of the inaugural Scientific Director and Executive Committee in 2007. In 2017, the Raine Study will see the implementation of: a new strong collaborative governance structure (Figure 6); improved human and technical infrastructure; participation for the first time of three generations of Raine Study participants. These activities will ensure the continued growth of the Raine Study's national and international reputation.

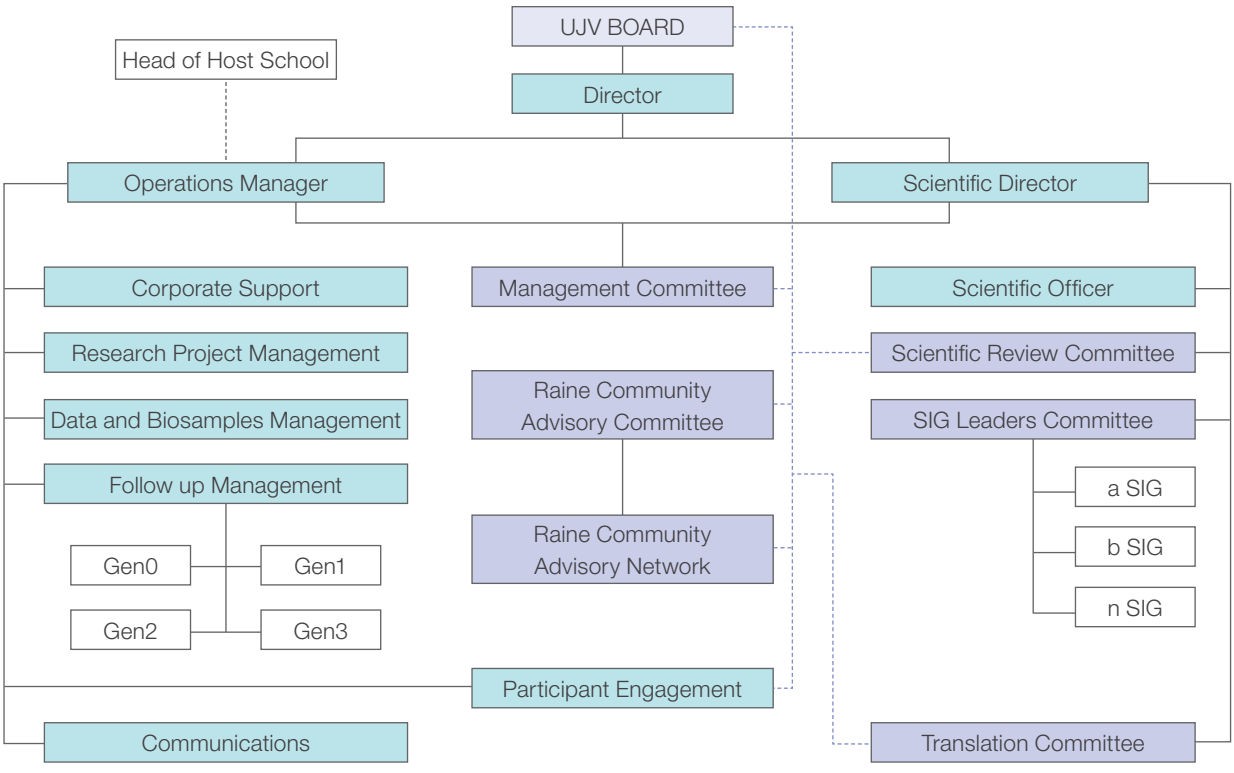

Figure 6: The new structure of staff, participants and portfolios.

RAINE STUDY PUBLICATIONS 2016

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Raine Annual Awards Ceremony

Tara Richman, Brigitte Tampin, Miranda Grounds.

Gavin Pereira, Melissa O'Donnell.

Dimitar Azmanov, Nigel Laing.

Peter Eastwood, Amanda Cleaver, Steven Mutsaers.

Karen Simmer, Michael Quinlan, Alan Robson.

Elizabeth Davis, Mariapia Degli-Esposti, Iona Schuster.

Lisa Wood, Benjamain Milbourn.

Babu Simon, Jodie Hegarty.

Financial Report

Investment Performance

The University's investment portfolio delivered positive returns during the year, primarily driven by capital appreciation in Long Term Pool investments, despite ongoing market volatility throughout the year. However, market growth in 2017 remains uncertain given market volatility as consequence of post US election outcomes and impact on global markets.

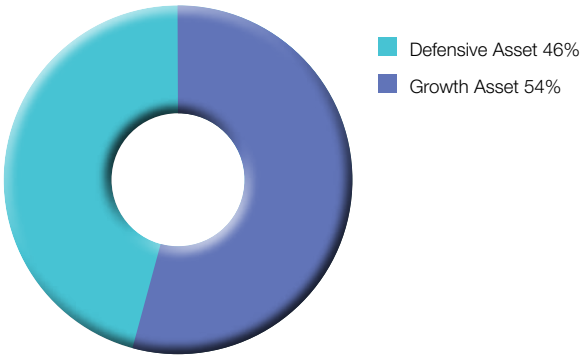
Investment Distributions

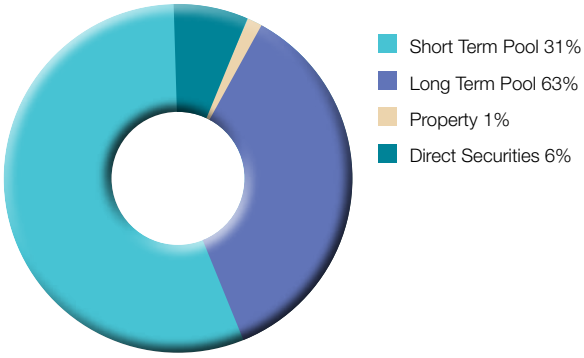
The Long Term Pool distributed 8.20% for the year and out-performed budget largely due to strong performance driven by equity capital appreciation post US Presidential Election. The Short Term Pool distributed 3.48% for the year which was in accordance with the original budget rate.

Investment Pool	Original Budget	Distribution Rate
LTP	7.42%	8.20%
STP	3.48%	3.48%

The University Investment Portfolio was transitioned to an Implemented Investment Solution with Mercer in December 2016. The LTP has predominately transitioned to its overall growth benchmark position Growth: 80%, Defensive: 20%. The STP now comprises only 100% Defensive assets.

Raine Investment Exposure and Asset Allocations





Raine Financial Update

The total carrying value of the Foundation assets as at 31 December 2016 was $38.4M, of which 76% is invested in the Long Term Pool (LTP), 19% in the Short Term Pool (STP) and 4% in Direct Securities and 1% in Property.

In May, 2016 the investment portfolio was rebalanced to 50/50 Growth versus Defensive across Long Term Pool and Short Term Pool and the Fluctuation Capital Fund capped at 10% of the total pooled investments. The Short Term Pool Raine Foundation Capital Account 2 ($3.8M) and the Raine Medical Research Fund Income & Expenditure Account 3 ($800k) were established for this purpose.

The Foundation distributed $1.4M to the Raine Medical Research Foundation for operating use, consisting of 90% of the Capital Distribution $1.1M, income from STP interest $119K, Fluctuation Capital interest $132k and dividend from DEXUS property Securities $98k. During the year the Foundation also received a $5,000 donation to establish the KY Wong Memorial Prize.

The Income and Expenditure Statement and Statement of Investments that follow show financial performance and position of the Foundation funds for the year ended 31 December 2016.

University Portfolio Asset Allocation

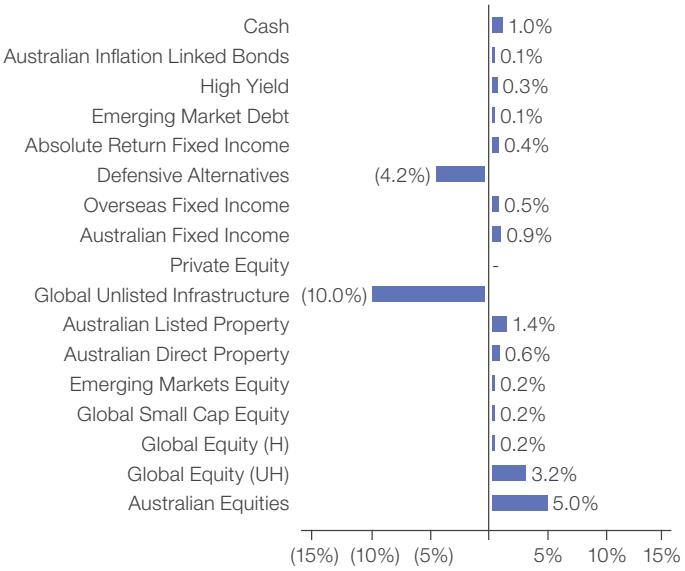
LONG TERM POOL (LTP) – STRATEGIC ASSET ALLOCATION

The LTP asset composition as at 31 December 2016 was held within the asset allocation ranges, except for underweight positions to Global Unlisted Infrastructure (-10%), Defensive Alternative (-4.2%) and actual holding of Australian Listed Property (+1%) due to AMP not having yet being transitioned to implemented investment solution.

Actual v Benchmark Portfolio Distribution (as per Investment Policy 2015)

	Strategic Asset Allocation	Benchmark	Actual
Growth	Australian Equities	35%	40%
	Global Equity (UH)	15%	18%
	Global Equity (H)	5%	5%
	Global Small Cap Equity	2%	2%
	Emerging Markets Equity	3%	3%
	Australian Direct Property	10%	11%
	Australian Listed Property	0%	1%
	Global Unlisted Infrastructure	10%	1%
	Private Equity	0%	0%
Defensive	Australian Fixed Income	5%	6%
	Overseas Fixed Income	0%	1%
	Defensive Alternatives	5%	1%
	Absolute Return Fixed Income	8%	8%
	Cash	2%	3%

Asset Class Deviation from Weighted Portfolio Benchmark



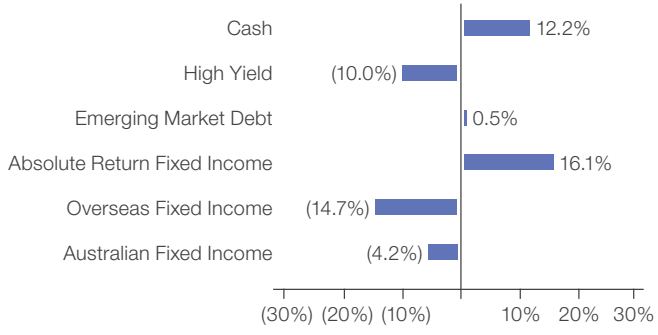
STRATEGIC ASSET ALLOCATION BENCHMARK – STP

The STP asset composition as at 31 December 2016 is currently held within the asset allocation ranges for all defensive assets, except for Absolute Return Fixed Income which is marginally above policy range IPS 2015.

Actual v Benchmark Portfolio Distribution (as per Investment Policy 2015)

	Strategic Asset Allocation	Benchmark	Actual
Defensive	Australian Fixed Income	25%	21%
	Overseas Fixed Income	25%	10%
	Absolute Return Fixed Income	15%	31%
	Emerging Market Debt	10%	10%
	High Yield	10%	0%
	Cash	15%	28%

Asset Class Deviation from Weighted Portfolio Benchmark



Raine Medical Research Foundation

Income and Expenditure for the year ended 31 December 2016

	Notes	2016 Actual $	2015 Actual $
INCOME			
Distribution from Raine Foundation		1,461,992	1,416,088
Other income:			
Funding retrieved from unspent grant		6,721	50,177
Management Fee (Bright Spark Raine Alliance)		25,000	
Total Income		1,493,713	1,466,265
EXPENDITURE			
Specific Activities:			
Raine Visiting Professors		63,690	49,233
Honorariums		8,160	21,598
Raine Research Prize and Travel Awards		306	6,500
Salary funding for Raine Study Scientific Directorship	1	65,000	65,000
Raine Priming Grants:			
2014 Grants			428,222
2015 Grants		425,000	425,000
2016 Grants		221,000	
Grants to Allied Institutions			
Other Expenses:			
Administration and Operating Expenses		68,936	23,780
Salary Expenses		275,654	193,624
TOTAL EXPENDITURE		**1,127,746**	**1,212,957**
NET OPERATING RESULT		**365,967**	**253,308**
Raine Medical Operating Funds:			
Opening Balance		2,839,270	2,585,962
Net Funds from Operating Activities		365,967	253,308
Closing balance as at the end of the year		**3,205,236**	**2,839,270**

Notes:

1 Committee meeting minutes 01/05/2014 approved $65k for further five year until 2019.

Raine Medical Research Foundation

Statement of Investments for the year ended 31 December 2016

	Notes	2016 Actual $	2015 Actual $
INVESTMENTS			
SHORT-TERM POOL	1		
Raine Medical Research Fund		3,205,236	2,839,270
Raine Foundation Fluctuation Capital Fund		3,464,878	4,264,878
Raine Foundation Capital Account 2		3,877,140	-
Raine Medical Research Fund I&E Account 3	4	800,000	-
Clinical Research Fellowships	5	284,965	229,162
Strachan Bequest		16,900	17,568
KY Wong Memorial Prize		5,044	-
TOTAL SHORT-TERM POOL		11,654,163	7,350,878
LONG TERM POOL	1		
Raine Foundation Capital Fund		24,003,029	26,888,300
Strachan Bequest		76,806	74,424
Other Bequests		50,773	50,773
TOTAL LONG-TERM POOL		24,130,608	27,013,498
TOTAL POOL INVESTMENTS		35,784,772	**34,364,375**
24/95 Monash Avenue (Hollywood) net carrying value		271,725	275,026
Dexus Property Securities	2	2,172,196	1,693,500
Total Other Investments		**2,443,921**	**1,968,526**
Total Investments at Carrying Value		38,228,693	**36,332,902**
Market Value – Other Investments			
24/95 Monash Avenue (Hollywood)	3	536,500	580,000
Dexus Property Securities	2	2,172,196	1,693,500
Artwork			
Total Other Investments – Market Value		2,708,696	**2,273,500**
Total Investments at Market Value		**38,493,468**	**36,637,875**

Notes:

1 2016 distribution rate : LTP at 8.20% and STP at 3.48%.

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 31/12/2016. The declined in value is aligned with current property market pricing.

4 Funds transferred from Fluctuation Capital Fund for the purpose of capping Fluctuation Capital Fund at 10%.

5 Interest earned on accrued funds (2012-2016).

Raine Medical Research Foundation

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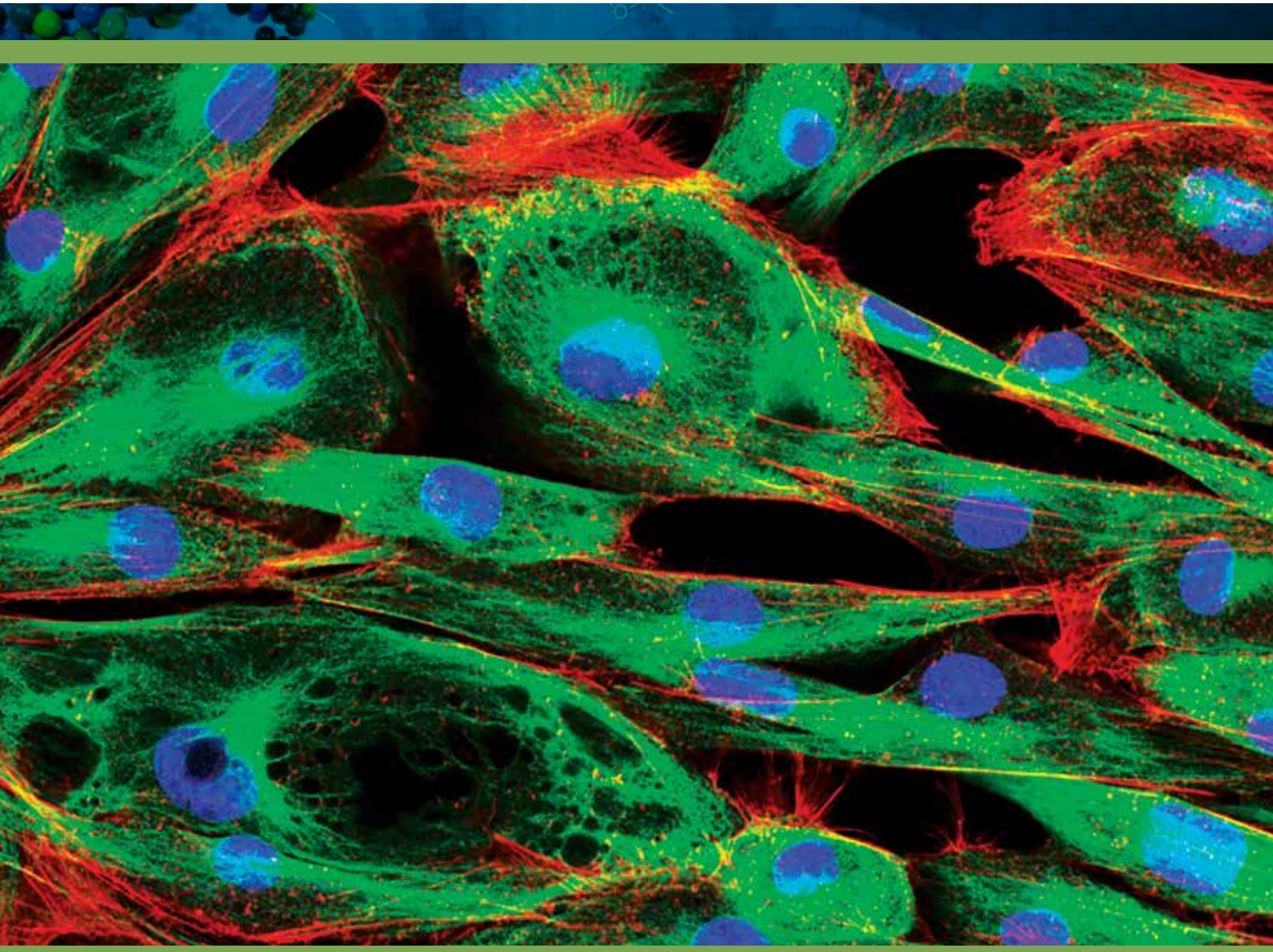
HEALY
MEDICAL RESEARCH FOUNDATION



Healy Medical Research Foundation

annual report

2016

HEALY
MEDICAL RESEARCH FOUNDATION

annual report 2016

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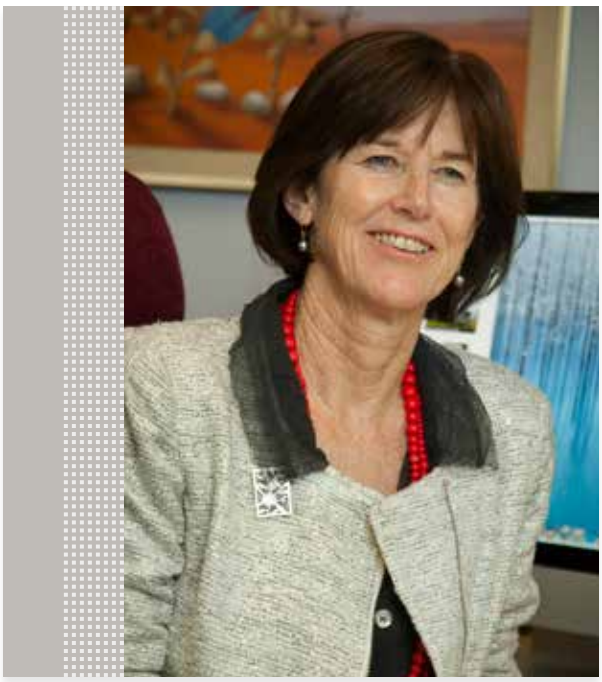
Chair's Address



It is my pleasure to present the research activities and funding position of the Healy Medical Research Foundation for 2016.

Established in 1970 through a generous bequest to The University of Western Australia by the late Patrick Burselum and Mary Estelle Healy, the Healy Medical Research Foundation is governed by a Deed of Trust, based on similar principles to the Raine Medical Research Foundation. It is administered by the same Research Committee and shares the same philosophy and commitment to medical research.

Mission Statement

In accordance with the terms of the Deed of Trust, income from the Capital Fund is intended for the purpose of: *seeking, diagnosing and investigating the nature, origin and causes of diseases in human beings and the prevention, cure, alleviation and combating of such diseases*.

Healy Research Collaboration Awards

The Healy Medical Research Foundation has a long history of supporting and advancing the careers of young investigators. In 2012 the Foundation introduced Research Collaboration Awards as a further commitment in support of early-career scientists. Since that time Healy has contributed in excess of $120,000 to encourage our young scientists to partner with national and international colleagues to further their research. These Awards are already showing significant benefits including: providing the opportunity for our early career researchers to visit top international research groups in their field; maximising knowledge and skill exchange; strengthening collaborative networks; submission of joint grants; co-authoring of published manuscripts; and achieving research outcomes that will progress to clinical translation. The Universities visited by our young scientists include Max von Pettenkofer Institut, LMU Muenchen, Germany and Texas A&M University, USA. The reports from their collaborative research and travel are on pages 6-7.

It is clear from the many success stories of young researchers supported by this program that the Research Collaboration Awards provide a valuable stepping stone to national and international success, through the facilitation of long-term collaboration and the promotion of research excellence.

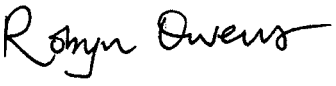
Financial Statement

The Healy Foundation has a sound capital base of approximately $1.4m and is well-placed to continue its annual commitment to medical research. It is pleasing to report that at this stage the annual distribution of funds to the Operational Account is sufficient to meet the continuation of our research activities and associated costs. This decision taken by the Raine Board will enable the consolidation and growth of the Healy Capital Fund.

I would like to take this opportunity to record my thanks and appreciation to the University office of Treasury and Investments for its high standard of financial management of the Healy portfolio in the administration of the Healy Foundation.

Research Committee

In concluding this address, I would also like to thank the members of our governing Board (Research Committee) for their commitment and willingness to oversee the research activities of the Foundation. We are fortunate to have a group of dedicated scientists, physicians and clinicians who bring a wealth of research knowledge and experience in the management of the Healy Medical Research Foundation. I look forward to working together to achieve another successful year in 2017.



Robyn Owens
UWA Deputy Vice-Chancellor (Research)
Chair, Research Committee

Research Committee

The Healy Medical Research Foundation is governed by a Committee of Senate, constituted in accordance with the requirements of the Deed of Trust. The 2016 Research Committee consisted of the following members:

Professor Robyn Owens
UWA 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 Garry Prendiville
Honorary Financial Consultant

Ms Lyn Ellis
Director

Dr Amanda Cleaver
Project Manager

Healy Research Collaboration Awards

The Research Committee introduced the Healy Research Collaboration Awards in 2012 to encourage early-career medical research scientists to establish and develop national and international research collaborations.

In 2017, two Awards were allocated with a total funding allocation of $19,474.

The Awards aim to increase opportunities for collaborative publications, joint grant submissions, sharing and advancement of research/clinical skills and industry linkages.

2016 Healy Research Collaboration Awards

	Chief Investigator	Project Title	Collaborating Institution
	Dr Aleksandra Debowski School of Biomedical Sciences, The University of Western Australia	Development of an inducible Helicobacter pylori cag-T4SS system for in vitro and in vivo studies	Max von Pettenkofer Institut, LMU Muenchen, Germany
	Dr Jessica Terrill School of Chemistry and Biochemistry, The University of Western Australia	Investigating the role of taurine in disease pathology of Duchenne Muscular Dystrophy (DMD) using the GRMD model	Texas A&M University, USA

2017 Healy Research Collaboration Awards

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

Healy Research Collaboration Awards

PROJECT TITLE

Development of an inducible Helicobacter pylori cag-T4SS system for in vitro and in vivo studies

INVESTIGATORS

Dr Aleksandra Debowski (Chief Investigator)
Professor Dr Rainer Haas (Collaborating Partner)

SCHOOL/INSTITUTE/CENTRE

School of Biomedical Sciences, The University of Western Australia
Max von Pettenkofer Institut, LMU Muenchen, Germany (Collaborating Institution)

SUMMARY

Chronic H. pylori infection represents the major cause of gastroduodenal pathologies including gastric cancer. The Type IV secretion system (T4SS) injects CagA, a toxin produced by H. pylori, into gastric cells and has been implicated in carcinogenesis. The Mongolian gerbil model recapitulates gastroduodenal diseases caused by H. pylori and is well suited to studying H. pylori-induced pathologies. This study aimed to use the synergistic effect of combining the gerbil infection model with a H. pylori inducible gene regulatory system (developed at UWA) to elucidate the role that cag-T4SS has in the development and progression of gastric cancer and furthermore investigate whether carcinogenesis can be reversed or halted by inhibiting specific bacterial products.

My role was to oversee the construction of several conditional H. pylori mutants using an inducible genetic system. I also travelled to Germany to establish the experimental protocol for using the inducible system in the Mongolian gerbil infection model together with team members of the Haas laboratory.

OUTCOMES

Collaboration

The collaboration between Professor Haas and my research has resulted in the establishment of important working parameters for the inducible gene regulatory system in the Gerbil infection model, such as identifying the inducer dosing range that can effectively regulate H. pylori gene expression in the Gerbil stomach and the time required to alter gene expression from ON to OFF.

This collaborative work resulted in the successful generation of unique H. pylori strains that can be specifically controlled, by way of a small molecule inducer, in their ability to inject CagA toxin into host epithelial cells using the T4SS. Implemented in the gerbil, these strains serve as a unique tool for studying the temporal requirements of specific cag-T4SS genes in carcinogenesis and the specific roles different immune effectors play in driving H. pylori pathogenesis. More importantly, these strains also enable the investigation into whether gastric cancer caused by H. pylori can be reversed or halted by inhibiting specific bacterial products.

Dissemination of knowledge and expertise

Collaboration and personal exchange between our two groups facilitated the exchange of respective expertise in microbial genetics and different infection models. I transferred technology that was developed at UWA and oversaw its successful application in both in vitro and in vivo infection models in the Haas laboratory. I acquired ‘in house’ knowledge regarding cell culture infection models, which are invaluable skills for studying additional H. pylori virulence targets of interest and in assaying cag-T4SS function and activity.

One of the core outcomes of the Award was in the area of research training. As part of the exchange, the supervision and mentoring of a PhD student dedicated to the project was undertaken, allowing me to pass on the skills and knowledge I had acquired. It also allowed me to learn valuable supervision skills. The exchange also facilitated scientific discussion with other postdoctoral fellows and laboratory heads at the Max von Pettenkofer Institut, allowing me to develop important network connections within the scientific community.

PROJECT TITLE

Investigating the role of taurine in disease pathology of Duchenne Muscular Dystrophy (DMD) using the GRMD model

INVESTIGATORS

Dr Jessica Terrill (Chief Investigator)
Professor Joe Kornegay (Collaborating Partner)

SCHOOL/INSTITUTE/CENTRE

School of Chemistry and Biochemistry, The University of Western Australia
Texas A&M University, USA (Collaborating Institution)

SUMMARY

Duchenne Muscular Dystrophy (DMD) is a devastating disease with no cure. My research has focused on preclinical drug research for the disease using the mdx mouse model. A compound of interest, taurine, is highly effective in treating the murine condition, however the phenotype of the mdx mouse is mild. This Award has allowed me to continue my research using the GRMD dog model, the phenotype of which closely resembles that of DMD.

By collaborating with Joe Kornegay at Texas A&M University, USA, I have furthered my research in the use of taurine in DMD. The research facilitated by this Award gained preliminary data for the potential effectiveness of the amino acid taurine in treating muse from the GRMD model, and established a role of inflammation-derived oxidants in the pathology. This project continues, with several grants submitted to advance the research performed, which plan to perform a formal pre-clinical trial of taurine in GRMD dogs. This research is an essential step before we advance our research to clinical trials in DMD boys.

OUTCOMES

Collaboration

My research has focused on the use of the mdx model for Duchenne Muscular Dystrophy (DMD) to identify cellular mechanisms of pathology and potential therapeutic interventions for this fatal disease. However the mdx mouse is not an ideal model (with a very mild phenotype), and the preferred model, the GRMD dog model, that more closely resembles the human condition, is not readily available. This Award allowed me to travel to Texas A&M University, to establish a collaboration with Professor Joe Kornegay, an expert in the use of the GRMD model who has established a colony. Through this collaboration, we have planned grant applications, received archival samples that have been used to generate preliminary data for these applications, and I have gained expertise in pre-clinical research using this model. Additionally, we have firmly established a role of inflammation-derived oxidants in the pathology of GRMD muscle, and these data form the basis of much of our continuing research.

Dissemination of knowledge and expertise

This Award allowed me to develop essential skills for working with the GRMD model for DMD, to facilitate research in this model essential to the further assessment and development of the use of taurine as a treatment for DMD. Also, it allowed advancement of our knowledge of the role of inflammation-derived oxidants in the pathology of DMD.

Publications

This Collaborative Award has resulted in the publication of preliminary data into the role of inflammation-derived oxidants in the pathology of GRMD muscle, and the potential use of the amino acid taurine as a therapeutic intervention.

Terrill JR, Duong MN, Turner R, Le Guiner C, Boyatzis A, Kettle AJ, Grounds MD & Arthur PG (2016). Levels of inflammation and oxidative stress, and a role for taurine in dystropathology of the Golden Retriever Muscular Dystrophy dog model for Duchenne Muscular Dystrophy. Redox Biology 9, 276-286.

Grants

Research performed from this collaboration formed the basis for a Fellowship application and a Grant application submitted to the French Muscular Dystrophy Association (AFM-Téléthon), entitled “Functional readouts of neutrophil mediated oxidative stress as biomarkers in plasma and urine from the Golden Retriever Muscular Dystrophy dog model for Duchenne Muscular Dystrophy”. Results of these applications are due for release in 2017.

Financial Statement

P B HEALY MEDICAL RESEARCH BEQUEST
Statement for year ended 31 December 2016

	Notes	2016 Actual $	2015 Actual $
Capital Fund			
Opening Balance		1,352,847	1,294,838
LTP Distributions		110,934	58,009
		1,463,781	1,352,847
Less:			
Senate Policy Distributions to I&E	1		-
Closing Balance		1,463,781	1,352,847
Income & Expenditure			
Opening Balance		239,500	301,134
Senate Policy Distributions from Capital		-	-
STP Distributions		8,760	14,232
Total Income		248,260	315,366
Less Expenditure:			
Healy Travel Awards		(18,400)	(41,626)
Operating Expense		(23,070)	(34,240)
Closing Balance		206,790	239,500

Notes:
1 2015 – Agreed with committee in meeting held on the 12 November 2015 to suppress the 5% distribution from capital.

HEALY
MEDICAL RESEARCH FOUNDATION

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