Auckland Medical Research Foundation

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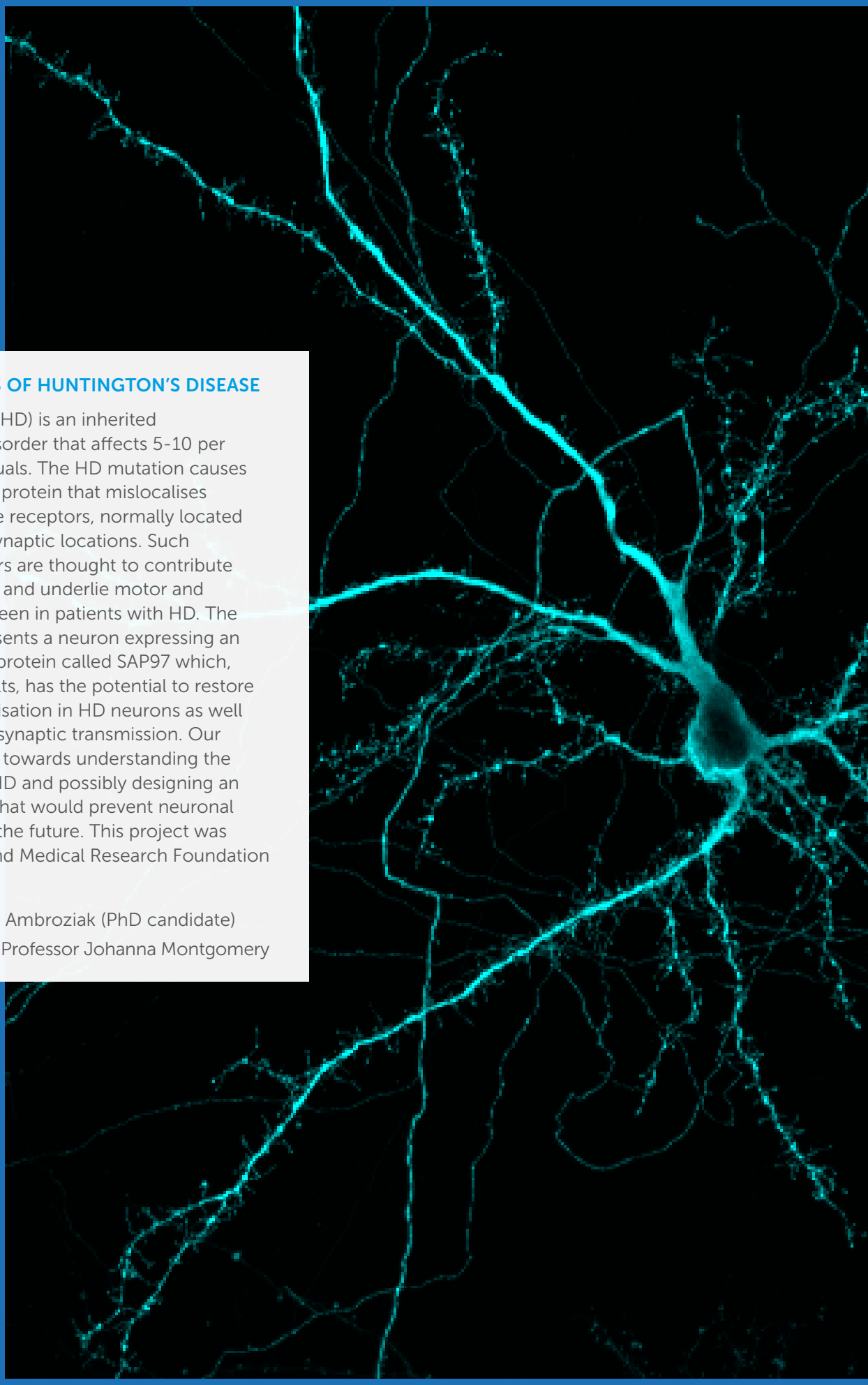
ANNUAL REPORT 2017

SUPPORTING MEDICAL RESEARCH FOR OVER *60 years*



THE SYNAPTIC BASIS OF HUNTINGTON'S DISEASE

Huntington's disease (HD) is an inherited neurodegenerative disorder that affects 5-10 per every 100,000 individuals. The HD mutation causes production of a faulty protein that mislocalises NMDA-type glutamate receptors, normally located at synapses, to non-synaptic locations. Such non-synaptic receptors are thought to contribute to the loss of neurons and underlie motor and cognitive symptoms seen in patients with HD. The image attached represents a neuron expressing an isoform of a synaptic protein called SAP97 which, according to our results, has the potential to restore normal receptor localisation in HD neurons as well as help retain normal synaptic transmission. Our findings provide clues towards understanding the pathomechanism of HD and possibly designing an effective HD therapy that would prevent neuronal loss in HD patients in the future. This project was funded by the Auckland Medical Research Foundation doctoral scholarship.

Researcher: Wojciech Ambroziak (PhD candidate)
Supervisor: Associate Professor Johanna Montgomery

AMRF Directorate

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REGISTERED OFFICE

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Charity Commission Registration Number: CC22674

President's Report & Medical Committee Report

YEAR ENDED 31 DECEMBER 2017

Jeff Todd

President's Report

The 2017 year brought with it another very sound financial performance by the AMRF and, equally, one of our stronger funding years with over $4 million awarded to medical research in the greater Auckland region.

Over the last five years, our Foundation has committed an average of $3.5 million of funding annually and we acknowledge and thank our generous supporters who enable this vital funding of research to continue to increase.

Our founding mission of funding high-quality medical research to provide genuine advances in medical and health sciences remains as rock solid as ever and, this year, we were delighted to welcome new major supporters including the Hugo Charitable Trust which established a Permanent Named Capital Fund with us.

A very significant bequest was received from the estate of Dr Shirley Tonkin, a much revered medical professional who, received funding from the AMRF during her career. It is so heartening to have the people we have funded give back to support our current researchers and their life-changing work of the future.

2017 was also a year of change as we bid farewell to Kim McWilliams, our Executive Director, who provided seven years of outstanding leadership to the AMRF team and welcomed Sue Brewster as our new Executive Director. A tribute to Kim is included in this report and on behalf of the Board, I thank Kim, Sue and the team at AMRF for their professionalism and tireless work which ensures the Foundation's operations run smoothly.

As this report goes to print, news of my retirement has been announced. After nearly 16 years as a Trustee and the last eight of those as President, it is time for me to step down. It has been a great privilege to serve the AMRF.

It is with mixed feelings that I write my final President's Report but with sincere gratitude that I leave the AMRF presidency role in the very capable hands of Richard Taylor. Richard has been a valued member of the AMRF Board for the last 14 years and is a senior partner of TGT Legal with extensive legal and corporate governance experience.

For this last time, I extend my grateful thanks to the trustees, committee chairs and members for their constant and generous support with gifts of time, experience and expertise. In particular, I thank the Board's Medical Committee, chaired by Professor Peter Browett, without whose work in reviewing funding applications, the AMRF could not fulfil its mission.

Finally, my heartfelt thanks to all our members and donors who have so generously and consistently ensured that AMRF funds important advances in medical research for future generations.

Jeff Todd
President

Prof Peter Browett

Medical Committee Report

The Medical Committee has been busy this year, assessing 186 grant applications over the course of the year split between five grant rounds. The AMRF successfully funded 60 grants at a total cost of $4.023 million – a success rate of 32.8% - which although is high in the arena of medical and health research funding, still means that many worthy applications are unable to be supported.

Within our funded grants the AMRF has continued to support researchers and clinicians in all stages of their careers. A particular highlight from this year was the awarding of the Douglas Goodfellow Repatriation Fellowship to bring back to New Zealand Associate Professor Sarah Hetrick, an exceptional clinical psychologist and researcher in the field of youth mental health. Another highlight was the continued relationship with the Kelliher Charitable Trust which provided the 2017 Kelliher Charitable Trust Emerging Researcher Start-up Awards for our top Postdoctoral Fellow and Doctoral Scholar from the previous year.

The awarding of these grants wouldn't be possible without the generous gifting of time and wide-ranging expertise of our Medical Committee who ensure the robust assessment of all the applications and provide recommendations to the AMRF Board of Trustees. In 2017 we welcomed three new members to our Committee: Associate Professor Anthony Phillips, School of Biological Sciences and the Department of Surgery, University of Auckland; Associate Professor Greg O'Grady Department of Surgery, University of Auckland, Auckland Bioengineering Institute and Auckland City Hospital; and Dr Justin Dean, Department of Physiology, University of Auckland. We also farewelled two exceptional members of our Committee: Associate Professor Nigel Birch and Dr Sue McGlashan, and we thank them both for their hard work and wish them well.

On behalf of the Medical Committee I would like to thank the AMRF team, led by Kim McWilliams and then by Sue Brewster in the latter part of the year, for the administration and background work that goes into our funding processes. In particular my thanks go to Dr Hannah Gibbons (Research Programme Manager) for her stewardship of the Grants Portfolio. I would also like to thank our Board of Trustees, under the superb Presidency of Jeff Todd, for their hard work and belief that funding the highest quality medical research will improve the health of New Zealanders and our loyal supporters who are a vital part of our AMRF mission.

Peter Browett
Chair, Medical Committee
Professor of Pathology,
Department of Molecular Medicine and Pathology,
University of Auckland

Thank you for joining us in the AMRF mission

This year and every year's achievements are attributable to the world-class researchers who receive our funding and work so tirelessly to create genuine advances in health science and medicine.

Their successes would not be possible without you, our loyal and generous supporters. Your support is the driving force behind our Foundation's vision to improve the health and quality of life for all New Zealanders. Gifts from you continue to transform people's lives.

In 2017, Ursula Elliott shared her story about her daughter, Kiriana's life-changing diagnosis of leukaemia and how thankful they all were for the care and treatment provided by Kiriana's specialist, Dr Andrew Wood.

Dr Wood works at Starship Hospital; is a Senior Research Fellow at the University of Auckland's Department of Molecular Medicine & Pathology and, along with his team, is undertaking vital research into childhood leukaemia treatments.

Andrew was awarded one of AMRF's Repatriation Fellowships to bring him back home after working in Philadelphia for many years and, in his words, "The AMRF Douglas Goodfellow Repatriation Fellowship Award has provided the critical start-up funds for establishing my position at the University of Auckland and the reputation of the AMRF review process is instrumental in helping to attract other research funding needed to carry on this project."

Kiriana during her treatment for leukaemia.

On 28th May 2017, Kiriana returned home to her family and is in full remission.

All of our operating and administration expenses are paid for by a separate charitable fund so **100% of all donations**, bequests, legacies and income from investments **directly** supports medical research.

AMRF Success Stories

THE CHALLENGES OF LIFE IN THE WOMB

DR CHRISTOPHER LEAR

"Simply knowing there are people personally willing to support researchers like me and our work makes us very grateful."

Recent PhD graduate Dr Christopher Lear was inspired by his supervisors Professors Laura Bennet and Alistair Gunn's work and the life changing benefit that it has had on the clinical care of newborn babies. He wants his research to answer questions that are helpful to the doctors treating sick newborns every day.

He says, "My elder sister has dyspraxia, a developmental disorder, and so the chance to contribute towards understanding the origins of this and other types of neurodevelopmental disability meant a great deal to me on a personal level."

With his prestigious **AMRF Barbara Basham Doctoral Scholarship**, Chris's PhD research has updated our understanding of what controls fetal heart rate during birth. "Heart rate is the only easily available way clinicians are able to determine whether a baby is coping well with the stress of labour, or not, and so my goal is to have the international labour guidelines updated with these concepts."

SOCIAL AND ECONOMIC COSTS OF HIGH BLOOD SUGAR IN NEWBORN BABIES

DR MATT GLASGOW

"As a father and premature baby myself, I have a personal interest in medical research that relates to improving life-long health by optimising the health of mothers and babies during pregnancy and immediately after birth."

Dr Matt Glasgow is a medically-trained doctor, recently working in health informatics where he develops computer applications that help other doctors and clinicians with clinical decision making.

Now, with his Douglas Goodfellow Medical Research Fellowship from the AMRF, he has been able to take time out from the workforce to pursue his PhD research full time.

Matt's fellowship will examine the long-term outcomes and social and economic costs of neonatal hypoglycaemia (NH), high blood sugars that can affect newborn babies shortly after birth. By determining the potential costs and cost savings of using dextrose gel to prevent NH in newborn babies at risk, he hopes to reduce the impact it has on babies as they grow up, and their families.

Matt says, "We investigate the uncertainties and gaps in knowledge associated with NH. This is a common condition that affects up to 50% of newborn babies in some at-risk groups (preterm babies, babies that are born large or small or to mothers with diabetes), and which can have severe consequences like epilepsy, cerebral palsy, or learning difficulties that affect the infant for the rest of their life.

"Funding provided by the AMRF is nothing short of essential to allow me to do this work."

PERSONALISED MEDICINE FOR CANCER PATIENTS

DR SANDAR TIN TIN

"New Zealanders can get better lung cancer treatment when their genetic subtype is known. If we can target their therapy, we can often improve their chances of survival."

After medical studies, residency and lecturing in her native Myanmar, Dr Sandar Tin Tin came to New Zealand to pursue her Masters and PhD in public health and epidemiology.

She is now focussed on improving treatments for lung, breast and endometrial cancer for patients in New Zealand through her **AMRF Postdoctoral Fellowship** supported by a **Kelliher Charitable Trust Emerging Research Start-up Award**.

Her work on gene mutation testing in patients with lung cancer is one of the very few population-based studies in this part of the world and fills an important gap in knowledge of the prevalence, demographic profiles and clinical outcomes of genetically-defined subtypes of lung cancer in New Zealand. She found that a considerable proportion of patients who did not get tested for mutation could in fact carry one, but went untested by current cancer treatment protocols and so missed the opportunity to be treated more appropriately.

Sandar says, "It will be so important to lung cancer patients when we develop a predictive tool for their mutation status. This tool will improve their access to appropriate treatment for their type of cancer and will therefore improve their survival."

She hopes to expand the models and tools she has developed to improve treatment for breast and endometrial cancer patients, too.

A SMARTPHONE APP TO REDUCE TEEN SELF HARM

ASSOCIATE PROFESSOR SARAH HETRICK

"These high tech tools are a small but important part of bigger programmes and efforts to prevent self-harm. Since they're developed by and with youth, we know there is likely to be high uptake and use by them and their peers."

A/Prof Sarah Hetrick has been registered as a clinical psychologist since 2007, gaining significant clinical experience within the youth mental health sector in Australia. Upon receiving her **Douglas Goodfellow Repatriation Fellowship** in late 2017, she has returned to New Zealand with her expertise and experience in mental health research methods and design.

Sarah aims to develop health research programmes relevant to understanding youth mental health in the New Zealand context, using high quality research to identify relevant, effective and scalable interventions for this population of vulnerable young people.

She says, "Given that most young people in New Zealand own a smart phone there is an enormous potential to make psychological self-care tools accessible when and where needed. Our app is specifically aimed to help adolescents manage distress and urges to self-harm, and ultimately to prevent episodes of self-harm.

"Importantly, we're using a co-design process with young people, including interviews about their needs, and design workshops where young people will develop the content, look and feel, format, functionality for the app.

"This fellowship is so important because it has allowed me to come home and use my skills to help youth at-risk here."

PERSONALISED MEDICINE THROUGH HEART IMAGING

Dr Avan Suinesiaputra and Professor Alistair Young, from the Department of Anatomy and Medical Imaging, University of Auckland, create 3D models of beating hearts to reveal major differences in the size of the left ventricle during its blood-pumping cycle after heart attack, or myocardial infarction (MI). As seen here, the heart can no longer contract efficiently in people who suffered a heart attack, which means that the heart cannot pump blood around the body as well as it should.

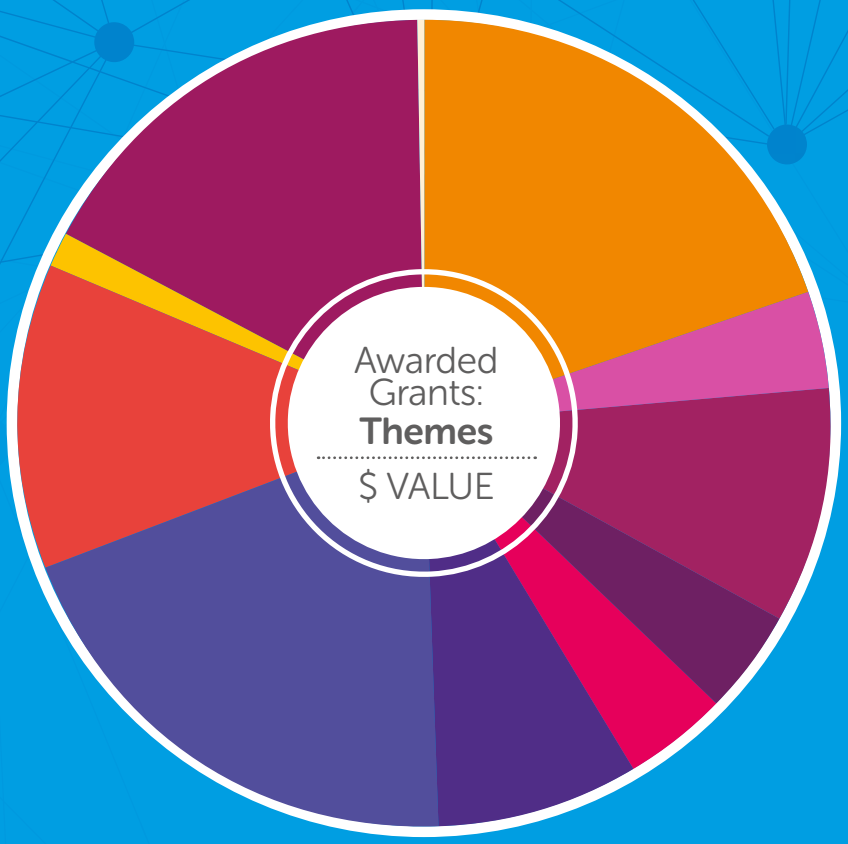
By using MRI and mathematical modelling to study the shape, size and function of the beating heart, this research shows the differences between healthy hearts and those that have suffered heart attacks. If this non-invasive technique becomes an established, routinely-used tool, doctors can use it to decide which heart attack patients should receive invasive surgical therapies that will benefit them, versus those who wouldn't see improvement.

The benefits will include saving money, time and, most importantly, patients' lives.

HEALTHY PATIENTS

MI PATIENTS

Grants Awarded



2017 AWARDED GRANTS THEMES : 60 GRANTS AWARDED TOTALLING $4,023,459

- Cancer (9) | $795,206 19.76%
- Cardiovascular Science (2) | $156,456 3.89%
- Cellular and Molecular Biology (4) | $382,994 9.52%
- Endocrinology, Metabolism and Nutrition (6) | $171,394 4.26%
- Infection and Immunity (2) | $163,000 4.05%
- Musculo-skeletal Science (3) | $318,947 7.93%
- Neuroscience (13) | $806,484 20.04%
- Other (7) | $489,774 12.17%
- Population Health (5) | $46,608 1.16%
- Reproduction, Development, Maternal and Newborn Health (8) | $689,902 17.15%
- Sensory Sciences (1) | $2,694 0.07%

$ Value each theme **% Total expenditure**
(n) Number of grants

Grants Awarded

PROJECTS

Improving Stenting Outcome ($153,456 - 2 years) 1117003

Dr Susann Beier, Prof John Ormiston, Prof Alistair Young, A/Prof Mark Webster, A/Prof Brett Cowan
Dept. of Anatomy with Medical Imaging, University of Auckland

Heart disease is the most common cause of death in New Zealand. To date, 169,000 New Zealanders are diagnosed with the disease, and every 90 minutes a person dies of its consequences. This fatal damage to the blood vessels around the heart is caused over time and risk factors include a poor diet, smoking, and a family history of heart disease. Stenting treatment is common, but more than 10,000 patients experience complications and 3,000 die suddenly from stent failure. The reason why treatment fails in some patients is because the current generic method is not suitable for every individual. Differences in shape and flow of the patient's blood vessel influence the success or failure of the treatment. We want to develop a personalised treatment, where individual differences are accounted for. We can achieve this by analysing the data of more than 600 patients. The individual differences can be explored by using a combination of sophisticated super-computer simulations, 3D-printing and radiographic imaging. This allows the testing of different treatment strategies for individuals in the lab, and can help to prevent complications and sudden death rates.

FUNDED BY: Bruce Cole Fund

LIN28B and Wilm's tumour ($159,999 – 1.5 years) 1117018

A/Prof Alan Davidson, Dr Zhenshen Peng
Dept. of Molecular Medicine & Pathology, University of Auckland

Wilms' tumour is the most common form of paediatric kidney cancer, affecting 1:10,000 children, and results from inappropriate growth and persistence of embryonic renal progenitors. While advances in treatment have enhanced overall survival, recurrence of Wilms' tumor is still a problem and there is a continuing need to understand the underlying oncogenic drivers. One such driver of Wilms' tumorigenesis that has recently been discovered is the RNA binding protein LIN28B, which is overexpressed in ~25% of high-risk Wilms' tumours. Understanding the effect of oncogenes such as LIN28B has been hampered by a lack of a physiologically relevant model to study cancer progression in the laboratory. Towards this goal, our group has pioneered a novel and simple protocol to generate fetal kidney tissue (organoids) from human induced pluripotent stem cells (iPSCs). In combination with CRISPR/Cas9 gene editing methods, this system provides an innovative new platform for modelling kidney diseases. Here, we propose generating kidney organoids from iPSCs that have been engineered to inducibly overexpress LIN28B with the goal of generating the first in vitro model of Wilms' tumour. This model will provide a novel platform to better understand the molecular basis of the disease and will be useful in the future as a tool to find biomarkers (to help with risk stratification) and to test new chemotherapy treatments.

FUNDED BY: Sir Lewis Ross Fund

Prognostic model for breast cancer ($68,223 – 1 year) 1117011

Prof Mark Elwood, Dr Sandar Tin Tin, A/Prof Vernon Harvey, A/Prof Roger Marshall, A/Prof Ian Campbell
Dept. of Epidemiology and Biostatistics, University of Auckland

This project continues our work funded by AMRF in 2016 (1 year) and will develop and assess methods to predict future outcome for women treated for breast cancer. These models will use data collected routinely in current clinical practice, and will be applicable to individual patients, particularly to identify those with likely very good or very poor outcomes. They will be helpful to doctors and patients in deciding on treatment options. This work is made possible by the information available in the high quality Auckland and Waikato clinical breast cancer registries, provided by over 14,000 women with breast cancer diagnosed since 2000. We will develop the first New Zealand-specific model to predict breast cancer outcomes, and compare its performance with existing models that have all been developed overseas.

FUNDED BY: Hugh Green Fund

Exploiting brain mechanisms to protect from preterm brain injury? ($159,263 - 2 years) 1117009

A/Prof Mhoyra Fraser
Dept. of Physiology, University of Auckland

Many preterm infants develop brain injury around the time of birth, with a high risk of life-long disability. Currently, we have no effective way of preventing disability. Our preliminary findings using a well-established animal model of preterm brain injury suggest for the first time that therapeutic manipulation of a critical endogenous neuroprotective anti-inflammatory mechanism can reduce damage to oligodendrocytes, the myelin-producing cells of the CNS. These findings suggest that it is possible to preserve myelination by supporting natural pathways in the brain. However, it remains to be proved whether this therapy will have a sustainable effect long-term. Thus, to replicate and extend our findings we will robustly test the long-term effects of this therapy and determine whether it improves survival of oligodendrocytes, improve myelination and reduce inflammation.

STRIDER NZAus Childhood Outcome Study ($75,061 - 2 years) 1117001

Dr Katie Groom, Prof Lesley McCowan, Prof Frank Bloomfield, Dr Christopher McKinlay
Dept. of Obstetrics & Gynaecology, University of Auckland

Being born too small poses significant risks of handicap and disease throughout a life time. There are no treatments available to improve growth before birth and so the only option is early delivery which adds further disadvantage to long

term health. The drug sildenafil may be the first ever in-utero therapy for fetal growth restriction and it is currently being investigated in the STRIDER NZAus clinical trial led by researchers from the University of Auckland. Sildenafil is being given to mothers with pregnancies affected by severe fetal growth restriction across New Zealand and Australia and compared to a similar group of mothers who receive a placebo tablet. The STRIDER NZAus Childhood Outcome Study will follow the surviving babies born to mothers in this clinical trial and will assess the development of these children at the age of 2-3 years. The study will assess whether the use of sildenafil in pregnancy improves the neurological and emotional-behavioural development of these children as well as effects on their cardio-metabolic, respiratory and general health. This study will provide highly valuable information on benefit (and/or harm) as a consequence of antenatal sildenafil therapy for the treatment of fetal growth restriction.

CO-FUNDED WITH: The Neurological Foundation of New Zealand

NEUROLOGICAL FOUNDATION OF NEW ZEALAND
PROGRESS THROUGH RESEARCH

Novel biomarker for cognitive impairments in PD ($159,294 - 2 years) 1117008

A/Prof Jian Guan, Prof Tim Anderson, Prof John Dalrymple-Alford, Dr Toni Pitcher

Dept. of Pharmacology & Clinical Pharmacology, University of Auckland

Insulin-like growth factor-1(IGF-1) is a hormone and plays a critical role in cognition. A large proportion of Parkinson disease (PD) patients develop mild cognitive impairment (MCI) in part due to poor IGF-1 function. PD with MCI has a 7-fold increased risk of developing dementia compared to those with normal cognition. Parkinson's dementia is recognised as a primary problem affecting patient and carer well-being and is a serious socio-economic issue worldwide. Earlier detection of MCI is critical for initiating effective interventions to delay the onset and slow-down progress of MCI. However there is no, yet an urgent need for, a biomarker to monitor IGF-1 function in order to identify individuals with high-risk to develop MCI and to track cognitive status. Our pilot trial suggested that the increase of plasma cyclic Glycine-Proline (cGP), a fragment of IGF-1 reflects the cognitive status prior to MCI in old people and the reduction of cGP links to PD patients with MCI. We speculate that the changes of plasma cGP may fulfil the role as the biomarker. We propose to evaluate differences in plasma cGP of PD patients with clinically defined normal cognition, MCI and dementia to assess the potential role of cGP as a marker of cognitive function in PD.

FUNDED BY: Anonymous Donor

Lipopeptides to treat neurological disease ($158,507– 2 years) 1117016

Dr Paul Harris, Dr Simon O'Carroll, Dr Sung Yan, Dist. Prof Margaret Brimble

School of Biological Sciences, University of Auckland

Neurological diseases affect almost one in six New Zealanders and encompasses a whole host of disorders including stroke, migraine, multiple sclerosis, spinal cord injury and epilepsy. Stroke currently ranks second after heart disease, and is the biggest cause of long-term disability in NZ. The treatment options for these diseases are very much limited and curing people is near impossible. Using medicinal chemistry and neurobiology we will create molecules that can act precisely at the site of injury or chronic disease and block the cellular signals that are responsible for progression of the disease. This builds on our previous work, where we have identified a peptide (chain of amino acids) capable of blocking cellular signals that would otherwise lead to inflammation, cell death and propagation of the injury – but these molecules were not stable enough to be used as a therapy. In this research we will construct new molecules that will be long-lasting and can be used to treat conditions of the central nervous system and neurodegenerative disease.

DNA-PK inhibitors ($159,981– 2 years) 1117020

A/Prof Michael Hay, Prof William Wilson, Ms Rosanna Jackson, Dr Yongchuan Gu

Auckland Cancer Society Research Centre, University of Auckland

Cancer cells use DNA repair mechanisms to escape the full effects of cytotoxic chemotherapy and radiotherapy. DNA-dependent Protein Kinase (DNA-PK) plays a crucial role in repairing DNA damage caused by radiotherapy and some chemotherapy drugs. We are designing new, selective inhibitors of this enzyme and combining these with a prodrug strategy that delivers the drugs selectively to tumours. It is important to evaluate how selective these new drugs are for DNA-PK, and how well the prodrugs deliver the drugs to tumours. We will compare existing antibody-based methods with new quantitative mass spectrometry methods to detect DNA-PK inhibition in both cells and tissues. The best method will be used to determine the selectivity of a DNA-PK inhibitor and the tumour delivery of the corresponding prodrug. Validation of the methodology will provide powerful tools to advance our drug discovery efforts for DNA-PK.

Sildenafil treatment of growth restriction and glucose metabolism ($33,538 – 18 months) 1117004

Dr Anne Jaquiery, Ms Hui Hui Phua, Ms Emma Buckels, Dr Charlotte Oyston

Liggins Institute, University of Auckland

Growth restricted babies have higher risks of perinatal complications in the short-term, and increased life-time risk of developing metabolic disease, such as type 2 diabetes. Thus, the effect of fetal growth restriction can have life-long implications for an individual beyond fetal and perinatal periods. Poor fetal growth often results from placental insufficiency, with the placenta unable to deliver adequate nutrients for fetal growth. Currently, there are no clinical treatments for pregnancies identified as having fetal growth restriction. One medication which may improve placental blood flow, thereby promoting

growth by improving fetal nutrient supply, is sildenafil citrate (Viagra). In parallel with the ongoing STRIDER (NZAus) clinical trial, we have completed an experimental study in sheep using an established model of growth restriction. Sildenafil treatment of a ewe carrying a growth restricted fetal lamb improved fetal and placental growth compared to non-treated control ewes. This study will address whether Sildenafil treatment can reverse the increased risk of metabolic disease after intrauterine growth restriction, by exploring the expression of key markers of glucose metabolism in the fetal pancreas, liver, and muscle. This will add to the growing body of knowledge suggesting Sildenafil treatment could ameliorate both fetal growth restriction and the long-term effects of the in utero environment.

SHON and endocrine therapy ($142,212 – 2 years) 5117014

A/Prof Dong-Xu Liu, Dr Yan Li, Prof Lai-Ming Ching

School of Sciences, Auckland University of Technology

Breast cancer is the most commonly diagnosed cancer for women in New Zealand and affects one in nine women during their life time, accounting for 44% of the top 5 cancers that most often affect women. Three-quarters of all breast cancers are estrogen receptor (ER) positive. Despite the well-known high rate of drug resistance, almost all patients with ER positive tumours are given anti-estrogen therapies as the front-line treatment for at least five years to reduce recurrence and mortality risks. One of the major reasons for this is the fact that there is no reliable means to determine who will or will not benefit from such treatments. A recent discovery shows that the presence of SHON protein in tumours markedly improves the prediction of patient response to anti-estrogen therapies. Experimental work has suggested that SHON may be an important determinant of the efficacy of antiestrogen therapy. We propose to investigate the relationship between SHON expression and drug resistance, to accelerate the development of improved therapeutic options to effectively treat ER positive breast cancer.

Understanding the CREBRF variant ($159,266 - 2 years) 1117006

Dr Troy Merry, Prof Peter Shepherd, Dr Rinki Murphy, A/Prof Lindsay Plank

Dept. of Molecular Medicine & Pathology, University of Auckland

Obesity and type 2 diabetes (T2D) are amongst the greatest health problems currently facing New Zealand. These diseases are disproportionately greater in Māori and Pacific people than in Europeans. T2D increases the risk of developing other health conditions, including heart disease and liver diseases, and certain cancers. Obesity is the greatest risk factor for the development of T2D and is partly caused by the environment but genetic factors also play a major role. Recently it has been shown that some Samoans have a small change in their CREBRF gene, and this is associated with an increased body mass index (BMI: surrogate measure for obesity), but protects from the development of T2D. We now know that this change in the CREBRF gene is also present in 30-40% of people of Polynesian descent in New Zealand. This study will investigate why people with this change in the CREBRF gene have increased BMI but a decreased risk of T2D. Understanding how genetic variation, particularly one that is unique to people of Polynesian descent, has the potential to determine what factors contribute to obesity and T2D in our population. Such findings are likely to lead to future novel therapeutic interventions in these specific populations.

Immune priming in rheumatic fever ($160,000 - 2 years) 1117002

Dr Nicole Moreland

Dept. of Molecular Medicine & Pathology, University of Auckland

Rheumatic fever is a serious autoimmune disease that can develop after a Group A Streptococcus (Strep A) infection in some children. The rates of rheumatic fever in Maori and Pacific children in New Zealand are unacceptably high and drivers for disease are still poorly understood.

This project will use contemporary laboratory techniques to study antibodies circulating in blood to determine the number of Strep A infections patients with rheumatic fever have experienced, compared with healthy children that live in the same area as the patients. The research will answer a fundamental question with respect to how rheumatic fever develops: do children that develop rheumatic experience more Strep A infections than those that do not? Remarkably, given the significant investment in rheumatic fever primary prevention programmes in New Zealand to treat sore throats, it is not known if the number of Strep A infections a child experiences increases their risk for developing rheumatic fever. Or alternatively, whether it is not the frequency of Strep A exposures, but an underlying susceptibility to autoimmune disease that is the driving force. Answering these critical questions will enable future prevention programmes and intervention strategies to be designed and implemented with the best chance of success.

Interactions between fat and tendons ($159,924 – 2 years) 1117019

Dr David Musson, Prof Jillian Cornish, Mr Brendan Coleman, Dr Dorit Naot

Department of Medicine, University of Auckland

There are over 4000 tendons in the body, each one a specialised tissue that connects muscle to bone and transmits tensile forces from muscle to generate movement. Tendon damage (tendinopathy) is a severe clinical problem that affects the quality of life of both young and aged persons, limiting movement and resulting in significant time off work. Recently, increased fat mass has been associated with an increased risk of tendinopathy. The traditional belief that this association was a result of increased load on the tendons, due to increased weight, has recently been reversed as upper limbs are also affected. Therefore, the mechanisms that are driving this increased risk of tendinopathy remain unknown. Fat is an endocrine organ, capable of releasing factors associated with a number of chronic diseases.

These factors have not been studied in relation to tendinopathy. Therefore, this study will examine the effects of fat-derived factors on tendons through a mix of basic, pre-clinical and clinical explorations.

FUNDED BY: Rose Richardson Estate

CaMK2 imbalance in osteoarthritis ($156,023– 2 years) 1117012

Dr Raewyn Poulsen, Prof Nicola Dalbeth

Department of Medicine, University of Auckland

Approximately one in four New Zealanders over the age of 65 years have the painful, disabling condition known as osteoarthritis. Currently incurable, osteoarthritis has a significant detrimental effect on quality of life. Loss of joint cartilage is a major cause of the symptoms of osteoarthritis. This cartilage loss is due in part to abnormal behaviour of cartilage cells. It is known that excessive activity of the enzyme calcium/calmodulin kinase 2 (CaMK2) can cause this cell behaviour change. Recently, we discovered that insufficient CaMK2 activity can also cause this cell behaviour change. This suggests that rather than inhibiting CaMK2 activity (and potentially causing CaMK2 insufficiency), targeting the cause of CaMK2 hyperactivity in osteoarthritis may be a more effective means to treat disease. In this project we will establish why CaMK2 activity is increased in osteoarthritis and how the level of CaMK2 activity affects cell behaviour. We suspect that CaMK2 hyperactivity in osteoarthritis is a result of other molecules binding to CaMK2, preventing its deactivation. If we find this is the case, there are already drugs under development for the treatment of other diseases which remove these molecules from CaMK2. These drugs may also be useful for treating osteoarthritis.

FUNDED BY: Rose Richardson Estate

Hyaluronan in neonatal seizures ($113,745- 2 years) 1117007

Dr Sumudu Ranasinghe, Dr Rashi Karunasinghe, Dr Justin Dean

Dept. of Physiology, University of Auckland

Seizures are the most common form of neurological emergency in newborn infants. Approximately 60% of these neonatal seizures are caused by hypoxic-ischemic encephalopathy, a lack of oxygen and blood flow to the brain, during birth. In New Zealand, approximately 1.3 in 1000 babies that are born at term experience hypoxic-ischemic encephalopathy. These neonatal seizures can increase the risk of developing further brain injury and causing life-long disabilities, including epilepsy. Although the proper management of neonatal seizures is crucial for improving the developmental outcomes for these children, there is currently no effective treatment for seizure inhibition. Indeed, the biological factors that contribute to seizure activity in neuronal cells following hypoxic-ischemic encephalopathy currently remain unclear. Our laboratory has novel evidence that an extracellular sugar called hyaluronan that surrounds neuronal cells may be important for controlling neuronal activity in the brain. We propose that hypoxia-ischemia reduces the levels of hyaluronan in the brain, and leads to increased seizure-like activity in neuronal cells. We aim to test our hypothesis using in vitro and in vivo experimental models. We will also explore whether a pharmacological inhibition of hyaluronan degradation may serve as a novel therapeutic strategy to minimise seizures after hypoxia-ischemia in the newborn.

CO-FUNDED WITH: The Neurological Foundation of New Zealand

Novel treatments for diabetic vascular complications ($159,582– 2 years) 1117015

Dr Ilva Rupenthal, Prof Colin Green, Mrs Odunayo Mugisho, Dr Monica Acosta

Department of Ophthalmology, University of Auckland

Diabetes is amongst the greatest health problems facing New Zealand with over 240,000 people estimated to have the disease. It is associated with a number of metabolic and vascular complications that affect a variety of organs including heart, kidneys and eyes. The damage of small blood vessels and neurons at the back of the eye, termed diabetic retinopathy, can lead to vision loss affecting up to 80 percent of people who have had diabetes for over 20 years. Current treatments mainly target late stage disease signs, but are less effective in slowing disease progression. Targeting an upstream inflammatory mechanism to restore vascular integrity, allowing proper tissue nutrition and oxygenation, will be substantially more beneficial. We have identified a channel that when targeted can ameliorate the condition by not only restoring retinal blood vessels to treat the signs, but also by promoting recovery of the affected tissues preventing further vision loss. We will be testing two drugs targeting this channel in a newly developed model of diabetic retinopathy and will perform ocular assessments comparable to those performed in clinics. While this study is primarily focused on the eye, the investigated drugs may also treat other vascular problems associated with diabetes.

FUNDED BY: Marion Ross Memorial Fund

Automatically identifying hypoxic ischemic, high-risk preterms with Machine Learning & Artificial Neural Networks. ($159,951 – 2 years) 1117017

A/Prof Charles Unsworth, Prof Laura Bennett, Prof Alistair Gunn

Engineering Science, University of Auckland

This research will develop an automated risk assessment system for hypoxic ischemic (HI) preterm infants, enabling them to be prioritised effectively for new clinical trials of potential neuroprotective therapies. Currently, preterm infants get missed by current clinical criteria since their neurological signs are more subtle than at term infants. In addition, the preterm EEG record is of limited range where the evolution of HI is not always known, making it very difficult to identify where temporally the infant is in the latent phase at birth, critical to the identification of how at risk they are. This is unlike in utero sheep models of HI where the full evolution of HI is available. Using our team's expertise in HI, 'Machine Learning' and 'Artificial Neural Network Approaches' we will derive a nonlinear map between the full evolution of HI of in utero sheep models and the limited unknown evolution of HI in preterms. Such a map will be translational, enabling us to 'bridge the gap' between experiment and cotside to predict where, temporally, a preterm infant is in its latent phase at birth, currently not possible. Thus, enabling the effective prioritisation of preterm infants for new randomised controlled clinical trials.

FUNDED BY: Curtis-Tonkin Paediatric Fund

SPACE cluster RCT in general practice ($150,012 - 2 years) 1117005

Dr Katharine Wallis, Prof Ngaire Kerse, Dr Linda Bryant, A/Prof C. Raina Elley

Dept. of General Practice & Primary Health Care, University of Auckland

Avoidable adverse drug event hospital admissions, adverse drug events and high-risk prescribing in general practice are common, costly and distressing. High-risk prescribing is prescribing that puts patients at increased risk of harm. The leading risk factor for high-risk prescribing and adverse drug events is the number of medicines a person is taking. Avoidable adverse drug event admissions are increasing as more people are living longer and taking more medicines for more long-term conditions. The most effective, cost effective, and practical approach to safer prescribing in everyday practice is not yet known. We propose a trial to test the effectiveness of an intervention designed to support safe prescribing decisions in everyday practice. The intervention comprises a practice audit to identify patients with high-risk prescribing, education and patient-specific feedback to doctors, and a practice mail-out to patients identified as having high-risk prescribing encouraging them to discuss their medicines when they next see their doctor. If proven effective, cost-effective, and practical, this simple intervention could be rolled out nationally and used routinely by Primary Health Organisations to improve the safety of prescribing and minimise adverse drug event hospital admissions in older people.

DOUGLAS GOODFELLOW REPATRIATION FELLOWSHIP

Co-design and pilot trial of a smartphone app to support young people who self-harm ($299,480 – 2 years) 1417001

A/Prof Sarah Hetrick

Dept. of Psychological Medicine, University of Auckland

Self-harm in adolescents is prevalent, and is a key risk factor for suicide. However, these young people rarely seek formal help. The urge to self-harm fluctuates, and is situation dependent. Therefore traditional face-to-face therapy cannot always offer a timely intervention. There is a pressing need for innovative treatments for self-harm in young people. Given that most young people in New Zealand own a smart phone there is an enormous potential to make psychological self-care tools accessible when and where needed. We propose to design a smart phone application (app) specifically aimed to help adolescents manage distress and urges to self-harm, and ultimately to prevent episodes of self-harm. We will use a co-design process with young people, including interviews about their needs, and design workshops where young people will develop the content, interface ('look and feel', format, functionality etc.), and wireframes (sketches that represent the interface) for the app. We will engage clinicians to ensure that the app can be meaningfully integrated into the face-to-face clinical work with young people who self harm. We will then pilot test the app with young people to ensure its usability and safety and to ensure that it decreases distress and urges to self-harm.

FUNDED BY: Douglas Goodfellow Charitable Trust

POSTDOCTORAL FELLOWSHIPS

EDITH C COAN RESEARCH FELLOWSHIP

Early changes in frontotemporal dementia ($198,225 – 2 years) 1317001

Dr Brigid Ryan

Dept. of Anatomy & Medical Imaging, The University of Auckland

Imagine that you are diagnosed with dementia. You're told that it will progressively deprive you of your ability to think, your personality, and your independence. Now imagine that your doctor tells you that your condition could have been treated if it was diagnosed 10 years earlier, but the damage to your brain now is too extensive. This is the problem that we are trying to solve: how to identify dementia years or decades before clinical diagnosis, so that intervention is possible. To do this we need to identify pre-clinical biomarkers of dementia. We have a unique opportunity to search for these biomarkers in a large Auckland family with a genetic mutation that is known to cause

frontotemporal dementia. We will search for biomarkers that are both non-invasive and time- and cost-effective, namely blood tests, tests of cognition, and sense of smell. This family has a mutation that causes clumping of the 'tau' protein inside brain cells, leading to cell death (this is known as 'tauopathy'). Our rationale is that biomarkers identified in this family may be generalisable to other tauopathies that cause dementia, including Alzheimer's disease. If not, they will still be useful biomarkers of frontotemporal dementia, a common cause of early-onset dementia in New Zealand.

FUNDED BY: Edith C Coan Trust / J & P Stilson Endowment Trust

perpetual guardian

DAVID AND CASSIE ANDERSON RESEARCH FELLOWSHIP

Genetic factors and beta-cell function ($218,656 – 2 years) 1317002

Dr Brie Sorrenson

Dept. of Molecular Medicine & Pathology, University of Auckland

The major function of pancreatic b-cells is to secrete insulin, which regulates blood glucose levels in the body. Diabetes arises when the function of these b-cells is compromised and they can no longer appropriately secrete insulin. Many factors contributing to defective insulin secretion are not known and while b-cell replacement therapies work well, there is a severe lack of donor tissue for transplant. This research will study how genetic factors influence b-cell function and whether gene-editing can improve function of patient derived cells. There is increasing evidence that insulin secretion is similar to synaptic vesicle release and we have preliminary data showing that the synaptic protein Shank3 affects insulin secretion from b-cells. The mechanism for this will be explored and the relevance to whole body metabolism studied using a mutant mouse model. We also have the unique opportunity to study a patient with an insulin gene mutation that causes diabetes very young in life. Cells from the patient will be reprogrammed back into stem cells, the genetic defect repaired and differentiated into b-cells to assess whether insulin secretion function is improved. This will provide proof-of-principle to indicate whether this approach has therapeutic potential for diabetes caused by single gene defects.

FUNDED BY: David and Cassie Anderson Medical Trust

perpetual guardian

DOUGLAS GOODFELLOW MEDICAL RESEARCH FELLOWSHIP

Economic Analysis of Neonatal Hypoglycaemia ($244,000 – 2 years, 6 months) 1417003

Dr Matthew Glasgow

Liggins Institute, University of Auckland

Low blood sugar in newborn babies (known as neonatal hypoglycaemia) affects half or more of babies in some groups in New Zealand, including those who are born early, are large or small at birth, or are born to mothers who have diabetes. Most often, this happens shortly after birth when the baby uses up its store of ready blood sugars and before it is able to burn its own fat stores. It can cause permanent brain damage if not treated promptly. Brain damage results in financial and societal costs that may persist across a lifetime. Treatment of neonatal hypoglycaemia itself also incurs financial cost, particularly if the baby is admitted to intensive care, which also separates the mother and baby and makes early breastfeeding difficult. An assessment of the long term health burden and costs of neonatal hypoglycaemia has not previously been undertaken. We will undertake a series of economic analyses looking at these aspects of neonatal hypoglycaemia, in order to better understand the costs and benefits of different management options, including the use of dextrose gel for treating or preventing neonatal hypoglycaemia. This will help guide healthcare policy and resource allocation, both nationally and internationally.

DOCTORAL SCHOLARSHIPS

Tumour heterogeneity: a patient-specific multilayered investigation ($128,000 – 3 years) 1217001

Ms Tamsin Robb

Dept. of Molecular Medicine & Pathology, The University of Auckland

Understanding tumour heterogeneity remains one of the most important questions in oncology. Tumour heterogeneity encompasses the differences between all of a patient's tumour cells in one or more tumours of their body. This variability covers genetic and molecular differences in the full range of cancer hallmarks, including metastasis and treatment resistance. We are now armed with genomic technology that may be used to answer some of the most pertinent questions in oncology. Why do some people's tumours spread rapidly around the body while others remain dormant and cause minimal harm? How do our differing genetic backgrounds affect our inherited cancer risk and the range of tumours developing in our families? What underlies the differences in individual patient responses to promising new drugs? By gaining a deeper understanding of cancer as a heterogeneous, varied, multifaceted disease within a single patient, we have greater hope of providing successful therapeutic strategies to that patient. The overarching aim of this research is to understand the effect and interplay of tumour heterogeneity in individual patients right down to the cell-level, in order to find new biomarkers for diagnosing and monitoring patients with neuroendocrine tumours in New Zealand, which will be widely applicable to cancer.

FUNDED BY: Anonymous donor

Grants Awarded continued

Enzyme-mediated stabilization of the blood-brain barrier ($128,000 – 3 years) 1217002

Mr James Hucklesby

School of Biological Sciences, University of Auckland

Stroke is a major cause of death and disability worldwide. If seen early enough patients with acute ischaemic stroke can be treated with a drug to dissolve the blood clot blocking circulation to the brain or the clot can be removed surgically. However, there is an urgent need to identify new therapies to increase the efficacy of these treatments and achieve higher levels of functional recovery. The blood-brain barrier is the gatekeeper of the central nervous system and functions as an interface separating the blood from the brain. Loss of blood-brain barrier integrity is a prominent pathological event in stroke resulting in uncontrolled entry of blood-borne products and fluid into the brain and contributing to a poor clinical outcome. This project explores new ideas on how the integrity of the blood-brain barrier is maintained. Our preliminary data suggest that an enzyme circulating in the blood can strengthen the barrier and may be able to reduce barrier damage following stroke. The proposed study will determine how this enzyme contributes to barrier integrity and may provide insight into whether it could be used as an adjunct therapy to improve health outcomes after stroke.

FUNDED BY: John Alfred Jarrett Trust

perpetual guardian

Cardiovascular medications and cancer outcomes in New Zealand ($128,000 – 3 years) 1217004

Mr Oliver Scott

Dept. of Epidemiology and Biostatistics, University of Auckland

The burden of cancer in New Zealand is high, and was one of the leading causes of death in 2013. There is a high and increasing prevalence of New Zealanders taking medication for high blood pressure and high cholesterol, as well as a high and increasing prevalence of risk factors for both cancer and IHD such as obesity, lack of physical activity, and unhealthy diets among New Zealand adults. As such, many New Zealanders are expected to suffer from both cancer and IHD in the coming years. Cardiovascular medications such as antihypertensive drugs, statins, and aspirin have tended to have positive effects on cancer outcomes in overseas studies, but this association may not be directly applicable to New Zealand patients. Hence, this PhD aims to examine the association between the use of cardiovascular medications and cancer outcomes in New Zealand, focusing on patients with breast cancer or lung cancer. The findings will inform health practitioners on what medications to prescribe cancer patients, and in turn, improve survival outcomes for cancer patients in New Zealand medicated for cardiovascular conditions.

GAVIN AND ANN KELLAWAY MEDICAL RESEARCH FELLOWSHIP

$34,895 1517001

Prof Boyd Swinburn

School of Population Health, University of Auckland

Validity testing of the findings of the Lancet Commission on Obesity

SIR HARCOURT CAUGHEY AWARD

$13,089 1717001

Prof Frank Bloomfield

Liggins Institute, University of Auckland

Role of the Intestinal Microbiome in Inflammation, Obesity, and Brain Health in Premature Infants

KELLIHER CHARITABLE TRUST EMERGING RESEARCHER START-UP AWARDS

$30,000 1717002

Dr Timothy Angeli

Auckland Bioengineering Institute, University of Auckland

Research support for his Edith C Coan Research Fellowship "Development and validation of endoscopic gastric electrical mapping as a diagnostic tool for digestive diseases"

$30,000 1717003

Mr Karan Govindpani

Dept. of Anatomy & Radiology, University of Auckland

Research support for his Brian de Luen Doctoral Scholarship "Understanding GABA Signalling in Human Pericytes in Healthy and Alzheimer's Disease Brains"

ALL KELLIHER AWARDS **FUNDED BY:** Kelliher Charitable Trust

Kelliher Charitable Trust

HEALTHEX EMERGING RESEARCHER AWARDS

$3,000 Travel Award 6717001

Mr Kenta Cho
Dept. of Physiology, University of Auckland

To attend a conference to present his research in the field of Reproduction, Development, Maternal and Newborn Health

$2,000 Travel Award 6717002

Mrs Melanie MacFarlane
Dept. of Paediatrics, University of Auckland

To attend a conference to present her research in the field of of Reproduction, Development, Maternal and Newborn Health

$2,000 Travel Award 6717003

Miss Sarah Mitchell
Liggins Institute, University of Auckland

To attend a conference to present her research in the field of Endocrinology, Metabolism and Nutrition

TRAVEL GRANTS

Dr Jesse Ashton
Dept. of Physiology, University of Auckland

To attend the Heart Rhythm Society (HRS) 38th Annual Scientific Sessions, 9-14 May 2017

Dr Marjan Askarian-Amiri
Auckland Cancer Society Research Centre, University of Auckland

To attend the 22nd Annual meeting of the RNA society, Prague, Czech Republic and the 2nd International Symposium on Frontiers in Molecular Science Non-coding RNAs and Epigenetics in Cancer, Basel, Switzerland, 30 May-23 June 2017

Dr Koray Atalag
Auckland Bioengineering Institute, University of Auckland

To attend the World conference MEDINFO 2017, Hangzhou, China, 21-25 August 2017

Dr Kathryn Beck
School of Food and Nutrition, Massey University

To attend the 21st International Congress of Nutrition, Buenos Aires, Argentina, 14-13 October 2017

Dr Karen Bishop
Dept. of Nutrition, University of Auckland

To attend the NCRI Cancer Conference, Liverpool, UK, 5-8 November 2017, and visit to the Experimental Cancer Medicine Centre, Cardiff University

Dr Benjamin Dickson
Auckland Cancer Society Research Centre, University of Auckland

To attend the 15th International Tumour Microenvironment Workshop 2017, Miami, USA, 27-29 April 2017

Dr Peter Freestone
Dept. of Physiology, University of Auckland

To attend the 47th Society for Neuroscience Annual Conference, Washington DC, USA, 11-15 November 2017

Dr Paulina Hanson-Manful
Dept. of Molecular Medicine & Pathology, University of Auckland

To attend the 20th Lancefield International Symposium on Streptococci and Streptococcal Diseases, Fiji, 16-20 October 2017

Dr Anna Howe
Dept. of General Practice and Primary Health Care, University of Auckland

To attend the Communicable Diseases Control Conference, Melbourne, Australia, 26-28 June 2017

Dr Kathryn Jones
Dept. of Pharmacology and Clinical Pharmacology, University of Auckland

To attend the International Society for Stem Cell Research, Boston, USA, 13-17 June 2017

Dr Rashi Karunasinghe
Dept. of Physiology, University of Auckland

To participate in the 2017 Woods Hole Neurobiology Course, Woods Hole, USA, 2 June-31 July 2017

Dr Hannah Kersten
Dept. of Ophthalmology, University of Auckland

To attend the American Academy of Optometry Meeting, Chicago, USA, 11-17 October 2017

Dr Dan Kho
Dept. of Pharmacology, University of Auckland

To attend the Progress in MS Research Conference, Sydney, Australia, 11-13 October 2017

Dr Andrea Kwakowsky
Centre for Brain Research, University of Auckland

To attend The Annual Scientific Meeting of the Australasian Neuroscience Society and an Imaging Workshop, Sydney, Australia, 3-6 December 2017

Dr Lydia Liew
Auckland Cancer Society Research Centre, University of Auckland

To attend the 15th International Tumour Microenvironment Workshop 2017, Miami, USA, 27-29 April 2017

Dr Amber Milan
Liggins Institute, University of Auckland

To attend the 10th Asia Pacific Conference on Clinical Nutrition, Adelaide, Australia, 26-29 November 2017

Dr Marta Paulino Silvestre
School of Biological Science, University of Auckland

To attend the 24th European Congress of Obesity 2017 and XVI Portuguese Congress of Food and Nutrition, Porto, Portugal, 4-20 May 2017

Dr Matire Harwood
Te Kupenga Hauora Maori, University of Auckland

To meet the Cochrane Heart Group and attend the ISQua Conference, London, UK, 1-4 October 2017

Grants Awarded continued

Dr Clare Reynolds
Liggins Institute, University of Auckland

To attend the DOHaD ANZ conference, Canberra, Australia, 4-7 April 2017

Associate Professor Grant Searchfield
Section of Audiology, University of Auckland

To attend the 11th TRI tinnitus Conference, Regensberg, Germany 14-16 March 2018, and present research to Sonova (Swiss hearing aid manufacturer)

Dr Ivana Sequiera
Biological Sciences, University of Auckland

To attend the Australia New Zealand Nutrition Society Annual meeting, Adelaide, Australia, 4-6 October 2017

Dr Giriraj Shekhawat
Section of Audiology, University of Auckland

To attend the 1st World Tinnitus Congress, Warsaw, Poland, 22-24 May 2017

Dr Brie Sorrenson
Dept. of Molecular Medicine and Pathology, University of Auckland

To attend the 12th Asia-Pacific Diabetes & Obesity Study Group Symposium, Hong Kong, 21-22 October 2017

Dr Sarah Stewart
Health and Rehabilitation Research Institute, Auckland University of Technology

To attend the 2017 Gout, Hyperuricaemia and Crystal-Associated Disease Network (G-CAN) Annual Scientific Meeting and the 2017 American College of Rheumatology (ACR) / Association of Rheumatology Health Professionals (ARHP) Annual Scientific Meeting, San Diego, USA, 2-9 November 2017

Dr Jennifer Utter
School of Population Health, University of Auckland

To attend the International Society for Behavioural Nutrition and Physical Activity annual meeting, Victoria, Canada, 7-10 June 2017

Dr Katharine Wallis
School of Population Health, University of Auckland

To attend the 22nd WONCA Europe conference, Prague, Czech Republic, 28 June - 1 July 2017, and the Society for Academic Primary Care, Warwick, UK, 12-14 July 2017

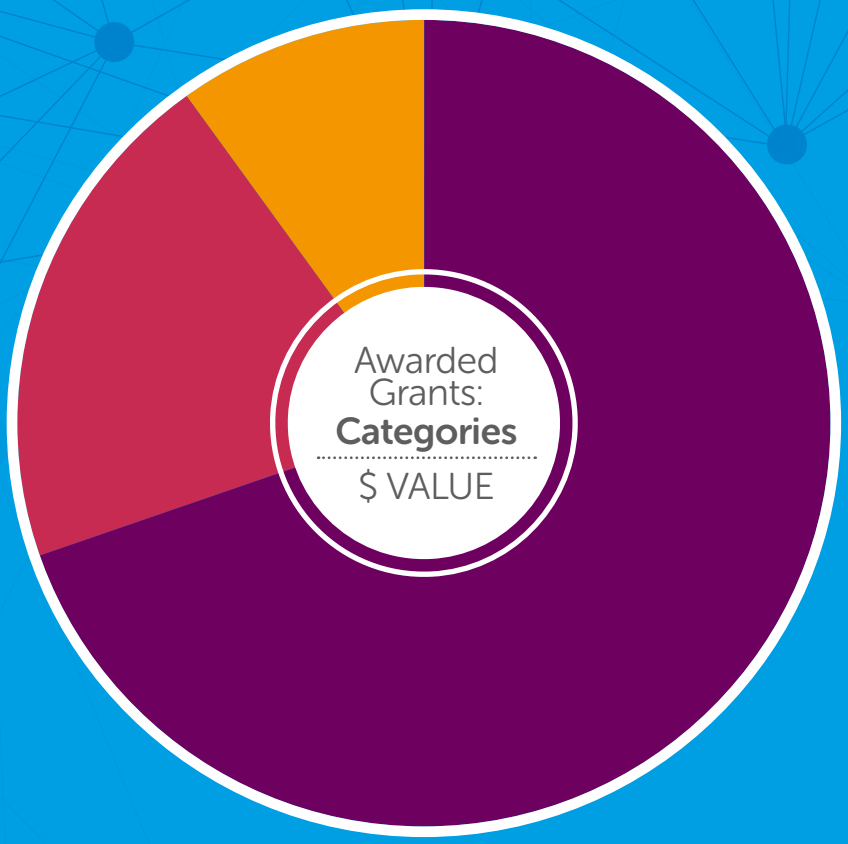
Dr Sarah Ward
Mechanical Engineering, University of Auckland

To attend RehabWeek, London, UK, 17 - 20 July 2017, Visit Imperial College London, and visit the Rehabilitation Institute of Chicago, USA, 24-28 July 2017

A/Prof Carol Wham
School of Sport, Exercise and Nutrition, Massey University

To attend the 21st International Congress of Nutrition, Buenos Aires, Argentina, 15-20 October 2017

Grants Completed



2017 AWARDED GRANTS - CATEGORIES:

60 GRANTS AWARDED TOTALLING $4,023,459

Biomedical (37) | $2,813,973 69.94%

Clinical (13) | $811,664 20.17%

Population Health and Community (10) | $397,822 9.89%

$ Value each category % Total expenditure
(n) Number of grants

Grants Completed

PROJECTS

TRANSLATIONAL REGULATION IN BREAST CANCER 1115003

Dr Marjan Askarian-Amiri,
Dist. Prof Bruce Baguley,
Dr Graeme Finlay
Auckland Cancer Society Research Centre,
University of Auckland

Dr Marjan Askarian-Amiri (front row, 3rd from left) with Dr Graeme Finlay (back left), Dist. Prof Bruce Baguely (back, centre) and their wider research team

Mammalian cells produce thousands of transcripts that are not translated into proteins despite having similar characteristics to mRNA. These transcripts known as non-coding RNA (ncRNA), have attracted intense interest over the last decade and are one of the fastest growing research fields in biology. Our focus in this project was the functional characterisation of a regulatory ncRNA that features in breast cancer. We have discovered an RNA species called ZFAS1 which we have implicated in mouse mammary gland development and human breast cancer. In this project we further investigated the function of ZFAS1 in human breast cancer. We have found that ZFAS1 is abundantly expressed in all cell lines tested, has a very long life time and is ribosome-bound. We showed that ZFAS1 was predominantly associated with the 40S small ribosomal subunit. The expression levels of ZFAS1 and of mRNAs encoding several ribosomal proteins that have roles in ribosome assembly, production and maturation were tightly correlated. ZFAS1 knockdown significantly reduced RPS6 phosphorylation. The results of this work were published in Biology Direct in Nov 2016. We have also established a CRISPR/Cas9 system to knock down ZFAS1 expression in cells, and are currently optimising the protocol for dual knockout.

FUNDED BY: Anonymous donor

BIOAVAILABLE ANALOGUES OF THIENO[2,3-B]PYRIDINES 1115004

Dr David Barker,
Dist. Prof Bill Denny,
Dr Johannes Reynisson
School of Chemical Sciences,
University of Auckland

Dr Barker in action

The aim of this project was to design and prepare bioavailable analogues of thieno[2,3-b]pyridines, a compound class which showed potent anti-proliferative activity in the nM range but exhibited poor aqueous solubility. It was envisioned that by incorporating polar, solubilizing groups to the thieno[2,3-b]pyridine structure, the bioavailability of these compounds could be increased. Initial synthetic endeavours prepared generation one compounds which replaced the sulfur with a nitrogen group. These were found to have increased solubility however not the high level of bioactivity desired for further study. Generation two compounds were therefore prepared with modifications at an alternative site in the core structure. This change pleasingly resulted in compounds which had increased solubility and also retained a high level of bioactivity against human cancer cell lines, including difficult to treat triple-negative breast cancer cell lines. This second generation of compounds will now be expanded with the aim of further improving both the solubility and bioactivity to a level suitable for clinical study.

FUNDED BY: Anonymous donor

NATURAL PRODUCT BASED ANTIBODY-DRUG CONJUGATES (ADCs) 1114016

Prof Margaret Brimble, Dr Paul Harris,
Dr Kuo-yuan (Greg) Hung,
A/Prof Adam Patterson, Dr Jeff Smaill
School of Chemical Sciences,
University of Auckland

Dist. Prof Margaret Brimble

Antibody-drug conjugates (ADCs) are an emerging class of drug that take advantage of the selectivity of an antibody to deliver a drug to a specific site of interest. The development of new toxins suitable for use in ADCs has been identified as an area in need of attention. Our group has recently synthesised a naturally-derived toxin culicinin D for potential use in ADCs. Given the difficulty of synthesis and uncertainty as to its importance, we were interested in development of structurally simpler analogues. A focused library of simplified building blocks were prepared and incorporated into the framework of culicinin D. The peptide analogues were then assessed for anti-proliferative activity at the Auckland Cancer Society Research Centre against a panel of cancer cell lines. Evaluation revealed that the C6-hydroxy group was essential for activity, whilst the C4-methyl and C8-keto substituents were not required. This finding allowed development of our lead analogues, which largely retain the potent activity of the natural product but are more synthetically tractable, and allow for efficient assembly of the peptide. Further refinement of analogues and work to uncover the mechanism of action of these potent anticancer peptides is currently underway.

FUNDED BY:
The Hugh Green Fund

MAXIMISING THE POTENTIAL OF IDO1 INHIBITORS TO INDUCE DURABLE, LONG-TERM REGRESSION OF TUMOURS 1114012

Prof Lai-Ming Ching, A/Prof Ian Hermans, A/Prof Brian Palmer

Auckland Cancer Society Research Centre, University of Auckland

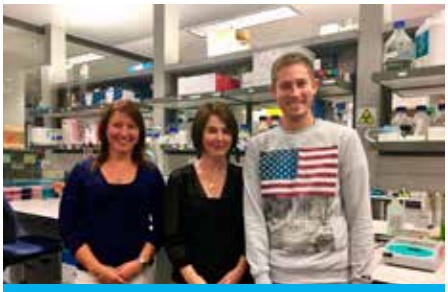
Prof Lai-Ming Ching (3rd from left) with her research team

Recent breakthroughs in cancer therapy, using agents that unleash the immune system, have enabled patients with advanced cancers, to live disease-free for more than 10 years. We have developed a new class of agents that inhibit an immunosuppressive enzyme called IDO1. In this research we explored the efficacy of our novel IDO1 inhibitors to impede the growth of murine models of glioma and lung carcinoma. As a monotherapy, IDO1 inhibitors slowed the growth of gliomas and lung carcinomas. Combining an IDO1 inhibitor with immune checkpoint blockades provided better than additive inhibition of glioma growth compared to monotherapies alone. No additive effect was observed when IDO1 inhibitors were combined with investigational whole cell vaccine against the glioma model. IDO1 accelerates the conversion of the essential amino acid tryptophan to kynurenine, and the ratio of kynurenine to tryptophan (K:T) increased in plasma and tumour as the glioma increased in size. Application of an IDO1 inhibitor reduced K:T ratios and could be a useful surrogate marker of activity.

A NON-INVASIVE TEST OF EMBRYO QUALITY 1114002

Dr Lynsey Cree, Dr Matthew VerMilyea, Professor Larry Chamley, Professor Peter Stone

Dept. of Obstetrics & Gynaecology, University of Auckland



Sophie Wicker, Dr Lynsey Cree (centre) and Brent McGillivray (PhD student)

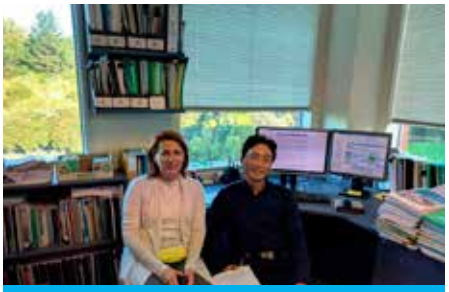
The number of couples seeking the help of assisted reproductive technologies to have children is increasing. During an IVF cycle there are multiple embryos produced, and a major challenge in reproductive medicine is selecting the best embryo for transfer back into the uterus of the intending mother. Our research was aimed at investigating if cell-free DNA (cfDNA) is released from human embryos into the culture media during IVF and to establish whether this DNA can serve as an objective and non-invasive biomarker of embryo quality to assist embryo selection in IVF. Furthermore, we aimed to test whether cfDNA represents a novel tool by which to detect genetic abnormalities in embryos.

Our results show that cfDNA is released into the media and this DNA is released in differing amounts in embryos of good and poor quality. The amount of DNA released varies throughout the time in culture. This DNA may be suitable for the detection of genetic abnormalities within the embryos however the reliability of this approach is currently being assessed. The development of an accurate, and non-invasive means by which to assess embryo quality and to select only genetically normal embryos would increase pregnancy success following IVF.

DURATION OF ESBLPE COLONISATION 7112007

Dr Dragana Drinkovic, Dr Hasan Bhally, Dr Susan Taylor, Dr David Holland, Dr Arlo Upton, Dr Simon Briggs, Ms Helen Heffernan, Dr Lifeng Zhou

Microbiology Laboratory, North Shore Hospital, Waitemata District Health Board



Dr Dragana Drinkovic and Dr Lifeng Zhou

Extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBLPE) are common gut bacteria which have become resistant to multiple antibiotics. Duration of ESBLPE gut carriage is not known, but is assumed to be very long. Hospital patients who carry ESBLPE are kept in isolation. This is costly and makes their management difficult because of limited availability of isolation rooms. The aim of this study was to investigate the duration of ESBLPE colonisation and factors that may influence it. Our preliminary results suggest that approximately half of the enrolled patients remained colonised with ESBLPE two years after their enrolment. Multiple antibiotic courses received during follow up seemed to contribute to continuous ESBLPE colonisation. We are now conducting in-depth analysis of collected data, which will give us better insight into our findings.

FUNDED BY:
Paul Stevenson Memorial Trust

Grants Completed continued

THE TUI STUDY 1113008

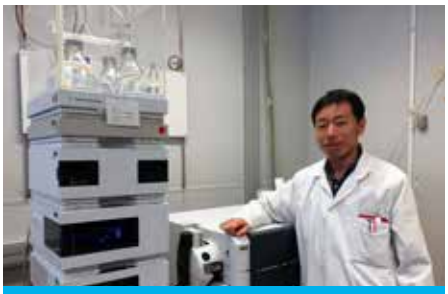
Prof Cindy Farquhar, Dr Emily Liu, Dr Nicola Arroll
Dept. of Obstetrics & Gynaecology, University of Auckland

Prof Cindy Farquhar

This study compared intrauterine insemination with ovarian stimulation with no treatment in 201 women with unexplained fertility. The study shows that the treatment has a small benefit similar to one started cycle of IVF with one fresh and one frozen embryo transfer. The number needed to treat is 6. That means that six women would need to have one cycle of IUI with clomiphene citrate to have one live birth. It is low cost treatment and should be offered to women with unexplained infertility as a first line treatment.

PROTEOMIC PROFILING OF PRODRUG-ACTIVATING ENZYMES IN LEUKAEMIAS 1114005

Dr Yongchuan Gu, Prof Peter Browett, Dr Frederik Pruijn, Prof William Wilson
Auckland Cancer Society Research Centre, University of Auckland



Dr Yongchuan Gu

The novel anticancer prodrug PR-104A, developed in the University of Auckland, was designed to be activated by enzymes under the hypoxic (low oxygen) conditions that prevail in many solid tumours. The bone marrow in patients with advanced leukaemia also becomes hypoxic, and some leukaemia cells also highly express an enzyme that activates PR-104A even in the presence of oxygen. This project developed a highly specific targeted proteomics assay for two key enzymes (POR and AK1C3) that activate PR-104A in low and normal oxygen, respectively. The expression of POR and AKR1C3 in human leukaemia cell lines was shown to predict metabolism of PR-104A to its active form, and the extent of subsequent DNA damage in these cells. The method also enables quantitation of 13 other enzymes that may play a role in PR-104A activation in some patients. A SWOG-funded multicentre clinical trial of PR-104 (the phosphate ester precursor of PR-104A) in relapsed refractory T-ALL, in the U.S.A, will utilise the methodology developed from the project to evaluate critically these potential predictive biomarkers. If successful this will enable use of the assay, in a personalised medicine context, to identify leukaemia patients who will benefit from treatment with PR-104.

FINDING INHIBITORS FOR MenD FROM A HUMAN PATHOGEN 1114013

Dr Jodie Johnston, Prof Margaret Brimble, Dr Daniel Furkert
School of Biological Sciences, University of Auckland

Dr Jodie Johnston (front, centre) with her team

Mycobacterium tuberculosis (Mtb) is the bacterium that causes tuberculosis (TB). Worldwide, TB is a big health problem, causing more deaths per year than any other infectious disease. In NZ, TB disproportionately affects migrants, lower socioeconomic groups and Māori. It is a difficult disease to eradicate as the bacterium can "hide" in the body in a latent state. Multi-drug resistant and extremely-drug resistant strains have also emerged; so new drugs are desperately needed. In this AMRF-funded project we developed an inhibitor discovery platform for MenD, an enzyme vital for production of vitamin K2 (menaquinone) and for the survival of the TB bacterium. We developed strong collaborations with scientists with complementary skills and used our MenD structures, combined with computational modelling and chemical synthesis, to select, design and synthesise several candidate inhibitors. We developed an assay to screen these for inhibition and were able to visualise the binding of several of them to their target by X-ray crystallography. In so doing, we identified new sites on the MenD enzyme that could be targeted by inhibitors. This is vital information for our future goals of making improved MenD inhibitors which would become part of the next line of anti-TB treatments.

PARKINSON'S DISEASE IN A DISH
1115023

Dr Kathryn Jones,
A/Prof Bronwen Connor
Centre for Brain Research,
University of Auckland

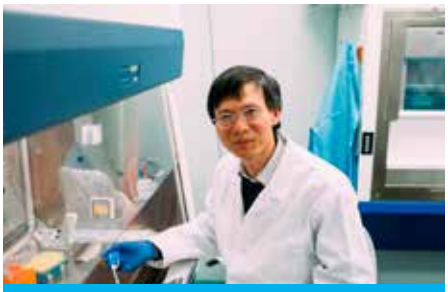
Dr Kathryn Jones

We used skin from adult human patients with Parkinson's disease (PD) to generate induced dopamine precursor cells (iDAPs) and ventral midbrain dopamine neurons (DA) through direct RNA reprogramming. We used these cells to investigate early disease-related changes in gene expression that could help explain the molecular mechanisms behind PD. Results showed that normal cells reprogrammed well into iDAPs and expressed gene and proteins expressed in the dopamine lineage. Control iDAPs differentiated into neurons that expressed dopamine markers and showed some functionality. iDAPs from PD patients however, showed altered growth factor genes, reduced neuroprotective genes and altered mitochondrial signalling genes. PD neurons differentiated from iDAPs also had reduced neuronal survival compared to controls. This reprogramming technology showed good promise for modelling a human neurodegenerative disease in a dish, and will lead to further study into ways to increase neuroprotection of diseased neurons and future treatments for this disease.

FUNDED BY:
Douglas Goodfellow Charitable Trust

SHON RECEPTOR IDENTIFICATION
1113022

A/Prof Dong-Xu Liu,
Dr Christopher Squire, Dr Yan Li
Liggins Institute, University of Auckland
and School of Science,
Auckland University of Technology



A/Prof Dong-Xu Liu

Breast cancer affects one in nine New Zealand females in their life time. Each year, more than 3000 women in New Zealand are diagnosed with breast cancer with over 650 deaths reported. Understanding the mechanisms by which oncogenes drive breast cancer is the first step to develop a better treatment for breast cancer in the future. Two thirds of breast cancer are estrogen receptor (ER) positive and treated with anti-estrogen therapy. However, up to 50% of the patients have or will develop drug resistance during treatment, thus do not benefit from this therapy and end up with devastating consequences. SHON is a human specific oncogene, which is widely expressed in human cancers including breast cancer. Moreover, the expression status of SHON in breast tumours has been shown to a biomarker, which can predict the response of patients to anti-estrogen therapy. In this study, we used a variety of techniques to identify the molecules that could bind or regulate the functions of SHON in cancer cells. We have identified a few potential candidate molecules that may play an important role in SHON-regulated cellular activities in breast cancer. The characterisation of these candidates are under way.

FUNDED BY:
The Breast Cancer Research Fund

MRI AS BIOMARKER FOR RHEUMATOID ARTHRITIS 1114001

Prof Fiona McQueen, A/Prof Anthony Doyle, Prof Nicola Dalbeth, Karen Lindsay, Peter Chapman
Dept. of Molecular Medicine & Pathology,
University of Auckland

Prof Fiona McQueen

The aim of this project was to investigate changes in joint inflammation that occur when rheumatoid arthritis (RA) patients change drug therapy using the "Treat to Target" (T2T) strategy. In this strategy it has been suggested that therapy should not only aim for clinical remission but aim to suppress all inflammation seen on MRI scans. For this study, two groups of patients were investigated; those on conventional oral therapy and those starting biologic agents (including "anti-TNF" injectable drugs). Wrist MRI scans and clinical assessments were performed a) just before and b) four months after intensification of therapy and a total MRI inflammation score was obtained. Patients were assessed clinically for changes in arthritis disease activity and correlations between clinical and MRI outcomes were sought. We found that there was minimal change in the MRI inflammation score over 4 months, despite clinical improvement. There was no difference in the MRI inflammation response between the two groups. For the entire group there was a significant but weak correlation between change in disease activity score and change in MRI inflammation score. We concluded that MRI outcomes should not be adopted to direct T2T escalation as clinically-driven strategies are already successful.
Most patients do not achieve imaging remission currently, even those taking biologic agents.

Grants Completed continued

THE ROLE OF INTRACELLULAR AGEs IN THE DIABETIC HEART? 1114004

Dr Kimberley Mellor, Dist. Prof Margaret Brimble, Prof Lea Delbridge
Dept. of Physiology, University of Auckland

Dr Kim Mellor with her research team

Diabetic patients have 2.5-fold increased risk of heart failure. Impaired ability of the heart to relax between beats is commonly observed in diabetic hearts, but the underlying mechanisms are poorly understood. In this AMRF funded research project, we aimed to investigate the role of sugar-modification of cellular proteins in mediating heart relaxation disturbance in diabetes. We have developed new chemistry tools for investigating advanced glycation end products (AGEs), a particular type of damaging sugar-modification of proteins, in the heart and have identified that glycation modifies key intracellular proteins inside the heart muscle cells which are important for muscle contraction and relaxation. We have provided the first evidence that heart proteins called troponins are glycated, these findings open up new leads for understanding disease mechanisms and for developing new diagnostic strategies for early intervention.

WHY ARE KNEE LIGAMENT SURGERIES FAILING IN YOUNG PEOPLE? 1114008

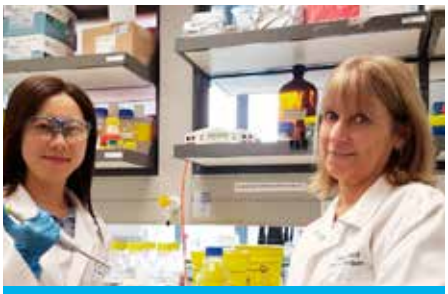
Dr David Musson, Dr Dorit Naot, Dr Mathew Street, Mr Brendan Coleman, Prof Jillian Cornish
Dept. of Medicine, University of Auckland

Dr David Musson

Injuries to the anterior cruciate ligament in the knee are incredibly common, especially in young active New Zealanders. To return our young sportsmen and women back to their active lifestyles orthopaedic surgeons will often rebuild their own ligaments with a small part of their hamstring tendon. However, it has recently been found that patients under the age of 20 are more likely to suffer a re-injury after this procedure, compared to patients over the age of 20, yet the reasons for this are unknown. We compared the biological properties of these tendons between the age groups and found that younger patient's tendons were structurally and mechanically different, and were also found to express higher levels of genes linked to the formation of tendon matrix. Our findings have provided biological evidence to the clinical observations recently found and have contributed to a change of practice by orthopaedic surgeons in Auckland who are now more likely to use a different, safer method to rebuild the knee ligaments of younger patients.

MUSCLE AS A SOURCE OF BONE ANABOLIC FACTORS 1115009

Dr Dorit Naot, Dr David Musson, Dr James Markworth, Dr Justin Fernandez, Prof Jillian Cornish
Dept. of Medicine, University of Auckland



Dr Dorit Naot (right) and colleague

Each year, over 80,000 people in New Zealand sustain a fracture, suffering acute pain and disability and sometimes long-term loss of independence. Thus, development of novel strategies for the improvement of fracture healing is a major public health priority. Studies have shown that when bone fractures, the adjacent muscle starts secreting factors that support the healing process. In addition, muscle stem cells can be recruited into the fracture site, transform into bone cells and help rebuild the damaged bone. Here, we developed an experimental system that models these interactions between bone and muscle cells. We found that when we induce inflammation, similar to the conditions created in early stages of fracture healing, bone cells recruit young muscle cells –inhibiting their maturation and inducing their directional movement towards the bone compartment. We also found that muscle cells respond to the presence of bone cells by secreting a large number of factors. We are now in the process of characterising these factors, and the molecular mechanisms involved in muscle cell recruitment into bone. These natural pathways and factors that support bone healing could be developed into therapeutics that assist the healing process when it is not optimal.

AUSTRALASIAN PAEDIATRIC HEAD INJURY RULES STUDY (APHIRST)

3112011

Dr Jocelyn Neutze, Dr Stuart Dalziel, A/Prof Franz Babl

Kidz First, Middlemore Hospital, Counties Manukau District Health Board

Dr Jocelyn Neutze

Clinical decision rules can assist in determining the use of computed tomography in children with head injuries. Three widely used high quality rules from the US (PECARN), from Canada (CATCH) and from the UK (CHALICE) have not been compared for accuracy in a large sample and it is not clear which rule, if any, should be used in Australasian emergency departments (EDs). With the support of the Auckland Medical Research Foundation the PREDICT (Paediatric Research in Emergency Departments International Collaborative) network undertook a prospective observational study of 20,000 children with head injuries of all severities at 10 EDs in Australia and New Zealand to assess the accuracy of the rules in the local setting. The key findings were that all three overseas rules were very accurate but that the PECARN rule did not miss a single patient requiring neurosurgery. These findings have implications for their wider implementation in Australasian EDs. In addition, a number of secondary analyses of this large data set have been conducted which provide an insight into important subsets of head injured children.

IMPROVING THE SURGICAL DRAINAGE OF NECROTIZING PANCREATITIS 1113013

A/Prof Anthony Phillips, Prof John Windsor, Dr Harvey Ho, Dr Lisa Brown

School of Biological Sciences, University of Auckland

Dr Lisa Brown in the laboratory

Percutaneous drains are tubes which drain infected fluid from inside the body. One such condition in which they are used is in infected dying pancreatic tissue. However, they are known to fail in 2/3rds of their use. This is usually due to drain blockage from particulate abscess material. We undertook to improve percutaneous drain success by investigating: 1) how to make the drains better by changing their design, and 2) what solutions could be flushed down the drains to help keep the open. We performed computer modelling and laboratory experiments to find out which parts of the drain design reduce fluid flow. Subsequently, we have developed new drain designs and have begun laboratory testing. We have also tested a total of 12 chemical solutions which could be used to liquefy tissues in the drains to enhance their drainage and prevent blockage. Our findings show that one of the best enzyme solutions is human gastric juice.

Gcn2 INTERACTOME

4113010

A/Prof Evelyn Sattlegger

Institute of Natural and Mathematical Sciences, Massey University

A/Prof Evelyn Sattlegger

The protein Gcn2 is an enzyme that is involved in many life-affirming biological functions, such as proper food selection, viral defence, the immune system, memory, and overcoming stress and starvation. Consequently, Gcn2 is a highly relevant protein, for medicine especially, as research has linked Gcn2 to various diseases/disorders such as aberrant feeding behaviour, dementia, cancer, and impaired viral defence. Given the significant impact these conditions have on health and quality of life, the need to find new drugs for their treatment is paramount. For this we first need to fully understand how Gcn2 is kept in check in cells, to ensure that Gcn2 executes the correct function at the correct time and appropriate location in the body. Our project contributed to filling a significant knowledge gap central to understanding Gcn2 regulation, which was the comprehensive identification of proteins that bind to Gcn2, and thereby keep Gcn2 in check.

MODEL-BASED LVD ASSESSMENT
1114006

Dr Avan Suinesiaputra, Prof Alistair Young, A/Prof Brett Cowan
Dept. of Anatomy with Radiology, University of Auckland

Prof Alistair Young & Dr Avan Suinesiaputra

Cardiac resynchronisation therapy (CRT) has been shown to be an effective treatment for heart failure. However, with such an expensive and invasive procedure, a significant proportion of CRT patients who do not respond to the treatment (about 30%) creates a burden in cost and management of heart failure patients. In this project, we developed a novel assessment method for cardiac dyssynchrony, which can be used to detect patients who will respond to CRT. The assessment is based on how different parts of the heart contribute to the global ventricular function. We derived this method by using finite element model of the heart, combined with continuous mathematical model of cardiac motion. The new method is being validated on 87 patients who were enrolled for CRT and have been followed for outcomes after 1 year.

POSTDOCTORAL FELLOWSHIPS

THE EDITH C. COAN RESEARCH FELLOWSHIP

Functional Characterisation of Cannabinoid Receptor SNPs Implicated in Mental Illness 1313001 & 1714001

Dr Natasha Grimsey Centre for Brain Research, University of Auckland

Dr Natasha Grimsey

Mental illnesses affect around 16% of New Zealanders and are difficult to diagnose and treat. Continued research is required to better understand these disorders. DNA variants called polymorphisms can alter proteins and cause them to function differently. Specific variants of Cannabinoid Receptor 2 (CB2), an immune system modulator, are more prevalent in patients suffering from mental illness than in the general population.

We have investigated what is different about the function of five these CB2 variants at a cellular level. While the majority of variants had no, or only subtle, effects on cellular responses, one of these had a profound influence on the longevity of CB2's effects following activation, which is likely to fundamentally influence the downstream functional effects on cells containing that variant. Further characterisation of the functional implications of this CB2 variant may ultimately lead to a better understanding of mental illness and will be important for further development of CB2-targeted therapeutics.

FUNDED BY: Edith C Coan Trust and the Kelliher Charitable Trust

perpetual guardian

Kelliher Charitable Trust

THE DAVID AND CASSIE ANDERSON RESEARCH FELLOWSHIP

Targeting neuropeptide receptors to alleviate the burden of pain 1314002 & 1715002

Dr Christopher Walker School of Biological Sciences, University of Auckland

Dr Christopher Walker

Pain is a prevalent and underappreciated factor in many diseases and conditions. Current treatments have significant side-effects which prohibit long term use or simply lack the required effectiveness. It is not surprising that many patients report inadequate pain management. This is particularly troubling as new pain treatments appear to suffer from similar draw-backs. New drug targets, which have new mechanisms of action, are required. Neuropeptide hormones are promising new targets for the treatment of chronic pain. To facilitate this research I established techniques for the culture of dorsal root ganglia and spinal cord neurons. These cultures were then optimised to utilize sophisticated miniaturized technologies to pharmacologically characterize neuropeptide signalling. This enabled me to explore how pain-modulating neuropeptides act on nerve cells at important sites for pain perception. Ultimately, I hope that the work will aid the development of drugs which target key receptors involved in chronic pain.

FUNDED BY: David and Cassie Anderson Medical Trust and the Kelliher Charitable Trust

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Kelliher Charitable Trust

DOCTORAL SCHOLARSHIPS

THE HENRY COTTON DOCTORAL SCHOLARSHIP

The Synaptic Basis of Huntington's disease 1213002

Wojciech Ambroziak Centre for Brain Research & Dept. of Physiology, University of Auckland

Dr Wojciech Ambroziak

In this project we sought to determine the source of synapse dysfunction in Huntington's disease (HD), a neurodegenerative disorder caused by a mutation in the huntingtin gene. It has been previously suggested that abnormal NMDA-type glutamate receptor distribution at synapses triggers cell death signalling pathways and might be responsible for the neuronal loss seen in HD. Here we studied the distribution of NMDA receptors in our established HD model, and determined whether a synaptic protein called SAP97 may be a potential therapeutic target for HD, as its acts as a regulator of glutamate receptor pools at synapses. Using super-resolution imaging and electrophysiology techniques, we found that the distribution of NMDA receptors is indeed altered in our HD model. Moreover, by co-expressing SAP97 in mutant HD neurons, we managed to prevent the abnormal NMDAR distribution and rescue normal synaptic transmission. Altogether the results allowed for the identification of SAP97 as a potential therapeutic target for HD and provide clues for the HD therapy in the future.

FUNDED BY: Henry Cotton Charitable Trust

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THE BARBARA BASHAM DOCTORAL SCHOLARSHIP

How does maternal glucocorticoid and MgSO4 treatment affect fetal neurodevelopment? 1213003

Christopher Lear Dept. of Physiology, University of Auckland

Dr Christopher Lear

Brain injury acquired before or during birth is significant cause of lifelong disability. Firstly, I investigated ways to identify fetuses at risk of infection and oxygen deprivation. We discovered a unique fetal heart rate pattern that may help identify severe infection. Furthermore, midwives and obstetricians ensure fetuses receive enough oxygen during labour by monitoring fetal heart rate. We showed that current clinical understanding of this is incomplete and based on outdated knowledge, which may explain the current poor ability to identify oxygen deprivation. Secondly, I investigated how a routine clinical treatment given to mothers at risk of premature labour, antenatal glucocorticoids, may influence brain injury in babies exposed to severe oxygen deprivation. This treatment vastly improves survival, but we found that it may worsen brain injury if given both before and after oxygen deprivation. One key mechanism for this is that glucocorticoids increase blood sugar levels. This finding may help explain the poor outcomes associated with maternal obesity/diabetes and suggests that excessive blood sugar levels may need to be prevented among babies that have suffered oxygen deprivation during birth.

FUNDED BY: Barbara Basham Medical Charitable Trust

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THE AMRF DOCTORAL SCHOLARSHIP

Imaging Mass Spectrometry of Metabolomic and Proteomic changes in Age-Related Lens Cataract 1213004

Mitchell Nye-Wood
Dept. of Physiology, University of Auckland

Dr Mitchell Nye-Wood

Cataract is primarily a disease of old age and Age-Related Nuclear (ARN) cataract is the leading cause of blindness in the world today. ARN cataract is characterised by protein modifications in the centre of the lens and antioxidant changes throughout the lens. This project studied an ARN cataract model using imaging technologies that map metabolic, protein, and optical changes in the lens. In the cataract model, the main lens antioxidant glutathione was seen to protect those proteins found in the outer lens regions, while in the lens nucleus, where this protection was not seen, proteins underwent a change in shape, in doing so releasing 'bound' water. This decreased the refractive index in the lens nucleus, making the lens less able to bend light into a focussed image. The effect this had on vision is reminiscent of presbyopia and the age-related loss of near-distance vision. This project was therefore successful in relating metabolic, proteomic, and optical changes in the aging and cataractous lens, leading to a more complete understanding of the role that oxidative stress plays in lens cataract formation.

Grants Completed continued

SIR HARCOURT CAUGHEY AWARDS

Role of the Intestinal Microbiome in Inflammation, Obesity, and Brain Health in Premature Infants 1717001

Prof Frank Bloomfield Liggins Institute, University of Auckland

Prof Jed Friedman

Through this award, we were delighted to welcome Professor Jed Friedman, Professor of Pediatrics at University of Colorado-Denver, to the Liggins Institute in August and September 2017. Professor Friedman is an internationally renowned expert in developmental programming, whose research primarily centres around the "Developmental Origins of Health and Disease" (DoHAD). Professor Friedman's work in maternal metabolic health and implications for offspring, childhood obesity and the microbiome are all highly relevant in the DoHAD space, and to research being undertaken at the Liggins Institute. In particular, his interest in how the microbiome interacts with host metabolism to impact upon liver metabolism and obesity is particularly relevant to clinical trials of microbiome transfer and on establishment of the new-born microbiome that are ongoing at the Institute. Professor Friedman spoke at several local and national events, ranging from meeting one-on-one with students and early career researchers within the Institute, to being an invited international speaker at the Queenstown Research Week 2017 in September, New Zealand's biggest annual scientific gathering. The Sir Harcourt Caughey Award offers a rare opportunity to invite international speakers of Professor Friedman's calibre to New Zealand. Such visits encourage international collaboration, stimulate constructive scientific discussion and importantly, provide students and early career researchers with a connection to the enormous, exciting global health research space to which they have begun to contribute.

Multicentre observational prospective study for the identification of prognostic factors in patients with mycosis fungoides/Sezary syndrome 2514003

Dr Bob (Cho Yui) Chan

Dept. of Dermatology, Auckland District Health Board

St John's Institute of Dermatology's Lymphoma team with Dr Bob Chan second on the left

The St John's Institute of Dermatology in London, UK, is a leading academic and clinical centre providing tertiary-level care across all aspects of Dermatology. St John's has the largest cutaneous lymphoma (a form of tumour in the skin) unit in the UK, caring for patients with a group of conditions which is uncommon yet can be associated with significant morbidity. I gained in-depth clinical experience in cutaneous lymphoma by working under some of the leading experts in this field. This included exposure to treatments not readily available in New Zealand. Furthermore, I helped implement the systems used at St John's to collect data for an international multicentre study looking at factors that might influence the outcome of patients with mycosis fungoides, a specific form of cutaneous lymphoma. Data collection for this study will be ongoing for another number of years and it is hoped that the findings of this collaboration will improve the care of patients with this condition. I also took the opportunity to gain experience across a wide range of dermatology subspecialty clinics during my time at St John's.

Challenges facing clinical trial design in medical oncology 2715001

Dr Michelle Wilson

Medical Oncology, Auckland District Health Board

Dr Michelle Wilson

Receiving the Sir Harcourt Caughey Award has helped me develop a number of projects here in Auckland. It allowed me time to complete seven projects that contributed to my MD on 'the challenges facing clinical trial design in oncology' which will be submitted at the end of May 2017. One of the projects was presented at the American Society of Clinical Oncology in June 2016, and two are currently under review for publication. The funding from this award has also created the opportunity for me to open the Auckland arm of the NEO clinical trial at Auckland hospital – a trial that has been key in the development of my passion for research. This award has helped create a solid foundation to build upon as I start my career as a clinician researcher. It has helped support me in taking the initial steps on the path I strive for my career to follow – a fine balance between clinical and translational research.

HEALTHEX EMERGING RESEARCHER AWARD

To attend the Genetic Association Course with Application to Sequence and Geotype Data at Max Delbrück Center for Molecular Medicine in Berlin, Germany, 22-26 June 2015

6714001

Mr Mohanraj Krishnan

Dept. of Obstetrics & Gynaecology, Auckland District Health Board

Attendees of the 2015 Genetic Association Course

I was very fortunate to have been awarded the AMRF HEALTHEX Emerging Researcher Award, 2014 as it provided me the funds to attend numerous leading universities and courses to promote my research and interests abroad. With this grant, I have presented a research poster at the INFANT symposium, University College Cork, Ireland, gave a seminar in the department of Women's Health, Kings College London, UK and attend the Genetic Association Course with Application to Sequence and Genotype Data at Max Delbrück Center for Molecular Medicine in Berlin, Germany. These events have nurtured my growth as a researcher creating a network of connections and opening up new international collaborations. I would sincerely like to thank AMRF for giving me the opportunity to pursue my ambitions and allowing me to develop my career in both clinical and research aspects of medical and evolutionary genetics.

BRINGING RESEARCH TO LIFE

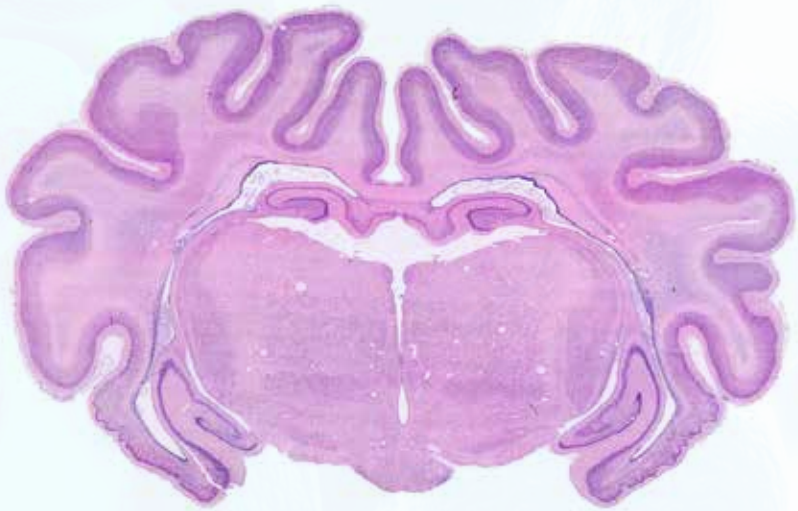
EVERY YEAR THE RESEARCHERS WHO HAVE BEEN AWARDED AMRF FUNDING GIVE BACK BY PRESENTING FREE PUBLIC LECTURES.

Dr Andrew Wood

On Thursday the 1st June 2017, AMRF were delighted to have Dr Andrew Wood present a public lecture on the topic of "New treatments of childhood leukaemia and paedeatric cancers". Dr Wood presented to a capacity crowd on his research into developing new treatments for childhood leukaemias with the goal of providing gentler and more effective treatments and improving cure rates.

In September 2017, Professor Peter Thorne presented to over 350 members of the public on the subject of "Hearing Loss, Tinnitus and Brain Health". With 18% of our New Zealand population impacted by hearing loss and tinnitus, Professor Thorne's talk was of great interest and many more people were able to view the lecture recording after the event on our website, www.medicalresearch.org.nz.

Professor Peter Thorne

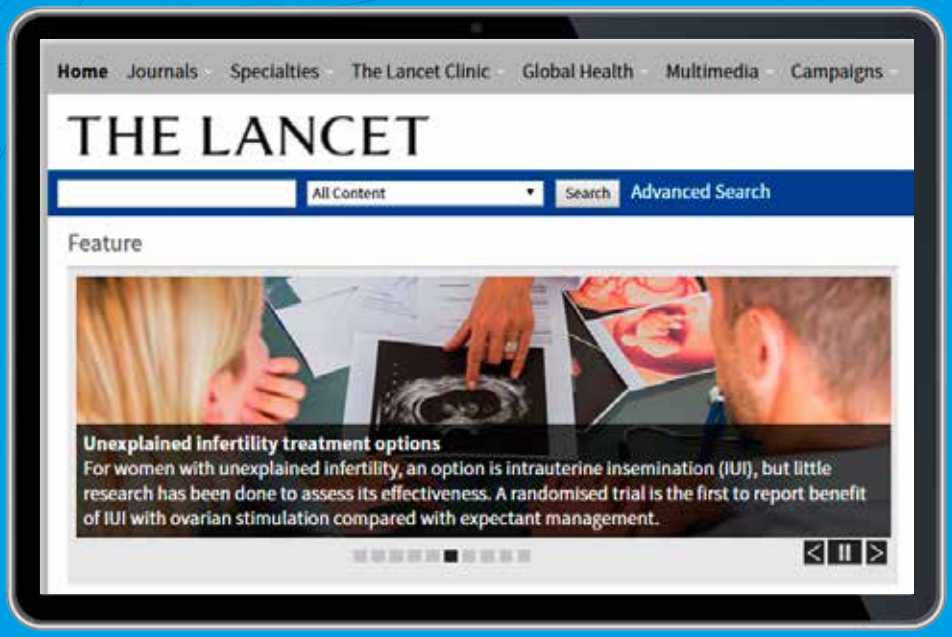


The folded outer layer of the brain (shown in dark purple) is the cerebral cortex and is the main part of the brain responsible for thinking. However, the cortex doesn't work alone, as it communicates and shares information with practically every region of the brain. This includes areas deep within the brain, like the hippocampus (the spiral-like structure found in the upper centre of the brain) which is critical in memory formation. The thalamus (the two large spheres at the centre of the brain) acts as a relay station for signals coming from different parts of the brain and also has the ability to control which messages are sent to the cortex, and which are not. The thalamus is therefore important in determining what information reaches our consciousness and whether we should be made aware of a sensation coming from elsewhere in the body. This impressive 'connectivity' linking the entire brain is what allows us to perform complex cognitive tasks. Unfortunately, these connections can be poorly formed or even damaged in babies born prematurely, leading to an increased risk of cognitive and learning disabilities. We are hopeful that treatments such as stem cells, anti-inflammatories or erythropoietin will help these connections repair and develop normally in these high risk babies.

Researcher: Christopher Lear (PhD candidate)

Supervisor: Prof Laura Bennet & Prof Alistair Gunn

Publications



The Lancet is one of the most prestigious general medical journals. Since its first issue in October 1823, the journal has "strived to make science widely available so that medicine can serve, and transform society, and positively impact the lives of people".[1]

AMRF-funded research has been, and continues to be, published in high ranking journals including *The Lancet*.

Here 'The TUI Study' led by Professor Cindy Farquhar, prominently featured in the rolling banner for the 23 November 2017 issue[2].

In Publication: Farquhar C, Liu E, Armstrong S, Arroll N, Lensen S, Brown J. (2018). Intrauterine insemination with ovarian stimulation versus expectant management for unexplained infertility (TUI): a pragmatic, open-label, randomised, controlled, two-centre trial. Lancet, 391(10119):441-450.

[1] www.thelancet.com/about-us
[2] www.the lancet.com, 23 November 2017

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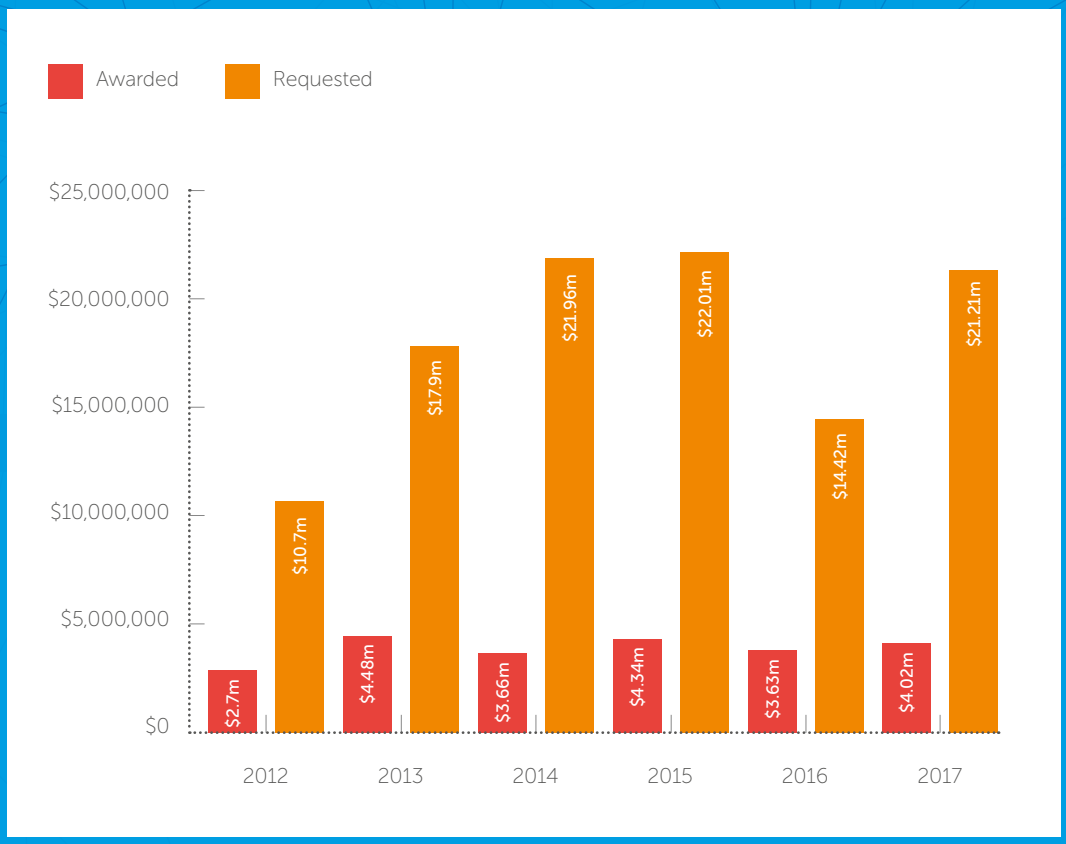
The generosity of the Rotary Club of Auckland Harbourside Inc., its members, and friends was on show at their annual Chinese New Year Ball, where over $70,000 was raised for research to find a blood test to predict premature birth.

Pictured: Right Honourable Bill English with Rotarians

The family and trustees of the Hugo Charitable Trust honoured the life of Chairman Mark Owens' father, Brian Owens, with both a named node in the AMRF Medical Sciences Learning Centre and a permanent named fund. The fund is specifically for pancreatic research and the gift enables significantly more pancreas-focussed research to be undertaken.

Financials 2017



There are many worthy requests for funding that we cannot support.

Thank you for your generosity.

Financial Highlights 2017

RESEARCH FUNDING 2017 $4,023,459 TOTAL RESEARCH FUNDING SINCE 1955 $71,600,000

FINANCIAL PERFORMANCE

	Note	2017 $	2016 $
Income			
Donations / Subscriptions	1	629,399	609,608
Investment Income		2,307,993	2,154,334
Trust Income / External Funding	1	879,118	731,277
Legacies/Bequests/Specific Donations	2	3,013,788	1,397,786
Net Gain on realisation of investments		451,959	107,698
Net Gain on currency fluctuations		16,010	(9,651)
Total		7,298,267	4,991,052
Expenditure			
Operational expenses		461,012	395,733
(Less Donation)	3	(461,012) Nil	(395,733) Nil
Research Grants	4	3,976,305	3,322,635
Depreciation on Grant Funded Assets		3,750	- 5,285
Reduction in value of investments		-	247,876
Total		**3,980,055**	**3,575,796**
Net Surplus / (Deficit)		**3,318,212**	**1,415,256**

The summary of financial highlights above have been extracted from the Audited Financial Statements which can be obtained by contacting the Foundation's office.

2017		2016
$629,399	Donations / Subscriptions	$609,608
$2,307,993	Investment Income	$2,154,334
$879,118	Trust Income and External Funding	$731,277
$3,013,788	Legacies / Bequests / Specific Donations	$1,397,786
$451,959	Net Gain on realisation of investments	$107,698

NOTES TO THE 2017 FINANCIAL REPORT

1. Donation & Trust Income includes grants, donations and external funding received from the following organisations:

Perpetual Guardian Administered Funds	
David & Cassie Anderson Medical Trust	205,000
N H Taylor Charitable Trust	40,000
The J & P Stilson Endowment Trust	100,000
Rose Richardson Estate	10,000
Edith C Coan Trust	120,000
John A Jarrett Trust	42,885
C E Lawford Estate	2,380

Public Trust Administered Funds	
Audrey Simpson Trust	4,000
Ralph Dingle Trust	3,000
Pauline Gapper Charitable Trust	6,500
Reed Charitable Trust	15,000

Other Trusts/Funds	
Douglas Goodfellow Charitable Trust	299,480
The Kelliher Charitable Trust	60,000
Marion Ross Fund	34,353
Maurice Paykel Charitable Trust	4,000

2. Legacies, Bequests and Specific Use Donations 3,511,407

Anonymous

The JI Sutherland Fund

Paul Stevenson Memorial Trust

Rotary Club of Auckland Harbourside Inc

Albert Frederick Strude

Estate of John Fleming

Estate of Shirley Tonkin

Estate of RG Beaver

Hugo Charitable Trust

Douglas Goodfellow Charitable Trust

3. Operational Expenses

The Foundation is grateful to the Harry, Hector, Douglas, and TB Goodfellow Funds for the external funding of operational expenses

4. Research Funding Approved 2017

PROJECT GRANTS (20)	2,488,036
POSTDOCTORAL FELLOWSHIPS (2)	416,881
David and Cassie Anderson Research Fellowship	
Edith C Coan Research Fellowship	
DOCTORAL SCHOLARSHIPS	
AMRF Doctoral Scholarships (3)	384,000
AMRF TRAVEL GRANTS (28)	76,078
OTHER GRANTS	
Kelliher Charitable Trust Emerging Researcher Start-up Grant (2)	60,000
Sir Harcourt Caughey Award	13,089
Gavin and Ann Kellaway Medical Research Fellowship	34,895
Douglas Goodfellow Repatriation Fellowship	299,480
Douglas Goodfellow Medical Research Fellowship	244,000
HealtheX Emerging Research Awards (3)	7,000
Less amounts required from previous years	(47,154)
TOTAL GRANT FUNDING 2017	3,976,305
TOTAL GRANTS AWARDED 2017	**4,023,459**

Members, Sponsors & Supporters 2017

WE ARE MOST GRATEFUL TO ALL THE INDIVIDUALS, TRUSTS AND ORGANISATIONS LISTED BELOW WHO HAVE GIVEN GENEROUS SUPPORT TO THE FOUNDATION DURING THE YEAR.

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Thanks also to our benefactors who wish to remain anonymous.

LEGACIES, SPECIAL ACKNOWLEDGEMENTS, SPONSORS, FUNDING PARTNERS 2017

Legacies and Bequests

Anonymous
Albert Frederick Strude
The Estate of John Fleming
The Estate of R.G. Beaver
The Estate of Shirley Tonkin

Special Acknowledgements

Anonymous Donors
Elliot Taylor
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Jean Lawry
Jeff Todd
JI Sutherland Fund
Murray & Sue Lee
Noel Davies
Paul Stevenson Memorial Trust
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The Douglas Goodfellow Charitable Trust
The Kelliher Charitable Trust
The Hugh Green Foundation
The Hugo Charitable Trust

Dr Shirley Tonkin OBE (pictured) had a medical and research career spanning over 60 years. Her findings in the 1980s led to an immediate 60% reduction in cot death in New Zealand, saving many infant lives. Her generous bequest to the AMRF ensures that life saving research into infant health will continue now and into the future.

Farewell To Kim McWilliams

In late 2017, AMRF said farewell to Executive Director Kim McWilliams after seven years in the role. Joining in 2011, Kim came from a largely commercial background, having managed the philanthropic and sponsorship portfolios of Westpac and the AMP Group of businesses in New Zealand. Her strengths include a wide variety of experiences in management, public relations, marketing, and philanthropy. Kim was on the Board of Philanthropy NZ as Deputy Chair and currently serves on the boards of the CatWalk Spinal Cord Injury Trust and Auckland Philharmonia Orchestra.

While at AMRF, Kim set the Foundation on a new path with innovative outreach programmes to broaden our member and supporter base and worked to ensure the Foundation is financially strong and well-equipped to meet our medical research challenges into the future. The partnerships she developed with Perpetual Guardian (Guardian Trust), among others, significantly increased the amount of medical research funding available to our applicants. Kim worked to establish the AMRF Senior Research Fellowship at the University of Auckland's Faculty of Medical and Health Sciences, helping to fill the gap in early career awards, the time when young and emerging researchers are most likely to struggle to secure funding.

Kim has established close ties with our many friends and supporters and has worked tirelessly with the large team of health and medical research professionals at the University of Auckland with whom the AMRF is closely associated. During her time as Executive Director, Kim built a talented and supportive team who assisted with the devlopment of the Foundation over that time.

Kim has joined the Private Wealth Network as Director – New Zealand, and we wish her all the very best.

AMRF welcomes Sue Brewster to the Executive Director role.

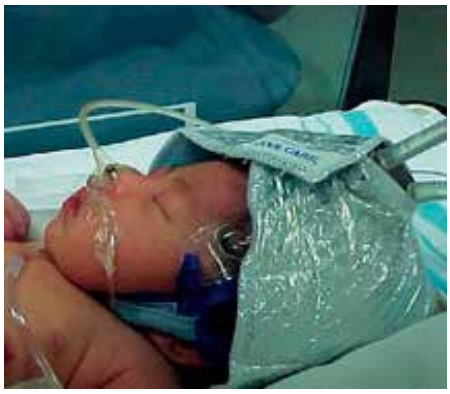
Recognition For Our World-Class Researchers

"If I hadn't had the sustained support from organisations like AMRF the cooling treatment simply would not have happened. It took years of intensive research to lead to this treatment and it has made a phenomenal difference to the mortality rate and health of babies all over the world."
Professor Alistair Gunn

2017 was a year that saw many of our New Zealand researchers deservedly recognised for their world-class research, both here and on the international stage.

In October 2017 Professor Alistair Gunn was awarded the prestigious Beavan medal for excellence in translational health research.

Professor Gunn's work into treatments to help protect a new-born baby's brain from brain damage started back in 1983 and, with the help of a grant from AMRF, he developed the world's first cooling machine. The cooling machine became a fundamental part of the research process that led to mild cooling becoming a global standard of care for treating babies with brain injury caused by low oxygen.



Similarly, Distinguished Professor Jane Harding has been leading research into babies but of a very different nature to that of Professor Gunn. Her work focuses on treating at-risk babies with a sugar gel to reduce the risk of low blood sugar - neonatal hypoglycaemia - which can lead to brain damage.

The sugar gel treatment has been widely adopted in New Zealand and in many other parts of the world and resulted in Professor Harding being the first person outside of the United States to win the acclaimed Norman J. Siegel New Member Outstanding Science Award from the American Pediatric Society.

AMRF first funded Professor Harding and her team early in her career and continue to fund this life-changing research with a new 'hPOD' trial underway.

HEALTHIER KIDS

Therapeutic hypothermia (cooling babies and their brains) reduces the rate of the most severe complications of low oxygen at birth by about 12%

How You Can Help

Since 1955, our supporters have contributed to establishing and retaining our best emerging research talent, repatriating key researchers and building capability in the New Zealand research community.

With 100% of all donations being invested directly into medical research, our supporters are confident that every dollar they gift goes towards funding research excellence.

Please join us in our mission and know you are at the heart of enabling ongoing, critical advances in medicine and improving the quality of life for all New Zealanders.

BECOME AN AMRF MEMBER

When you become an Annual or Life Member of the Foundation, you will receive access to the latest information in the research world, a hard copy of our biannual newsletter and our Annual Report, a classic AMRF pin and invitations to lectures and member only events.

MAKE A DONATION

Donations are a vital part of our annual funding programme. You may choose to give annually, monthly or to pledge an amount over time. Ann Kellaway, who together with her late husband Gavin, donated towards the creation of a fellowship fund. Ann explains why:

"Gavin and I chose to do this in our lifetimes to feel the excitement of giving. I encourage those of you thinking of giving to do so in your lifetime to be able to see what's happening, to see the research that you are hoping for."

Contact us:

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If you would like to speak to us, phone 09 923 1701.

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You may consider a donation in remembrance of someone special or in celebration of a special occasion such as a birthday or anniversary. We will always send a personalised letter advising that you have made this special donation.

MAKE A BEQUEST OR MAJOR GIFT – A LASTING INVESTMENT IN MEDICAL RESEARCH

"Giving a major gift to the AMRF was a natural choice by the Hugo Charitable Trust. Our Trust donations are given to organisations that build on my father's legacy of creating future benefit for Aotearoa New Zealand and the work that the AMRF funds is all about the current and future health of our people. We know too that the AMRF has a very rigorous assessment process for all applications and have real trust the money will be invested wisely, based on robust medical criteria." **Maryanne Owens, Founder, Hugo Charitable Trust.**

Your support, no matter how big or small, is invaluable in helping to make life-changing improvements in the field of medical and health. Please consider supporting us and the future of medicine by either signing up as a member or providing a donation through:

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