Auckland Medical
Research Foundation

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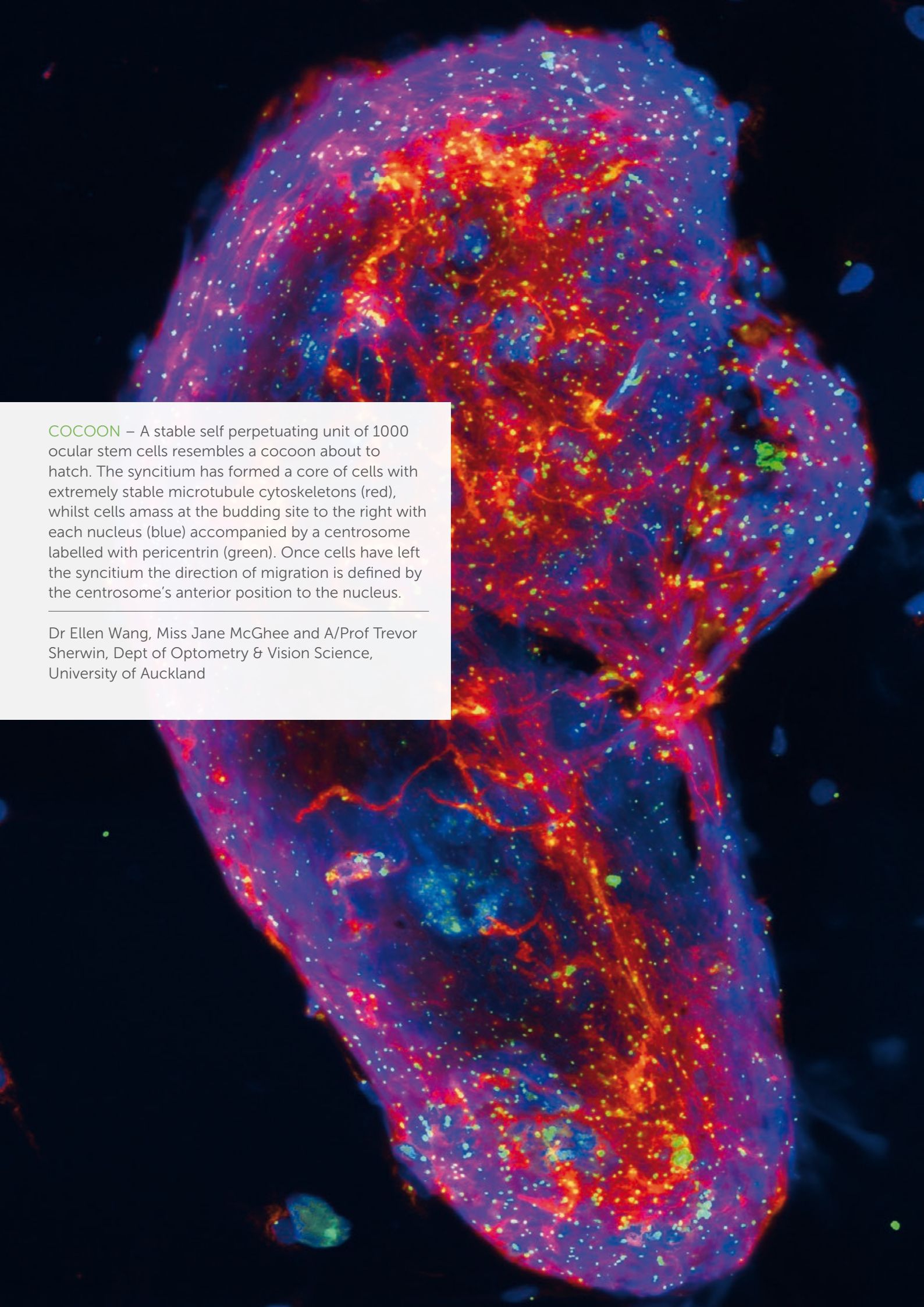

COCOON – A stable self perpetuating unit of 1000 ocular stem cells resembles a cocoon about to hatch. The syncitium has formed a core of cells with extremely stable microtubule cytoskeletons (red), whilst cells amass at the budding site to the right with each nucleus (blue) accompanied by a centrosome labelled with pericentrin (green). Once cells have left the syncitium the direction of migration is defined by the centrosome's anterior position to the nucleus.

Dr Ellen Wang, Miss Jane McGhee and A/Prof Trevor Sherwin, Dept of Optometry & Vision Science, University of Auckland

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Mr WD Goodfellow, OBE

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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 2014

Jeff Todd.

Board Report

The AMRF believes that significant advances in medicine can only come about through quality research.

The Foundation strives to improve the health of New Zealanders through funding the highest quality medical research of all kinds – $56 million distributed since our inception in 1955. 2014 saw $3.62 million awarded. We'd like to thank our external funding partners including Perpetual Guardian, Public Trust, Kelliher Charitable Trust, Manchester Trust, and the Paul Stevenson Memorial Trust. Their additional funds make a significant difference in a difficult funding environment.

Building capacity and capability for a world-class research community in New Zealand is also at the heart of our philosophy and vision. We encourage personal research development gained through overseas experience but also support the repatriation of researchers home to New Zealand through the prestigious Goodfellow Repatriation Fellowship.

The Foundation is most grateful for all contributions made in 2014 and in particular for the generous annual endowment which covers our operating expenses.

Our Executive Director, Kim McWilliams, and her small team have ensured the Foundation's operations have been conducted with professionalism and efficiency. The team has been tireless in its efforts and innovative in its approach to growing our capital base and in turn our support, in a very competitive philanthropic environment.

My personal thanks are extended to Trustees, Board Committee Chairs and Members who all contribute generously with their time and experience. In particular, I pay tribute to the Medical Committee, under the Chairmanship of Professor Peter Browett, whose demanding but essential work in reviewing applications for grants absorbs many hours in evaluation and assessment.

With the continuing commitment of Trustees, staff, members, grant holders, funding partners and donors the future success of the Foundation is assured.

Jeff Todd

President

Prof Peter Browett.

Medical Committee Report

Once again, a tough funding environment has kept the number of applications to the AMRF in 2014 high, with a total of 74 grants being awarded from 260 applications across a broad range of grant categories. As always, many worthy applications were unable to be supported, but we can proudly announce that the Auckland and Northland research community has benefited from the AMRF awarding $3.62 million to support world class biomedical, clinical and population health research being undertaken within our catchment area.

In a similar manner to 2013, this year we were able to support a high number of new and emerging researchers through the awarding of two post-doctoral fellowships, four doctoral scholarships, and importantly in memory of our patron who sadly passed away, we awarded the Douglas Goodfellow Medical Research Fellowship to an outstanding medical graduate to undertake his PhD studies. In addition to this, five of our sixteen project grant recipients were deemed to be 4 or less years post senior qualification (PhD and MD), highlighting the strength of emerging researchers and the AMRF's support of them in the early stages of their careers.

This would not have been possible but for the hard work of the Medical Committee who voluntarily dedicate their time and expertise to our robust peer review process. In 2014 we welcomed A/Prof Nigel Birch, from the School of Biological Sciences, University of Auckland to our committee as a full member, and farewelled Prof Ngaire Kerse who provided valuable insight through her background in general practice and primary care and great entertainment during the five years she sat on the committee.

2014 was also the first year of the AMRF operating a fully web-based electronic application and assessment system. The AMRF Portal was well received by applicants, referees, medical committee members and AMRF staff, and I wish to thank Leigh Harrison of ElseApps Ltd and our Research Programme Manager, Dr Hannah Gibbons, for their hard work in making this a success. My thanks also extend to the AMRF Office staff for their support of the Medical Committee throughout the year.

Peter Browett

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

KNOWLEDGE GAINED THROUGH RESEARCH MEANS BETTER PATIENT CARE AND IMPROVED MEDICAL TREATMENTS

AMRF EXISTS FOR ONE PURPOSE: to improve the health of New Zealanders through funding the highest quality medical research. We believe that such research is vital to making genuine advances in patient care and medical treatments. But that research comes at a cost...

GROWING A SUSTAINABLE FUND

Funding for medical research in New Zealand is critical for our future health. In 1955 a group of Auckland medical and business leaders, united in their concerns about serious shortfalls in funding for medical research, came together to form the AMRF. From small beginnings, they grew a sustainable and enduring investment fund to provide research grants every year.

OUR COMMITMENT TO FUNDING EXCELLENCE

Our Medical Committee (comprised of clinical and biomedical scientists) appraises every request for funding and will consider applications from every field of modern medicine. Only the best applications meet our rigorous standards when assessing the medical and scientific importance of new research proposals.

SUPPORTING THE BEST NEW ZEALAND RESEARCH TALENT

AMRF have supported many successful scientists in New Zealand including Prof Sir Peter Gluckman, Sir Brian Barratt-Boyes and Prof Sir Graham Liggins.

Through our funding, we help to establish and retain our best emerging talent, repatriate key researchers and build capability in the New Zealand research community.

YOUR DONATION IS APPLIED ONLY TO MEDICAL RESEARCH

We apply 100% of donations, bequests, legacies and income from investments to medical research. Our operating expenses are met by a separate charitable fund. So if you donate to the AMRF, you can be assured that every cent of your donation is applied to advancing the highest quality medical research.

A SELECTION OF FIELDS SUPPORTED BY YOUR DONATIONS

Arthritis | Asthma | Biomedical Imaging | Bones & Muscles | Cancer | Cardiovascular | Cellular & Molecular Biology | Diabetes | Gastrointestinal | Endocrinology | Hearing | Immunology | Infectious Disease & Vaccine Development | Kidney | Liver | Lungs | Maternal & Newborn Health | Mental Health | Neuroscience & Neurological Disease | Nutrition | Pancreatitis | Population Health | Reproduction | Skin Biology & Wound Healing | Stem Cell Biology | Surgery | Vision.

An AMRF success story

DEVELOPING NEW TREATMENTS FOR TINNITUS – BY DR GRANT SEARCHFIELD

Dr Grant Searchfield with a model of the ear.

Tinnitus, also known as ringing in the ears or head, is a highly prevalent condition afflicting 7% of New Zealanders. Severe tinnitus can lead to disruption of work, social activities and sleep; and lead to anxiety and depression. In the last decade there have been tremendous advances in understanding the mechanisms underlying tinnitus, but the search for a cure continues. Tinnitus is complex; studies of brain activity indicate auditory, memory, attention and emotional parts of the brain work together to create it.

Effective medications for tinnitus have not yet been found, and surgery is seldom successful. Tinnitus lacks a specific site of generation and there is no reliable method for identifying its presence or absence. Tinnitus research relies heavily on circumstantial evidence, changes in brain activity in EEG or MRI activity when tinnitus is present and absent, and self-reported tinnitus handicap using questionnaires.

Tinnitus can be reduced in some people by low levels of electrical current applied to the scalp, while the most effective clinical treatment for tinnitus is a combination of counselling to reduce tinnitus distress and sound stimulation using hearing aids or masking sounds to make the tinnitus difficult to hear.

Grant Searchfield and his team have successfully studied many aspects of tinnitus from its auditory-neural mechanisms to its clinical management and prevalence in New Zealand.

Q1. Please can you tell us about yourself and how you came to be in this area of research?

I'm a graduate of the audiology program at the University of Auckland. I first worked in public and then private audiology practice where I discovered the catastrophic effect tinnitus could have on people's lives, and how difficult it was to treat. I was encouraged by Dr Ron Goodey, a well known ENT specialist, to develop clinical skills in this area, and eventually to return to University to undertake a PhD. My PhD in Professor Peter Thorne's auditory physiology lab investigated how damage to the ear could translate into activity that the brain might interpret as sound. Towards the end of my PhD I also became the inaugural director of the University's Hearing and Tinnitus clinic, enabling transfer of research into clinic practice. I've been very lucky in being able to combine my passion for research with clinical roles. The combination of clinical practice and research has enabled the development of a successful translational research program.

Q2. How has AMRF funding allowed your research to evolve or progress to the next stage?

The AMRF funding we have received has been critical for the success of my research group. The funding has aided trial of new methods, laying the foundations for future studies. There are few funding opportunities internationally specific to tinnitus and the competition for these is very high. Recent funding we have been awarded by AMRF through the J M Cathie Trust (administered by Perpetual Guardian) has facilitated research on the mechanisms behind a theoretical framework of tinnitus called Adaptation Level Theory. We have used sound stimulation and non-invasive brain stimulation to try and piece together mechanisms responsible for tinnitus suppression, in a hope to identify targets for future therapies.

Q3. Please can you tell us about how your research outcomes are being used in New Zealand, and the benefit to New Zealanders from your research:

The treatment framework that we have developed is now being used in New Zealand and Australia, as are hearing aids based on some of our concepts. Assessment tools, such as the Tinnitus Functional Index (a USA questionnaire that I collaborated in developing) has now been validated for use in New Zealand. Probably the most direct benefit to New Zealanders is the quick translation of research from our lab to the University of Auckland's Hearing and Tinnitus clinic. The clinic has an international reputation as a leading clinic

Dr Grant Searchfield using a hearing aid testing machine.

in tinnitus management. In collaboration with Auckland UniServices I plan to launch a website soon through which clinicians and patients will be able to access some of our latest research and sound therapy.

Q4. Have there been significant overseas breakthroughs or collaborations resulting from your research? Please can you describe your team's contribution to the global research effort in your area:

Our research has been well received internationally and is recognised as leading the field in some areas. Importantly, it is seen as being undertaken in a careful, rigorous manner. I'm regularly invited to speak at international tinnitus conferences and I'm on the scientific advisory board of both the American Tinnitus Association and the Tinnitus Research Initiative, the two largest tinnitus organisations internationally. We've collaborated in clinical trials of tinnitus sound therapy with researchers in Italy and regularly undertake work with hearing aid manufacturers in the USA and Europe. Most recently we've begun an exciting collaboration with Professor Marom Bikson's lab at The City University of New York exploring what happens in the brain with non-invasive stimulation. Work that we are currently undertaking with Behavioral Medicine and Pharmacy in Auckland, exploring the use of a psychoactive substance on tinnitus, has also gained a considerable amount of international attention. New Zealand is recognised as a hotbed of tinnitus research, with wonderful work happening in Otago as well. An indication of the mana of NZ tinnitus research was the very successful hosting of the TRI International Tinnitus conference in Auckland in early 2014.

Q5. What is the next step in your research plan?

Tinnitus research has traditionally used quantitative group designs, measuring a few variables across a group of tinnitus patients, sometimes before and after an intervention. However in considering the very variable nature of tinnitus, it is likely that individual differences are not properly accounted for, leading to misinterpretation of results. A solution is to make use of multiple case studies investigated in depth over an extended period of time. This research will use short-term (brain stimulation) and long-term (hearing aid) use to perturb tinnitus. We plan to use a mixed model design consisting of multiple behavioural (psychoacoustic, psychometric, and qualitative) and objective (fMRI) measures along with modelling to follow patients for two years. To achieve this we are learning new techniques from colleagues in the CBR, BRNZ and in New York; we are incredibly grateful for their support.

Q6. What is your greatest hope or dream for research in this field?

An end goal would be to find a cure(s) for the millions worldwide with tinnitus. If my work can contribute to this I'd be very happy. In the meantime we will continue to explore new and imaginative ways of trying to reduce tinnitus suffering.

FUNDED BY: Jean Cathie Research Fund

perpetual guardian

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Join AMRF as an Annual or Life Member and receive reports and newsletters, and invites to special events and presentations.

See our website www.medicalresearch.org.nz or call us on (09) 923 1701 for further details.

GRANTS AWARDED

75 Grants Awarded Totalling $3,655,372

- Neuroscience (13) | $420,341 11.50%
- Other (5) | $12,644 0.35%
- Population Health (1) | $2,500 0.07%
- Pulmonary, Renal, Nephrology and Gastrointestinal Sciences (3) | $19,082 0.52%
- Reproduction, Development, Maternal and Newborn Health (8) | $259,180 7.09%
- Sensory Sciences (1) | $2,958 0.08%
- Stem Cell Biology (1) | $3,254 0.09%
- Surgery (3) | $439,320 12.02%
- Biomedical Imaging (4) | $413,798 11.32%
- Cancer (7) | $532,590 14.57%
- Cardiovascular Science (4) | $226,498 6.20%
- Cellular and Molecular Biology (9) | $316,666 8.66%
- Endocrinology, Metabolism and Nutrition (2) | $205,863 5.63%
- Infection and Immunity (7) | $358,312 9.80%
- Musculo-skeletal Science (7) | $442,366 12.10%

$ Value each theme
% Total expenditure

Grants Awarded

PROJECT GRANTS

MRI AS BIOMARKER FOR RHEUMATOID ARTHRITIS ($159,560 – 2 years) 1114001

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

The management of rheumatoid arthritis (RA) has undergone a revolution in the past decade. New drug therapies can markedly reduce joint pain and many patients can achieve clinical remission with reduction in long-term joint damage. It is important to assess patients' responses to different drug regimens. MRI scanning is an ideal imaging biomarker as it reveals inflammation affecting the lining of the joint (synovitis) and the bone beneath (bone oedema or BME) plus joint damage (erosions and cartilage thinning). The Auckland Rheumatology Imaging group has an established track record in MRI research in RA. We now plan to move our expertise into the clinical arena. New Zealand rheumatologists use specific drug regimens (conventional and biological), to try and achieve remission in a "Treat-to-Target" approach. They monitor patients' progress using the Disease Activity Score (DAS) which quantifies joint inflammation clinically. The aim of this study is to obtain MRI inflammation scores (synovitis, BME, tenosynovitis) before and after each drug intervention, to see whether changes in MRI scores mirror changes in the DAS. We intend to compare MRI and DAS responses between 2 groups of patients: those receiving conventional disease-modifying antirheumatic drugs (cDMARDs) and those receiving biological therapies (bDMARDs).

A NON-INVASIVE TEST OF EMBRYO QUALITY ($120,285 - 2 years) 1114002

Dr Lynsey Cree, Prof Larry Chamley, Prof Peter Stone, Dr Matthew VerMilyea
Dept of Obstetrics and Gynaecology, University of Auckland

In vitro Fertilisation (IVF) is a commonly used technique for infertility and its use is rising due to women delaying child bearing. Annually 350,000 babies are born using this technique, however success rates are still low. Developing techniques to select the best embryo for transfer in order to maximise the likelihood of a healthy live baby represents one of the major challenges in reproductive medicine. Recent data suggests that embryos expel genetic material into the media in which they are cultured. This is a novel finding that has the potential to provide a non-invasive way to look at the genetic complement of the embryo. Current techniques used to do this are invasive and some may harm the embryo. Our research aims to investigate whether this genetic material, located within the media, can give meaningful data of embryo quality and whether it can be used to select only those embryos with the correct chromosomal makeup. This is particularly important for older women whose embryos are more likely to have an incorrect chromosomal makeup. Selecting embryos with the correct chromosomal makeup will increase IVF success rates. This novel research project has the potential to change the future of embryo screening in New Zealand and internationally.

EFFECTIVENESS OF FOOTWEAR IN PEOPLE WITH GOUT ($106,553 – 2 years) 5114003

Prof Keith Rome, A/Prof Nicola Dalbeth, Prof Peter Gow, Prof Peter McNair, A/Prof Alain Vandal
Dept of Podiatry, Auckland University of Technology

Gout is a major cause of musculoskeletal disability in Aotearoa New Zealand. Foot pain occurs in most people with gout. There is strong evidence that many people with gout wear inappropriate or poor quality footwear, and that ill-fitting footwear may contribute to further foot problems. We have shown in a recent feasibility study that footwear with good cushioning, motion control and adequate width reduces foot pain and disability in the short term. We propose a long-term randomised controlled trial examining the effects of a footwear intervention on foot pain and disability. The trial will assess the effect of standard podiatric care and a relevant footwear intervention against standard podiatric care only. The study findings will be used to make evidence-based recommendations regarding footwear intervention for people with gout.

THE ROLE OF INTRACELLULAR AGES IN THE DIABETIC HEART ($159,335 – 2 years) 1114004

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

In New Zealand, more than 200,000 people are currently diagnosed with diabetes and the burden falls disproportionately on the Maori and Pacific Island populations, with the prevalence and death rates approaching double those of Pakeha. Diabetic patients have 2.5-fold increased risk of heart failure. The prevalence of diastolic dysfunction in type 1 and type 2 diabetes is estimated to be as high as 40-75% without overt coronary artery disease. The myocardial origins of this vulnerability are poorly understood and effective treatment strategies are lacking. This study aims to establish that in diabetes – glycation of intracellular proteins in the heart is a pathology to target therapeutically. In characterising intracellular glycation as a novel component of diabetic cardiomyopathy, this project has potential to contribute a highly significant advance in knowledge in this field – and to prompt an innovative paradigm shift in thinking about causation of diabetic cardiopathology. It is anticipated

that this research will translate into specific fundamental outcomes relating to the science and the treatment of heart failure in diabetic patients.

FUNDED BY: Marion Ross Memorial Fund

PROTEOMIC PROFILING OF PRODRUG-ACTIVATING ENZYMES IN LEUKAEMIAS ($158,973 – 2 years) 1114005

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

The anticancer prodrug PR-104, developed in the University of Auckland, was designed to be activated by reductase enzymes in tumours under conditions of low oxygen (hypoxia), which is a hallmark of tumours. During its evaluation in clinical trials with solid tumours, pre-clinical research identified a reductase, AKR1C3, which also activates PR-104 in the presence of oxygen. AKR1C3 is highly expressed in some leukaemias. Given that the bone marrow becomes hypoxic in advanced leukaemias, it was suggested that PR-104 might exploit both AKR1C3 and hypoxia, leading to a phase I/II trial of PR-104 in relapsed acute myeloid and lymphocytic leukaemias. The trial showed good although variable responses, but only limited evaluation of biomarkers was undertaken. We will develop a targeted proteomics assay for PR-104 reductases, using a powerful mass spectrometry approach that allows simultaneous quantification of large numbers of proteins in clinical samples. The assay will be optimised for bone marrow and blood samples from patients and its ability to predict metabolic activation of PR-104 will be evaluated. If successful, the assay will be used in subsequent trials of PR-104 in human leukaemias to assess its role in identifying responsive patients in a personalised medicine context.

FUNDED BY: Pritchard-Coutts Charitable Trust

MODEL-BASED LVD ASSESSMENT ($125,014 – 2 years) 1114006

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

Ventricular dyssynchrony is the main predictor for cardiac resynchronisation therapy (CRT), an invasive procedure that can dramatically improve the morbidity and mortality of patients with chronic heart failure. However, 30% of patients who undergo CRT do not receive any benefit due to the lack of appropriate selection criteria, including current assessment technique. We aim to develop a more accurate and reproducible left ventricular dyssynchrony (LVD) assessment method based on mathematical modelling of the left ventricle derived from cardiac MRI. We are also investigating a novel prognostic prediction method based on multi-dimensional analysis of shape, motion and auxiliary diagnostic information, such as scar tissue location and electrical timing. This project will provide a valuable clinical tool to assess ventricular dyssynchrony prior to CRT procedure.

FUNDED BY: AC Horton Estate

SELECTIVE INHIBITORS OF MRSA PYRUVATE KINASE AS STRUCTURALLY UNIQUE, NEXT-GENERATION ANTIBIOTICS ($12,000 – 2 years) 1114007

Dr Jonathan Sperry
School of Chemical Sciences, University of Auckland

This research will have implications in the treatment of infections caused by antibiotic resistant bacteria. Successful collaborative efforts with The University of British Columbia (UBC) have identified a small molecule inhibitor of methicillin-resistant staphylococcus aureus (MRSA) pyruvate kinase (PK) that exerts this inhibitory activity selectively over human isoforms. We will use these preliminary results to guide the rational design of a focused compound library, which will be sent to UBC for further biological analysis against MRSA PK. By conducting several iterations of this synthesis/biological evaluation process, we will develop potent, selective inhibitors of MRSA PK well-suited for in vivo evaluation as structurally unique antibiotics that work on a novel biological target compared to existing therapies.

WHY ARE KNEE LIGAMENT SURGERIES FAILING IN YOUNG PEOPLE? ($149,171 – 2 years) 1114008

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

Tears of the anterior cruciate ligament, an important stabiliser of the knee joint, are a significant clinical problem in active, young individuals, with surgeries costing over $18 million per year in New Zealand. Recent data has highlighted that patients under the age of 20 undergoing surgical reconstruction of their anterior cruciate ligament are more prone to re-tearing. This study aims to understand the biological mechanisms behind this phenomenon by comparing the mechanical strength, structure and gene expression profile of biopsies from patients under the age of 20 and biopsies from those over the age of 20 undergoing anterior cruciate ligament reconstruction.

TARGETING THE MECHANISM OF HOST RECOGNITION TO PREVENT BACTERIAL INFECTIONS ($53,580 – 1 year) 4114009

Dr Xue-Xian Zhang, A/Prof John Harrison, Dist. Prof Paul Rainey, Dr Stephen Ritchie
Institute of Natural and Mathematical Sciences, Massey University

With the widespread increase of bacterial resistance to antibiotics, new strategies to prevent and treat healthcare-associated infection are urgently required. This proposal addresses a crucial gap in our current understanding of how bacteria cause disease - namely, how pathogenic

Grants Awarded continued

bacteria recognise vulnerable hosts for successful colonisation and immune evasion. To date, our research has focused on Pseudomonas aeruginosa, an environmental pathogen that causes a wide range of healthcare-associated infections and pulmonary infections in people with chronic lung diseases, particularly cystic fibrosis. Recent progress has led us to a novel hypothesis that P. aeruginosa recognises urocanate in human tissues and use it as a trigger for bacterial invasion. To test this hypothesis, we will develop the analytic techniques that are essentially required for the detection of urocanate in chemically complex human samples (e.g., sputum, urine and wound fluid). Next, we will screen ~200 specimens from patients with various diseases (including asthma, diabetes and cystic fibrosis) in order to identify the urocanate-containing tissues for further investigation into the association between urocanate concentration and predisposition to bacterial infection. The data will form the basis for the development of new strategies to prevent bacterial infection through interrupting the urocanate-mediated host recognition.

CREATING NEURAL BRIDGES: A CONDUCTING POLYMER NEUROTRANSMITTER RELEASING SYSTEM ($150,215 – 2 years) 1114010

Dr Darren Svirskis, A/Prof Johanna Montgomery, Prof Jadranka Travas-Sejdic
School of Pharmacy, University of Auckland

Advancements at the Brain-Machine interface have enhanced human life, for example cochlear implants to enable hearing and deep brain stimulation to alleviate symptoms of Parkinson's disease. We hypothesise that neurotransmitter loaded Conducting Polymers (CPs) can function as neural bridges, modifying neuronal action potential firing patterns and facilitating neuronal communication. We propose to develop a glutamate releasing CP responsive to the intrinsic electrical activity of neurons. We will culture neurons together with CPs in vitro, forming neural bridges. For the first time, we will study how action potentials in living neurons alter the properties of stimuli-responsive CPs. Using these neural bridges, we will determine if the firing of one neuron can trigger a CP to release a neurotransmitter and subsequently influence the firing rate of a second neuron. The data from this research will provide a platform to develop new treatment strategies for conditions of abnormal neuronal signalling, such as autism, epilepsy, nerve injuries and hereditary sensory impairments. The methods developed in this research could be used to study and manipulate other electrically active cells such as those found in the heart and gastro-intestinal tract.

IMPROVING PATIENT RECOVERY AFTER ABDOMINAL SURGERY USING A LONG ACTING LOCAL ANAESTHETIC IMPLANT ($154,940 – 2 years) 1114011

Dr Manisha Sharma, Prof Andrew Hill, Dr Darren Svirskis
School of Pharmacy, University of Auckland

Major abdominal surgery is associated with post-operative pain, fatigue, long hospital stays and significant resource consumption. Currently, patients are commonly administered analgesics (opioids), or local anaesthetics during and after surgery. The use of opioids is associated with serious systemic side effects. Local anaesthetics have shown better patient recovery as they act by blocking nerve conduction from the site of surgery. However, the local anaesthetics are administered as a solution using an elastomeric infusion-catheter device. These infusion devices use bulky, expensive pumps, and require technical expertise of trained staff throughout the period of therapy. In addition, this system may also be complicated by microbial infection or blockage. This not only causes patient inconvenience but also increases the duration of stay in the hospital further adding to healthcare costs. This proposal aims to develop polymeric non-biodegradable implantable system loaded with local anaesthetic to treat post-operative complications. These bioactive implants will release drug at desirable rates, over an extended period of time. Drug delivery technologies like these would not only benefit patients in New Zealand, but will also have high impact globally by enhancing recovery after surgery.

MAXIMISING THE POTENTIAL OF IDO1 INHIBITORS TO INDUCE DURABLE, LONG-TERM REGRESSION OF TUMOURS ($159,300- 2 years) 1114012

A/Prof Lai-Ming Ching, A/Prof Ian Hermans, A/Prof Brian Palmer
Auckland Cancer Society Research Centre, University of Auckland

Recent breakthroughs in cancer therapy, using agents that unleash the immune system, have enabled patients with previously incurable cancers such as metastatic melanoma, 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 aim to explore multiple approaches that may increase the potential of these IDO1 inhibitors to treat cancer. We aim to combine these novel IDO1 inhibitors with other investigational immunotherapies; to identify the best combinations that will provide the most durable responses against preclinical models of lung carcinoma, melanoma and glioblastoma. We will test IDO1 inhibitors in combination with antibodies to immune checkpoint antigens as well as in combination with anti-cancer vaccines being developed for treatment of melanoma and gliomas.

FINDING INHIBITORS FOR MenD FROM A HUMAN PATHOGEN ($141,280 – 2 years) 1114013

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

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 apart from HIV. 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. We aim to develop inhibitors for MenD, an enzyme vital for production of vitamin K2 (menaquinone) in Mtb and essential for the survival of the bacterium. No MenD enzyme exists in humans, so drugs targeted against this enzyme are less likely to be toxic. Our recent 3D structure of MenD, combined with computational modelling, gives us a knowledge base on which to select a set of potential inhibitor compounds. We will then develop an assay to screen these compounds and find those that are inhibitors. We will then use X-ray crystallography to discover how the best inhibitors bind to MenD, characterise their interactions and see how to improve them. The Mtb MenD inhibitors we discover could become part of the next line of anti-TB treatments.

PERIOPERATIVE VASCULAR EVENTS IN UNRECOGNISED OBSTRUCTIVE SLEEP APNOEA ($157,880 – 2 years) 2114014

A/Prof Timothy Short, Dr Ivan Bergman, Dr Joyce Tai, Dr Maartje Tulip
Dept of Anaesthesia & Perioperative Medicine, Auckland City Hospital

Obstructive sleep apnoea (OSA) is the most common sleep-related breathing disorder. It is increasing in prevalence. OSA is estimated to be present in 9% of women and 17% of men, but is frequently undiagnosed. OSA has been associated with cardiovascular problems including stroke, heart attack, cardiac arrest and abnormal heart rhythms, and patients with untreated OSA are more likely to die from these conditions. There is currently little data about the effect of OSA in surgical patients, although there is a trend towards increased risk of cardiovascular complications. The Postoperative Vascular Events in Unrecognized Sleep Apnoea Study (POSA) is an international multi-centre study of the effects of undiagnosed OSA on vascular complications in patients undergoing major surgery. The study will include patients over the age of 45 who are undergoing major non-cardiac surgery, and who have at least one risk factor for post-operative vascular events. All patients will have an overnight sleep study pre-operatively to assess whether they have OSA, and to determine its severity. Post-operatively the patients will be followed closely post-operatively for the first three nights to assess the impact of breathing on postoperative complications.

PAIN IN THE BACK! DECIPHERING WHICH CELLS DRIVE INTERVERTEBRAL DISC DEGENERATION ($147,194 – 18 months) 1114015

Dr Sue McGlashan, Ms Taryn Saggese, A/Prof Ashvin Thambyah
Dept of Anatomy with Radiology, University of Auckland

Intervertebral disc degeneration is a major cause of back pain. The intervertebral disc consists of an outer fibrous ring, the annulus fibrosus, which surrounds an inner gel-like centre, the nucleus pulposus. Strong annular fibers contain the nucleus pulposus and distribute pressure evenly across the disc, whereas the nucleus pulposus acts as a shock absorber. With degeneration, the nucleus pulposus becomes fibrous and stiff, unevenly transferring loads to the annular walls creating areas of high stress, increasing the risk of disc herniation. Although changes in the nucleus pulposus are thought to initiate disc degeneration, how this occurs is still poorly understood. This study will examine the role of the 2 major cell types present in the nucleus pulposus to determine which cells are susceptible to changes in nutrient supply to the disc (which occurs with ageing) and excessive/inappropriate mechanical loads (e.g. such as poor posture or lifting heavy weights). The findings of this study will advance our understanding of how disc degeneration develops and help develop cell based therapies.

NATURAL PRODUCT BASED ANTIBODY-DRUG CONJUGATES (ADCs) ($158,317 – 2 years) 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

Breast cancer is a common cancer that affects approximately 1 in 9 women in New Zealand. Current breast cancer treatments include surgery, radiotherapy, and chemotherapy. Patients undergoing breast cancer chemotherapy often experience unpleasant side effects as healthy cells are also targeted by the cytotoxic drugs used in the treatment. Antibody-drug conjugates (ADCs) serves as a powerful tool to deliver cytotoxic compounds selectively to tumour cells without causing significant damage to healthy tissues. The antibodies incorporated within the ADC system specifically bind to the corresponding antigens present on cancer cells, hence leading to a significant reduction of the common systemic toxicities associated with chemotherapy. With ADCs being the future "holy grail" for cancer therapy, there is an urgent need to identify novel potent and selective cytotoxins for conjugation to monoclonal antibodies. Culicinin D is a naturally occurring peptide that exhibits potent toxicity against PTEN-negative cancerous breast cells thus providing

Grants Awarded continued

an exciting new cytotoxin for further development. The synthesis of culicinin D and analogues thereof, will be undertaken in order to evaluate their potential for use as ADCs. In this study we aim to ultimately create effective ADCs that can be used to treat patients with PTEN-negative breast cancer.

NAMED FELLOWSHIPS

DOUGLAS GOODFELLOW MEDICAL RESEARCH FELLOWSHIP

DETERMINANTS OF SERIOUS SKIN AND SOFT TISSUE INFECTION IN NEW ZEALAND CHILDREN ($282,500 – 3 years) 1414001

Dr Mark Hobbs
Centre for Longitudinal Research, University of Auckland

New Zealand children experience a high rate of hospitalisation for serious skin and soft tissue infections (SSSTI), with Maori and Pacific children disproportionately affected. This project aims to determine the relative contribution of social, economic, ethnic, environmental, genetic and microbiological factors to the incidence of SSSTI in children aged less than 5 years. I will complete this project within the Growing Up in New Zealand cohort study. The cohort is large (n = 6853) and ethnically and socioeconomically diverse. I will identify all cohort children who were admitted to hospital with an SSSTI, and compare them to cohort children not admitted to hospital with an SSSTI. I will analyse data describing the host (demographics, health status, variations in the genes that determine immune responses to infection); the organism (variations in the bacteria resident in the nose, throat and skin of cohort children at age 4 years) and the environment (household environment, socioeconomic deprivation, access to healthcare) and determine the relative contribution of host, organism and environmental factors to SSSTI. The results will provide new knowledge to guide future efforts to reduce the incidence of SSSTI in New Zealand children.

DOCTORAL SCHOLARSHIPS

J I SUTHERLAND DOCTORAL SCHOLARSHIP

THE MESENCHYMAL CELL SUBSETS IN NORMAL AND MALIGNANT HUMAN TISSUE ($126,500 – 3 years) 1214002

Miss Jennifer Eom
School of Biological Sciences, University of Auckland

Tumours consist of malignant cancerous cells as well as normal cells that help the cancer cells survive and grow. As well as targeting cancer cells, modern approaches to cancer therapy are targeting these normal cells in tumours. Cells that are sometimes called Cancer-Associated Fibroblasts - or more correctly "mesenchymal cells" - are one class of these normal cells that support tumour development in a number of ways. Unfortunately, these cells remain poorly characterised. It is unclear which normal cells they originate from, and how their characteristics change in response to invasion by cancer cells. This research aims to increase our knowledge of the different types of mesenchymal cells in normal human tissues and in tissues infiltrated by the skin cancer malignant melanoma. Results will enable development of new cancer therapies that target the right types of mesenchymal cells and the molecules they use to support cancer cells.

BARBARA BASHAM DOCTORAL SCHOLARSHIP

HUMAN GENETIC STUDIES OF FAMILIAL KIDNEY DISEASE ($126,500 – 3 years) 1214003

Miss Rachel Dodd
Dept of Molecular Medicine & Pathology, University of Auckland

Focal segmental glomerulosclerosis (FSGS) is a form of kidney injury where patients show scarring or 'sclerosis' of the major filtrational unit of the kidney, the glomerulus. This results in an inability to filter the blood normally. FSGS is a relatively common form of kidney injury, and onset can occur in childhood or adulthood, accounting for 5% of adult and 20% of children with end stage renal disease (ESRD) worldwide. This research project is based on preliminary work looking at the genetics of a New Zealand family with FSGS, which identified a mutation in a novel candidate gene RADIXIN (RDX), occurring only in affected individuals. RDX is expressed in mesangial cells, which are smooth muscle cells that regulate blood pressure within the glomerulus. The gene plays a key role in regulating the contractile machinery of the cell, and we therefore hypothesise that abnormal gene function could lead to abnormalities in the ability of mesangial cells to relax, resulting in increased intra-glomerular blood pressure, which has been implicated in FSGS. If confirmed, our study will be the first to demonstrate that a genetic defect in mesangial cells causes FSGS.

FUNDED BY: Barbara Basham Medical Charitable Trust

perpetual guardian

HUMAN TROPHOBLAST STEM CELLS IN HEALTHY AND GROWTH RESTRICTED PREGNANCIES ($126,500 – 3 years) 1214004

Ms Teena Gamage
Dept of Obstetrics & Gynaecology, University of Auckland

The placenta is a vital foetal organ essential to the nourishment and survival of the baby within the mother. Inadequate placental development in early pregnancy is often the cause of pregnancy complications including intrauterine growth restriction where, due to poor placental function, the foetus does not grow properly. This condition affects approximately 5,000 pregnancies each year in New Zealand. Currently there is no cure for this condition. Very little is known about early placental development and how or why the placental development and function are impaired in foetal growth restriction but problems with the growth and maturation of specialised placental cells; called trophoblasts, are likely to be a major contributing factor. We have, for the first time, isolated a population of trophoblast stem-like cells from both early and late gestation placentas. This project aims to learn how to control the growth and maturation of these stem cells. If we can control the growth/maturation of these stem cells, that raises the exciting possibility that we may finally develop a treatment to improve the growth of diseased placentas leading to improved foetal growth thus reducing a burden on New Zealand's healthcare system.

RISK FACTORS, PATHOPHYSIOLOGY AND MANAGEMENT OF DIVERTICULAR DISEASE ($126,500 – 3 years) 1214005

Dr Rebeka Jaung
Dept of Surgery, University of Auckland

Diverticulosis is an abnormal out-pouching of the lining of the colon, and when symptomatic is known as diverticular disease (DD). DD is becoming recognised as a chronic disease and confers a substantial financial burden on healthcare institutions. Acute diverticulitis (AD) describes the condition where inflammation occurs within a diverticulum and is a common acute surgical problem often requiring emergency surgery. The main objectives of this doctoral research are as follows: 1) To formulate a scoring system to assess severity in AD and predict need for operative intervention and increased patient support. This is intended to be a tool to help prioritise imaging and operations, especially for clinicians practising in hospitals with limited resources. 2) High resolution manometry (HRM) will be used to characterise large bowel motility in patients with DD. HRM has already provided revolutionary insights into bowel function in both normal bowel and in slow transit constipation. HRM has not been used in DD before and we hope that this project will improve our current understanding of DD. 3) A trial will be carried out to evaluate efficacy of steroid therapy in AD. This is a novel intervention for AD which we hypothesise could lead to earlier symptomatic recovery.

POSTDOCTORAL FELLOWSHIPS

EDITH C COAN RESEARCH FELLOWSHIP

EFFECTS OF CALCIUM ON INDICES OF BONE AND CARDIOVASCULAR HEALTH ($175,863 – 2 years) 1314001

Ms Sarah Bristow
Dept of Medicine, University of Auckland

Osteoporosis affects 50% of women and 30% of men, representing an enormous health and economic burden on New Zealand. Calcium supplements are widely recommended to treat or prevent osteoporosis; however, they have recently been shown to increase the risk of a heart attack. The reason for this is unclear. In a recent study, we found calcium supplements had some adverse effects on blood pressure and blood clotting shortly after they were taken. These effects could explain the increased risk of a heart attack; however, this study was too small to be definitive. The aim of this project is to examine these effects in a larger clinical trial. Without the use of calcium supplements, most people find it difficult to meet the recommended intakes of calcium through diet alone. Many adults may therefore be at an increased risk of osteoporosis. However, the relationship between dietary calcium intake and the risk of developing osteoporosis or having a fracture is unclear. The second aim of this project is to thoroughly examine the relationship between dietary calcium intake and bone health. The findings of this study will provide information that will assist with the clinical management of osteoporosis in New Zealand and elsewhere.

FUNDED BY: Edith C Coan Trust

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DAVID AND CASSIE ANDERSON RESEARCH FELLOWSHIP

TARGETING NEUROPEPTIDE RECEPTORS TO ALLEVIATE THE BURDEN OF PAIN ($205,261 – 2 years) 1314002

Dr Christopher Walker
School of Biological Sciences, University of Auckland

Every New Zealander suffers from pain and for many this is an intolerable daily burden. Pain is a prevalent and underappreciated factor in the pathogenesis of many diseases and conditions, including arthritis, chronic headache, chronic lower back, and tumour induced pain. Current pain 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. The current strategies for developing new pain treatments are inadequate. New classes of drugs, which have new mechanisms of action, are required. This project will utilise sophisticated miniaturised technologies to quantitatively explore how a pain-

Grants Awarded continued

modulating factor acts on nerve cells at important sites for pain perception. Discovering how this factor acts will allow a new mechanism of action to be targeted and lead to a new class of pain treatments.

FUNDED BY: David and Cassie Anderson Medical Trust

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OTHER GRANTS AWARDED

GAVIN AND ANN KELLAWAY MEDICAL RESEARCH FELLOWSHIPS

($39,663) 1514001

Dr Darren Hooks
Auckland Bioengineering Institute, University of Auckland

To extend research collaboration between the University of Auckland (Bioengineering Institute) and the University of Bordeaux (LIRYC Institute), France, in the field of cardiac rhythm management.

($21,800) 1514002

Dr Vickie Shim
Auckland Bioengineering Institute, University of Auckland

To develop a research collaboration between the University of Auckland (Bioengineering Institute) and the University of California, Berkley, USA, to develop a computational microscope for investigating cell matrix interactions in the Achilles tendon for tissue engineering applications.

($13,082) 1514005

A/Prof Alan Davidson
Dept of Molecular Medicine & Pathology, University of Auckland

To spend 3 weeks at University of Southern California in the laboratory of Professor Andrew McMahon in order to get trained in state-of-the-art CRISPR genome editing technologies.

($36,800) 1514007

A/Prof Michelle Glass
Dept of Pharmacology, University of Auckland

Fellowship in the laboratory of Dr Giovanni Marsicano, Neuroscience Magende, Inserm Institute, Bordeaux, France.

SIR HARCOURT CAUGHEY AWARDS

($25,000) 2514003

Dr Cho Yui Bob Chan
Dept of Dermatology, Auckland District Health Board

Multicentre observational prospective study for the identification of prognostic factors in patients with mycosis fungoides/ Sezary syndrome. St John's Institute of Dermatology, London, UK.

($25,000) 2514006

Dr Soizick Mesnage
Dept of Medical Oncology, Auckland City Hospital

Fellowship combining translational research in the genomics of high grade serous ovarian cancer, phase I clinical trial work, and clinical oncology training in gynaecological malignancies at the Institute Gustave Roussy.

KELLIHER CHARITABLE TRUST EMERGING RESEARCHER START-UP AWARDS

($30,000) 1714001

Dr Natasha Grimsey
Research support for her Edith C Coan Research Fellowship

"Functional Characterisation of Cannabinoid Receptor SNPs Implicated in Mental Illness"

($30,000) 1714002

Dr Clare Reynolds
Research support for her David and Cassie Anderson Research Fellowship

"Maternal Diet Induced Programming of Offspring Immune Function"

AMRF HEALTHEX EMERGING RESEARCHER AWARD

($5,000 Travel Award) 6714001

Mr Mohanraj Krishnan
Dept of Obstetrics and Gynaecology, University of Auckland

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

TRAVEL GRANTS AWARDED

Dr Jane Alsweiler
Dept of Paediatrics, University of Auckland

To attend the Perinatal Society of Australia and New Zealand, Perth, Australia, 5-9 April 2014

Dr Nicola Anstice
Dept of Optometry & Vision Science, University of Auckland

To attend the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting, Orlando, Florida, 4-8 May 2014

Dr Matt Boyd
Centre for Medical and Health Sciences Education, University of Auckland

To attend the SimHealth 2014 Conference, Adelaide, Australia, 25-28 August 2014

Dr Yan Chen
Centre for Medical and Health Sciences Education, University of Auckland

To attend the 12th Asia Pacific Medical Education Conference (APMEC), Singapore, 4-8 February 2015

Dr Ashika Chhana
Dept of Medicine, University of Auckland

To attend the 1st Biennial International Bone & Mineral Society (IBMS) Herbert Fleisch Workshop, Brugge, Belgium, 16-18 March 2014

A/Prof Nathan Consedine
Dept of Psychological Medicine, University of Auckland

To attend the 36th Annual Society for Behavioral Medicine Conference and Departmental Symposia, Philadelphia, PA (SBM), and visit to UPenn, Temple, Georgetown, & Rutgers, 11 April-4 May 2014

Dr Lynsey Cree
Dept of Obstetrics and Gynaecology, University of Auckland

To attend the Euromit 2014, International Meeting on Mitochondrial Pathology, Tampere, Finland, 15-19 June 2014

Dr David Cumin
Centre for Medical and Health Sciences Education, University of Auckland

To attend the SimHealth 2014 Conference, Adelaide, Australia, 25-28 August 2014

A/Prof Alan Davidson
Molecular Medicine and Pathology, University of Auckland

To attend the American Society of Nephrology Meeting, Philadelphia, USA, 11-16 November 2014

Dr Joanne Davidson
Dept of Physiology, University of Auckland

To attend the Annual Congress of the Fetal and Neonatal Physiological Society, Italy, 31 August-3 September 2014

Dr Justin Dean
Dept of Physiology, University of Auckland

To attend the 9th Hershey Conference on Developmental Brain Injury, St Michaels, MD, USA, 4-6 June 2014

Dr Victor Dieriks
Dept of Anatomy with Radiology

To attend the 9th FENS Forum of Neuroscience, Milan, Italy, 5-9 July 2014

Dr Peter Freestone
Dept of Physiology, University of Auckland

To attend the Federation of European Neuroscience Societies Meeting, Milan, Italy, 5-9 July 2014

Dr Robert Galinsky
Dept of Physiology, University of Auckland

To attend the Fetal and Neonatal Physiological Society (FNPS) - 41st annual meeting, St Vincent, Italy, 31 August-3 September 2014

A/Prof Michelle Glass
Dept of Pharmacology, University of Auckland

To attend the International Cannabinoid Research Society (ICRS) Meeting, Baveno, Italy, 29 June-3 July 2014

Dr Scott Graham
Dept of Pharmacology, University of Auckland

To attend the International Cannabinoid Research Society (ICRS 2014), Baveno, Italy, 28 June-2 July 2014

Dr Jiwon Hong
School of Biological Sciences, University of Auckland

To visit a lab in the University of Manchester and to attend the International Society for Extracellular Vesicles (ISEV) meeting, Rotterdam, the Netherlands, 23 April-4 May 2014

Mr Francis Hunter
Auckland Cancer Society Research Centre, University of Auckland

University of Toronto collaboration: High-throughput shRNA screening to discover bioreductive prodrug sensitivity genes, Toronto, Canada, 26 August-28 October 2015

Dr Joanna James
Dept of Obstetrics and Gynaecology, University of Auckland

To attend the Society for Reproductive Investigation (SRI) annual meeting (including the Placenta Association of the Americas Satellite Meeting), San Francisco, USA, 25-28 March 2015

Mr Oliver Knight-West
National Institute for Health Innovation, University of Auckland

Two conferences and several meetings will be attended, Spain and UK, 10-20 September 2014

Dr Euphemia Leung
Auckland Cancer Society Research Centre, University of Auckland

To attend the Gordon Research Seminar and Gordon Research Conference-Mammary Gland Biology, Lucca (Barga), Italy

Dr Christine McIntosh
Centre for Clinical Research and Effective Practice, Counties/Manukau District Health Board

To attend the 2014 International Conference on Stillbirth, SIDS and Baby Survival, Amsterdam, The Netherlands

Dr Verity Oliver
Dept of Ophthalmology, University of Auckland

To attend The Association for Research in Vision and Ophthalmology (ARVO) Annual Conference, Denver, Colorado, USA, 3-7 May 2015

Dr Justin O'Sullivan
The Liggins Institute, University of Auckland

To attend the Advanced Workshop on Interdisciplinary Views on Chromosome Structure and Function, Trieste, Italy, 15-19 September 2014

Dr James Pau
Dept of Mechanical Engineering, University of Auckland

American Congress of Rehabilitation Medicine, Toronto, Canada, 7-10 October 2014

A/Prof Thomas Proft
Dept of Molecular Medicine, University of Auckland

To attend the Microbiology & Infectious Diseases Asia Congress, Singapore, 10-11 June 2014

Grants Awarded continued

Dr Chinthaka Samaranayake
General Medicine, Auckland District Health Board

To attend the Sleep DownUnder 2014 Conference, Perth, Australia, 9-11 October 2014

Dr Emma Scotter
Dept of Pharmacology, University of Auckland

To attend the "Neurodegenerative Diseases: Biology & Therapeutics"; and "Blood Brain Barrier" Conferences, New York, USA, 2-14 December 2014

Dr Giriraj Shekhawat
Section of Audiology, University of Auckland

To attend the NYC Neuromodulation 2015 meeting, New York and Dallas, USA, 7-18 January 2015

Dr Matthew Street
Dept of Medicine, University of Auckland

To attend The 23rd Annual Conference of the Australasian Society for Biomaterials and Tissue Engineering, Victoria, Australia, 22-24 April 2014

Dr Simon Swift
Dept of Molecular Medicine and Pathology, University of Auckland

To attend the ASM general meeting and ASMCUE, Boston, USA, 15-20 May 2014

Dr Ejsan Vaghefi
Dept of Optometry and Vision Science, University of Auckland

To attend the 2014 Annual Meeting of Association for Research in Vision and Ophthalmology (ARVO), Orlando, Florida, 4-8 May 2014

Dr Francisco Javier Virues-Ortega
School of Psychology, University of Auckland

To attend the Annual Conference of the Association for Behavior Analysis International, Chicago, USA, 23-27 May 2014

Dr Christopher Walker
School of Biological Sciences, University of Auckland

To attend two conferences: The 8th International Symposia on the CGRP Family; All roads take to the brain: neural control of human energy homeostasis in health and disease, Ascona, Switzerland, 21-28 September 2014

Dr Grace Wang
Department of Psychology, University of Auckland

To attend the International Pharmaco EEG-Society (IPEG) Meeting, Leipzig, Germany, 25-28 September 2014

Dr Tom Kay Ming Wang
Greenlane Cardiovascular Service, Auckland District Health Board

To attend the World Congress of Cardiology (World Heart Federation Scientific Sessions), Melbourne, Australia, 4-7 May 2014

Dr Guido Wassink
Dept of Physiology, University of Auckland

To attend the Fetal and Neonatal Physiological Society Conference 2014 (41st FNPS), Saint Vincent, Italy, 31 August-3 September 2014

Dr Harriet Watkins
School of Biological Sciences, University of Auckland

Visit to the laboratory of Professor Thomas Sakmar at the Rockefeller University, New York followed by attendance at 'CGRP 2014' The 8th International Symposia on the CGRP Family; CGRP, Adrenomedullin, Amylin, New York, USA, Ascona, Switzerland and London, UK

Dr Siouxsie Wiles
Dept of Molecular Medicine and Pathology, University of Auckland

To attend the 1st American Society for Microbiology Conference on Experimental Microbial Evolution, Washington DC, USA, 19-22 June 2015

Prof John Windsor
Department of Surgery, University of Auckland

To attend the Combined European Pancreatic Club and International Association of Pancreatology Meeting, and the Nutrition Symposium, Southampton, England, 24-28 June 2014

Dr Ju Zhang
Auckland Bioengineering Institute, University of Auckland

To attend the World Congress of Biomechanics 2014, Visiting Fellowship at Imperial College London, Boston, USA and London, UK, 6-10 October 2014

An AMRF Success Story

MEDICAL IMAGING: POWERFUL NEW TOOLS REVEAL MORE ABOUT THE CAUSE OF ARTHRITIS – BY PROFESSOR FIONA MCQUEEN

Prof Fiona McQueen.

Over the last 20 years there has been a quantum leap forward in the development of medical imaging, especially when applied to the specialty of rheumatology. Where previously there were only X-Rays to help us image the joints, we now also have magnetic resonance imaging (MRI), ultrasound (US), computed tomography (CT) scanning, dual energy CT (DECT) scanning and positron emission tomography (PET) scanning to name a few. New modalities are constantly emerging, all developed using highly specialised and often expensive technology. Considerable expertise is required of radiographers to help perform scans and radiologists to help interpret them. Now it has also become important for physicians including rheumatologists, to use and interpret these scans so that they can learn more about diseases affect the body and how well medical treatments are working.

My research over the last 25 years has concentrated on how these advanced imaging techniques can help us better understand the pathological processes that lead to arthritis. In particular, my focus has been on rheumatoid arthritis, psoriatic arthritis and more recently gout. In all these diseases, advanced imaging has provided not only pretty pictures but important, quantifiable information that can be used for making a diagnosis, determining prognosis and measuring responses to therapy. It is exciting that these great leaps forward in medical imaging have occurred at the same time as huge advances in drug therapy. Biological disease-modifying anti-rheumatic drugs (bDMARDs) have been designed using molecular techniques to mimic natural mediators within the body. Often these mediators cause inflammation and joint damage and bDMARDs of various types have been designed to block disease pathways extremely effectively. Thus, patients' symptoms, including joint pain and swelling, can be ameliorated and long-term joint damage can be prevented. Imaging gives us the tools with which to see into the joint (Figure 1) and observe these effects.

Much has been learned about the processes that drive joint damage. MRI allows inflammation to be visualised (something that is not possible with X-Rays). Inflammation can be found within the lining of the joint (where it is called "synovitis"), around tendons (tendonitis) and, interestingly, within the bone itself (osteitis). Osteitis is particularly important as it is a strong predictor of erosive joint damage that may develop years or even decades later and result in deformity of the hands and feet. The bone was not suspected as a site of inflammation until MRI scanning showed this to be the case and this major discovery was made in the 1990s by our research team (now called the Auckland Rheumatology Imaging Group). Our studies compared sections of bone taken from rheumatoid joints at the time of joint replacement, with MRI scans of the same region. Indeed, microscopic examination of bone slices did show inflammation. Interestingly, certain cells called plasma cells were present within this inflammatory infiltrate and these cells are increasingly suspected to be important in triggering rheumatoid arthritis. Osteitis or "MRI bone oedema" is now recognised by rheumatologists all around the world as a "red flag", indicating that the patient's rheumatoid arthritis is aggressive and should be treated actively before further damage can occur. I and other members of the Auckland MRI group have been described as "pioneers" in this field.

Q1. Please can you tell us about yourself and how you came to be in this area of research?

I graduated from the University of Otago with MBChB in 1980 and worked as a junior doctor in Wellington and Auckland during the 1980s before going overseas to pursue advanced training, initially in General Medicine (Western Australia) and later in Rheumatology (Edinburgh). I returned to take up a consultant rheumatologist post at Auckland Hospital in 1991. My postgraduate degree (MD) was awarded in 1996 in Immunology. I first became interested in medical imaging when MRI scanning was included in our first cohort study of rheumatoid arthritis begun in 1996 and now known as the "Auckland MRI study". This aimed to identify factors that could predict prognosis over the long-term. This line of research continued over the next 2 decades, helping to define the imaging features of rheumatoid arthritis. Later imaging projects have explored the pathological changes associated with inflammation and damage in psoriatic arthritis and gout.

Q2. How has AMRF funding allowed your research to evolve or progress to the next stage?

The AMRF has been one of the main funders for my research from the late 1980s to the present day. The Auckland MRI study mentioned above ran for an 8 year period and has been followed by further imaging studies of other groups of patients using MRI, CT scanning and most recently DECT scanning. We have explored the role of imaging in defining joint pathology in various cohorts of patients with rheumatoid arthritis, psoriatic arthritis and gout. I feel that "public good" funding such as is provided by the AMRF, is of immense importance to prevent medical research being skewed by commercial interests. There is always a risk of this happening when drug companies sponsor clinical trials of agents that they have developed themselves and this also applies

An AMRF Success Story continued from previous page

to research exploring the value of imaging. Most of my research has been "clean" in this respect and as such is well respected internationally.

Q3. Please can you tell us about how your research outcomes are being used in New Zealand, and the benefit to New Zealanders from your research:

The focus for the Auckland Rheumatology Imaging Group is now on translating imaging findings into the clinic to benefit our patients in New Zealand. Our current research project explores using an " MRI inflammation score" as an outcome marker to guide therapy. We are exploring the relationship between imaging features and clinical indicators of arthritis activity such as joint pain and swelling. We aim to compare the effectiveness of different therapies (including bDMARDs), using MRI as a tool. Increasingly, MRI scanning is being used to determine whether bDMARD therapies are truly effective in individual patients. Our research should help to guide clinicians in deciding whether to order these expensive scans and how to interpret them.

Q4. Have there been significant overseas breakthroughs or collaborations resulting from your research? Please can you describe your team's contribution to the global research effort in your area:

Our imaging research has led to a number of international collaborations, the most important being within the framework of the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) group. As one of the first researchers in the world to develop an interest in MRI in rheumatoid arthritis, I was invited to join the OMERACT MRI imaging group in 1998. At that stage there were just 6 members from NZ (myself), Australia, US, UK and Denmark. We endeavored to create a scoring system to quantify MRI features of joint inflammation and damage. This involved devising and validating a scoring system and then testing and retesting this so that it could be widely applicable for rheumatologists and radiologists practicing in this area. That was published in 2003 and led to many further OMERACT publications and projects as well as numerous spin-off projects in related fields. NZ rheumatology is now well represented in OMERACT with many of my colleagues working within international collaborations, most recently in the field of gout imaging where NZ is an acknowledged leader from a global perspective.

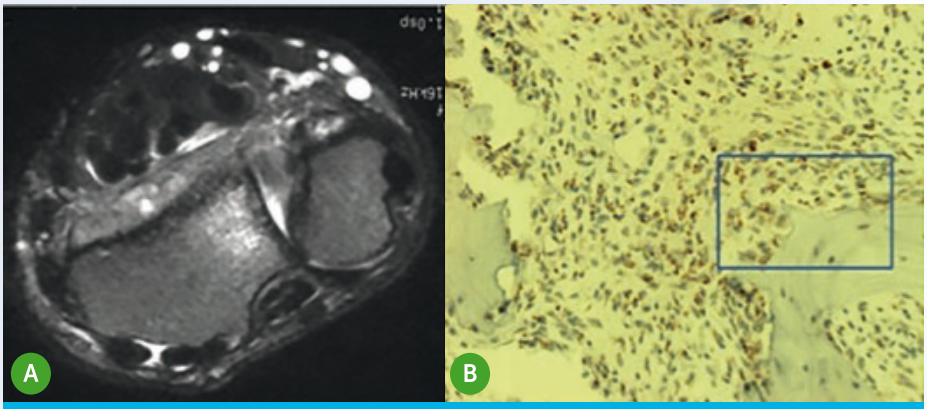


Figure 1. A) MRI scan of the wrist (axial) showing bone oedema (osteitis) within the radius (arrow). B) Bone resected from a region of MRI osteitis shows multiple plasma cells (brown stain) adjacent to osteoclasts sited within lacunae on bony trabeculae.

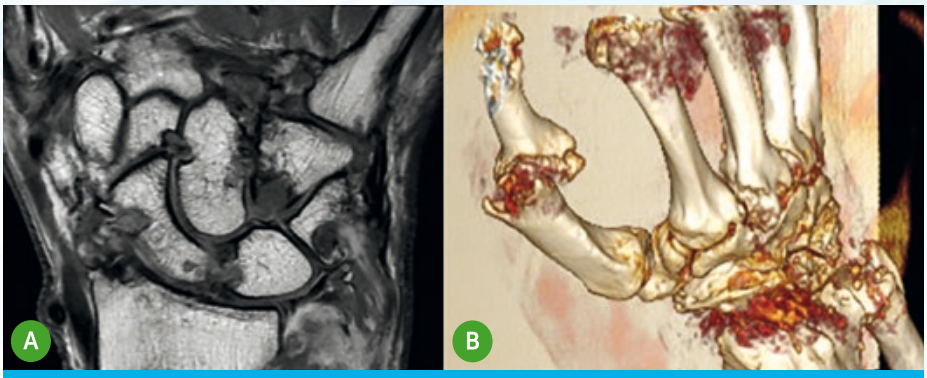


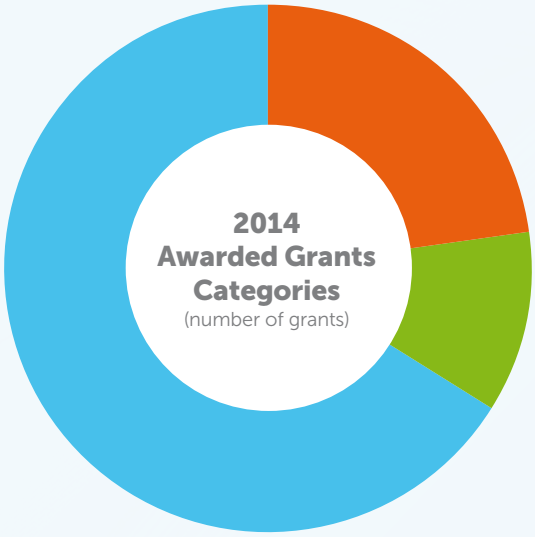
Figure 2. Imaging of the wrist in a patient with gout A) Coronal MRI scan shows multiple erosions. B) Matching CT scan shows tophaceous deposits.

Q5. What is your greatest hope or dream for research in this field?

My greatest hope is that advanced imaging will become not only more widely used in rheumatology but also better understood by clinicians. Ideally patients need to have access to the most appropriate form of imaging to answer the clinical questions that will affect their management. This does not always mean that they need the most expensive type of scan and learning how to use this complex technology is increasingly becoming important. Imaging helps us understand how disease processes work by revealing pathology within the joint and this area has always been of special interest to me. Molecular imaging holds promise for the future in that it may allow very early abnormalities to be picked up in the joints and other organs, long before clinical arthritis actually develops.

GRANTS COMPLETED

75 Grants Awarded Totalling $3,655,372



Clinical Total (17) | $828,207 23%

Population Health and Community Total (4) | $393,852 11%

Biomedical Total (54) | $2,433,313 66%

$ Value each theme % Total expenditure

Grants Completed

PROJECTS

LONG NON-CODING RNA IN BREAST CANCER (1111011)

Dr Marjan Askarian-Amiri, Prof Bruce Baguley, Dr Cherie Blenkiron
Faculty of Medical and Health Sciences, University of Auckland

Dr Marjan Askarian-Amiri (front row, second from left) with Prof Bruce Baguley (back row, left) and team.

Human and other vertebrates have about 20,000 protein-coding genes. However, these make up only around 1.5% of the total genome and it has been shown recently that more than 75% of the human genome is functional, comprising mainly so-called non-protein-coding genes. In this project we have focused on the functions of two of these genes. Results obtained here showed that these genes play important roles in gene regulation in breast cancer cell lines. We have shown that two non-protein coding genes are involved in two different mechanisms in gene regulation. One has the potential to be used as a biomarker while the other can be used as a target for novel therapeutic approaches in breast cancer.

IDENTIFICATION OF GENES INVOLVED IN TUMOUR-INDUCED LYMPHATIC GROWTH (1111015)

Dr Jonathan Astin, Prof Kathryn Crosier, Prof Phil Crosier
Dept of Molecular Medicine & Pathology, University of Auckland

Prof Phil Crosier, Dr Jonathan Astin and Prof Kathryn Crosier in the FMHS zebrafish facility.

Currently, one in three New Zealanders will die of cancer. Frequently, the cause of death is due to metastasis, where cancer cells spread from the primary tumour and invade other parts of the body. Cancer cells are able to spread from the primary tumour by entering either the blood or, in many cases, the lymphatic vasculature. One of the first steps in lymphatic-mediated metastasis is the growth of lymphatic vessels towards and within the primary tumour, however many of the signalling pathways that underlie this response remain unknown.

We have developed transgenic zebrafish in which the lymphatic vessels are marked with fluorescent proteins. Funding from this project grant allowed us to isolate these fluorescent lymphatic cells and use them to identify genes involved in lymphatic vessel growth. We also developed a model of tumour-induced lymphatic growth in zebrafish embryos that will allow us to understand how lymphatic vessels form around tumours and also as a platform to test for drugs that prevent this process. This work forms an important first step in developing therapies to prevent or limit lymphatic-mediated metastasis.

POST OPERATIVE GUT DYSFUNCTION (1112012)

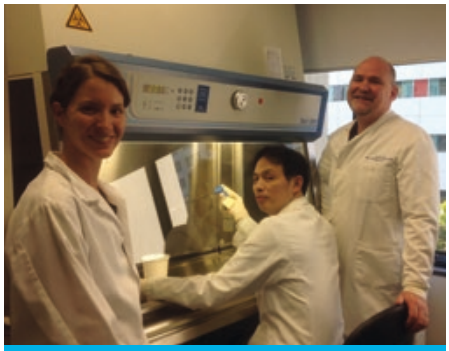
A/Prof Ian Bissett, Dr Ryash Vather
Dept of Surgery, University of Auckland

Ryash Vather (centre) meeting with Associate Professor Ian Bissett (second from left) and other research students.

Post-operative ileus is an important health problem, which affects a considerable proportion of patients following abdominal surgery. It slows recovery, increases morbidity and prolongs length of hospital stay. We have used a new technique – "high resolution manometry" to shed light on how the bowel recovers after surgery and hope this informs our understanding on what causes abnormalities of post-operative function. We have also shown via randomised controlled trial that gastrografin, a medication thought to be of benefit in treating ileus, is not clinically useful in shortening its duration after elective bowel surgery. We are thankful for the financial and academic support of AMRF, without which this research would not have been possible.

DANGEROUS DEBRIS (1113002)

Prof Larry Chamley, Dr Qi Chen
Dept of Obstetrics and Gynaecology, University of Auckland



Prof Larry Chamley (right) with Dr Qi Chen (centre – applicant) and PhD student Chez Viall.

Preeclampsia affects approximately 3,000 New Zealand women and their babies annually causing high blood pressure in the mother and often requires the premature delivery of the baby to prevent death of either the mother or the baby. Antiphospholipid antibodies are a key risk factor for preeclampsia. We had evidence that antiphospholipid antibodies induce excessive death of cells from the placenta. The dead cells break apart and we think the resulting fragments of dead placental cells trigger preeclampsia via "danger signals" that are released when the cells break open. Our aim was to investigate whether danger signals are more abundant in placentas from preeclamptic women and whether antiphospholipid antibodies increase the amount of danger signals in placental cell fragments. We have shown that preeclamptic placentas contain more of an important danger signal called HMGB-1 and that antiphospholipid antibodies increase the amount of HMGB-1, in fragments of dead placental cells. We have also shown that cells from maternal blood vessels contain a receptor (called RAGE) that is able to recognise and respond to the HMGB-1 danger signal. This work shows a mechanism by which placental cell fragments can disrupt the function of maternal vascular cells resulting in the high blood pressure seen in preeclampsia. Future investigations will determine whether we can block the interaction between HMGB-1 and its receptor RAGE with the aim of preventing the high blood pressure of preeclampsia.

TRAFFICKING OF THE CREATINE TRANSPORTER IN LIVE NEURONS (1110002)

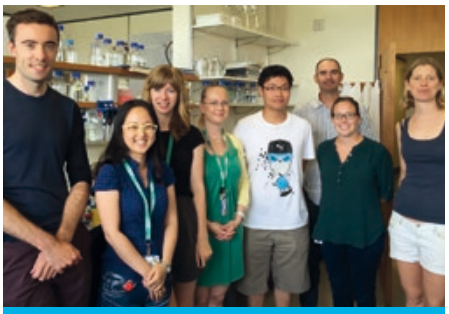
A/Prof David L Christie, Ms Joanna R Dodd
School of Biological Sciences, University of Auckland

Joanna Dodd and David Christie at the live cell microscope.

Creatine plays a key role in energy metabolism and is well known as a dietary supplement. It plays a critical role in brain function. Absence of the creatine transporter, the protein required for creatine uptake by neurons, results in intellectual disability, and the absence of creatine in the brain. The research investigated the idea that the creatine transporter is located in neurons near energy-producing mitochondria. We introduced differently coloured fluorescent tags for the creatine transporter and mitochondria into neurons grown in culture and studied their movement by live-cell microscopy. Both markers appear to be localised to regions of neurons that receive nerve signals. We were able to track the movement of the both the creatine transporter and mitochondria. While we did not find evidence that the movement of the creatine transporter and mitochondria were co-ordinated, the results were consistent with a delivery mechanism for creatine that would support mitochondria to produce the energy required for the function of neurons. Creatine may be important to maintain the function of mitochondria to reduce metabolic stress found in neurodegenerative diseases, such as Parkinson's and Huntington's disorders.

ROLE OF THE NOVEL PROTEIN PGAF IN RENAL DISEASE (1111001)

A/Prof Alan Davidson
Dept of Molecular Medicine & Pathology, University of Auckland



Professor Alan Davidson and his research team.

Our laboratory seeks to better understand renal disease in order to develop new therapies. We use the zebrafish (which has a kidney similar to our own) to test the importance of novel proteins discovered in the kidney. The major goal of this project was to characterise the function of a new protein we discovered, called PGAF, which we found is needed to maintain the integrity of the kidney's blood filters. Loss of PGAF function causes the blood filters to become leaky (much like they do in various kidney diseases) and is associated with dramatic changes in the shape of the blood filtering cells. We found that PGAF binds to another protein that controls how the cell responds to stress and inflammation. Consistent with this, stressing cells leads to increased protein levels of PGAF. Based on these results, we believe that PGAF acts as a novel anti-stress protein that keeps kidney cells healthy. PGAF may be a useful drug target to develop new therapies to treat kidney disease and inflammatory disorders.

Grants Completed continued

TARGETING EXTRACELLULAR MATRIX IN PRETERM BRAIN INJURY (1112002)

Dr Justin Dean
Dept of Physiology, University of Auckland

Developmental Brain Injury Laboratory. Dr Justin Dean (PI) and team.

Babies born prematurely have very high rates of disability, including cerebral palsy, for which there is no cure. Low oxygen and blood flow (hypoxia-ischemia) in the newborn is an important cause of these disabilities. In this study, we used a model of preterm hypoxia-ischemia that mimics the brain pathology observed in the human condition. In this model, we have identified that abnormal accumulation of the extracellular matrix molecule, hyaluronan, plays an important role in controlling the degree of brain cell injury. Further, using a pharmacological treatment based on inhibiting the actions of hyaluronan, we found that we could promote recovery of brain cell function. Thus, pharmacological blockade of abnormal hyaluronan signalling may be a potential therapeutic strategy for treatment of neonatal hypoxic-ischemic brain injury.

PAIN RELIEF AFTER HIP REPLACEMENT SURGERY: A COMPARISON OF TWO APPROACHES (7110010)

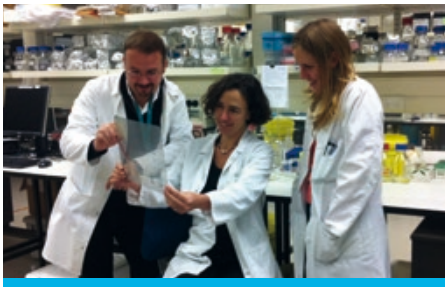
Dr Michael Frederickson
Anaesthesia Institute

Dr Michael Frederickson

Following elective hip replacement, both continuous lumbar plexus block and spinal anaesthesia (with adjunctive morphine) have shown early outcome benefits over traditional methods. However, the 2 techniques have not been compared in a prospective randomised manner. 50 patients undergoing elective hip replacement were randomised to receive spinal anaesthesia (with adjunctive morphine) and patient controlled continuous lumbar plexus block. All surgery was conducted under general anaesthesia. Measured outcomes included numerically rated postoperative pain, supplemental analgesic consumption, indices of mobilisation together with complications. Block placement time was marginally shorter for the spinal group. Patients in the lumbar plexus group required more pain relief during surgery and in recovery, with correspondingly higher pain scores. Pain scores during the subsequent 24 hours were similar between groups, however, more patients receiving spinal anaesthesia required rescue morphine. Physiotherapy mobilisation indices were similar between groups. More spinal group patients reported itchiness, but nausea, disorientation, and falls were all similar between groups. We concluded that following elective hip joint replacement, compared to continuous lumbar plexus block, spinal anaesthesia incorporating adjunctive morphine provides better pain relief in recovery. Subsequently, however, these patients required more rescue morphine and experienced more itchiness. These results will assist caregivers and patients in tailoring the method for each patient.

CB2 IN THE DISEASED HUMAN BRAIN (1113011)

A/Prof Michelle Glass, Dr Scott Graham
Dept of Pharmacology, University of Auckland



Dr Scott Graham, AP Michelle Glass and Mrs Christa MacDonald examine an in situ hybridisation film image from their study examining the distribution of the CB2 cannabinoid receptor in the brain.

Cannabis has been proposed as a potential therapy in a very wide range of disorders. While the role of FB1 cannabinoid receptors in mediating the psychoactive properties of cannabis are well established, the CB2 receptor has remained something of an enigma, with conflicting studies on whether this receptor is even expressed in the brain. Our research has aimed to use in situ hybridisation to address the localisation of CB2 in the brain. The final analysis is ongoing but it appears that our work agrees with those studies that suggest that CB2 is not widely found in human brain. This is important as increasingly drugs are being developed to target CB2; it is therefore critical that its distribution is understood.

CANNABINOID RECEPTOR TRAFFICKING (1110018)

Dr Natasha Grimsey
Centre for Brain Research, University of Auckland

Dr Natasha Grimsey at a fluorescence microscope, utilised to visualise subcellular structures.

In order for the environment outside a cell to influence the inside of a cell, special proteins called receptors are required. Receptors usually sit on the surface of cells but can move between various compartments within the cell via "intracellular trafficking pathways" that are strictly controlled. The number of receptors on the surface at any one time determines to what extent the cell can respond to signals from outside the cell, such as drug treatments. Two such drug receptors are the type 1 and 2 Cannabinoid receptors (CB1 and CB2). As well as mediating the effects of cannabis, these receptors modulate a large number of normal brain and bodily functions and have been implicated as potential drug targets in a wide variety of diseases from cancer to neurodegenerative disorders. We have used molecular techniques to alter specific parts of these receptors; by observing how receptor trafficking changes we have obtained novel information regarding how trafficking is controlled. These findings included evidence for receptor-specific interactions in intracellular regions which control cell surface expression, as well as an exciting "chaperone" effect which enhances cell surface expression and has strong potential to be exploited for therapeutic benefit.

VITAMIN D STATUS IN MAORI AND NON-MAORI (1111017)

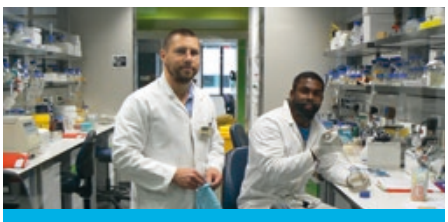
Prof Ngaire Kerse, Ms Catherine Bacon, Mr Avinesh Pillai, Dr Mark Bolland, Ms Karen Hayman, Dr Mere Kepa, Dr Lorna Dyall
Dept of General Practice & Primary Health Care, University of Auckland

Professor Ngaire Kerse and LILACS team.

This grant provided funding for assays and some research fellow time to further the aims of a cohort study of 80 – 90 year old Māori and 85 year old non-Māori living in the Bay of Plenty and Lakes Districts of New Zealand (LiLACS NZ). The aims were to determine the effect of Māori ethnicity and other predictors of vitamin D status in people in their 80s. These data were presented at the New Zealand Nutrition Society Conference in Queenstown in August, 2014. A manuscript draft is in the final stages of preparation for publication. An additional aim was to determine prospective outcomes associated with baseline status. Research outputs arising from this grant are still forthcoming.

PEPTIDE TECHNOLOGY TO COMBAT BREAST CANCER (1112003)

A/Prof Geoffrey Krissansen, Mr Glenn Bell, Ms Yi Yang
Dept of Molecular Medicine & Pathology, University of Auckland

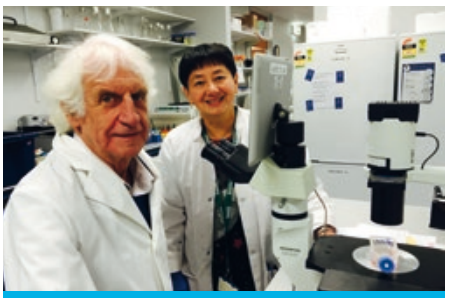


Glenn Bell (foreground), PhD student on the project, in the lab with another colleague.

We have developed novel technology which is capable of delivering protein-based anti-cancer drugs to cancer cells. As proof-of-principle we have shown that it can deliver protein-based drugs capable of destroying or inhibiting various oncoproteins required for the proliferation/survival of breast cancer cells. Targeting and downregulation of the oncoproteins by our novel agents inhibited tumour cell survival/proliferation. The technology has been further developed to restrict the delivery of anti-cancer drugs to tumours, thereby sparing healthy tissue. Two novel approaches have been devised and tested, which demonstrate that drug delivery will only take place when anti-cancer drug conjugates are activated by molecules released by the tumour.

TRIPLE NEGATIVE BREAST CANCER (1112006)

Dr Euphemia Leung, Prof Bruce Baguley
Auckland Cancer Society Research Centre, University of Auckland



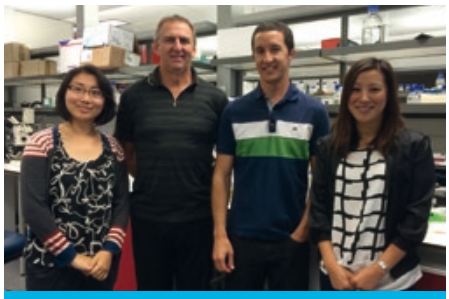
Prof Bruce Baguley and Dr Euphemia Leung in the Auckland Cancer Society Research Centre tissue culture laboratory.

Breast cancer is the major malignancy in women and is known to exist in several forms, including "luminal cell" and "basal cell". Many basal cell breast cancers are called "triple negative" because they lack the appropriate hormone receptors and are particularly difficult to treat. We have cultured human luminal breast cancer cells and found that they also contain small populations of cells with "triple negative" character. We have shown that different response of these cells to targeted anticancer drug treatment.

Grants Completed continued

CYSTEINE DELIVERY TO THE LENS (1112005)

Dr Julie Lim, Dr Angus Grey, Prof Paul Donaldson
Dept of Optometry & Vision Science, University of Auckland



Members of the Molecular Vision laboratory: from L-R; Ms Ivy Li, Prof Paul Donaldson, Dr Angus Grey and Dr Julie Lim.

Age related nuclear (ARN) cataract is the leading cause of blindness in the world. Despite effective procedures to restore sight, the number of people afflicted by cataracts is estimated to reach 30 million as the world's population ages. Faced with a looming cataract epidemic, research efforts have focused on developing novel anti-cataract therapies to prevent or delay the onset of cataract. Since ARN cataract is associated with oxidative damage to cells in the centre or nucleus of the lens, our research efforts have concentrated on identifying pathways that could be used to enhance antioxidant levels and protect against cataract. In this research proposal, we have developed a bovine model of nuclear cataracts in which high pressure oxygen is used to replicate the changes seen in human nuclear cataract. These changes include a massive depletion of antioxidants in the lens centre, an increase in protein aggregate formation and an increase in lipid peroxidation, a marker of oxidative stress. Having established this model in our laboratory, we are now in an exciting position to test the effectiveness of different antioxidant formulations in preventing or slowing down the progression of cataracts thereby reducing the need for expensive surgical intervention.

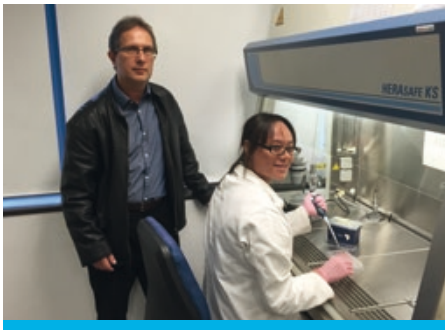
HEALING WITH HOLOCONES (1111010)

A/Prof Trevor Sherwin
Dept of Opthalmology, University of Auckland

This project aims to define groups of human stem cells that can be isolated from the patient and expanded in the laboratory aiming to heal corneal diseases associated with stem cell loss or with corneal dystrophies. The cornea is the front transparent surface of the eye and its transparency is crucial for vision. A/Prof Trevor Sherwin's group have shown that corneal stem cells can be isolated from human tissue and expanded to form spheres that are self-replenishing and capable of responding to injury. Further research will focus on using these stem cell spheres as elements that can be transplanted back into patients with corneal stem cell deficiencies to restore vision.

HAIR CELL SURVIVAL UNDER STRESS (1110013)

Dr Srdjan Vlajkovic, Prof Peter Thorne, Prof Gary Housley
Dept of Physiology, University of Auckland



Assoc Prof Srdjan Vlajkovic and student Ms Shelly Lin.

According to the World Health Organization, hearing loss is a major contributor to the global burden of disease and significantly affects over 280 million people world-wide. The vast majority of hearing loss occurs because of the degeneration or death of either hearing sensory hair cells or auditory nerves. Mammalian hair cells do not regenerate, so the hearing loss resulting from hair cell loss is permanent. Clearly with this background of terminal injury it is essential to maintain the functional sensory cell population through disease and aging. The proposed study drew on recent findings that there are specific molecules secreted in the ear that orchestrate protective or reparative responses to stress in the inner ear. In this study, we used cochlear tissue culture models to investigate therapeutic interventions directed at hair cell survival after exposure to ototoxic drugs. Findings from this study will aid pharmacological interventions to protect and repair the sensory structures of the inner ear, and thus protect from hearing loss.

SPUTUM PROCALCITONIN IN BRONCHIEACTASIS (3110015)

Dr Conroy Wong, Ms Sarah Mooney, Dr Susan Taylor, Dr Lata Jayaram, Dr David Holland, Dr Stuart Jones, Dr Irene Zeng
Dept of Medicine, Middlemore Hospital

Bronchiectasis is a chronic, debilitating disease characterised by productive cough, and repeated respiratory infections that require frequent courses of antibiotics. Procalcitonin is a marker of infection that is useful for distinguishing bacterial from viral infections. This study evaluated the clinical utility of sputum procalcitonin following our discovery of markedly elevated procalcitonin levels in *sputum* compared with serum in patients with acute exacerbations of bronchiectasis. We evaluated the levels of sputum procalcitonin in patients with stable bronchiectasis, the repeatability of the test, and compared the different methods of collecting sputum samples (spontaneous and induced). Thirty patients with stable bronchiectasis and fifteen healthy subjects had sputum and serum procalcitonin levels measured. The tests were repeated after 7 days in the patients with bronchiectasis. We found that sputum procalcitonin levels were increased in patients with stable bronchiectasis. This was in contrast to serum levels that were undetectable.

Procalcitonin levels in spontaneously expectorated sputum were higher than those in induced sputum in patients with bronchiectasis. Sputum procalcitonin levels remained stable in patients with bronchiectasis when repeated one week later. We conclude that sputum procalcitonin has the potential to be used as a marker of bacterial infection and to guide antibiotic therapy in patients with bronchiectasis.

EXECUTIVE FUNCTION IN METHAMPHETAMINE EXPOSED CHILDREN (1112004)

Dr Trecia Wouldes, A/Prof Linda LaGasse, Prof Barry Lester
Dept of Psychological Medicine, University of Auckland

A/Professor Trecia Wouldes and team.

Methamphetamine "P" use during pregnancy is a serious public health problem in NZ. As children begin their formal education it is important to determine whether prenatal exposure to methamphetamine will affect some important skills needed for school success. These include the ability to delay gratification, control impulses, and modulate emotional expression so that they can get along with their peers and attend to solving novel problems. Children who do not have these skills are more likely to be disruptive in the classroom and unable to pay attention in class and be at risk for later conduct problems and substance abuse. Early results of our research show that children exposed prenatally to methamphetamine may have more problems mastering these skills which may in turn affect their early learning and their ability to pay attention in the class room and get along with their peers.

FUNDED BY: AC Horton Estate

ROBOTIC GAIT REHABILITATION SYSTEM (1111014)

Prof Shane Xie, Dr John Parsons
Dept of Mechanical Engineering, University of Auckland

Prof Shane Xie (centre) in the lab.

Neurological disorders such as stroke and incomplete spinal cord injuries (ISCI) often result in lower limb disability and loss of mobility. Robot driven physiotherapy has been actively researched in the past two decades to help physiotherapists provide better treatment. However, existing designs of robotic gait orthoses are extremely heavy and rigid and are not suitable to work with human users. Moreover, these orthoses force the subject's limbs on predefined tracks without taking into account the patient's disability level. In order to advance the present state of robotic physiotherapy, this project has developed a new design of robotic orthosis which will be more flexible, lightweight and with the use of special muscle like actuators; the actuation of robotic orthosis will be more compliant, soft and human friendly. Besides design improvements, we have also developed an intelligent controller based on "assist-as-needed" approach whereby the robotic assistance to the subjects can be attuned to their neurological impairment levels. Brain control methods have been developed to allow users to operate the robotic exoskeleton in a natural way. Physiotherapy, employing our new robotic orthosis design and intelligent controller will be natural, safe, objective and evidence based.

MAPPING STUDY OF PERSISTENT ATRIAL FIBRILLATION (1112020)

Dr Jichao Zhao, Prof Bruce Smaill, Dr Nigel Lever
Auckland Bioengineering Institute, University of Auckland

Atrial fibrillation causes rapid/chaotic activation of the atrial chambers of the heart and impacts ~88,000 New Zealanders each year. Long term success rate of reversing persistent atrial fibrillation (PeAF) in patients is very disappointing (<30%). We proposed an innovative global atrial electrical mapping method for better understanding and ablation of PeAF. A suite of innovative signal processing tools have been developed to characterise spatio-temporal atrial activation patterns. A robust forward/inverse approach has been proposed and tested on varied sizes of sheep left atrial geometries extracted from magnetic resonance imaging. Our research outcomes will lead to better treatment of PeAF.

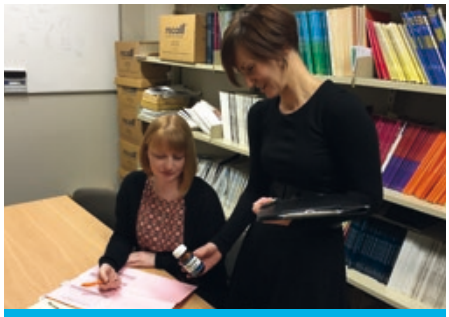
Grants Completed continued

POST DOCTORAL FELLOWSHIPS

EDITH C COAN POST DOCTORAL FELLOWSHIP

ARE GENERIC MEDICINES ACTUALLY LESS EFFECTIVE AND MORE LIKELY TO CAUSE SIDE EFFECTS? (1312001)

Dr Kate Faasse
Dept of Psychological Medicine, University of Auckland



Dr Kate Faasse (right) discussing how to make medicines more effective by utilising the placebo effect with lab group member and PhD Candidate Annie Jones.

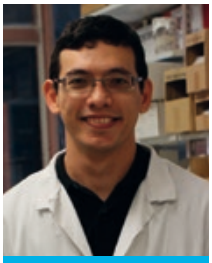
The two studies looked at the influence of branding as well as how seeing another person report medication side effects impacts on the effectiveness and side effects of medicines. The results of the first study show that seeing another person report side effects after taking a placebo tablet increases the number of side effects experienced by the viewer, as well as reducing the effectiveness (placebo effect) of the tablet. The second study found that having a brand name label on a pain relieving medicine (some tablets were active ibuprofen, some were placebos) can enhance the effectiveness of the tablet when compared to generic labelling, as well as increasing medication side effects when the tablet is a placebo. Both studies have now been completed, study one has been published, and study two has been written up and submitted to a major health psychology journal for consideration.

FUNDED BY: The Edith C Coan Trust

perpetual guardian

MICROTUBULE DYNAMICS AND NEUROSERPIN (1310002)

Mr Tet Woo Lee
School of Biological Sciences, University of Auckland

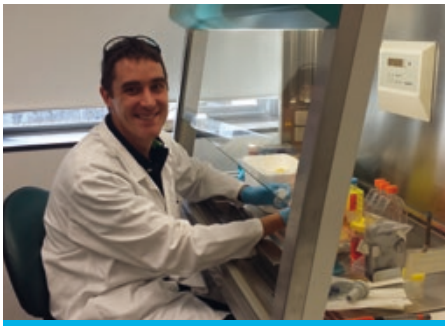


Mr Tet Woo Lee

Research to investigate the function and dysfunction of the nervous system is important for understanding the causes and possible treatments for the various neurological diseases that devastate the lives of many individuals. One method used by scientist to study the nervous system is to grow nerve cells, or neurons, in the laboratory. This method of culturing neurons provides a means to investigate how these cells grow and form connections, as well as how they are affected by various chemicals and drugs. In our laboratory studies, we have inadvertently discovered that the growth of cultured neurons is strongly altered by chemicals that leach from plastic syringes and filters, which are commonly used in laboratory research to sterilise solutions. Our findings provide an important warning to the scientific community to ensure that the use of these consumables does not compromise scientific experiments. We have also been studying the protein neuroserpin, which is known to protect neurons from death in stroke and is linked to several neurological diseases. We have identified the key parts of the neuroserpin molecule that mediate its biological activity. These results will be beneficial in the design of potential therapeutic agents based on neuroserpin.

EVALUATION OF SCAFFOLD MATERIALS FOR TENDON REGENERATION (1311002)

Dr David Musson
Dept of Medicine, University of Auckland



Dr David Musson making up collagen gels to seed cells in.

The aim of this project was to identify materials that could be used to improve the surgical outcomes of tendon repair. Tears of the rotator cuff, for example, affect approximately 50% of those over the age of 50 and in the past 10 years the number of surgical repairs has increased 4-fold. However, due to the tendon's inherent lack of healing, re-tear rates can be as high as 69%. Therefore, tissue engineering, where a biomaterial scaffold can be placed at the site of injury to aid the repair process, has been highlighted as a way of improving this high re-tear rate.

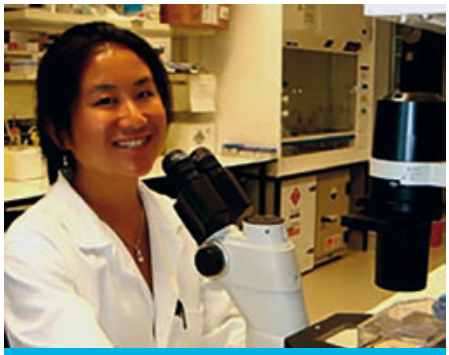
During this project five novel scaffold materials, ranging from naturally derived products to synthetic polymers, were assessed in a series of in vitro studies. Two particularly impressive scaffolds were selected to continue through to carefully designed pre-clinical models of rotator cuff augmentation. Both scaffolds significantly improved the healing outcomes and are now being considered for clinical application by our orthopaedic collaborators.

DOCTORAL SCHOLARSHIPS

BRIAN DE LUEN DOCTORAL FELLOWSHIP

THE REGULATION OF STEM CELL MIGRATION IN PARKINSON'S DISEASE (1210001)

Miss Sheryl Tan
Centre for Brain Research, University of Auckland

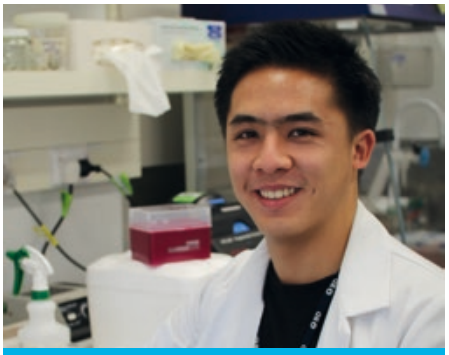


Sheryl Tan investigating olfactory dysfunction in Parkinson's disease.

Hyposmia, or the diminished capacity to smell, is a robust precursor to the motor symptoms of Parkinson's disease (bradykinesia, rigidity, a resting tremor, and a shuffling gait), preceding these by 4-10 years. In pursuit of what causes hyposmia in the virtually unstudied human olfactory bulb, a computerised 3D model of the olfactory bulb was created using a combination of automated, fluorescent immunohistochemistry and 3D reconstruction methods that provided quantitative parameters and a unique method for visualisation of the constituents of the olfactory bulb and its functional units (olfactory glomeruli). Antibodies to V-GLUT2 (vesicular glutamate transporter type 2) and NCAM (neural cell adhesion molecule) enabled the identification of olfactory glomeruli. The number of glomeruli, as counted from the 3D model, was highly variable amongst four normal cases (2,436 – 9,999 glomeruli) and not significantly different from three Parkinson's disease bulbs (1,840 – 8,341 glomeruli). Total glomerular and bulb volume was also measured but no significant differences were observed. Nonetheless, the experimental and analytical approach employed in these studies represents a unique and powerful method for visualisation and objective quantification. The second major aspect to this thesis was an experimental approach to understanding the control mechanism of polysialic acid-neural cell adhesion molecule (PSA-NCAM), a post-translational modification that aids cellular migration and dendritic foraging. The putative role of sialidase IV (NEU4) in the downregulation of PSA-NCAM was examined; the removal of polysialic acid being a critical step for correct positioning of neuroblasts upon migrating into the olfactory bulb. To do this, NEU4 was expressed in the TE671 rhabdomyosarcoma cell line, and its effects on PSA-NCAM expression were measured. No significant changes in overall PSA-NCAM levels were seen in cells expressing either the short or long isoform of NEU4. This was seen under conventional culture conditions and also when cells were cultured in an extracellular matrix. In order to detect more subtle changes that may be occurring at the cell surface, the same experiments were performed and analysed using immunocytochemistry and high content analysis. Depending on the mode of analysis small changes were detected suggesting that NEU4 may be involved in reducing the amount of PSA-NCAM present at the cell surface. However, owing to the experimental design, I was not able to definitively implicate or exclude NEU4 from involvement in the down-regulation of PSA-NCAM. Collectively, the findings of this thesis are of relevance when elucidating the mechanisms of olfactory bulb wiring and organisation, and how neural progenitors serve to maintain this brain region over a lifetime.

COCHLEAR INFLAMMATION: MECHANISMS AND THERAPIES (1209003)

Dr Winston Tan
Dept of Physiology, University of Auckland



Dr Winston Tan

There are 360 million people worldwide (over 5% of the world's population) with disabling hearing loss. In New Zealand, up to 25% of the burden is generated from excessive noise exposure in occupational and leisure settings. Although oxidative stress has been postulated as the key mechanism of noise-induced hearing loss, emerging evidence suggests that cochlear inflammation may also be a major contributor. This project aimed to improve our understanding of the underlying mechanisms and dynamics of the noise-induced cochlear inflammatory response. We demonstrated a substantial inflammatory response in the mouse cochlea following exposure to acute and chronic noise exposure, with increased expression of various inflammatory mediators and the recruitment of inflammatory cells. We speculate that inflammatory cells are recruited to the noise-exposed cochlea by these mediators to mop up debris from noise damaged cells, but also cause significant bystander tissue injury, thus exacerbating the noise-induced damage. In addition, we investigated the protective role of adenosine signalling in noise-induced cochlear inflammation. Adenosine is a ubiquitous signalling molecule that shows

Grants Completed continued

strong anti-inflammatory effects via the adenosine A2A receptor (A2AR). We showed that post-exposure treatment with a drug that selectively stimulates A2ARs mitigated cochlear inflammation, which could represent a potential treatment for noise-induced cochlear inflammation.

OTHER GRANTS

SIR HARCOURT CAUGHEY AWARD

FUNDING FOR VISITING ACADEMIC PROF CHRISTINA PUCHALSKI (1712001)

Dr Peter Huggard
School of Population Health, University of Auckland

Dr Peter Huggard

Christina Puchalski is a palliative care specialist and Director of the George Washington Institute for Spirituality and Health, Washington, DC, and a Professor of Medicine and Health Sciences at The George Washington University School of Medicine. Her presentations and seminars focused on teaching spirituality in medical and health programmes. Sessions included three at the University of Auckland, seminars on "Spirituality in Palliative Care" seminar at The Selwyn Foundation and Mercy Hospice Auckland, plus a public evening seminar. In a programme organised by colleagues at Otago University, she presented to five groups of staff and public in Dunedin.

SIR DOUGLAS ROBB MEMORIAL FUND

GLOW WORM ANIMATION OUTREACH PROJECT (6712002)

Dr Siouxsie Wiles
Dept of Molecular Medicine & Pathology, University of Auckland

Award-winning scientist and communicator Dr Siouxsie Wiles has teamed up with animator Luke Harris to make another animation - this time about the New Zealand glow worm and how scientists use bioluminescence to understand circadian rhythms.

Online videos are the fasting growing source of content on the internet, and are becoming an increasingly popular format for communicating science. In this project, award-winning scientist Dr Siouxsie Wiles is working with professional graphic artist Luke Harris, and his team, to create a short animation using the New Zealand glow worm to introduce the public to exciting scientific research that exploits bioluminescence, in this case to study our circadian rhythm, otherwise known as our body clock.

GAVIN & ANN KELLAWAY MEDICAL RESEARCH FELLOWSHIP

TO BUILD ON EXISTING AND ESTABLISH NEW COLLABORATIONS IN THE UNITED KINGDOM AND USA AND ATTEND CONFERENCES IN GERMANY (1513001)

Dr Bruce Russell
School of Pharmacy, University of Auckland

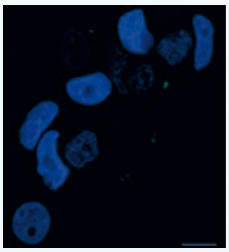
Dr Bruce Russell was awarded the Fellowship to travel to the UK and USA during later 2013 to build on existing and establish new collaborations. After meeting researchers at the Institute of Psychiatry, Kings College, in London for the first time they offered to co-author publications arising from a dataset that his group finished collecting last year. In addition there are now plans to seek undertake joint collaborative study based both here and in London. While based at the University of Cambridge Dr Russell also attended conferences in both Munich and Berlin to observe recent trends in schizophrenia research. During his subsequent visit to the University of California, San Diego, additional planning was undertaken to carry out collaborative research within the next two years.

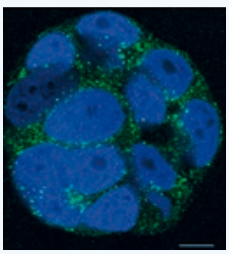
AMRF MEDICAL SCIENCES LEARNING CENTRE

University of Auckland
Faculty of Medical and Health Sciences

Opened by the Prime Minister Helen Clark in 2005, the AMRF Medical Sciences Learning Centre was funded by the AMRF to celebrate the Foundation's 50th Anniversary. The centre has won a national architecture award and houses the medical school's anatomy and pathology collections. It is used extensively by undergraduates in medicine, science and nursing from the University of Auckland and other tertiary education institutions, as well as registrars in pathology and radiology.

PUBLICATIONS





The Xentry sequence of amino acids allows proteins to become cell penetrating, and can be used to deliver drugs and imaging agents specifically to tumour cells. Top: Breast cancer cells do not take up an inactivated peptide containing both the Xentry sequence and a blocking sequence. Bottom: After the peptide is treated so that the blocking sequence is removed, the Xentry sequence-containing protein (green) can now enter the cell. Both images show the nuclei of the breast cancer cells stained blue and the scale bar represents 10 μm.

Publications

Askarian-Amiri, **ME**, Seyfoddin, V, Smart, CE, Wang, J, Kim, JE, Hansji, H, Baguley, BC, Finlay, GJ, Leung, EY (2014). Emerging role of long non-coding RNA SOX2OT in SOX2 regulation in breast cancer. *PLoS One,* 9:e102140.

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Yoon, JJ, Ismail, S, **Sherwin**, **T** (2014). Limbal stem cells: Central concepts of corneal epithelial homeostasis. *World Journal of Stem Cells,* 6(4):391-403.

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The University of Auckland Centre for Brain Research's Prof Louise Nicholson discusses promising new findings in the quest to find a cure for spinal cord injuries.

AMRF AUDITORIUM

University of Auckland
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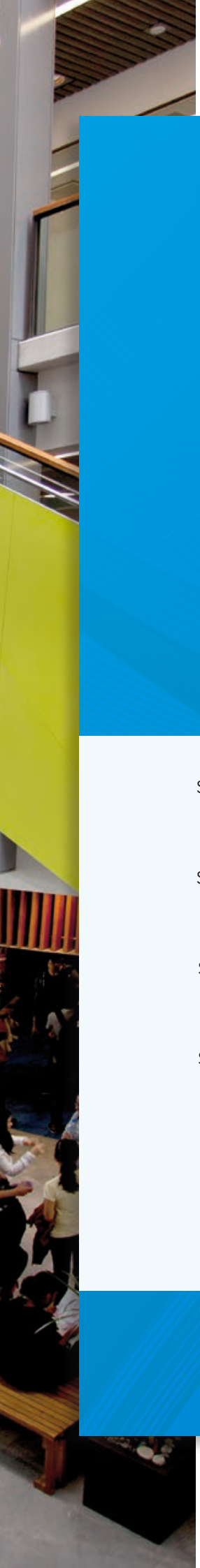
The AMRF Auditorium was made possible through a generous donation from an AMRF benefactor.

AMRF holds two free public lectures each year on topics of interest. See www.medicalresearch.org.nz for past and current lectures.

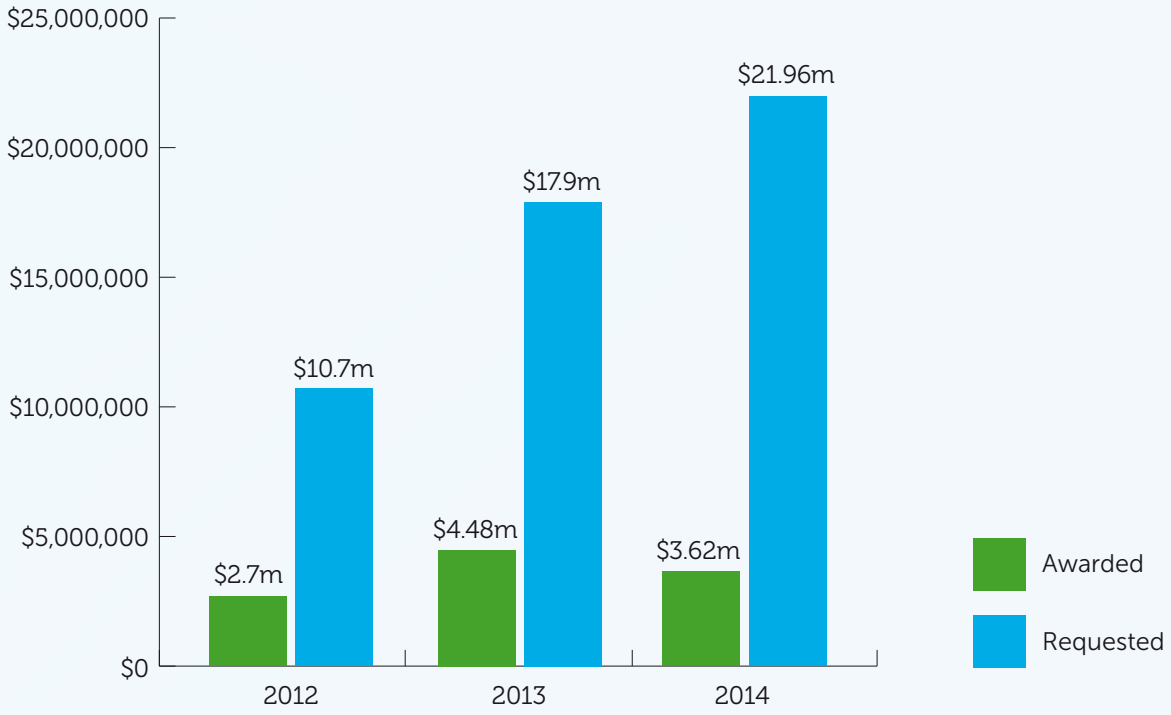


FINANCIALS 2014

THERE ARE MANY WORTHY REQUESTS FOR FUNDING THAT WE CANNOT SUPPORT

2014 SAW A 23% INCREASE IN APPLICATIONS TO THE AMRF

2013 – $17.9 million requested, $4.48 million awarded
2014 – $21.96 million requested, $3.62 million awarded



Financial Highlights 2014

RESEARCH FUNDING 2014 $3.62M **TOTAL RESEARCH FUNDING SINCE 1955 $55.8M**

FINANCIAL PERFORMANCE

	Note	2014 $	2013 $
Income			
Donations / Subscriptions	1	402,712	173,132
Investment Income		2,100,067	2,147,370
Trust Income and External Funding	1	769,765	1,800,509
Legacies/Bequests/Specific Donations	2	153,818	444,080
Net Gain on realisation of investments		600,119	82,437
Net Loss on currency fluctuations		(2,097)	(7,250)
Total		4,024,384	4,640,278
Expenditure			
Operational expenses		354,437	340,278
(Less Donation)	3	(354,437) Nil.	(340,278) Nil.
Research Grants 2014	4	3,425,927	4,263,479
Depreciation on Grant Funded Assets		5,231	4,857
Reduction in value of investments		335,599	461,791
Total		**3,766,757**	**4,730,127**
Net (Deficit) / Surplus		**257,627**	**(89,849)**

The summary financial report above has been extracted from the full Audited Financial Statements which can be obtained by contacting the Foundation's office. Tel: 09 923 1701 or Email: amrf@medicalresearch.org.nz

	2014	2013
Donations / Subscriptions	$402,712	$173,132
Investment Income	$2,100,067	$2,147,370
Trust Income and External Funding	$769,765	$1,800,509
Legacies / Bequests / Specific Donations	$153,818	$444,080
Net Gain on realisation of investments	$600,119	$82,437

NOTES TO THE 2014 FINANCIAL REPORT

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

Perpetual Guardian Administered Funds	
David & Cassie Anderson Medical Trust	205,261
Barbara Basham Medical Trust	126,500
NR Thomson Charitable Trust	70,000
NH Taylor Charitable	28,500
Ethel Reed Hitchen Estate	3,589
J&P Stilson Endowment Trust	165,000
Richardson Trust	31,915
Rose Richardson Estate	40,000
Edith C Coan Trust	120,000
John A Jarrett Trust	40,000
Public Trust Administered Funds	
Acorn Charitable Trust	20,000
Tennyson Charitable Trust	10,000
Pauline Gapper Charitable Trust	8,000
Audrey Simpson Trust	3,750
Ralph Dingle Trust	1,750
Other Trusts/Funds	
The Kelliher Charitable Trust	60,000
Paul Stevenson Memorial Trust	25,000
Anonymous	128,700
Joan Mayes Charitable Trust	25,000

2. Legacies, Bequests and Specified Donations 153,818

Estate of CF Hall

Estate of EM Robinson

Estate of A Schutt

Estate of FH Sims

3. Operational Expenses

The Foundation is very grateful for the Harry Goodfellow Fund, Hector Goodfellow Fund and TB & WD Goodfellow Funds for the external funding of operational expenses in 2014.

4. Research Funding Approved During Year

RESEARCH PROJECT GRANTS (16)	
AMRF General Purpose & Named Funds Supporting Research Projects	2,113,597
A C Horton Estate	
Breast Cancer Research Fund	
Brian Jones Fund	
Doug Brown Fund	
GS Blanshard Fund	
Hugh Green Diabetes & Breast Cancer Fund	
LH Corkery Fund	
Marion Ross Memorial Fund	
MJ Merrilees Fund	
Sir Henry Cooper Fund	
Sir Lewis Ross Fund	
Sir William Goodfellow Fund	
W & WAR Fraser Fund	
MEDICAL RESEARCH FELLOWSHIP (1)	
Douglas Goodfellow Medical Research Fellowship	282,500
POSTDOCTORAL FELLOWSHIPS (2)	
David and Cassie Anderson Research Fellowship	205,261
Edith C Coan Research Fellowship	175,863
DOCTORAL SCHOLARSHIPS (4)	
AMRF Doctoral Scholarships (2)	253,000
Barbara Basham Doctoral Scholarship	126,500
J I Sutherland Doctoral Scholarship	126,500
AMRF TRAVEL GRANTS (42)	**110,806**
OTHER GRANTS (9)	
OTHER GRANTS (9)	
Kelliher Charitable Trust Emerging Researcher Start-up Grants (2)	60,000
Gavin and Ann Kellaway Medical Research Fellowship (4)	111,345
HealtheX Emerging Research Award (1)	5,000
Sir Harcourt Caughey Fund (2)	50,000
Total Grants Committed 2014	**3,620,372**
Less amounts allocated but not required	(194,445)
TOTAL GRANT FUNDING 2014	**3,425,927**

Members, Sponsors & Supporters 2014

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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Estate of FH Sims

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AMRF have a proven track record of growing world class medical research, and it is our belief that research is the only way we can ensure genuine advances in medicine and outcomes for patients. To this end, we rely on the generosity and support of our donors to help us grow a sustainable fund for the future.

Become an AMRF Member

A recent quote from Elspeth Mount QSM, about becoming an AMRF member:

"I am absolutely in awe of the work of AMRF to date and would certainly encourage every member to help spread the word and seek to grow the membership among their family, friends and colleagues".

When you become an Annual or Life Member of the Foundation you will receive access to the latest information in the research world, hard copies of the AMRF's biannual Newsletter and Annual Report, and access to lectures and member only events. Sign up online or complete the form below.

Make a Donation

Donations are a vital part of our development and annual funding programme. You may choose to give annually, monthly, or to pledge an amount over time. Donations of $5 or more are receipted and tax deductible. A generous endowment to the AMRF funds our administrative overheads and running costs, which means that your support goes directly to funding research.

Make a Remembrance or Special Occasion Donation

You may consider a Remembrance Donation in lieu of flowers or may wish to honour a special occasion such as the birthday of a friend or family member. The Foundation will send a personalised letter advising that you have made this type of donation. Such donations are appreciated by the individuals or families as this is a dignified and practical way of expressing your condolences or celebrating a special occasion.

Make a Bequest or Major Gift – a lasting investment in medical research

A bequest is a gift of cash or assets (shares, property, or other assets) made through your Will. A bequest or major gift to the AMRF is an investment in the health of future generations. You can choose to leave your gift for a specific area of research or for general purposes, allowing the Foundation to determine the greatest area of need. If you are considering this option please contact us, as we are happy to assist.

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