Media Release
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Auckland Medical Research Foundation Awards over $3.62 million to Medical Researchers

The Auckland Medical Research Foundation (AMRF) has recently announced $2,335,306 in funding to medical researchers in the last three funding rounds for 2014, reaching a total of $3.62 million distributed in 2014.

Foundation Executive Director, Kim McWilliams says, “We have a long-standing commitment to support high-quality research, research talent, and help our grant holders develop world class research portfolios. Congratulations to these outstanding recipients”.

The successful grants included 7 research projects ($1,069,126), 4 Doctoral Scholarships ($506,000), 2 Postdoctoral Fellowships ($381,124), 1 Douglas Goodfellow Medical Research Fellowship ($282,500) 2 Gavin and Ann Kellaway Medical Research Fellowships ($49,882), 1 Sir Harcourt Caughey Award ($25,000) and 7 travel grants ($21,674) for researchers to present their research overseas. Grants were awarded over a variety of biomedical and clinical research areas including Cancer, Cellular and Molecular Biology, Endocrinology, Neuroscience, Surgery and Musculo-skeletal Science.

See Below for Grant Summaries

The Auckland Medical Research Foundation is a major independent funding agency and charitable trust that provides contestable funding for medical research across the complete spectrum of modern medicine. Over the last 59 years we have distributed over $56 million in funding to a wide range of research activities – currently around $3-4 million annually.

Our Foundation is unique in the charity sector, in that every dollar donated from within the community goes directly and fully (100%) to research. Our administration costs are generously supported by benefactors.

For further information on the current grants awarded and application forms for future grant rounds see our website at www.medicalresearch.org.nz

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For further information please contact:

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Grants Awarded November and December 2014

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 a polymeric non-biodegradable implantable systems 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.

MAXIMIZING 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
A/Prof Timothy Short, Dr Ivan Bergman, Dr Joyce Tai, Dr Maartje Tulip ($157,880 – 2 years) 2114014
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 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.

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.

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 – Perpetual Guardian_

**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 drawbacks. 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 utilize sophisticated miniaturized technologies to quantitatively explore how a pain-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 – Perpetual Guardian_

**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 Science, 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 5000 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 raise the exciting possibility that we may finally develop a treatment to improve the growth of diseased placentas leading to improved foetal growth thus reducing 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.

**GAVIN AND ANN KELLAWAY MEDICAL RESEARCH FELLOWSHIPS**

*These fellowships are awarded to support senior medically qualified, or established medical research persons, who would gain value from further study abroad, or in furthering their research expertise and knowledge at an approved overseas research institution.*

**A/Prof Alan Davidson ($13,082) 1514005**  
Dept of Molecular Medicine & Pathology, University of Auckland

To spend 3 weeks at The 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.

**A/Prof Michelle Glass ($36,800) 1514007**  
Dept of Pharmacology, University of Auckland

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

**SIR HARCOURT CAUGHEY AWARDS**

*These awards are granted to researchers who may (i) be New Zealand graduates who are returning to a part-time appointment in Auckland; or (ii) be an Auckland-based New Zealand medical graduate who is deserving of assistance to train and perform research in a specific field overseas, especially where there is a deficiency in local expertise in that field; or (iii) be sufficiently prestigious in a particular field of medical knowledge and/or research to visit Auckland, normally for 3-4 weeks, to foster interest and research in that specialty.*

**Dr Soizick Mesnage ($25,000) 2514006**  
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.