Auckland Medical Research Foundation
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# Successful AMRF Grant recipients December 2012

**OTOPROTECTION BY ADENOSINE RECEPTORS - $146,752**
**Dr Srdjan Vlajkovic, Prof Peter Thorne, Dr Detlev Boison, Prof Gary Housley**
Dept of Physiology, The University of Auckland

Hearing loss affects 10-13% of New Zealanders and this prevalence will increase with the aging population. Exposure to noise and drugs toxic to the inner ear are major contributing factors to this disability. Prosthetic rehabilitation via hearing aids and cochlear implants is the only current treatment for hearing loss. Hence, it is essential to develop therapies that can ameliorate or repair injury to the delicate structures of the inner ear. We have shown that hearing loss in experimental animals exposed to traumatic noise can be substantially restored by administration of drugs acting on adenosine receptors. Here we propose a set of studies that will utilize transgenic mice that lack genes for the two main types of adenosine receptors found in the inner ear to assess their responses to aging, noise stress and drug toxicity. This is critical translational research for therapeutic management of noise, age and drug-induced hearing loss.

**THE PEOPLE STUDY**
**Prof Robert Doughty, Dr Mayanna Lund - $70,000**
Dept of Medicine, The University of Auckland

Heart failure is a common condition with high rates of hospitalisation and death. Most clinical trials involving patients with HF have focused on patients with poor heart pump function (low LV ejection fraction). However, the heart pump function may be normal among a significant subset of patients with heart failure. Currently, there is uncertainty regarding which patients with heart failure with preserved pump function will be at risk of dying or being re-admitted to hospital. The objectives of this study are to determine which of these patients will be at risk of these events. This large-scale, multicentre international study will recruit 2500 patients with HF in New Zealand and Singapore. The patients will then be followed for 2 years. The study results will impact on the clinical management of patients with HF in New Zealand and Singapore and will lead to the development of clinical trials to test newer treatments for patients with heart failure.

**AUSTRALASIAN PAEDIATRIC HEAD INJURY RULES STUDY (APHIRST) - $114,000**
**Dr Jocelyn Neutze, Dr Stuart Dalziel**
Kidz First
Counties Manukau District Health Board

Many children sustain head injuries and present to emergency departments (EDs) for evaluation. Although head computer tomography (CT) identifies all important injuries, radiation from CTs can increase the risk of fatal brain and blood cancers. However, failure to quickly identify significant intracranial injury may have disastrous consequences including long-term neurological disability and/or death. This study aims to develop a pathway to assist doctors in deciding who should have a CT scan after head injury. Several evidence-based head injury clinical decision rules (CDRs) have been developed to identify patients at risk of significant head injury. None have been validated outside their original settings. We propose to prospectively validate and compare performance of the three highest quality CDRs from the United Kingdom, United States and Canada in 10,000 children presenting to

13 major paediatric EDs in Australia and New Zealand. Identification of optimal CDRs for implementation will help minimise risks of missing clinically significant intracranial injury and radiation exposure from cranial CT scans. The results will have a major impact on head injury management in children both in New Zealand and worldwide.

**POSTOPERATIVE GUT DYSFUNCTION - $63,500**
**A/Prof Ian Bissett, Dr Ryash Vatehr**
Dept of Surgery, The University of Auckland

Postoperative ileus (POI) is an important health problem which affects a considerable proportion of patients following abdominal surgery. It slows patient recovery, increases postoperative morbidity and prolongs length of hospital stay, thereby significantly impacting quality of life and patient-perceived outcomes of surgery. It also confers a significant fiscal burden on healthcare institutions, with its management in the USA alone being estimated at $US1.5 billion annually. The objectives of this research are to characterise for the first time pressure wave movement in the human large bowel peri-operatively and after tissue healing has occurred, and to investigate the therapeutic value of gastrografin in the management of POI. The use of gastrografin for POI has not been previously evaluated. The principal methodologies used will be prospective in vivo observational studies using novel fibre optic technology, and a double-blind placebo-controlled randomised trial. It is hoped that these projects will facilitate a clearer understanding of the pathophysiologic basis of POI and functional tissue healing, and appraise the therapeutic value of an economical, safe and readily available intervention.

**WRITTEN EMOTIONAL DISCLOSURE AND SURGERY - $151,616**
**Dr Elizabeth Broadbent, Prof John Windsor, Prof Andrew Hill, A/Prof Roger Booth**
Dept of Psychological Medicine, The University of Auckland

Surgery is a psychological stressor, with patients' concerns including fear of pain, death, and separation from family. Psychological stress has been shown to impair the production of cytokines involved in wound healing and to slow the healing of small experimental wounds. Psychological stress has also been associated with altered levels of pro- and anti-inflammatory cytokines and metalloproteinases involved in wound repair in surgical patients. Furthermore, relaxation exercises have been found to improve indices of wound healing and levels of fatigue following surgery. More research is needed to investigate the effects of other types of interventions on healing after surgery. There is evidence that three, 20-minute sessions of writing about personal emotional events can improve the healing of small experimental wounds, but no research has investigated the effects of expressive writing on the healing of wounds in surgical patients. This research aims to test whether written emotional disclosure can improve wound healing in surgical patients. We will randomise 90 patients scheduled to undergo abdominal surgery to either write about traumatic events or to a control group. We will measure stress, mood, cytokines, fatigue, and wound healing. This research has implications for the delivery of pre-operative care to optimise outcomes.

**IMPROVING TEAM COLLABORATION IN THE OPERATING ROOM - $123,626**
**A/Prof Jennifer Weller, Prof Alan Merry, Mr Ian Civil, Ms Wendy Guthrie, Dr Craig Webster, Dr Jane Torrie, Mr Andrew MacCormick, Ms Kaylene Henderson, Dr David Cumin, Dr Matt Boyd**
Dept of Anaesthesia, Auckland City Hospital

Recent, important studies have shown that failures in teamwork and team communication in the operating theatre (OT) lead directly to clinical errors and patient harm. Research also suggests that training as a team for those who are expected to work in teams can significantly reduce these teamwork errors. These findings form the basis of the United States Institute of Medicine's directive that such team-based training is needed. Despite this, training in healthcare tends to occur within professional specialties (professional "silos") rather than in genuine interprofessional teams. Simulation provides a risk-free opportunity to

train teams in a realistic environment, yet simulation activities at present remain focussed on single specialities. The current project will engage complete multiprofessional clinical teams comprising surgeons, an anaesthetist, an anaesthetic technician, and theatre nurses in a highly realistic simulated OT environment. The simulated environment and scenarios developed by our group will create a "laboratory" where multidisciplinary team interactions can be systematically studied in ways not possible in the clinical OT. We will measure the effect of a full-day simulation course intervention on surgical complications in the clinical setting. Ultimately these simulations will lead to development of definitive strategies to improve performance, OT productivity, and patient safety.

**WNT SIGNALLING AS A LINK BETWEEN DIABETES AND ATHEROSCLEROSIS - $78,071**

**Dr Peter Shepherd, Dr Brie Sorrenson**
Dept of Molecular Medicine & Pathology, The University of Auckland

Atherosclerotic cardiovascular disease is a leading cause of death and risk of cardiovascular disease is greatly increased in type-2 diabetics. Despite strong evidence linking the high glucose levels observed in diabetics with atherosclerosis, the molecular mechanism linking these states remains elusive. Atherosclerosis is largely the result of lipid accumulation in the arterial wall and we have previously observed that glucose alters lipid metabolism in macrophages, which are the cells responsible for initiating atherosclerosis through the trapping of lipid within the arterial wall. We have also observed that glucose regulates the Wnt signalling pathway in macrophage cells and this study aims to determine whether regulation of Wnt signalling components by high glucose levels could be contributing to the increased rate of atherosclerosis in diabetics. We will test how glucose regulates Wnt signalling factors, such as LRP5/6 and β-catenin, and determine whether such regulation promotes lipid accumulation in cells of the arterial wall. Overall, this work will expose a mechanism by which cells sense and respond to high glucose levels and will provide important new information on the mechanisms linking diabetes with cardiovascular disease.

**MELANOCORTIN TREATMENT FOR OBESITY - $166,636**

**Dr Kathy Mountjoy, Dr Ailsa McGregor**
Dept of Physiology, The University of Auckland

Stress, weight gain and glucose metabolism are influenced by a group of hormones called melanocortin peptides. These peptides comprise chains of amino acids, of varying length, and are derived from one large precursor protein found in the brain and pituitary gland, called proopiomelanocortin (POMC). Special enzymes chop-up POMC to form the melanocortin peptides, according to the body's requirement. We have developed a mouse that lacks a particular 13 amino acid melanocortin peptide called adrenocorticotropic hormone (ACTH1-13). These mice can be used to study what effects of ACTH1-13 on physiological function. The mice appear normal until they reach puberty and then they develop obesity, but not diabetes. Treatment of these obese mice with ACTH1-13 or a natural variant that is slightly chemically altered, called α-melanocyte stimulating hormone (α-MSH), reduced mouse body weight and fat mass when mice were fed a normal diet. In light of the worldwide obesogenic environment, we will now test whether obesity and diabetes in these mice is exacerbated by a feeding a high-fat diet, and whether melanocortin hormone treatment can reverse obesity while animals feed on a high-fat diet. These studies should aid the development of improved tests and treatments for obesity and type 2 diabetes.

**MOLECULAR DEFECTS IN COMMON VARIABLE IMMUNE DEFICIENCY - $54,913**

**A/Prof Rohan Ameratunga, Dr Klaus Lehnert, Dr See-Tarn Woon, Ms Wikke Koopmans, Dr Anthony Jordan**
Dept of Virology and Immunology, LabPLUS

Common variable immune deficiency (CVID) is the commonest symptomatic primary immune deficiency disorder in adults and children. CVID patients are susceptible to multiple and severe infections. Serious infection episodes often require hospitalisation. Up to 90% of CVID patients do not have confirmed genetic diagnoses. Securing a genetic diagnosis can assist with patient management and expand our understanding of this disorder. We present two groups of patients that could benefit from the next generation sequencing technology. Group one are seven patients from a kindred. We conclude another gene, not the commonly known mutation TACI C104R, is the cause of CVID. Group two comprises of a family with two affected siblings but asymptomatic parents and brother. The proposed whole exome sequencing project will help identify novel genes, which may be causative. We will use our knowledge of the immune response-associated molecular pathways associated with CVID to help prioritise the mutations we identify. Identifying these genes will result in much improved patient management including family studies, early diagnosis and better prognosis. In the future we will use this technology as the discovery and diagnostic tools for other primary immune deficiency disorders with undefined genetic defects.

**THE SYNAPTIC BASIS OF HUNTINGTON'S DISEASE - $141,154**
**Dr Johanna Montgomery, Dr Ailsa McGregor**
Dept of Physiology & Centre for Brain Research, The University of Auckland

All neurodegenerative diseases have direct or indirect effects on synapses in the brain. Therefore a major step towards understanding what goes wrong in the diseased brain is to understand how synapse function is altered by disease. In this proposal we seek to determine the source of synapse dysfunction in Huntington's Disease (HD). Previous work on HD mouse models has shown that receptors on the surface of neurons are mis-localised, inducing changes in synapse function. Here we will focus on two synaptic proteins, bSAP97 and aSAP97, which we have recently shown can control the distribution of receptors on neurons (Li et al., 2011, J. Physiology 589, 4491-4510). We will utilise a cellular and an animal model of HD to determine whether changing the expression levels of bSAP97 or aSAP97 can rescue normal receptor distribution, and whether this subsequently rescues normal synapse function. These cellular data will identify whether a and/or bSAP97 are part of the pathological signature for HD and also whether they could be potential therapeutic targets.

**TARGETING THE HUMAN GROWTH HORMONE RECEPTOR IN ER+ BREAST CANCER - $138,193**
**Dr Jo Perry, Dr Dong-Xu Liu, Dr Stephen Jamieson, Prof William Wilson**
Auckland Bioengineering Institute, The University of Auckland

Humans and animals born with a deficiency in the cell surface receptor for human growth hormone (hGH) have a dramatically reduced, almost absent, risk of developing cancer. Conversely, increased levels of hGH and the hGH receptor are detectable in a variety of different human cancers, including breast cancer, and this is associated with reduced survival for breast cancer patients. However, studies investigating the efficacy of inhibiting the hGH receptor for the purposes of treating cancer are limited. We will use pre-clinical models of human breast cancer to test the hypothesis that hGH receptor inhibition will restrict the growth of tumours, and improve response to the anti-estrogen drug, tamoxifen. A clinically available hGH receptor inhibitor will be used in this study. Thus a successful outcome has the potential for rapid translation into the clinic, with the ultimate aim of significantly impacting on treatment outcomes for breast cancer patients.

**MAPPING STUDY OF PERSISTENT ATRIAL FIBRILLATION - $107,426**
**Dr Jichao Zhao, Prof Bruce Smaill, Dr Nigel Lever**
Auckland Bioengineering Institute, The University of Auckland

Atrial fibrillation (AF) causes rapid and chaotic activation of the atrial chambers of the heart. It impacts ~37,000 New Zealanders each year and the prevalence of AF in a population

increases with age, with 10% of people over 80 having AF. Māori experience morbidity and mortality due to AF at a higher rate and at an earlier stage of life than the general population. AF is associated with a range of clinical conditions including hypertension, valvular disease and heart failure. AF itself is not generally life threatening, but it can cause stroke and exacerbate heart failure. Percutaneous catheter ablation is widely used to treat patients with AF. However, results for persistent AF are much less impressive due to lack of effective technique to detect and analyse AF pattens. We propose a novel approach to atrial electrical mapping in which activation will be mapped simultaneously in both atrial chambers using novel basket catheters and test it on sheep. These data will then be referred to 3D atrial endocardial surface reconstructed from magnetic resonance images (MRI) or computed tomography (CT). A suite of real-time signal processing tools will be developed so that spatio-temporal atrial activation patterns can be analysed in real time.

## DOCTORAL SCHOLARSHIPS

### DEVELOPMENT OF BIOMARKERS FOR IMPROVED EMBRYO SELECTION IN IVF – $122,000

**Miss Elizabeth Hammond**
Dept of Obstetrics & Gynaecology, The University of Auckland

In New Zealand, there is an increasing trend for women to delay child bearing. This is a significant health issue as female fertility declines during ageing, due to both the loss of eggs and lowering of egg quality. Consequently, there has been increasing use of In Vitro Fertilisation (IVF), a technology which uses drugs to stimulate the ovaries to produce mature eggs which are then collected and fertilised outside the body. One fertilised egg is then put back into the uterus to hopefully establish a successful pregnancy. Clinically, there is a need for improved markers of egg quality so that only the best embryo is transferred into the uterus. We will investigate how egg quality is affected by ageing and ovarian stimulation drugs, which could lead onto the development of a marker of egg quality and improved IVF protocols. We aim to find ways to improve IVF success rates, especially in older women. Premature menopause (under 40 years) is also becoming more of an issue as woman delay child bearing. We wish to identify some genetic causes of premature menopause, and search for early clinical markers that provide a better opportunity for intervention.

### THE EFFECT OF NEONATAL HYPOGLYCAEMIA ON VISUAL DEVELOPMENT - $97,250

**Mr Nabin Paudel**
Dept of Optometry & Vision Sciences, The University of Auckland

Newborn babies commonly experience low blood sugar, a condition known as neonatal hypoglycaemia. As glucose is the brain's main energy source, this condition may impair neurological function, however, at present, very little is known about the effect of neonatal hypoglycaemia on brain development. As a consequence, the level of neonatal hypoglycaemia that requires treatment in early infancy is currently unknown. This PhD project forms part of a large multidisciplinary study known as the Children with Hypoglycemia and their Later Development (the CHYLD study) which aims to assess the developmental effects of neonatal hypoglycaemia in a cohort of 500 children whose blood glucose levels were measured continuously for several days after birth. The aim of this specific project is to assess visual function in these children at the ages of 2 and 4.5 years. Vision is of particular interest as neonatal hypoglycaemia may preferentially affect visual brain areas. The assessments include a range of vision tests targeting specific regions of the visual cortex and will therefore provide new insights into the effect of neonatal hypoglycaemia on the rate and extent of visual cortex development. The study will also provide important information regarding the treatment and management of hypoglycaemia in newborns.

### LIVER APCS – $ 83,000

**Dr Otto Strauss**
Dept of Surgery, The University of Auckland

Antigen presenting cells (APCs) are critical in initiating and directing the immune response in humans. Detailed description of APCs in skin, blood, and lymph nodes has proven their importance in normal and diseased states and has identified them as targets for therapies in disease. Despite this, APCs have not been appropriately characterized in human liver. The liver is unique in that it promotes a state of tolerance and in doing so is not only the most readily accepted transplanted organ, but also harbours infection such as hepatitis and malaria, and malignancy that is both malignant and originating within the organ. In certain situations it can still mount a potent immune response, such as to clear infection of hepatitis A, or in the autoimmune diseases of primary sclerosing cholangitis and autoimmune hepatitis. The project will use modern techniques to accurately describe APC populations in the liver in detail. Improving our knowledge of these cells will help us to understand the biology of health and disease in the liver, but will also define targets on liver APCs to allow for their use in future therapies and drugs to combat disease not only of the liver, but the entire body.

## POSTDOCTORAL FELLOWSHIPS

### ARE GENERIC MEDICINES ACTUALLY LESS EFFECTIVE AND MORE LIKELY TO CAUSE SIDE EFFECTS? - $165,060

**Dr Kate Faasse**
Dept of Psychological Medicine, The University of Auckland

The proposed studies will investigate the impact of branding on medication effectiveness and side effects. Study 1 will look at the impact of branding in a social context in which participants may or may not see another person experience medication side effects. Study 2 will investigate whether generic painkillers work as well as branded painkillers when people know which medication (branded or generic) they are taking compared to when they do not know. This research is relevant to a wide range of medical treatments. As more and more medications become available, government budgets must find ways to accommodate this growth, often through funding generic alternatives rather than branded drugs. Public perceptions of generic medications are generally negative, and these perceptions may influence expectations about medications. Previous research suggests that changing medications can reduce how well a medication works, and changing to a generic can increase side effects. Additionally, social information transmitted through television and the internet can increase side effect reporting, and may also spread negative expectations about generic medications.