Auckland Medical Research Foundation
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Auckland Medical Research Foundation awards over $1.3 million to medical researchers in the first half of 2016

The Auckland Medical Research Foundation (AMRF) has recently announced $1,311,018 in funding to medical researchers in its first two of five funding rounds in 2016.

Foundation Executive Director Kim McWilliams says, “It is really pleasing to see such great research projects and talent across the full spectrum of medical science. More research is the only way we can ensure genuine advances in medicine and outcomes for patients. Congratulations to all recipients.”

The successful grants include 11 research projects ($1,271,264) and 16 travel grants ($39,754) for researchers to present their research both in New Zealand and overseas. Grants were awarded in a variety of biomedical, clinical, and population health research areas including: Cancer; Cellular and Molecular Biology; Infection and Immunity; Neuroscience; Population Health; Psychology; Reproduction, Development, Maternal and Newborn Health; Sensory Sciences; and Musculo-skeletal Science.

See Below for Project 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 60 years we have distributed over $67 million in funding to a wide range of research activities – currently around $4-5 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 a benefactor.

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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Project Grants Awarded June 2016

Perioperative Atrial Fibrillation and Postoperative Stroke (PAFS) study ($30,743 - 2 years) 2116003
Dr Doug Campbell, Dr Tom Burrows, Dr Cornelius Kruger, A/Prof Timothy Short
Dept of Anaesthesia, Auckland District Health Board

Atrial fibrillation is an abnormal heart rhythm, which is common in older people. It is associated with increased risk of stroke, which can have devastating consequences. Patients who have episodes of atrial fibrillation frequently receive anticoagulant medicines (such as warfarin) to reduce the risk of stroke. After surgery, it is common for older patients to have an episode of atrial fibrillation. We do not know how commonly this occurs, or what the consequences are. The Perioperative Atrial Fibrillation and Postoperative Stroke (PAFS) study will determine the incidence and consequences of atrial fibrillation after surgery. Patients will wear a heart monitor before surgery, and for two weeks after surgery. They will undergo MRI scan of their brain several days after surgery looking for any evidence that they have had a small stroke. This study will be performed across several hospitals internationally, including Auckland City Hospital. The Principal Investigator is based in Canada, and has published multiple studies looking at heart disease in patients having major surgery. The PAFS study might change how we treat patients who have an episode of atrial fibrillation after an operation, in order to protect them from complications such as stroke.

Measuring in vivo activity in the auditory cortex and its link to Autism Spectrum Disorders ($159,250 - 2 years) 1116009
Dr Juliette Cheyne, Prof Peter Thorne, A/Prof Johanna Montgomery
Dept of Physiology & Centre for Brain Research, University of Auckland

Autism Spectrum Disorders (ASD) are developmental disorders defined by learning difficulties, sensory issues, communication difficulties, social deficits and stereotyped behaviours. Because ASD symptoms appear during infancy, it is crucial to examine how brain development is altered, as this could cause behavioural deficits. The social and communication difficulties in ASD are thought to be due to abnormalities in the processing of sounds, which in turn impairs language abilities. We hypothesise that this impaired sound processing is due to connections between brain cells in the auditory cortex forming incorrectly during development. We will utilise state-of-the-art cellular recording techniques in live mice to determine how the development of the auditory cortex is affected in ASD. We will reveal developmental differences in brain activity in ASD mice, which could lead to deficits later in life. We will also determine whether cortical organisation of tones (from high to low frequency) and plasticity in the auditory cortex are altered in ASD mice. The information obtained in this study is essential to advance knowledge of how changes in the activity in the developing brain link to deficits in sensory processing later in life, which could also be relevant to other neurodevelopmental disorders.

Overcoming drug-resistant bacteria ($154,847 - 2 years) 1116001
A/Prof Brent Copp, Prof Jean Michel Brunel, Dr Siouxsie Wiles
School of Chemical Sciences, University of Auckland

For several decades the routine use of antibiotics has saved countless lives. Recently, the World Health Organisation described how antibiotic-resistant bacteria are present in every region of the world, including New Zealand, and called for drastic action to prevent a return to the pre-antibiotic era.

New antibiotics are needed, or alternatively, new methods are needed to restore the activity of antibiotics against drug-resistant bacteria. We have recently discovered a class of compounds that do the latter – enhancing the activity of the antibiotic doxycycline towards the normally drug resistant bacterium Pseudomonas aeruginosa. This project involves the synthesis and biological evaluations of new molecules based around our discovery, where we will optimize the antibiotic enhancing activity of this compound class and determine how such enhancement is achieved. This will provide proof of concept as to whether such compounds can be used to 'rehabilitate' old antibiotics, and to thereby restore their effectiveness to aid in the fight against drug-resistant bacterial infections.

IGF-1 and Preterm Brain Injury ($158,997 - 2 years) 1116008
Dr Justin Dean, Prof Alistair Gunn
Dept of Physiology, University of Auckland

In New Zealand, approximately 500 babies are born prematurely every year, and around half survive with life-long disabilities. These disabilities often result from infection and inflammation around the time of birth. Excitingly, we now know that the brains of preterm babies can recover rapidly from injury, but may then fail to develop normally. Using a new rodent model of very preterm brain injury, we found that inflammation can impair normal brain development. Further this was associated with a reduction in the levels of insulin-like growth factor (IGF-1), a molecule critical for normal brain growth. In this proposal, we will test whether restoring normal levels of IGF-1 in the brain during or after infection will promote brain maturation, and thus restore normal brain development. We will compare direct treatment of the brain using IGF-1 with an agent that can improve availability of locally produced IGF-1.

CB1 in brain cancer ($157,272 - 2 years) - 1116011
A/Prof Michelle Glass, Dr Scott Graham, Dr Graeme Finlay
Dept of Pharmacology, University of Auckland

Is cannabis a cure for brain cancer? This question is appearing with increasing frequency in the popular media, but the scientific evidence is still undecided. In studies investigating cannabinoid ligands that target the cannabinoid receptors in cancer cells the outcome has been quite mixed, with some reports of tumour cell death, but others that have observed an increase in cell proliferation. We have some evidence to suggest that the level of cannabinoid CB1 receptors expressed in cells influences the signal that is produced by activation of the receptors – and hypothesize that this observation is the reason for the diverse findings in the field. Here we aim to utilise human brain cancer cells to investigate if the expression and function of cannabinoid receptors in these cells and determine if CB1 receptors are a valid therapeutic target.

Cystine/cysteine redox signalling in the aging eye ($106,260 - 2 years) 1116006
Dr Julie Lim, Prof Paul Donaldson, Dr Monica Acosta
Dept of Physiology, University of Auckland

With advancing age, oxidative stress results in redox imbalance and eye diseases which threaten the sight of the elderly. We propose that the cystine/glutamate antiporter (CGAP) in the eye is important for maintaining redox balance and minimising oxidative stress. Clinical assessments on CGAP knockout mice reveal the early onset of eye diseases. To elucidate the underlying pathways that result in these pathologies, molecular and functional tests will be performed and this information used to guide the design of effective therapies that target a specific tissue of the eye against oxidative

stress to delay the onset of age related eye diseases.

Epigenetics of progesterone resistance in endometriosis ($157,141 - 2 years) 1116005
Dr Anna Ponnampalam, Prof Cynthia Farquhar
Liggins Institute, University of Auckland

Endometriosis is characterised by the presence and growth of endometrium (the lining of the uterus) outside the uterus. It is a common cause of infertility and chronic abdominal pain in reproductive age women. While the incidence is approximately 10%, the actual prevalence is much higher because many women and girls are initially misdiagnosed. Endometriosis-related pain is serious, debilitating and episodic. Current treatment modalities have major limitations and are only successful in half the patients and these women generally develop resistance to repeated treatments with the same agent over a period of 6 months to 3 years. Hence the clear need to identify novel molecular pathways that can provide early identification of developing resistance, inform current therapies and enable future targeted therapy development. The project is to test the hypothesis that DNA methylation plays a crucial role in the aberrant oestrogen priming of the endometrium that lead to progesterone resistance and development of endometriosis. The overall objective of this project is to understand the mechanisms involved in progesterone resistance generally seen in endometriosis, thereby improving identification and potentially enabling the development of effective therapeutic interventions.

Mucosal vaccination against S. aureus with PilVax ($100,650 - 2 years) 1116007
Dr Fiona Radcliff, A/Prof Thomas Proft
Dept of Molecular Medicine & Pathology, University of Auckland

Effective delivery of approved vaccines typically requires qualified personnel, defined storage conditions and injection of the materials. Using live organisms, such as food grade bacteria, for vaccine production and needle-free delivery (e.g. by ingestion) is a promising alternative. A novel vaccine delivery vehicle, called PilVax, has been developed by researchers at the University of Auckland. The basis of PilVax is a bacterium found in yoghurt, called Lactococcus lactis, which has been modified to express large quantities of foreign proteins including vaccine candidate antigens, on its surface. Preliminary studies in mice have shown that delivery of PilVax into the nasal cavity can indeed stimulate robust immune responses. The goal of this project is to build on that work by testing whether PilVax mediated delivery of vaccine candidate antigens from Staphylococcus aureus, an important bacterial pathogen that is very common in New Zealand, can stimulate protective immunity to this pathogen. If PilVax proves to be effective in these tests it will establish this delivery platform as a promising and flexible approach for non-invasive vaccination against not only S. aureus but also other mucosal pathogens.

Stereotactic body radiotherapy in lung metastases SAFRON II. ($25,000 - 2 years) 2116004
Dr Giuseppe Sasso, Dr Shankar Siva, Mrs Rebecca Montgomery
Radiation Oncology, Auckland District Health Board

Stereotactic ablative body radiotherapy (SABR) is a high-precision, non-invasive and low-toxicity alternative for treatment of small lung lesion. Due to early reports of excellent control rates (comparable to surgery) and minimal associated toxicities, SABR is being rapidly implemented worldwide and in New Zealand in the treatment of small peripheral lung lesions. Approximately 30% of all cancer patients will develop secondary spread to the lung during the course of their disease. In patients with limited secondary cancer in the lung, SABR can result in long-term survival and even

cure. As it is non-invasive, delivered in as little as a single outpatient visit and without the need for hospitalisation, SABR is an attractive and potentially very cost-effective treatment option. Additionally, emerging evidence suggests that large doses of precision SABR may evoke a strong immune response to recognise and attack remaining tumour cells in the body. SAFRON II is a randomised phase II clinical trial comparing single treatment versus multi-treatment SABR techniques (ie. 4 fractions). This research will be the first comprehensive evaluation of SABR techniques integrating the assessment of (1) clinical outcomes, (2) quality of life (3) cost-efficacy and (4) translational immunological investigation.

Epigenetic targeting of metastasis ($106,725 - 2 years) 1116002
Dr Dean Singleton, A/Prof Adam Patterson
Auckland Cancer Society Research Centre, University of Auckland

Breast cancer is the most common cancer in New Zealand women accounting for nearly 3000 new registrations and over 600 deaths each year. Although breast cancer outcomes are improving with earlier detection and more effective treatments, most patients die when their cancers spread (metastasize) into secondary organs. The blood vessels that supply breast tumours are poorly developed and are unable to deliver sufficient oxygen to the tumour. This results in regions of low oxygen (hypoxia) forming within the tumour. Hypoxia is critically important because it causes cancer cells to become more invasive, resulting in an increased risk of metastasis and poorer patient survival. This occurs because certain enzymes sense low oxygen and respond by switching on genes that promote invasion. We are developing new drugs to target these changes. In this work we will investigate the potential of these drugs to prevent hypoxia signalling in tumour models and reduce tumour growth and metastasis. The results of this study will help to develop effective strategies to prevent cancer metastasis and improve patient survival.

miRNAs as early predictors of preterm birth ($114,379 - 2 years) 1116010
A/Prof Mark Vickers, Prof Lesley McCowan, Dr Katie Groom, Dr Clint Gray
Liggins Institute, University of Auckland

At a global level, more than one in 10 babies are born too early (<37 weeks of pregnancy) equating to over 15 million preterm births and more than one million new-born deaths. Preterm birth also increases the risk of death due to other causes including neonatal infections. In New Zealand, nearly 8% of babies are born preterm and, of those, approximately 60% occur after spontaneous onset of labour. Preterm birth rates are higher in Maori women at around 14%. Although women with a previous spontaneous preterm birth (SPTB) are considered to be at high risk for recurrence, the majority occur in women without prior history. Accurate prediction of SPTB risk, before the clinical event, would allow for improved care and the potential for targeting novel and existing therapies to prevent SPTB, which may result in improved outcomes for both infant and mother. We have preliminary data showing that miRNA signatures in maternal blood as early as 20 weeks gestation can differentiate between those that go on to deliver at term or experience early SPTB (28-32 weeks). This project will expand on these findings to work towards development and validation of effective non-invasive biomarkers to identify women at risk for SPTB.