The Queensland Health and Medical Research Awards

FINALISTS ANNOUNCED

The Queensland Health and Medical Research Awards, an initiative of ASMR, honour the quality of scientific endeavour in Queensland. Announcing the finalists today, convenors Dr Jill Larsen applauded the overall quality of scientific research in the many excellent applications received.

> **Winners and runners-up for all categories will be announced at the**
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> **ASMR Medical Research Week® Gala Dinner**
> **Friday May 29th**
> **The Sky Room, Brisbane Convention Centre, South Brisbane**

Postgraduate Student Award Finalists

Jonathon Fanning, Prince Charles Hospital

Transcatheter aortic valve implantation (TAVI)

Aortic stenosis (AS) is the most common heart valve disease in the western world. One-half of patients with severe AS are rejected for valve surgery because of excessive risk. Transcatheter aortic valve implantation (TAVI) is an innovative life-saving treatment for these patients. However, the possibility of brain injury from TAVI has limited its use. This study performed the most comprehensive neurological/cognitive assessment to date to characterize the brain injury associated with TAVI and identify strategies to minimize its occurrence. While no patient had symptoms of stroke or cognitive dysfunction, 60% had silent strokes detected by brain imaging.

Shani Stuart, Queensland University of Technology

Mitochondria, the energy producing organelles of the body are linked with migraine susceptibility

Sufficient energy production to enable our neural system to function correctly could be related to migraine, a common neurological disease affecting approximately 12% of the general adult population. Mitochondria are found in all mammalian cells to supply the tissues of our body with energy, especially muscle and neural cells which have the highest energy requirements. This study investigated the link between mitochondrial dysfunction and migraine susceptibility by studying the underlying genetic variation in migraine sufferers compared to healthy controls. The Norfolk Island genetic isolate population was used as a discovery cohort and follow up studies were undertaken in large Australian Caucasian migraine case control populations. The latest genomic next generation sequencing technology was used to perform whole mitochondrial sequencing and subsequent statistical modelling analysis was used to identify significant findings. This analysis showed a clear link between mitochondrial function and migraine pathogenesis, which may lead to the identification of new therapeutic targets.

Mitchell Stark, QIMR Berghofer Medical Research Institute

MicroRNA Expression Regulates the Sensitivity of Targeted Therapy in Melanoma

Melanoma is the 4th most common cancer in Australia. Targeted therapy in patients with stage IV melanoma (distal spread of disease) is one of the first-line treatments for advanced disease. However, most patients do not have a durable response to the treatment due to either inherent or acquired resistance to therapy. One of the many mechanisms for this resistance is due to loss of a 'tumour-suppressor' gene called NF1. We found that loss of NF1 function can be explained in part via regulation by a microRNA called miR-514a. MicroRNAs are small ribonucleic acid sequences that control protein levels in the cell. We found that when miR-514a was turned on, melanoma cells were resistant to the main targeted therapy. On the other hand, when miR-514 was 'turned off', melanoma cells responded well to the therapy. Results from this study will help to devise better treatments for late stage melanoma patients.

Gillian Fisher, Griffith University

Investigating the Antimalarial Potential of Primary Sulfonamide Compounds

Malaria is a significant infectious disease, causing ~600,000 deaths annually, mainly in African children under the age of five. Unfortunately all current antimalarial drugs are failing due to the widespread emergence of drug resistant parasites. Thus, new antimalarial drugs are urgently needed, particularly those that act differently to current drugs as this may help

prevent treatment failure due to resistance. Primary sulfonamides are a type of chemical compound not yet exploited for malaria, but with proven efficacy and safety as drugs for other diseases. In this study novel primary sulfonamides with antimalarial activity were identified and one of these compounds was used to generate laboratory resistant malaria parasites. These resistant parasites are an important new tool that will allow us to determine whether these compounds kill malaria parasites differently to current antimalarials, potentially identifying a novel target in the parasite that can be used to develop new antimalarial drugs.

Laure Martine, Queensland University of Technology

Tissue-engineered humanised xenograft models to dissect mechanisms of breast cancer-induced bone metastasis

Bone metastasis occurs in 80% of women suffering from advanced breast cancer (BC) and remains incurable to date. The development of new therapies is hampered by the lack of appropriate models to mimic this disease. Current studies use human BC cells grown in the mouse skeleton, but due to differences between both species the results are often not transferable to the clinical situation. We have developed a model that reproduces the interactions of human BC cells and human bone in vivo. Human bone-forming cells obtained from adult patients are transplanted under the skin of immune-deficient mice with a biomaterial carrier and bioactive factors promoting bone formation. This tissue engineering approach leads to the formation of a human-derived bone tissue in mice. We have applied this "humanised" bone model to reproduce the development of metastases from injected human BC cells and investigate biological mechanisms involved in human BC metastasis to bone.

Arabella Young, QIMR Berghofer Medical Research Institute

Targeting immunosuppressive adenosine to promote an immune response against cancer

Within the clinic, recent advances in immunotherapies that aim to reinvigorate the immune system's fight against cancer have shown great success. Nevertheless, variation in treatment efficacy is evident and while some patients respond well, others show resistance. By combining therapies that inhibit a diverse range of immunosuppressive pathways it is predicted that patient's will receive durable benefits. However, identifying synergistic combination approaches remains a significant challenge. Notably, production of the immunosuppressive metabolite adenosine is increased within the tumour microenvironment. This suppresses tumour cell killing performed by immune cells allowing for disease progression. We identified that targeting adenosine improves survival and reduces tumour burden in preclinical models. Importantly, by combining clinically utilised immunotherapies with targeted therapies against adenosine we further improve disease control. Our studies advocate that targeting adenosine in immunotherapeutic combinations, has potential to reduce tumour burden and progression, increasing patient life expectancy and quality of life.

Postdoctoral Researcher Award Finalists

Dr. Andrea Schuessler, QIMR Berghofer Medical Research Institute

A new immunotherapy for brain cancer

Glioblastoma multiforme (GBM) is the most aggressive human brain cancer and affects almost 1000 Australians each year. Most patients survive only little more than one year after diagnosis and this grim prognosis has hardly changed despite decades of research into better medications. We have developed a new immunotherapy that aims to help a patient's own immune system fight the cancer more effectively. We tested this new therapy in 10 patients with recurrent GBM and could show that the treatment is absolutely safe and has no major side effects. Our patients survived longer than would be expected after tumour relapse, for example one patient was still alive more than 4 years after therapy. Most importantly, 4 out of 10 patients showed no signs of the disease recurring. This study was an essential first step in the development of new treatments to improve the outlook for patients with brain cancer.

Dr. Amirali Popat, Mater Research Institute, University of Queensland
Programmable Nanoparticles for the treatment of Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is affecting over 2.2 million people in Europe, 1.4 million people in USA and around 70,000 Australians with an annual net disease burden of $2.7 billion on the Australian economy. A key challenge in current treatment for IBD is achieving localised delivery of drugs, reducing effective systemic dose and side effects associated with non-targeted therapy. The overarching aim of this research is to target intestinal inflammation using programmable nanoparticles and to understand the mechanism of the same. Our results suggest that these smart nanoparticles can release anti-inflammatory drugs in the colon avoiding systemic side effects and improving bioavailability of these drugs. Outcomes of this research can lead to improved therapeutic efficacy and has the potential to have a large impact on the quality of life of millions of patients suffering from IBD and other colonic disease such as colon cancer around the world.

Dr Shin Foong Ngiow, QIMR Berghofer Medical Research Institute

A threshold level of intratumor CD8+ T cell PD1 expression dictates therapeutic response to anti-PD1

Tumors hijack immune regulatory mechanisms, known as immune checkpoint pathways to suppress anti-tumor immunity, facilitating tumor progression. Excitingly, these immune checkpoint pathways can be blocked using specific monoclonal antibodies (mAbs), reactivating the host anti- tumor immunity to combat the disease. The recently approved anti-PD1 mAbs (Pembrolizumab and Nivolumab) are the revolutionising immunotherapy agents of this class, currently used to treat melanoma and non-small cell lung cancer patients. Unfortunately, while some patients are presented as exceptional responders, a proportion of the anti-PD1-treated patients with various malignancies do not respond. This new survival profile now raises questions about how to predict and increase the number of patients who receive long-term clinical

benefit from PD1-targeted therapy. However, it remains hard to study the differences between responder and non-responder in patients. Using mouse tumor models, we have now determined which tumor types are responsive to anti-PD1 therapy.

Senior Researcher Award Finalists

Dr Shyuan Ngo, University of Queensland

Fuelling the fight against neurodegenerative disease: translational studies in motor neuron disease

Nerve cells (neurons) in the brain are normally lost as we age. The unnatural loss of these cells however, is a hallmark of diseases like Motor Neuron Disease (MND). In MND, the loss of neurons in the brain and spinal cord leads to muscle paralysis and death. Research from my laboratory suggests that glucose is not properly used to generate energy in the brains and muscles of mouse models of MND. This change in how the body generates energy might starve the neurons and muscle cells, leading to their death. Using a chemical compound to improve glucose use, we have delayed the disease in our mice. We are now studying how changes in the way the body generates energy can affect how quickly the disease progresses in MND patients. Thus, our studies have the potential to treat diseases that occur due to the loss of neurons, including MND.

Dr Sarah Medland, QIMR Berghofer Medical Research Institute

Common genetic variants influence human subcortical brain structures

At the individual level, genetic variations exert lasting influences on brain structures and functions associated with behaviour and predisposition to disease. Within the context of the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Consortium, we conduct collaborative large-scale genetic analysis of magnetic resonance imaging (MRI) scans to identify genetic variants that influence brain structure. Our recent findings will be discussed focusing on genetic variants influencing volumetric measures derived from a measure of head size (intracranial volume, ICV) and seven subcortical brain structures corrected for ICV (nucleus accumbens, caudate, putamen, pallidum, amygdala, hippocampus, and thalamus). In addition, we will present the first findings from joint meta-analyses of ICV and hippocampal volume from 26,577 participants from the ENIGMA and CHARGE cohorts. These new analyses have identified novel variants influencing brain structure and have revealed substantial overlap between genetic variants influencing hippocampal volume and those influencing risk for Alzheimer's disease.

Dr Kyle Upton, Mater Research Institute University of Queensland

Single cell genomics demonstrates somatic mosaicism in development and disease

Mobile Genetic Elements (MGEs) are DNA sequences which use a copy and paste mechanism to replicate within our DNA, generating mutations which can cause genetic disease. Understanding the impacts of this process has been limited by technical difficulties in identifying mutations. To overcome this obstacle, I have played a lead role in the development and application of a sensitive and accurate technique to map MGE mutations. Using this technique, I have previously demonstrated that MGE mutations occur extensively as part of normal brain development, and contribute to tumour evolution. To better understand the prevalence and impact of MGE mutations, I have developed single cell DNA sequencing techniques. I have now demonstrated that MGEs generate a large number of mutations in all neurons in normal development, and are likely to impact neuronal function. I am currently investigating the role of MGE mutations in driving tumour evolution and chemoresistance in ovarian cancer.

Clinical Researcher Award Finalists

Dr Yogavijayan Kandasamy, The Townsville Hospital & The University of Newcastle

The effects of preterm birth on renal development

The World Health Organization estimates that every year 15 million babies are born premature and this number is rising. Three-quarters of these babies could be saved with current, cost effective interventions. In Australia, approximately 25,000 babies (8%) are born premature each year. Survival of these babies has dramatically improved and majority of them now survive to adulthood but often with long-term health complications. Recent research indicates that these babies may also have an increased risk of developing kidney diseases as adults. We therefore carried out a study to determine the effects of prematurity on kidney growth in a group of premature babies admitted to a specialist baby unit. From this study, we found that prematurity decreases kidney growth and kidney function compared to full term babies. We concluded that these babies need to be followed regularly to monitor the kidney growth and function.

Dr Christopher Carty, QLD Children's Gait Laboratory & Griffith University

Informing medical intervention for movement disorders using innovative musculoskeletal modelling technology

Throughout my career I have contributed to medical research by applying engineering principles in the clinical management of patients with movement disorders. These patients include young adults with bone cancer, older adults with an increased falls risk and children with cerebral palsy. Currently I am appointed in a consultant clinical role in the Queensland Children's Gait Laboratory and my vision is to use computer modelling techniques to identify optimal surgical interventions for the paediatric population. My current projects are focused on incorporating medical images from MRI with 3D motion of children during walking. The ultimate purpose of these projects is to predict outcomes from surgery using 'virtual surgery' simulations. This will allow the surgical team to have access to better information for surgical decision

making for children who require surgery and also will assist in determining that those children who do not need surgery will not be subjected to surgery.

Dr Alwyn Todd, Griffith University

The effect of dietary sodium modification on blood pressure in studies of subjects with systolic blood pressure less than 140mmHg: A systematic review of quantitative evidence

In healthy individuals with normal blood pressure excess dietary salt is excreted by the kidney. Through this process normal blood pressure can be maintained despite changes in dietary salt intake. However, in the presence of hypertension (high blood pressure), blood pressure may rise in response to salt intake as the kidney is not able to effectively get rid of excess salt. The Australian Dietary Guidelines currently state that sodium reduction can change blood pressure in healthy individuals with normal blood pressure. This statement is based on analyses of data including both healthy subjects with normal blood pressure and some subjects with hypertension. This paper has analysed data from studies that only include healthy individuals with normal blood pressure (not individuals with hypertension), and found that blood pressure does not change by more than 1% when dietary sodium intake is varied.

Abstracts and biographical information are available from http://asmr.org.au/MRWMedia

For further information about the finalists and announcement of the winners/for interviews contact

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