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Australian Society for Medical Research

Queensland Health & Medical Research Awards

May 2011

Organised by the ASMR Qld Branch Committee

Funded by Queensland Health

ASMR Foreword 2011 from the Minister for Health

The Bligh Government is committed to putting Queensland at the forefront of medical research and innovation in health.

Medical Research saves lives. It's vital that we support and encourage the scientists and researchers making the discoveries that put Queensland on the cutting edge.

That's why the Bligh Government has committed more than $20 million over four years to the Health Research Fellowship Program through the Office of Health and Medical Research.

This fellowship program has attracted world class researchers and clinicians to Queensland, and recognises those outstanding professionals already working here.

Queensland researchers have achieved great things.

Thousands of at risk Queensland women are being protected against cervical cancer each year thanks to the vaccine discovered by University of Queensland researchers.

Scientists from Queensland Institute of Medical Research and Peplin Inc developed an anti-cancer drug which has delivered excellent results in human clinical trials in Australia and the US of non-melanoma skin cancer and solar keratoses.

These are the kind of world first discoveries that we want to see more of in Queensland and with the help of our researchers I believe we can achieve even more.

Congratulations to the finalists and recipients. I look forward to seeing the positive impact the outcomes of their research will have on patients in Queensland throughout Australia and ultimately the world.

Sincerely,
Geoff Wilson –
Minister for Health

Queensland Government

A/Prof Michael Breakspear

A diagnostic brain imaging protocol for recent onset psychosis based on free viewing of movie clips

Early and accurate diagnosis of schizophrenia, a major mental illness, is key to effective intervention and reducing the overall burden of illness. This work presents early progress on a novel brain imaging test for schizophrenia which is based on the characterization of brain activity whilst subjects view clips from popular film clips. This idea is to capture complex brain activity during visual and auditory perception whilst young subjects view interesting and naturally engaging media.

Although schizophrenia is usually conceptualized of as a disorder of well formed hallucinations and delusions, its onset is more typically characterized by heightened arousal, a vague but pervasive feeling of unease and poorly formed misperceptions. This unstable constellation of symptoms challenges clinical diagnosis at a time when properly guided interventions are most likely to have the greatest long-term benefits. It is possible to frame this clinical picture as a disturbance in the capacity of the cortex to optimally form predictive models of the environment, to appropriately sample visual scenes in order to estimate the likelihood of such models and to hence minimize surprise in a dynamic social landscape. This approach suggests that manipulating the relationship between visual search strategies and natural scene statistics might be a sensitive means of quantifying core neurobiological deficits early in the course of emerging psychotic disorders. We are developing a diagnostic tool for the prodromal phase of these disorders which involves experimentally disturbing the relationship between visual saccades and the stream of natural images in well directed films. I will outline the conceptual and computational bases and early experimental results thus far obtained, including a canonical example of paranoia and theory of mind in a spaghetti western.

Prof Suzanne Chambers

Who is a cancer survivor? Antecedants, prevalence and outcomes

Over the past two decades the paradigm of the *cancer survivor* has come to dominate and lead not only supportive care programs in cancer but also the focus and direction of psychosocial cancer research. In the first large scale population-based assessment of *cancer survivor* identity we found almost half of colorectal cancer patients did not see themselves as a survivor; but that those who did reported more personal growth as a result of their illness experience. These results will inform the design of clinical and community support interventions for cancer patients in the future.

Background Cancer survivor identity has become a dominant paradigm in describing people with cancer and driving the focus of programs and research in supportive care. However, antecedents of survivor identity adoption and population-based prevalence are not well described.
Methods A prospective survey of a population-based sample of 1966 (57% response) colorectal cancer patients assessed socio-demographic variables, health behaviours, optimism, benefit finding, cancer threat appraisal, psychological distress and satisfaction with life at five months post-diagnosis as predictors of survivor identity five years subsequently. Prevalence of survivor identity at 5 years post-diagnosis and psychological and lifestyle outcomes (n=786) were later assessed.
Results 55.0% of people identified as a cancer survivor; 39.4% as a person who had had (or has) cancer; 1.4% as a cancer patient; and 1.2% as a cancer victim. People who were older and who reported higher personal growth after diagnosis were more likely to assume a survivor identity at five years. At five years survivors had higher benefit finding and better satisfaction with life. Cancer survivors uniquely reported a significant decrease in somatisation and acceptance; and increases in satisfaction with life and physical activity over time.
Conclusions For colorectal cancer patients the cancer survivor identity is common, but not universal, five years after **diagnosis**; and may evolve from looking for benefit after cancer through personal growth. People who adopt a cancer survivor identity report more positive adjustment outcomes after cancer and this has implications for the design of clinical and community support interventions.

Dr Eduardo Pimenta

The interplay of salt and aldosterone in determining ill-effects of aldosterone excess

Aldosterone is a steroid hormone that contributes importantly to the maintenance of sodium and fluid balance. Aldosterone excess is a common condition (5-15% of patients with hypertension) in which autonomous aldosterone production increases blood pressure and causes target organ damage. Experimental studies have indicated that the effects of aldosterone excess are dependent upon concomitant high dietary salt intake. However, an interaction between aldosterone and dietary salt has not been studied in humans. We have demonstrated that, in patients with aldosterone excess, high-salt diet causes kidney and heart damage and is an important cause of high-blood pressure which is resistant to treatment. Strategies to substantially reduce dietary salt intake should be part of the overall treatment in patients with hypertension and aldosterone excess.

Hypertension is the leading cause of mortality and the third largest cause of disability in both developed and developing countries. Aldosterone, which is a steroid hormone produced in the adrenal cortex, contributes importantly to the maintenance of sodium and fluid balance and, when in excess, can cause hypertension. Although experimental data indicate that the deleterious effects of aldosterone excess are dependent upon concomitant high dietary salt intake, such an interaction of endogenous aldosterone and dietary salt has not been previously observed in humans. We tested the hypothesis that aldosterone excess and high dietary sodium intake interact to cause resistant hypertension and worsen kidney damage and cardiac structure in patients with hypertension. We found that aldosterone excess and high dietary salt combine to increase proteinuria[*] and left ventricular hypertrophy. Although correction of hyperaldosteronism reduced target organ deterioration, it did not completely resolve the detrimental relation between salt and aldosterone. Furthermore, in a randomized cross-over study, we showed that excessive dietary sodium ingestion contributes importantly to resistance to antihypertensive treatment.[*] Low-salt diet decreased office, daytime, nighttime, and 24-hr systolic and diastolic blood pressure by 22.7/9.1 mm Hg. In conclusion, our findings emphasize the importance of dietary sodium in determining the degree of blood pressure, cardiac and renal damage, in patients with hypertension and aldosterone excess, and suggest that aldosterone excess may play a more permissive role. Since high-salt diet is associated with target-organ deterioration and resistant hypertension, strategies to substantially reduce dietary salt intake should be part of the overall treatment in patients with hypertension and aldosterone excess.

Nobel Laureate Barry J Marshall AC

Clinical Professor, University of Western Australia

A medical pioneer whose work transcends all boundaries

In 2005 Barry J. Marshall and J. Robin Warren were awarded the Nobel Prize for Physiology or Medicine in recognition of their 1982 discovery that a bacterium, *Helicobacter pylori*, causes one of the most common and important pathologist interested in gastritis, during internal medicine fellowship training at Royal Perth Hospital in 1981.

Photo courtesy: Adrienne Marshall

The pair studied the presence of spiral bacteria in association with gastritis. The following year (1982), *Helicobacter pylori* was cultured for the first time and they developed their hypothesis related to the bacterial cause of peptic ulcer and gastric cancer. In 1984, while at Fremantle Hospital, Marshall proved that the new germ was harmful in a well-publicised self-administered experiment, in which he drank a culture of *H.pylori.*

Persevering despite widespread scepticism, Marshall also came up with combinations of drugs that killed the *H.pylori* bacteria and eliminated ulcers permanently. The hypothesis that *H.pylori* is a causative factor of stomach cancer was accepted in 1994 by the World Health Organisation. This work has now been acknowledged as the most significant discovery in the history of gastroenterology and is compared to the development of the polio vaccine and the eradication of smallpox. Affecting 50% of the global population, *H.pylori* is recognized as the most common chronic infection in the world. "Like a trail of crumbs, the DNA of our *Helicobacter pylori* can show where we were born and where our ancestors travelled from over the past 60,000 years" says Marshall.

In 2008 Professor Marshall was elected into the prestigious US National Academy of Science, an institution that was established in 1863 by President Abraham Lincoln. This recognition further establishes Barry's international scientific credentials.

Barry was born in Kalgoorlie in 1951 and attended Marist Brothers College in Perth from 1960-68. He completed his undergraduate medical degree at The University of Western Australia in 1974. He is married with four children and four grandchildren and lives in Subiaco, Western Australia.

Barry's numerous awards and fellowships are listed on the next page.

Awarded in conjunction with Dr Robin Warren

- Nobel Prize for Physiology or Medicine 2005
- Western Australian Citizen of the Year 2006
- Western Australian of the Year 2007
- Companion in the General Division of the Order of Australia (AC) in 2007.
- The Paul Ehrlich Prize 1997
- Warren Alpert Prize 1995

Current appointments

- Clinical Professor of Medicine UWA
- Clinical Professor of Microbiology UWA
- Consultant Gastroenterologist (Sir Charles Gairdner Hospital)
- co-Director of the Marshall Centre for Infectious Diseases Research & Training UWA Founder and Director of ONDEK, a biotechnology company
- Founder and Director of TRI-MED a diagnostics company
- Ambassador for Life Sciences for Western Australia
- Western Australian Technology and Industry Advisory Council
- Honorary Patron of Scitech
- Visiting Professor, Wake Forest University, North Carolina
- Fellow of the Australian Academy of Science 1999
- Member of the Royal Society, UK 1999
- Patron of the Monash Centre for Synchotron Science
- Francis R & Helen M pentz professor of Science at Penn State University, USA

Awards and Fellowships

- Honorary Professor at the Third Military Medical University, Chongqing, China
- Honorary Degree of Doctor of Science, *honoris causea*, University of Oxford, UK
- Honorary Doctorate in Medicine at Örebro University, Sweden
- Galen Medal, The Worshipful Society of Apothecaries, London
- Lennon K. Black Prize for Excellence in Biomedical Research, Jefferson College, USA
- Elected Foreign Member to the National Academy of Sciences
- Guest Professor of Internal Medicine at Keio University, Japan
- The William Beaumont Prize – AGA
- Honorary Degree of Doctor of Science, *honoris causea*, Polish Academy of Medicine
- *The Bulletin* Smartest 100 – Health & Medicine winner
- Silver Seal, University of Bologna, Italy
- Australian Centenary Medal
- The Keio Medical Science Prize
- Inaugural Premier's Prize for Achievement in Science, WA
- Prince Mahidol Award for Public Health
- Clunies Ross National Science and Technology Award
- Inducted as a Fellow of Australian Academy of Science
- Inducted as a Fellow of the British Royal Society
- Benjamin Franklin Medal for Life Science
- Buchanan Medal, The British Royal Society of Medicine
- The Dr A.H. Heineken Prize for Medicine
- The Florey Medal, Australia
- Kilby Prize, Dallas Texas
- The Gairdner Award, Toronto Canada
- The John Scott Award, City of Philadelphia
- The Albert Lasker Award

Dr Thiruma Arumugam

Novel pharmacological agents to target stroke-induced brain injury

In Australia, stroke is the leading cause of serious, long-term disability with more than 60,000 strokes occurring each year. Two decades of basic research targeting single stroke injury mechanisms in single cell types or single injury mechanisms in multiple cell types have failed when applied in clinical trials of human strokes. We have identified γ-secretase inhibitors as a novel and potent stroke therapy by targeting diverse pathogenic mechanisms in multiple cell types. This work investigates how γ-secretase inhibitors protect against ischaemic stroke-induced brain injury at the molecular level in multiple cell types to promote the development of γ-secretase inhibitors as a novel anti-stroke therapy.

Notch-1 is a cell surface receptor that regulates cell-fate decisions in the developing nervous system and it may also have roles in synaptic plasticity in the adult brain. Binding of its ligands results in the proteolytic cleavage of Notch by the γ-secretase enzyme complex, thereby causing the release of a Notch intracellular domain (NICD) that translocates to the nucleus, where it regulates transcription. Here we show that activation of γ-secretase mediated Notch signalling modulates ischemic neuronal cell death *in vitro* and *in vivo*. Our findings from the use of Notch-1 siRNA or the over expression of NICD indicate that Notch activation contributes to cell death. Using modified NICD, we demonstrate an apoptosis-inducing function of NICD in both the nucleus and the cytosol. NICD transfection-induced cell death was reduced by blockade of calcium signalling, caspase activation and Janus kinase signalling. Inhibition of the Notch-activating enzyme, γ-secretase, protected against ischemic neuronal cell death by targeting an apoptotic protease, cleaved caspase-3, nuclear factor kappa B (NFκB), and the prodeath BH3-only protein, Bim (Bcl-2-interacting mediator of cell death). Mice transgenic for antisense Notch and normal mice treated with inhibitors of the Notch-activating enzyme γ-secretase showed reduced damage to brain cells and improved functional outcome in a model of focal ischemic stroke. Furthermore, γ-secretase inhibition reduced NICD, p-P65 and Bim levels *in vivo*. These findings suggest that Notch signalling endangers neurons following ischemic stroke by modulating the NFκB, prodeath protein Bim, and caspase pathways. The current lack of effective stroke treatments requires a novel conceptual approach, and that γ-secretase inhibition may represent an important new piece in the puzzle. By understanding how γ-secretase inhibitors protect against ischaemic stroke-induced brain injury at the molecular level, we will be in a position to promote the development of γ-secretase inhibitors as a novel anti-stroke therapy.

Dr Kristen Radford

Targeting the cross-presenting dendritic cells for immunotherapy

Dendritic cells are rare white blood cells that initiate and direct immune responses. Dendritic cell-based vaccines have been shown to improve survival in diseases such as metastatic prostate cancer, for which there are currently no effective treatments. However, as this approach relies on first extracting the dendritic cells from the patient and then reinfusing them, they are costly, labour intensive and not suitable or effective for many patients. We recently identified a rare subtype of dendritic cell in humans and showed that it is specialised at inducing anti-cancer immune responses. This now allows for the development of new vaccine strategies that target the "cancer fighting" subset of dendritic cells directly, without requiring their removal from the patient. Our goal is to now apply this finding to make dendritic cell therapy more efficacious, practical and adaptable for the treatment of a wider range of patients and malignancies.

Immunotherapy using dendritic cells (DC) is a promising approach to treat a variety of malignancies for which there are currently no effective alternatives. Notably, the Provenge (Dendreon) vaccine is one of few new treatments to significantly improve survival in metastatic prostate cancer patients and has received US Food and Drug Administration approval. DC therapy involves extracting DC from the patient, loading them with tumour antigens ex vivo and reinfusing them into the patient, where they instruct cytotoxic T lymphocytes (CTL) to destroy the tumour. However, this approach is costly, labour intensive and not suitable or effective for many patients. Understanding the complexity of the human DC network and DC subset specialisation is essential to develop new vaccines. There is compelling evidence that the mouse $CD8\alpha^+$ DC subset plays an essential role in the induction of anti-tumour and anti-viral CTL responses by their unique capacity to cross-present exogenous antigen (such as dying tumour cells). However, clinical translation of these findings has been limited as homologies between mouse and human DC subsets have not been forthcoming. We developed the isolation procedures and performed the first functional analysis on the rare human $CD141^+$ DC subset. $CD141^+$ DC are characterised by high expression of Toll-like receptor (TLR)-3 and production of IL-12 and IFN-β in response to the TLR3 ligand, poly I:C. Importantly, $CD141^+$ DC are superior to DC subtypes currently used clinically, in their capacity to cross-present exogenous antigen. These findings identify $CD141^+$ DC as the human equivalent of the mouse $CD8\alpha^+$ DC and as such, the key subtype to target for vaccination. This now allows us to develop new vaccines that specifically target $CD141^+$ DC directly in vivo, that have the potential to be more efficacious, practical, cost effective and adaptable to treat a wider range of patients and malignancies.

Dr Susan Woods

miR-380-5p represses p53 to control cellular survival and is associated with poor outcome in MYCN-amplified neuroblastoma

We study a childhood cancer of the nervous system called neuroblastoma. We found that these cancers disable one of our main natural defences against cancer by over-producing a microRNA. This results in a reduction in the amount of protection against cancerous changes in that cell – leading to the growth of tumours. However when we blocked the microRNA, the cancer cells died and the tumours became much smaller. MicroRNAs originate from part of our DNA that has long been thought of as junk DNA. Much is still unknown but we know they can interfere with the functioning of genes and can control the production of proteins in the body. What is really exciting about this research is it is the first time that anyone has blocked the growth of a primary tumour by the simple, systemic delivery of a microRNA inhibitor and suggests a new therapeutic target for neuroblastoma patients.

Inactivation of the p53 tumour suppressor pathway allows cell survival in times of stress and occurs in many human cancers; however, normal embryonic stem cells and some cancers such as neuroblastoma maintain wild-type human *TP53* and mouse *Trp53* (referred to collectively as *p53* herein). We identified a miRNA, miR-380-5p, that repressed p53 expression via a conserved sequence in the *p53* 3′ untranslated region (UTR). miR-380-5p was highly expressed in mouse embryonic stem cells and neuroblastomas, and high expression correlated with poor outcome in neuroblastomas with neuroblastoma derived v-myc myelocytomatosis viral-related oncogene (*MYCN*) amplification. This was the first microRNA identified whose expression predicts outcome in neuroblastoma patients. Furthermore we investigated the mechanism of action of miR-380: miR-380 over expression cooperated with activated HRAS oncoprotein to transform primary cells, block oncogene-induced senescence and form tumours in mice. Conversely, inhibition of endogenous miR-380-5p in embryonic stem or neuroblastoma cells resulted in induction of p53, and extensive apoptotic cell death. *In vivo* delivery of a miR-380-5p antagonist decreased tumour size in an orthotopic mouse model of neuroblastoma. This was one of the first reports of systemically delivered anti-miRNA treatments to successfully decrease the size of a primary tumour, a significant step in the development of microRNA targeted therapeutics. We have demonstrated a new mechanism of p53 regulation in cancer and stem cells and uncovered a potential therapeutic target for neuroblastoma.

- Peak professional society representing Australian health and medical researchers
- Direct members and 57 affiliated professional societies and medical colleges
- Corporate and disease related foundation memberships bringing an additional 100,000 Australians into the ASMR network
- Long established role in public, political and scientific advocacy
- Plannning for the future of Health and Medical research in Australia

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2008 Access Economics Report
"Exceptional Returns: The Value of Investing in Health R&D in Australia II"

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- Draft ethical guidelines on the use of ART in Clinical Practice & Research

Recent Initiatives
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Dr Kerry-Ann O'Grady

Lung health in Aboriginal and Torres Strait Islander Queenslanders

Acute and chronic lung diseases are major contributors to the health gap between Indigenous and non-Indigenous Australians. Despite this, there has been little work focussing on the delivery of culturally appropriate services to "close the gap." This project, for the first time, comprehensively mapped chronic lung disease burden in Indigenous Queenslanders and the services available to prevent and manage disease. It found that, overall, Indigenous Queenslanders were 2.7 times more likely to be hospitalised with chronic lung disease and 2 times more likely to die from these diseases than non-Indigenous Queenslanders. There was substantial variation in disease burden between Queensland regions.

Background Respiratory illnesses in Indigenous Australians are major causes of morbidity and mortality yet scarce attention has been paid to this burden and the services available to prevent and manage disease. This project aimed to, in Indigenous peoples in Queensland, (a) determine the disease burden of common chronic lung diseases and (b) identify areas of need with respect to lung health services. **Methods** Literature reviews and analyses of data available on hospitalisations and mortality were used to describe disease epidemiology, with a focus on asthma, chronic obstructive pulmonary disease, lung cancer and obstructive sleep apnoea. Key stakeholder interviews and an online survey of health professionals were used to quantify lung health services across the state and to identify the available services, needs and gaps. **Results** Morbidity and mortality from respiratory diseases in the Indigenous population is substantially higher than the non-Indigenous population across all age groups and regions. There are inadequate clinical services, material and human resources to address disease prevention, detection, intervention and management in an evidence-based and culturally acceptable fashion. There is a lack of culturally appropriate educational resources and disease management programs, insufficient access to appropriately engage Indigenous health professionals, a lack of multi-disciplinary specialist outreach teams, fragmented information systems and inadequate coordination of care. **Conclusions** Major initiatives are required at all levels of the health care system to adequately address service provision for Indigenous Queenslanders with lung diseases, including high quality research to investigate the causes for poor lung health, which are likely to be multifactorial. **Significance/impact** This is the first statewide comprehensive analysis of lung health services for Indigenous Queenslanders. The work is currently contributing to policy, service delivery and research planning in Queensland, and was the basis for the development of a new lung health outreach programme to Indigenous communities in Queensland.

Dr Kelly Smith

Discovery of a novel gene in cardiac valve development

The heart is an essential, life-supporting organ, required to separate oxygenated and deoxygenated blood and distribute it around the body. The cardiac valves are critical for maintaining this separation. The valves develop when we are embryos and mistakes occurring during their formation result in congenital heart defects, the most common cause of infant death from a birth defect. I am using the zebrafish to understand how the heart and valves development. Zebrafish hearts develop similar to humans but zebrafish are born external to the mother and are transparent organisms so we can observe and study the heart as it forms. I have identified a zebrafish with a genetic mutation causing a valve defect. The gene responsible for this defect has never been identified previously and understanding its function may give us insight into the diagnosis and treatment of congenital heart disease.

The atrioventricular canal (AVC) physically separates the atrial and ventricular chambers of the heart and plays a critical role in the development of the valve and septa. Defects in AVC development result in aberrant heart morphogenesis and are a significant cause of congenital heart malformations (the most prevalent form of birth defect). I study the zebrafish to interrogate the genetic and cellular morphogenesis events that take place during heart development. Zebrafish embryos are optically transparent and develop externally, permitting live-cell imaging during organogenesis. This also makes zebrafish highly amenable to large-scale forward genetic screens. Using this approach, a mutant (dubbed *wickham*) was isolated from a forward genetic screen that was indistinguishable from siblings at early stages of heart development but exhibited cardiac dysmorphology at the stage of valvulogenesis. Positional cloning revealed that the *wickham* locus encodes transmembrane protein 2 (Tmem2), a single-pass transmembrane protein of previously unknown function. Expression analysis demonstrated myocardial and endocardial expression of *tmem2* in zebrafish as well as conserved *Tmem2* expression in the endocardium in mouse embryos. Detailed phenotypic analysis identified an up regulation and expansion of expression of known AVC markers in both the endocardium and myocardium of *wickham* mutants. These analyses identify *wickhamm/tmem2* as a novel regulator of cardiac development that functions to restrict chamber-AVC boundary formation in zebrafish and displays conserved expression in the mammalian heart. This research has already contributed to our understanding of how this organ develops, from the genetic regulators to cellular modifications. Future outcomes are likely to impact on our understanding of congenital heart disease, contributing to both diagnostics and therapeutics.

Dr Michael Tallack

Exploring the control of erythropoiesis by next generation ChIP-seq and mRNA-seq technologies

T Whitington, E Glazov, M Dinger, TL Bailey and AC Perkins

Healthy adults produce about 2 million red blood cells (erythrocytes) every second of their lives. These red blood cells transport oxygen from our lungs to all the tissues of the body using a protein molecule called hemoglobin. The production of red blood cells needs to be carefully controlled, too little production results in various forms of the disease anemia. The gene *KLF1* is a master controller of red blood cell production and also ensures that red blood cells are healthy and functional. Recent studies have described mutations in *KLF1* that result in a particular form of human anemia called CDA (for congenital dyserythropoietic anemia). We have investigated the different roles that *KLF1* plays to ensure healthy red blood cells are produced in adequate numbers. By utilizing recent advances in DNA technology we have described that *KLF1* regulates all aspects of red blood cells, including size, shape, survival and hemoglobin content.

The production of healthy red blood cells (erythrocytes), known as erythropoiesis, is a process tightly controlled by a suite of unique extracellular signals, cell-niche interactions, and lineage restricted transcription factors. The transcription factor KLF1 (formerly known as EKLF, erythroid Krüppel-like factor) is expressed only in erythroid cells and their precursors and regulates all aspects of erythrocyte development and biology. Loss of *Klf1* in mice leads to death *in utero* due to severe anemia, caused by defects in hemoglobin production, the integrity of the cytoskeleton and membrane, and iron metabolism. Recent human mutations in *KLF1* have been discovered and result in altered expression of blood group antigens, persistence of fetal hemoglobin, and congenital dyserythropoietic anemia (CDA). In particular, the pathology of CDA, which results in distortion to the size, shape and hemoglobin content of erythrocytes, accurately reflects the roles of KLF1 in erythrocyte biology that have been described in mice. We have taken advantage of the advances in DNA sequencing technology (so called "next-generation" DNA sequencing) to comprehensively characterize the functions of Klf1 in erythropoiesis. We have performed chromatin immunoprecipitation followed by DNA sequencing (ChIP-seq) to determine all of the *in vivo* binding sites for endogenous Klf1 in mouse erythroid precursors. This has revealed new insights into the mechanism of Klf1 gene activation, co-operation with other transcription factors, and previously unappreciated erythroid genes. We have also characterized the erythroid transcriptome in the presence ($Klf1^{+/+}$) and absence ($Klf1^{-/-}$) of Klf1 by performing mRNA-seq. This has provided a more comprehensive set of Klf1 target genes than was possible using traditional microarray technology and uncovered the existence of previously undescribed transcript variants, in particular alternative promoters that are erythroid specific and Klf1 dependent. Our studies illustrate for the first time the full repertoire of Klf1 dependent events that underpin erythroid cell development and homeostasis.

Office of Health and Medical Research

The Queensland Government has provided $25.65 million for a Health and Medical Research Program that comprises the following key initiatives:

Initiative 1: Support our people – recruit, develop and retain a skilled health research workforce

Initiative 2: Promote the transfer of knowledge into improved health and wealth

Initiative 3: Provide clear leadership and promote collaboration

Office of Health and Medical Research, Queensland Health

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Dr Kylie Alexander

Macrophages are novel and critical participants in bone healing

Alexander KA, Kohler T, Hume DA, Sweet MJ, Raggatt LJ and Pettit AR

Bone disease and injury are national and international health and research priorities costing the Australian health system over $10 billion annually. Current treatments target bone destruction but do not restore bone that has been lost, creating an unmet therapeutic need for new bone building treatments. Macrophages are commonly known for their roles in immune response to infectious organisms. Less acknowledged are sub-groups of macrophages present in virtually all organs of the body playing ongoing roles in organ development, repair, and maintenance. We recently demonstrated that a population of macrophages is present in specialized tissues lining bones (osteomacs). Importantly, we discovered that osteomacs not only promote bone formation in normal growth but are pivotal for bone formation during bone repair.

Bone dynamics is achieved through the coordinated actions of bone resorbing osteoclasts and bone matrix producing and mineralizing osteoblasts. The mechanisms controlling this balancing act are not completely understood, limiting our ability to manipulate outcomes for bone repair. Current anti-resorptive drugs for complex fractures and osteoporosis do not restore bone that is already lost, generating a therapeutic need for new anabolic bone treatments. This project investigates a novel mechanism where the immune system controls bone formation. We demonstrated that osteal tissues contain a resident macrophage population (osteomacs) that are intimately associated with osteoblast bone forming surfaces (ObS). Depletion of osteomacs using the Macrophage-Fas-Induced Apoptosis (Mafia) transgenic mouse induced complete loss of ObS suggesting a novel role for osteomacs in regulating anabolic bone activity. To investigate the requirement of osteomacs for *in vivo* bone formation a tibial defect model was employed. Macrophage depletion resulted in a striking reduction in $F4/80^+$ osteomacs and $CT1^+$ osteoblasts. Quantitative micro-CT analysis confirmed significantly impaired bone healing at 7 days post surgery ($p=0.036$). Delayed depletion of macrophages indicated that failure in bone formation was not due to loss of early macrophage-mediated inflammatory events. Clodronate liposome mediated depletion also significantly compromised bone healing ($p=0.026$). Osteoclasts are also susceptible in these depletion strategies, however osteoprotegerin treatment during bone healing had no effect on bone formation. The differentiation, proliferation and survival of macrophages are dependent on colony stimulating factor-1 (CSF-1), and its administration during bone healing resulted in an increase in $F4/80^+$ osteomacs ($p=0.002$) and new $CT1^+$ matrix deposition ($p=0.026$). Micro-CT analysis confirmed active mineralization of this woven bone matrix. This study has discovered a novel regulatory mechanism that alters bone dynamic paradigms.

Laura Bray

Fibroin-based materials support co-cultivation of human limbal epithelial and stromal cells for ocular tissue reconstruction

Bray, LJ, George, KA, Ainscough, SL, Chirila, TV, Hutmacher, DW and Harkin, DG

Approximately 10 million cases of blindness worldwide are due to diseases affecting the cornea. The future supply of adequate corneal tissue for transplantation is uncertain, and this problem is further compounded by a current global shortage of corneal tissue for transplantation in countries without access to tissue banking facilities. This project studies the use of limbal stem cells in conjunction with a fibrous material known as fibroin, a protein which can be readily isolated from silkworm cocoons (*Bombyx mori*). We found that limbal stem cells can produce a corneal surface transplant equivalent on fibroin-based materials. This research represents a step forward in the development of limbal tissue transplants for the treatment of severe eye injuries and common diseases such as pterygium, and also in the quest for whole transplantable ocular tissue grown from the patient's own cells, thus addressing a wider international need for transplantable eye tissue.

Introduction Membranes prepared from a protein (fibroin) isolated from domesticated silkworm (*Bombyx mori*) silk, support the cultivation of human limbal epithelial (HLE) cells and thus display significant potential as biomaterials for ocular surface reconstruction. We presently extend this research by evaluating the attachment, morphology and phenotype of HLE cells grown on fibroin in direct comparison with donor amniotic membrane (AM), the current clinical standard substrate for HLE transplantation. Also, we investigate the ability to produce a bi-layered scaffold of fibroin with an upper HLE layer and lower mesenchymal stem cell (MSC) layer. **Methods** Primary cultures of HLE and MSC were established in DMEM/F12 medium with 10% fetal bovine serum (HLE culture included irradiated 3T3 feeder cells). Cultures were subsequently passaged onto transparent fibroin membranes, AM, or within 3D scaffolds prepared from partially-solubilised fibroin. HLE and MSC cells were also co-cultured upon bi-layered silk fibroin. Tissue constructs were paraffin-embedded and analysed via immunohistochemistry. **Results** Epithelia constructed from HLE cells on fibroin maintained evidence of corneal phenotype (K3/K12 expression) and displayed a comparable number and distribution of $\Delta Np63^{+}$ progenitor cells to that seen in cultures grown on AM. HLE and MSC were able to be co-cultivated on composite fibroin scaffolds.**Conclusions** These results confirm the suitability of membranes constructed from *Bombyx mori* silk fibroin as substrata for HLE and MSC cultivation and encourage progression to studies of efficacy in preclinical animal models.

Brooke Coombes

Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials

Tendon problems, such as tennis elbow or Achilles tendon pain, are common afflictions of middle-aged men and women, affecting day-to-day activities, sport and work. In a comprehensive and systematic manner, this study identified and analysed 41 published reports on the use of injections in nearly 2700 patients with tendon injuries. It showed that corticosteroid injections, provide short-term pain relief but may be worse than other treatments in the long-term. However patients can be reassured that corticosteroid injection rarely causes serious harm. Other newer increasingly popular injections, such as botox or injection of a person's blood, have not been thoroughly researched. While some of these may be helpful in the long term, it appears that none offer a magic bullet for tendon pain. This study helps answer questions raised by both doctors and patients as to which injections are beneficial or harmful in treating tendon pain.

Background Few evidence-based treatment guidelines for tendinopathy exist. We undertook a systematic review of randomised trials to establish clinical efficacy and risk of adverse events for treatment by injection. **Methods** We searched eight databases including randomised trials assessing efficacy of peritendinous injections with placebo or non-surgical interventions for tendinopathy, scoring more than 50% on the modified physiotherapy evidence database scale. We undertook meta-analyses and estimated relative risk and standardised mean differences. The primary outcome of clinical efficacy was protocol-defined pain score in the short, intermediate, or long term. Adverse events were also reported. **Findings** 3824 trials were identified and 41 met inclusion criteria, providing data for 2672 participants. We showed consistent findings between many high-quality randomised controlled trials that corticosteroid injections reduced pain in the short term compared with other interventions, but this effect was reversed at intermediate and long terms. Only one patient (0.1%) had a serious adverse event (tendon rupture). By comparison with placebo, reductions in pain were reported after injections of sodium hyaluronate (short, intermediate and long terms), botulinum toxin (short term), and prolotherapy (intermediate term) for treatment of lateral epicondylalgia. Lauromacrogol, aprotinin, and platelet-rich plasma were not more efficacious than was placebo for Achilles tendinopathy, while prolotherapy was not more effective than eccentric exercise. **Interpretation** Despite the effectiveness of corticosteroid injections in the short term, non-corticosteroid injections might be of benefit for long-term treatment of lateral epicondylalgia. However, response to injection should not be generalised because of variation in effect between sites of tendinopathy. **Significance** This research warrants attention by physicians and health professionals attempting to keep pace with important advances in medicine. It comprehensively addresses the benefits and harms of a commonly used practice with that of emerging clinical interventions for a condition that significantly impacts on both individual and society.

Kate Miller

Playing away pain

Children accessing hospital for medical care frequently undergo painful procedures in their management of their injury or illness. With increasing numbers of children accessing hospitals and increased time and work pressures on staff, alternatives to support children undergoing medical procedures are necessary to promote both physical and emotional care and recovery. Working alongside a Brisbane technology company, a hand held distraction device was developed aimed for 3-12 year olds. The device was designed to meet the developmental (cognitive, physical and emotional) needs of children, as well as the clinical needs of staff. Using the device children could choose (1) procedural preparation stories that talked them through what to expect during their procedure, and (2) distraction stories and games that diverted their attention during the actual procedure. Using 2 clinical trials, at the Royal Children's Hospital, the impact of this device on children's pain and distress levels was compared to standard practice and off the shelf videogames. Children who accessed the purpose designed device had significantly reduced pain and distress during procedures as well as reduced treatment times. Preliminary results showed faster healing times with children with burn injuries. This has led to reduced short and longer term pain experiences for children and increased delivery and efficiency of medical procedures.

Background Non-pharmacological approaches to supporting young children through painful medical procedures are an essential component of burn pain management protocols. However their uptake into clinical practice remains adhoc due to restrictions within acute hospital settings and in ensuring developmental appropriateness. A new technology device (Multi-Modal Distraction(MMD)) was developed by healthcare professionals and information technology team enhancing the quality and uptake of these approaches Two studies were undertaken to determine whether levels of pain and distress using the MMD device could be reduced and lead to reduced treatment length. **Methodology** Two prospective randomised control trials were completed. One hundred and twenty children (3-10 years) undergoing acute burn wound care procedures were randomised to various groups: (1) Standard Distraction (SD) Group; (2) MMD Distraction Group; (3) MMD Procedural Preparation group; (4) Combined MMD Distraction and Preparation Group and (5) Off the shelf video games group. Pain intensity and child distress were measured prior to and during the procedure. Clinical utility end points included length of treatment, days to healing and adverse pain events. **Results** Across the two trials MMD (preparation, distraction and combined protocols) significantly reduced pain intensity ($p<0.05$) and distress scores ($p<0.05$) when compared to SD and off the shelf technology. Length of treatment ($p<0.05$), days to healing and the number of pain adverse events were also reduced ($p<0.05$) with the use of MMD pain protocols. **Conclusions** MMD use reduced young children's pain experiences during burn wound care procedures. The use of procedural preparation was found to be an essential component of non-pharmacological approaches. In addition to minimizing pain and distress, MMD reduced treatment length and pain adverse events. In addition it may lead to reduced days to healing. These results are providing evidence of clinical efficacy and utility.

Tracy O'Mara

A genome-wide association study to identify genetic markers associated with endometrial cancer grade

T O'Mara, D Duffy, DJ Thompson, S Ahmed, K Ferguson, CS Healey, ANECS, G Montgomery, M Shah, J Morrison, PP Pharoah, AM Dunning, PM Webb, DF Easton, AB Spurdle

Endometrial cancer (cancer of the uterus) is the most commonly diagnosed gynaecological cancer. Although the majority of cases diagnosed experience good prognosis, there are some patients who will relapse unexpectedly. Identifying genetic variation associated with prognosis could inform decision-making for disease management at diagnosis and provide avenues for the development of agents targeting aggressive disease. We have recently performed a study to identify genetic variations associated with endometrial cancer grade in Caucasian Australian and British women. Two variants were identified as having an association with higher endometrial cancer grade and will be explored in more samples for validation. These variants are distinct from those previously reported be associated with endometrial cancer risk and suggest that this research is beneficial to improve understanding of biological pathways that influence outcome for endometrial cancer patients.

Endometrial cancer is the most commonly diagnosed gynaecological cancer. Although endometrioid endometrial cancer (80% of cases) generally carries a good prognosis, some patients with this tumour subtype relapse within two years. Identifying genetic variants associated with prognosis could inform clinical decision-making for management at diagnosis, and inform development of chemotherapeutic agents targeting aggressive disease. Genome-wide association studies (GWAS) have been successful in identifying common genetic variation involved in cancer susceptibility. Presently there are limited published studies using GWAS data to identify single nucleotide polymorphisms (SNPs) associated with tumour prognostic indicators, such as grade. We used case data from an endometrial cancer case-control GWAS to assess association of SNPs with endometrial cancer grade. Genome-wide genotyping of 1285 Australian and British women with endometrioid endometrial cancer and reporting Caucasian ethnicity was performed using the Illumina 610K BeadChip. After applying quality control measures, data on 519,655 SNPs for 1233 cases with grade information were used in the analysis. Regression analyses assessing SNP association with grade (1, 2 or 3), adjusting for study group (Australian or British) were performed using PLINK software. Fifty-three SNPs were found to be significant at $<10^{-4}$. Two variants with evidence of association with higher endometrial cancer grade (p-trend$<10^{-6}$) have been selected for validation in independent sample sets. These SNPs are located in or near genes not previously reported to be involved in cancer aetiology or prognosis and, if confirmed, would represent novel gene targets. Neither of these SNPs fall into the top 1500 SNPs prioritised for validation of association with risk. Results to date suggest that genetic alleles associated with prognostic features, such as cancer grade, may be distinct from those associated with predisposition.

Diwakar Pattabiraman

Requirement of Myb-CBP/p300 interaction for the development of acute myeloid leukemia

DR Pattabiraman, V Barbier, K Krishnan, P Mukhopadhyay, K Shakhbazov, P Leo, SM Grimmond, AC Perkins, I Winkler, J-P Levesque, TJ Gonda

Acute myeloid leukaemia (AML) affects the blood and bone marrow and is characterised by an overproduction of white blood cells. It is caused by a large number of well-documented alterations in the DNA. Despite being one of the better-studied cancers, very few targeted therapies are used in the clinic, with chemotherapy still being mainstay. This study aims to translate basic laboratory findings into a novel targeted therapy for AML by the inhibition of c-Myb function. C-Myb is a protein essential for blood cell development. C-Myb interacts with another protein, CBP/p300, to carry out its normal function. Preliminary results show that this interaction is essential for normal cells to acquire leukemic properties. Establishing a better understanding of the mechanisms of Myb function in AML would enable development of novel targeting strategies, which could have therapeutic potential. These could potentially be used in combination with currently employed chemotherapy agents to enhance the efficacy of treatment and minimize their side effects.

Acute myeloid leukaemia (AML) is a disease of disordered haematopoiesis that results from the acquisition of mutations in haematopoietic stem/progenitors that impair normal differentiation. Very few targeted therapies are used in the clinic to treat AML, with chemotherapy still being mainstay. This study aims to translate basic laboratory findings into a novel targeted therapy by the strategic inhibition of Myb function. The Myb oncoprotein is a key regulator of haemopoietic cell proliferation and differentiation, expressed at high levels in human myeloid leukaemias. *c-myb* expression is essential for the proliferation of human AML. Our previous work has shown that interaction of Myb with the co-activator CBP/p300 is essential for its transforming ability (Pattabiraman et al, *Mol Cancer Res* 2009). To study the significance of this interaction in AML, we have employed a newly generated mouse model, *Booreana*, which harbours a mutation in the transactivation domain of c-Myb (Papathanasiou et al. *Blood* 2010) that renders it unable to interact with CBP/p300. We have shown that AML1-ETO and MLL-ENL, oncogenes known to be causative of several sub-types of AML, are unable to transform haematopoietic cells from *Booreana* mice, thus demonstrating that Myb-CBP/p300 interaction is required for the development of AML. We are currently carrying out experiments to study the *in vivo* leukaemogenic transforming ability of *Booreana*. This will involve isolating donor haematopoietic cells from *Booreana* mice, ectopically expressing AML1-ETO and MLL-ENL, and studying the time taken for leukaemia development when transplanted into recipient wild-type mice. In summary, we observe a significant impairment in the ability of certain oncogenes to transform haematopoietic cells from mice that have a mutation in c-Myb rendering it unable to interact with CBP/p300. This provides compelling evidence for targeting the Myb-CBP/p300 as a therapeutic strategy for treating human AML if not singly, at least in combination with treatment regimes currently in use.

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ASMR works tirelessly to raise the profile of health and medical research in Australia through its public, political and scientific advocacy.

The Society has a 50 year history of responsible, well articulated and evidence based submissions to government. ASMR played a pivotal role in the doubling of the NHMRC Budget in 2000 and again in 2006.

Our landmark publications (Access Economics reports, "Exceptional Returns: The Value of Health R&D in Australia I and II, Workforce Survey 2007 and the 2009 publication "Planning the Health and Medical Research Workforce 2010-2019", Case Studies Series I, II and II) are advocacy tools which underpin the critically important grass roots campaigns which have been the hallmark of the Society for many years and were instrumental in maintaining investment in NHMRC in the 2011 Federal Budget.

ASMR will continue its advocacy role, informing our politicians and the wider community about the value of Health and Medical Research and its part in bringing better health and economic outcomes to all Australians.

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We encourage you to participate in ASMR activities:

Join us at the **Queensland ASMR Medical Research Week® Dinner** to celebrate the achievements of health and medical researchers. The dinner will be held on **Friday, June 3rd,** 7pm at the Sebel and Citigate Hotel where the ASMR Medallist for 2011, Nobel Prize Laureate Prof Barry J Marshall, AC will be the keynote speaker.

In 2005 Barry J Marshall and Robin Warren were awarded the Nobel Prize for Physiology or Medicine in recognition of their 1982 discovery that a bacterium, *Helicobacter pylori*, causes one of the most common and important diseases of mankind, peptic ulcer disease.

Attend the **50th ASMR National Scientific Conference**, this year to be held in Cairns, November 13-16th. The theme of this year's conference is "Indigenous health: ACTION on Prevention". Topics covered will include:

- Primary and Preventative Health Care
- Mental and Psychosocial Health
- Early Intervention and Good Clinical Care: Maternal and Child Health
- Chronic Disease
- Infectious disease
- Amplifiers of Chronic Disease
- Research Methodologies

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About the QLD Postgraduate Student Conference

As part of ASMR Medical Research Week®, the Australian Society for Medical Research holds a student conference to showcase the high quality of research undertaken by students in universities and other institutions. The work presented at this conference is that of postgraduate students and the conference is well attended by a broad range of researchers and academics. The 2011 ASMR Queensland Postgraduate Student Conference will take place at the Princess Alexandra Hospital on the 31st May 2011.

As well as having many students present their work as oral and poster presentations, the conference is held in conjunction with the Postgraduate Student category of the ASMR Queensland Health and Medical Research Awards. This year the six finalists for this award are: Kylie Alexander (UQ Centre for Clinical Research), Laura Bray (Institute of Health and Biomedical Innovation & Queensland Eye Institute, QUT), Brooke Coombes (School of Health and Rehabilitation Sciences, UQ), Kate Miller (Queensland Children's Medical Research Institute, UQ), Tracy O'Mara (Institute of Health and Biomedical Innovation, QUT) and Diwakar Pattabiraman (Diamantina Institute, UQ).

The organising committee would like to take this opportunity to thank our keynote speakers, Associate Professor Christine Wells (Australian Institute for Bioengineering & Nanotechnology, UQ), Professor David Whiteman (Cancer Control Group, Queensland Institute of Medical Research), Dr Kerry Manton (Institute of Health Biomedical Innovation, QUT), Dr Brian McEvoy (Queensland Blood Management Program, Clinical and Statewide Services, Queensland Health) and Ms Sarah Tennant (Science Communication Manager, Queensland Institute of Medical Research) for volunteering their time to present at this conference.
We would also like to show our appreciation to all of our judges, sponsors, presenters, supervisors and registrants; without you, this conference would not be possible.

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Many thanks to our judging panels

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