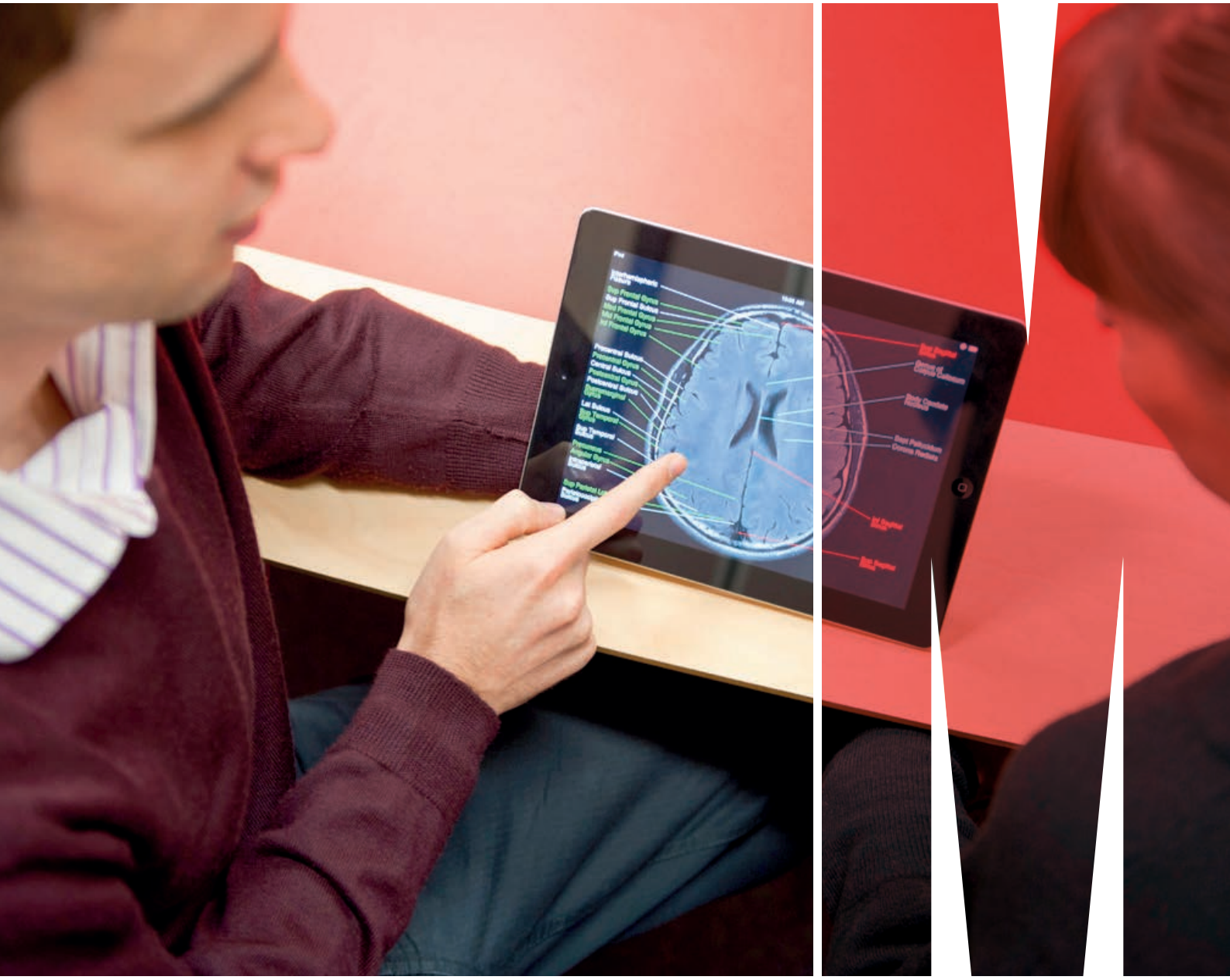
MONASH University

MONASH
MEDICINE,
NURSING AND
HEALTH SCIENCES

3RD ANNUAL MONASH UNIVERSITY CLINICAL SCHOOLS TRANSLATIONAL RESEARCH SYMPOSIUM

HOSTED BY CENTRAL CLINICAL SCHOOL



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Mail

Central Clinical School

Monash University @ Alfred Medical Research and Education Precinct

Reception: Level 6, Alfred Centre

99 Commercial Road

Melbourne VIC 3004

Front cover image

Monash Alfred Psychiatry research centre staff discussing a brain scan

Contents

Program timetable

Invited Speakers	
09.00 am	Professor Kathryn North AM - Genomics and the brave new world of personalised medicine: A global and local perspective Director, Murdoch Children's Research Institute, and the David Danks Professor of Child Health Research at the University of Melbourne
09:40 am	Doctor C. Glenn Begley - Challenges to translational science around the world (and even across the Yarra) Chief Executive Officer, BioCurate, Melbourne
10:30 am Tea/Coffee	
11:00 am	Professor Paul Myles - Large clinical trials and reverse translation Central Clinical School/Alfred Health
11:30 am	Associate Professor Menno C Van Zelm - Primary immunodeficiencies: Immunology lessons from nature Central Clinical School
11:55 pm	Professor Mark Cooper AO - The changing face of managing diabetes and its complications Central Clinical School/Alfred Health
12:20 pm Lunch	
1:25 pm	Professor Helen Dewey - The long walk to effective therapies in acute stroke Eastern Health Clinical School
1:50 pm	Doctor Claudia Nold - Translating a cytokine into a therapeutic: From promise to product School of Clinical Sciences, Hudson Institute, Monash Health
2:15 pm	Doctor Sarah Zaman - Primary prevention of sudden cardiac death after myocardial infarction School of Clinical Sciences, MonashHeart, Monash Health
2:40 pm	Professor Peter Gibson - Low FODMAP diet: The road from ideas to implementation across the world Central Clinical School/Alfred Health
3:05 pm	Professor Melissa Southey - Towards massively parallel translation: The breast cancer example School of Clinical Sciences at Monash Health
3:30 pm Tea/Coffee	
4:00 pm	Professor Richard Kitching - A New Mechanism Determining the Risk of Autoimmune Disease School of Clinical Sciences at Monash Health
4:25 pm	Professor Terence O'Brien - Developing treatments that address the treatment gap for the sacred disease The Royal Melbourne Hospital
4:50 pm	Professor Eva Segelov - The role of aspirin in modulating response to cancer Professor/Director Oncology School of Clinical Sciences and Monash Health
5:15 pm	Summary and announcement of Translational Research Young Investigator Poster Presentation Award Professor Stephen Jane, Head of Central Clinical School and Director Translational Research Program
6:00 pm	Drinks
7:00 pm	Close

About Translational Research at Monash University

This year sees Monash University's 3rd annual Translational Research Symposium. The symposium showcases our achievements and current activities, and looks to the future. We warmly invite you to join us for an informative and entertaining occasion. This is a unique opportunity to meet with some of Melbourne's eminent biomedical researchers and the young and upcoming talent being mentored by our clinical schools at Monash University.

In 2015, a translational PhD and Graduate Certificate program were launched, the first of their kind in Australia. Monash's clinical schools and their partner hospitals provide a vigorous and lively scientific environment with seamless translation to clinical environments and applications. The large cohorts of research students contribute significantly to the clinical schools' productivity, and in turn, the clinical schools mentor and train our future leaders in medical research. This environment is further enriched with the continuing recruitment of highly talented research leaders, addition of departments, and maintaining investment in research platforms at Monash University clinical sites.

See more:

www.med.monash.edu.au/cecs/education/translational/

Monash University's Clinical Schools

Central Clinical School, Eastern Health Clinical School and School of Clinical Sciences, Monash's three clinical schools all offer collaboration with a range of health facilities including The Alfred Hospital, Monash Health, Box Hill Hospital and many other hospitals and residential care facilities.

All three schools offer an innovative approach to research with a large focus on translation and collaboration, working closely with world leaders in biomedical and clinical research. The three schools offer a diverse range of subject areas for undergraduate and post graduate study programs. Through the close ties with health care providers, research at Monash University is able to move rapidly towards health outcomes in improved patient care.

Each school offers a great breadth of research themes as outlined below.

Central Clinical School (CCS)

Head of CCS
Professor Stephen Jane

CCS offers opportunities for research in a variety of different areas through its collaborations with the Alfred Hospital, Australian Centre for Blood Diseases, Baker Institute and Burnet Institute, as well as its many departments including the newly established Department of Diabetes. The CCS departments provide cutting edge research covering a variety of research themes. These include: blood diseases, allergy and respiratory diseases, gastroenterology, immunology and pathology, infectious and inflammatory diseases, psychiatric research, diabetes and its complications, clinical neuroscience, anaesthesia and perioperative medicine, and sexual health.

www.med.monash.edu.au/cecs/

Eastern Health Clinical School (EHCS)

Head of EHCS
Professor Ian Davis

EHCS has ties with a large range of facilities including seven hospitals, and rehabilitation, community and mental health facilities. As well as these ties which are vital for medical students, EHCS also offers a wide range of research areas, with a particular focus on clinical trials. Some of these areas include: cardiology, haematology, hepatology, oncology, renal, respiratory and sleep medicine, and rheumatology.

www.med.monash.edu.au/ehcs/

School of Clinical Sciences (SCS) at Monash Health

Head of SCS
Professor Eric Morand

SCS provides opportunities for research, education and clinical practice. It has a strong connection with Monash Health, Victoria's largest hospital network. SCS therefore also provides a broad variety of research areas, with focuses including: critical care, obesity and endocrinology, emergency medicine, genetic diseases, imaging, inflammatory diseases, nutrition and dietetics, rehabilitation, palliative care, and women's and children's health.

www.monash.edu/medicine/scs

Speaker Abstracts

Professor Kathryn North AM

Director, Murdoch Children's Research Institute
Director, Victorian Clinical Genetics Service
David Danks Professor of Child Health Research,
University of Melbourne

Genomics and the brave new world of personalised medicine: A global and local perspective

Genomics is already having a huge impact on our ability to diagnose and understand a range of disorders, and to target therapies to the individual. However, effective integration of this "disruptive technology" into everyday clinical practice will require a "whole-of-system" approach that builds on existing expertise. In Australia, we also need to overcome the "state/federal divide" in the funding of genetic testing to develop a cohesive national approach that is cost effective and provides equitable access.

The Australian Genomics Health Alliance (AGHA) is an NHMRC-funded national collaborative network committed to implementing genomic medicine within Australia and providing evidence to inform policy and practice. AGHA comprises over 50 partner organisations including the diagnostic pathology and clinical genetics services of all Australian States and Territories, along with the major research and academic institutions and peak professional bodies. By approaching clinical genomics at a national rather than state-based level, we increase our critical mass and offer a single point of contact for government and for national and international consortia. Our approach – starting with the patient and developing a system that is focussed on improving patient care and outcomes – provides us with a unique opportunity to lead internationally in the integration of genomics into healthcare.

AGHA is also a leading member of the Global Alliance for Genomics and Health (GA4GH), an organisation of over 470 of the world's leading biomedical research institutions, healthcare providers, information technology and life science companies, funders of research, and disease and patient advocacy organisations. The Global Alliance aims to accelerate the world-wide effort to responsibly aggregate, analyse and share large amounts of genomic and clinical information to advance the understanding, diagnosis, and treatment for cancer, inherited diseases, infectious diseases, and drug responses.

Doctor C. Glenn Begley

Chief Executive Officer, BioCurate, Melbourne

Challenges to translational science around the world (and even across the Yarra)

As scientists and physicians, we all want to make an impact on the lives of patients. We all want to see our research translated into something of lasting value.

Sadly however, the vast majority of findings published in high-profile journals are fundamentally flawed and cannot be reproduced. Many groups have come to this shocking conclusion. This is important because the ability to reproduce a result is fundamental to establishing its legitimacy, and it is these early-stage results that provide the foundation for studies that will ultimately be performed in people. Yet the majority of research studies cannot be used to drive a drug development program. Furthermore the time invested in attempting to confirm an irreproducible result has a real opportunity cost; it distracts scientists and physicians from other more fruitful areas of endeavour.

A review of the details of irreproducible experiments provided the explanation. Experiments were not performed using what most would regard as standard scientific methodology (blinding researchers to their data during experiments; repeating experiments; reporting all results; use of appropriate controls; avoiding inappropriate data-selection or "cherry picking"; appropriate data analysis).

The lack of robust data represents a real challenge to the world's clinical development and, despite the substantial therapeutic advances that have taken place over recent decades, is a major contributor to the failure of drugs in the clinic.

Monash University and the University of Melbourne have come together to create an independent new, company, BioCurate. The goal of this new company is to be part of the solution in terms of translational research and new drug development. BioCurate will harness the research output of these two outstanding Universities with the intent of turning discoveries into treatments. A key element of this process will be ensuring rigorous, robust science.

This presentation will dissect several highly cited publications published in high profile journals to illustrate the systemic problem of irreproducible science that currently exists within the academic community.

Speaker Abstracts

Professor Paul Myles

Department of Anaesthesia and Perioperative Medicine, CCS and Alfred Hospital

Large Clinical Trials and Reverse Translation

Clinical practice should be guided by medical research, typically starting with basic science, then small studies in humans - translation from bench to bedside – and finally large clinical trials. Yet most clinical trials do not change practice; this suggests that their results are either unreliable or that such trials are irrelevant to clinical practice. The use of surrogate, or intermediate, outcome measures in surgery and anaesthesia is widespread. Such surrogate markers are of questionable significance and often have no convincing relationships with patient outcome. Severe complications leading to death or chronic disability are rare, but it is these that patients (and doctors!) are concerned about. Such low event rates have important implications for trial design.

Because most improvements in medicine are modest and incremental, large numbers of patients need to be studied in order to have adequate statistical power to detect a clinically important difference in serious adverse outcomes. Such studies require a sample size in the many thousands to provide sufficient statistical power and reliable estimates of effect. Large trials with straightforward requirements reflecting standard practice are sometimes called effectiveness, pragmatic, or practical trials. They thus optimize generalisability and so are clinically relevant.

But it must be kept in mind that large clinical trials are focused on the question, “Does this intervention work” (i.e. improve outcome)? They are not designed to investigate how or why a drug or techniques does or doesn’t work – that is, underlying mechanisms and explanations often remain unclear.

Large trials offer two key, frequently under-utilised benefits for those engaged in basic science. First, they offer a great opportunity to embed one or more substudies, with additional blood and other sampling in a subgroup of patients, to provide mechanistic insights. Second, there are often unexpected findings in large clinical trials, and these can inform the design of follow-up secondary studies to investigate how or why such effects occur. That is, reverse translation.

It should be kept in mind that most medical discoveries are serendipitous, identified through the inquisitive minds of attentive investigators.

I will outline examples from some of our large, high-impact clinical trials.

Associate Professor Menno C Van Zelm

Department of Immunology and Pathology, CCS

Primary Immunodeficiencies: Immunology lessons from nature

Primary immunodeficiencies are rare inherited disorders of the immune system. Typically, patients present at a young age with recurrent and severe infections. However, there is enormous clinical heterogeneity that includes late-onset of disease and non-infectious complications such as auto-immunity and malignancies. Treatment is mostly symptomatic using antibiotics and intravenous immunoglobulin substitution. Corrective treatment is only possible with stem cell transplantation or gene therapy.

Over the past three decades, advances in the field of immunology and genomics have uncovered the genetic basis of disease in many patients. Such genetic diagnoses are critical for decisions regarding stem cell transplantation and gene therapy, and in several cases have formed the rationale for treatment with small molecule inhibitors.

On top of these clinical implications, functional and genetic analysis of patients with primary immunodeficiencies have provided new insights in human immunology, with the presence of a single mutant gene providing a unique human model system.

In my talk, I will present our approach for uncovering functional and genetic defects in patients with antibody deficiencies, and how these have advanced our understanding of human immune responses.

Speaker Abstracts

Professor Mark Cooper AO

Head of Department of Diabetes, CCS

The changing face of managing diabetes and its complications

After over 50 years managing diabetes primarily with insulin, sulphonylureas and metformin as well as diet and exercise, the treatment options have been greatly expanded over the last decade.

New drugs that surprisingly do not target the pathways that are considered critical in the pathogenesis of type 2 diabetes ie insulin resistance and beta cell dysfunction now have entered the armamentarium for the treatment of diabetes.

We have three major classes of drugs that not only lower glucose levels but also appear to have better side effect profiles and in certain circumstances may confer specific actions to reduce diabetic micro and macrovascular complications. These agents include DPP-IV inhibitors, GLP-1 analogues and SGLT2 inhibitors. In addition, there has been rapid progress in our understanding of the underlying pathophysiology of diabetic complications which it is hoped will lead to new targets and ultimately new therapies to reduce the major burden of both type 1 and type 2 diabetes and their complications.

Professor Helen Dewey

Director of Neurosciences, EHCS

The long walk to effective therapies in acute stroke

Over the last 25 years, stroke care has undergone a revolution with the introduction of a number of effective therapies leading to much better outcomes for stroke sufferers. Translation of promising ideas into every day clinical practice is often very slow and this is well illustrated with respect to the implementation of intravenous thrombolysis for acute ischaemic stroke (AIS).

Conversely, the establishment of the Victorian state wide endovascular clot retrieval service for patients with AIS very soon after publication of the pivotal large randomised controlled trials in 2015, provides an example of effective translation of research into practice. A Very Early Rehabilitation Trial in Stroke (AVERT) will be used to provide an example of how clinical observations inform clinical trial design and how outcomes are translated into practice.

Doctor Claudia Nold

National Heart Foundation of Australia – Fellow
Hudson Institute of Medical Research
Monash University

Translating a cytokine into a therapeutic: From promise to product

The discovery of the anti-inflammatory function of IL-37, which Dr Nold published in Nature Immunology in 2010, had a major impact on the interleukin field and necessitated a reorganisation of the IL-1 family nomenclature. Five years later, she discovered the IL-37 receptor complex, as again reported in Nature Immunology. Next, she and her team identified critical regions in the IL-37 structure and generated a modified IL-37 biologic with enhanced anti-inflammatory properties. Besides publication in Science Immunology, this research led to an industry collaboration that aims to develop immunotherapeutics for a range of inflammatory diseases.

Speaker Abstracts

Doctor Sarah Zaman

SCS, MonashHeart, Monash Health

Primary prevention of sudden cardiac death after myocardial infarction

The Patients who have survived a myocardial infarction (MI) with resultant impaired cardiac function are at high risk of sudden cardiac death (SCD). The risk of SCD is 6 times higher in the first month post-MI then thereafter, with a substantial risk in patients with more preserved cardiac function. However, current guidelines exclude such patients form receiving a primary prevention implantable-cardioverter-defibrillator (ICD).

The PROTECT-ICD Trial aims to prevent SCD through use of an electrophysiology study (EPS) to identify high risk patients early-post MI who may benefit from an ICD.

This is an international, multi-centre, randomised controlled trial of 1,058 patients with a left ventricular ejection fraction (LVEF)≤40% post-MI. Patients are randomised 1:1 to either early (3-40 days after MI) ICD implantation guided by electrophysiological study, or to standard care (ICD implanted >3 months post-revascularisation for MI if LVEF≤30% or ≤35% with heart failure). The primary outcome is SCD or non-fatal arrhythmia at 2-years.

The trial commenced in 2014 with 15% of target participants already recruited from 18 active sites across the AsiaPacific. With a further 10-20 sites being initiated in 2017, complete patient recruitment and 2-year follow up is projected to finish in 2020.

The PROTECT-ICD Trial is unique in being the only study to target the important issue of early prevention of SCD in post-MI patients through the use of an electrophysiology study. The trial has the potential to change national and international guidelines for primary prevention of SCD and selection for defibrillator therapy.

Professor Peter Gibson

Department of Gastroenterology, CCS

Low FODMAP diet: The road from ideas to implementation across the world

Irritable bowel syndrome (IBS) is characterised by recurrent/chronic symptoms of abdominal pain, bloating and change in bowel habits without serious underlying pathology. It affects up to 15% of people across the world, and has a big impact on quality of life and performance at school/work.

Therapy has been challenging – there is no quick-fix with drugs. Patients with IBS have been telling us for decades that symptoms are triggered by eating, but such observations were not converted to rational and efficacious dietary therapy, even though slowly absorbed sugars, like fructose, and indigestible oligosaccharides, like fructans, were known individually to induce symptoms.

By thinking more broadly, our group came up with a new concept that required a new term for such short-chain carbohydrates ('FODMAPs). We proposed that all FODMAPs be reduced in the diet of people with IBS. The consequent diet, the low FODMAP diet, proved to be highly effective in up to 3 out of four patients in randomised controlled trials and in clinical real-world practice.

To underpin such an approach, we needed to measure the FODMAP content of a vast array of foods and this enabled a unique database to be developed. The problem was how to get such information accurately to the end-user. This was achieved by digital technology and the resultant Monash University low FODMAP Diet App quickly became the #1 medical app across the world.

Thus, the combination of hypothesis, science, dietary knowledge, high-quality clinical trials, infrastructure development, education, digital innovation and sensible commercialisation in a multidisciplinary group has led to changes in the paradigm of management of patients with IBS and considerable improvement in quality of life for a large number of people.

Speaker Abstracts

Professor Melissa Southey

SCS, Monash Health

Towards massively parallel translation: The breast cancer example

Given current evidence, it is no longer appropriate to practice breast cancer clinical genetics in the context of limited "high risk" gene testing aimed at placing women into a limited number of estimated risk-defined groups; breast cancer risk is a continuum. It is now known that a woman's genetic risk is defined by her mutation (or more broadly variant) status for multiple genomic regions, and not just the "major" susceptibility genes. Genetic variants and risk scores generated by a genome-wide association study modify risk for mutation carriers, as well as non-carriers.

Heterogeneity in risks associated with mutations exists within, and across, the "major" genes. Furthermore, even if mutations are found, family history can still be important. This poses many challenges for clinicians and women who undertake genetic testing using gene panel testing. With the exception of BRCA1 and BRCA2, the magnitude of risk associated with almost all of the genetic variation identified via gene panel testing for breast cancer susceptibility is unknown and how these might be modified by common genetic variants has not been investigated.

Research, genetic testing and risk assessment modelling is no longer limited by technology and increasing amounts of data are available to address these issues – but how can this data be used to provide information sufficient to start routinely placing women on the risk spectrum (rather than categories) and advance strategies for personalised risk management.

Professor Richard Kitching

SCS, Department of Nephrology and Paediatric Nephrology, Monash Health

A new mechanism determining the risk of autoimmune disease

The highly polymorphic HLA system is critical to foreign and self-protein recognition by the immune system. A key question in autoimmune disease is how this HLA system, genetically linked to almost all autoimmune diseases, mediates disease risk. Furthermore, conditions such as type I diabetes mellitus, multiple sclerosis and Goodpasture's disease (GPD) not only feature risk MHC Class II (HLA) alleles, but also exhibit dominant HLA-mediated protection, i.e. some HLA alleles are protective, even when inherited with a risk allele.

We used GPD that causes life-threatening glomerulonephritis and pulmonary haemorrhage, to address this fundamental question. GPD is caused by autoimmunity to the non-collagenous domain of the a3 chain of type IV collagen, a3(IV)NC1, found in glomerular and pulmonary basement membranes, with the dominant CD4+ T cell epitope being the a3135-145 peptide. HLA-DR15+ people have a relative risk of GPD of 8.5, but HLA-DR1+ only 0.3. This HLA-DR15-associated risk is abrogated by HLA-DR1 co-inheritance.

We used in vitro and in vivo systems in HLA-DR15, DR1 and DR15/DR1 transgenic mice, together with samples from both GPD patients and from fully HLA-typed health donors. CD4+ a3135-145-specific T helper cells are central to disease and a3135-145 responses define HLA-DR1's dominant protection. The molecular structure of the a3135-145-HLA-DR complex differs markedly between HLA-DR15 and of HLA-DR1, resulting in different a3135-145-specific T cell selection.

Furthermore, most a3135-145-specific CD4+ T cells in HLA-DR15+ mice and humans are conventional T cells (with the potential to become autoreactive pro-inflammatory cells). However, when educated by HLA-DR1, the resultant a3135-145-specific CD4+ cells are anti-inflammatory regulatory T cells (Tregs) that maintain tolerance to a3(IV)NC1. Even in the presence of HLA-DR15, it is these -a3135-145-specific specific Tregs, generated by HLA-DR1-peptide interactions, that potently protect from autoimmunity and GPD.

These findings answer a central question in autoimmune disease, providing a mechanistic basis for understanding HLA-mediated susceptibility and protection. Peptide-HLA/T cell interactions could be used in disease diagnosis and risk stratification, and the potency of Tregs specific for immunodominant autoepitopes mean that they may be more specific therapies for autoimmune diseases.

Speaker Abstracts

Professor Terence O'Brien

James Stewart Professor of Medicine, The Royal Melbourne Hospital, The University of Melbourne

Developing treatments that address the treatment gap for the Sacred Disease

Epilepsy, known to the ancients as the "Sacred Disease", is the most common serious chronic neurological condition worldwide.

There is no medical cure for epilepsy, but anti-epileptic drugs (AEDs) can symptomatically suppress seizure occurrence, and if taken on an ongoing basis can control the seizures in approximately two-thirds of patients. However, despite more than 15 new AEDs being introduced into clinical practice over the last three decades, there has been minimal impact on the major current treatment gaps for epilepsy. These are:

1. Drug resistant epilepsy,
2. Medication tolerability,
3. Lack of disease modifying/anti-epileptogenic therapies, and
4. Lack of treatment for psychiatric comorbidities.

The explanation for the lack of impact of these new therapies is likely that the traditional drug development paradigm has been focused on identifying drugs that suppress seizures, rather than treatments that incrementally impact the gaps in care over currently available AEDs.

Over the last decade there has been a refocusing of therapy development in the epilepsy field, utilizing true animal models of epilepsy, to identify drugs that are disease modifying and therefore fundamentally mitigate the epileptic condition, thereby have potential to address the current gaps in epilepsy treatment.

Two such treatments are sodium selenate, targeting the accumulation of hyperphosphorylated tau that occurs in acquired epilepsy, and Z944, a selective T-Type calcium channel blocker that inhibits epileptiform neuronal burst firing. However, translating the promising results in animal models of these compounds to demonstrate effective anti-epileptogenesis in human clinical trials represents a significant challenge.

Professor Eva Segelov

Professor/Director Oncology School of Clinical Sciences and Monash Health

The role of aspirin in modulating response to cancer

This talk will discuss two main aspects of aspirin in cancer-prevention of primary and secondary cancer; and modulation of the immune response to cancer. Aspirin has been shown in large cohort and population-based studies to prevent a variety of cancers (primary prevention) and additionally to prevent recurrence, including for bowel, prostate and breast cancer.

The 'gold standard' randomized controlled Phase III trials comparing aspirin with placebo are underway in multiple tumour types. The mechanism of action is not fully described but is likely to relate to immune modulation rather than antithrombotic effect. There are putative predictive biomarkers, at least for some cancers such as colorectal cancer.

In addition, aspirin holds promise for patients with in situ cancers as an immune modulator which may enhance response particularly of radiotherapy as well as modern immune-oncology agents.

Young Investigator Award Poster presentations

Dr Jun Yang, Hudson Institute

Optimising care for patients with primary aldosteronism: Putting research into practice

Background: Primary aldosteronism (PA) is the most common endocrine cause of hypertension, affecting 5 – 10 % of hypertensive patients and up to 20% of those with resistant hypertension. Early diagnosis is crucial as it is potentially surgically curable. Unfortunately very few centers have established protocols or expertise in its diagnosis. Objectives: Building on our established expertise in aldosterone research, this project aims to develop center-specific guidelines for the diagnosis of PA and offer an evidence-based pathway of care for patients. Methods: An extensive literature review was performed of the diagnosis of PA using PubMED. The information was collated into a center-specific protocol after consultation with all the stakeholders involved in the pathway of care, including endocrinologists, radiologists, chemical pathologists and endocrine surgeons. The PA protocol was introduced in January 2010. Subsequent patient outcomes were audited in 2016 to evaluate the impact of the protocol on clinical practice. Results: Introduction of the PA protocol led to an exponential increase in the number of PA diagnostic procedures being performed, from 2 in 2010 to 31 in 2016. There was also a 50% increase in the success rate of the procedures. The multidisciplinary approach to care has led to more standardized reporting by Diagnostic Imaging and Chemical Pathology. Analysis of patient outcomes has resulted in refinement of the protocol to optimize diagnosis. The significant increase in the number of PA diagnoses has necessitated the establishment of a dedicated Endocrine Hypertension Clinic at Monash Health. Conclusion: An evidence-based center-specific protocol developed from PA research has been successfully implemented in clinical practice, leading to increased diagnoses and optimal patient care. Further research to evaluate PA prevalence and

Ms Maria Zaldivia, Baker Institute

Renal denervation reduces monocyte activation and monocyte-platelet aggregate formation: An anti-inflammatory effect relevant for cardiovascular risk

INTRODUCTION: Over-activation of renal sympathetic nervous system and low-grade systemic inflammation are common features of hypertension. Renal denervation (RDN) reduces sympathetic activity in patients with resistant hypertension. However, its effect on systemic inflammation has not been examined. METHODS: We prospectively investigated the effect of RDN on monocyte activation and inflammation in patients with uncontrolled hypertension scheduled for RDN. Ambulatory blood pressure, monocyte as well as monocyte subsets activation and inflammatory markers were assessed at baseline, 3 and 6 months post-procedure in 42 patients. RESULTS: RDN significantly lowered 24-hour ambulatory blood pressure at 3 months (50.5±11.2/81.0±11.2 mmHg to 144.7±11.8/77.9±11.0 mmHg), which was sustained at 6 months (144.7±13.8/78.6±11.0 mmHg). Activation status of monocytes significantly decreased at 3 months ($p<0.01$) and 6 months ($p<0.01$) post-procedure. In particular, classical monocyte activation was reduced at 6 months ($p<0.05$). Similarly, we observed a reduction of several inflammatory markers including monocyte-platelet aggregates (3 months $p<0.01$), plasma MCP-1 (3 months $p<0.0001$; 6 months $p<0.05$), IL-1β (3 months $p<0.05$; 6 months $p<0.05$), TNF-α (3 months $p<0.01$; 6 months $p<0.05$) and IL-12 (3 months $p<0.01$; 6 months $p<0.05$). A positive correlation was observed between muscle sympathetic nerve activity and monocyte activation before and after the procedure. CONCLUSIONS: These results indicate that inhibition of sympathetic activity via RDN is associated with a reduction of monocyte activation and other inflammatory markers in hypertensive patients. These findings point to a direct interaction between the inflammatory and sympathetic nervous system, which is of central relevance for the understanding of beneficial

Ms Katrina Woodford, Department of Surgery , CCS

Feasibility of stereotactic ablative radiotherapy (SABR) for locally-advanced non-small cell lung cancer (NSCLC)

Background SABR has enabled a curative treatment for elderly patients or those with significant comorbidities diagnosed with early-stage NSCLC who would have otherwise gone untreated. As a result population-based survival has improved. If SABR could be utilized in the treatment of locally-advanced NSCLC in the same way, the public health impact would be greater, as twice as many patients are diagnosed with advanced disease. We assessed the feasibility of SABR for locally-advanced NSCLC. Methods Twenty three patients with N2 and/or N3 locally-advanced lung cancer were retrospectively replanned. Three planning approaches were assessed; conventional; SABR and a hybrid approach. We assessed the feasibility of three dose regimes, with PTV doses all having a biologic equivalence of 60Gy in 30 fractions (α/β=10). The planning aim was to determine the least number of fractions to deliver an acceptable plan. Results The hybrid approach generated acceptable plans in 48% of patients, while the conventional and SABR approaches achieved 26% and 4% respectively. Of the 18 patients who had an acceptable plan generated, one was achieved with the 8-fraction regime, with the remaining needing the 12-fraction regime. Conclusion SABR was feasible for approximately half of the locally-advanced NSCLC patients we assessed and for these patients a 30-treatment course can be reduced to 12 treatments. If the alternative to SABR is no treatment at all, compromises to tumour coverage or organ-at-risk tolerances may be acceptable, increasing feasibility. This data will inform a phase I study testing the safety of SABR for locally advanced NSCLC.

Young Investigator Award Poster presentations

Mr Paul Jansons, SCS

Trial-based comparative cost effectiveness analysis of gym versus home-based exercise with telephone follow-up for adults with chronic health conditions

Aim To investigate the comparative cost effectiveness of gym versus home-based exercise programs with telephone follow up for adults with chronic health conditions who had previously completed a short term, supervised group exercise program. Method A two-group 12 month intervention, randomised controlled trial. One group received a gym based exercise program, the other a home-based exercise program with telephone follow up. The economic evaluation took the form of a trial-based, comparative, incremental cost-utility analysis undertaken from the societal perspective with a 12 month time horizon. Health care costs were collected from government databases and participant self-report, productivity costs from self-report, and health utility was measured using the EQ-5D-3L. Sensitivity analyses were conducted to vary the perspective of the evaluation to both the patient and health service perspectives separately. Results 105 participants included in this trial. The gym-based follow-up approach would cost an additional $491,572 AUD from the societal perspective to gain one quality adjusted life year compared to the telephone-based approach. There was considerable uncertainty in this finding in that there was a 37% probability that the telephone-based approach was both less costly and more effective than they gym-based approach. Conclusion The gym-based approach was more costly to implement. These additional costs are unlikely to be justified by differences in health outcomes attained. Further research conducted across multiple socioeconomic groups and with an additional no-intervention comparison group is warranted to further inform clinical decision-making in this area.

Ms Rose Brazilek, ACBD

Microfluidic device characterisation for von Willebrand Disease screening

von Willebrand Disease (VWD) is the most common inherited bleeding disorder in Western populations. The chief pathology involves quantitative or qualitative deficiency of von Willebrand Factor (VWF), the function of which is highly-dependant on elevated shear rates in blood flow. Contemporary screening assays lack sufficient sensitivity for rapid assessment, and requires relatively large blood volumes and do not incorporate the modulating effects of blood flow. AIM: To characterise a new microfluidic device with the potential to improve point-of-care screening of VWD by improving reliability, reducing sample volume sizes, and provide more rapid screening of VWF-dependant platelet function. METHODS: Whole blood samples from 11 adults with suspected or confirmed VWD (4 type 1 patients, 5 type 2 patients and 2 type 3 patients) aged 18-62 years, with mean VWF levels of 46.67% (SD 38.8) was perfused through the device incorporating stenosis that generate well defined blood shear gradients. Resulting aggregate size was monitored in real-time using epifluorescence microscopy. Aggregate area for control donors and samples taken from patients with confirmed or suspected VWD was assessed to determine the device's diagnostic potential. RESULTS: We present data demonstrating that platelet aggregation in the device is dependent on platelet GPIb/V/IX and integrin aIIbb3 engagement of VWF and platelet activation. Device output directly correlates with VWF antigen levels and is able to sensitively detect vWD aggregation defects. CONCLUSION: This novel device has the potential to improve VWD screening by reducing sample volumes and providing a rapid and reliable assessment of VWF-specific platelet function.

Mr Alexander Rodrigues, SCS

Effect of long-term leptin replacement therapy on bone mass in a pre-menopausal woman with genetic leptin deficiency

Background: Leptin is important for musculoskeletal development. Genetic leptin deficiency, from Leptin gene mutations, is extremely rare and causes severe metabolic abnormalities. Here we report a case of a 33y Turkish female with leptin deficiency due to missense Lep mutation (C105T), who had received seven years of metreleptin (synthetic leptin analogue) therapy. Case: Patient presented with severe obesity (body mass index, BMI 64.3 kg/m2), hypogonadotropic hypogonadism, and dyslipidaemia. She was started on metreleptin 4.2 mg/day (0.04 mg/kg), subcutaneously. Doses were titrated during follow-up, according to weight variations. Serial BMD and bone mineral content (BMC) measurements were made utilising DXA (Hologic QDR4500). Results: At first consultation, total hip, femoral neck and L1-L4 spine BMDs were 0.915 g/cm2, 0.949 g/cm2 and 1.098 g/cm2 respectively. T-scores for these regions were all normal (-0.2, 0.9 and 0.5, respectively). BMCs were 15.36 g/cm, 4.75 g/cm and 16.19 g/cm, respectively. After 7 years, dose was reduced progressively to 2.5 mg/day. BMI fell to 39.3kg/m2. Total hip, femoral neck and lumbar spine BMDs were 0.966g/cm2, 0.931g/cm2 and 1.221g/cm2, respectively. T-scores remained unchanged and normal (-0.3, -0.8 and 0.3). Hip BMC increased (29.99 g/cm), femoral neck BMC decreased (3.31 g/cm) and spine BMC remained unchanged (16.67 g/cm). Conclusions: Despite significant weight loss, BMD was maintained following leptin supplementation suggesting leptin possibly had a positive impact in the prevention of a decrease in BMD that is associated with weight loss. These findings support other work that leptin may influence the skeleton in a mechanism independent of fat mass.

Young Investigator Award Poster presentations

Dr Atul Malhotra, SCS

Allogenic amnion epithelia cell use for bronchopulmonary dysplasia in preterm infants

Background: Bronchopulmonary dysplasia (BPD) is a relatively common morbidity in preterm infants, especially in those born before 28 weeks of gestation. Current management of BPD, which has a significant impact on the patient, family and community, is largely supportive and no cure exists. Over the last decade, our group has shown that human amnion epithelial cells (hAECs), derived from healthy amniotic membranes can prevent and reverse lung injury in small and large animal models of adult and neonatal lung disease, including BPD. Aim: To assess the safety of intravenously administered allogeneic hAECs in preterm infants with established BPD. Methods: Preterm infants born before 28 weeks of gestation were eligible if they were still significantly dependent on ventilatory support and oxygen at 36 weeks postconceptional age. Primary safety outcome parameters included short term measures, i.e. local reaction, anaphylaxis, infection, systemic rejection effects, and long term measures, i.e. tumorigenesis. CGMP-compliant hAECs were isolated from healthy term placenta donors and delivered to infants using a slow intravenous infusion at a dose of 1 million/ kg suspended in saline. Secondary outcomes included changes in respiratory function, other morbidities and death. Results: Five preterm infants (median birth weight 814 (450- 990) grams, gestation 27 (25-28) weeks) with established severe BPD have been recruited into the trial. There were no immediate or short term adverse effects. Respiratory support parameters in the first few days after cell infusion either improved or showed no significant change from pre-treatment levels. Long term results of the first recruit are satisfactory, while the others are pending. Conclusion: hAECs seem to be well tolerated when given to preterm infants with established severe BPD. This first-in-human study will inform future clinical

Ms Christie Bennett , SCS

Interventions designed to reduce gestational weight gain can reduce the incidence of gestational diabetes mellitus: Systematic review and meta-analysis

Excessive gestational weight gain (GWG) increases the risk of gestational diabetes mellitus (GDM). Many interventions have reduced GWG. However, the effect on GDM is still unknown. This systematic review (SLR) aimed to (i) evaluate the impact of interventions designed to prevent excessive GWG on the incidence of GDM, and (ii) examine if effects differ by geographical region and body mass index (BMI). A SLR of randomised controlled trials (RCTs) was conducted without date limits using seven international databases and three Chinese databases. RCTs that reported a primary/secondary aim to reduce excessive GWG and the incidence of GDM were considered. Two authors independently identified and assessed the included studies. Meta-analysis data are reported for GDM incidence with interventions covering diet, physical activity (PA) and lifestyle (diet plus PA).Of 20,517 manuscripts screened, 37 were included for analysis (n=12,942). Diet interventions reduced the risk of GDM by 44% (RR: 0.56, 95% CI: 0.36-0.87), while PA interventions reduced the risk by 38% (RR: 0.62, 95% CI: 0.50-0.78). Both lifestyle interventions and BMI did not significantly alter the risk. PA interventions from Southern Europe reduced GDM risk by 37% (RR: 0.63, 95% CI: 0.50, 0.80). Both diet and lifestyle interventions conducted in Asia resulted in a 62% (RR: 0.38, 95% CI: 0.24, 0.59) and 32% (RR: 0.68, 95% CI: 0.54, 0.86) reduction in GDM, respectively. Interventions designed to prevent excessive GWG can reduce the risk of GDM. However, due to physiological and/or behavioural responses to interventions, the 'one size fits all' approach is not supported.

Mr Mitchell Sarkies, Physiotherapy

Conceptualising and evaluating implementation success: The efficacy standardised effect

INTRODUCTION Health outcome changes should be the standard by which implementation success is judged. However, the success of implementation strategies in delivering treatments may be constrained or amplified by the efficacy of the treatment being introduced to practice. This study proposes a new conceptual approach to evaluating the success of research implementation strategies as applied to health outcomes: The efficacy standardised effect. METHODS The efficacy standardised effect expresses the change in health outcomes from treatments delivered by implementation strategies (implementation studies), relative to the treatments efficacy (treatment efficacy studies). This is conceptualised as a ratio of implementation success and treatment efficacy. RESULTS In the case example, a ratio of mortality reduction observed when an algorithm-based implementation strategy was used to deliver early enteral feeding treatment and when early enteral feeding was evaluated in highly controlled efficacy studies resulted in an efficacy standardised effect of 0.6. This on mortality rate represents the relative benefit of using evidence-based algorithms to improve nutritional support for critically ill patients. CONCLUSION The efficacy standardised effect provides a mechanism to account for variable treatment efficacy when ascertaining the success of an implementation strategy. Using a ratio to present the quantitative success of research implementation strategies in an easily interpretable, uniform scale may allow the pooling of implementation study results

Young Investigator Award Poster presentations

Dr Hui Liew, EHCS

Endothelial glycocalyx damage in kidney disease is reflected by serum biomarkers but not the perfused boundary

Background: Disruption of the endothelial glycocalyx (EG) is an early indicator of vascular damage and a potential novel marker of endothelial dysfunction in CKD. Biochemical markers and an increased perfused boundary region (PBR) in sublingual capillaries using the novel Glycocheck device may reflect EG damage. Aim: We aimed to assess correlation of EG damage with endothelial dysfunction (ED) measured by albuminuria and biochemical markers. Methods: Healthy controls, CKD patients (eGFR 15-60mL/min), and kidney transplant recipients had a Glycocheck measurement performed. Urine and blood were collected for urine albumin:creatinine ratio (ACR), serum hyaluronan, syndecan-1 (markers of EG), von Willebrand factor (vWF) and vascular cell adhesion molecule, VCAM-1 (markers of ED) using commercial ELISA kits. Results: 24 healthy controls, 26 CKD patients, and 27 transplant recipients were recruited. eGFR negatively correlated with age (r=-0.707, p<0.001), systolic blood pressure (p=-0.529, p<0.001), body mass index (-0.529, p<0.001), hyaluronan (r=-0.521, p<0.001), vWF (p=-0.520, p<0.001), and VCAM (p=-0.540, p<0.001). PBR did not correlate with any markers of EG or ED. Syndecan-1 correlated with vWF (r=0.291, p=0.01), while hyaluronan correlated with vWF (r=0.581, p<0.001), VCAM (r=0.623, p<0.001) and ACR (r=0.435, p<0.005). Hyaluronan, vWF and VCAM all positively correlated with age and systolic blood pressure. In multivariate analysis, significant predictors of (a) hyaluronan were age (β=1.69, p<0.001) and ACR (β=0.250, p<0.001), R2=0.432; (b) vWF were age (β=19.95, p=0.003) and hyaluronan (β=7.24, p<0.001), R2=0.411; and (c) VCAM were hyaluronan (β=2.34, p=0.003) and vWF (β=0.137, p=0.002), R2=0.522. There were no significant predictors of PBR or syndecan-1. Conclusions: Serum markers of EG damage correlated closely with markers of endothelial damage (vWF, VCAM and ACR and ACR) in this cohort. PBR showed no additional

Mr Michael Keating, Baker Institute

A systems-biology approach to identifying and characterising a novel regulator of lipid metabolism

Utilising a cutting-edge discovery platform, we identified many potential novel regulators of lipid metabolism. One such novel target we named proteosomal associated protein (PAP) was strongly correlated with hepatic diacylglycerol (DAG) species across 107 strains of mice. Utilising two hepatic cells lines Hep3B and HepG2 we sought to validate PAP as a regulator of lipid metabolism, through manipulation of free fatty acids (FFAs). Furthermore, we examined the effect of acutely over expressing PAP in C57Bl/6J and DBA/2J mice subjected to a normal chow diet via adenoviral expression. PAP overexpression in Hep3B/HepG2 cells resulted in a reduction in DGAT2 mRNA expression, which is involved in triacylglycerol synthesis, and an increase CGI-58 which is involved in DAG hydrolysis. Overexpression of PAP also led to an increase in mRNA expression of the marker of ER stress, CHOP, and an increase in mRNA expression of TNF-α, a marker of cellular inflammation. Moreover, chow-fed C57Bl/6J mice over expressing PAP result in a 75% reduction (p=0.035) in hormone sensitive lipase compared to control mice. Furthers studies overexpressing PAP in both C57B1/6J and DBA/2J showed that PAP could drive changes in many lipid species, most notably DAGs and ceramides in both plasma and liver. Our findings demonstrate that PAP plays a role in FA metabolism with possible effects on ER stress and inflammation due to increased levels of toxic lipid intermediaries. Furthermore, it validates the discovery platform to identify novel regulators of lipid metabolism.

Ms Mehnaz Pervin, SCS

Post-translational modifications of GILZ: Implications for new anti-inflammatory therapies

Background: Glucocorticoid-induced leucine zipper (GILZ) is a transcriptional regulatory protein, emerged as a mediator of Glucocorticoids (GC) due to its anti-inflammatory actions, theoretically lacking GC side-effects. Down-regulation of GILZ is associated with cell activation and inflammation, and boosting the level of GILZ expression is a desirable outcome for enhancing the anti-inflammatory effects of GILZ. Methods: Macrophages stimulated with various stimuli were treated with the protease inhibitor MG-132 or the lysosome blocker bafilomycin. GILZ expression levels were analysed by western blotting and/or RT-qPCR. Lysine to arginine mutations were introduced into GILZ at K37, K77 and K108 and were overexpressed in human microvascular endothelial cells (HMECs) to determine the effect on proteasomal degradation of GILZ. Results: Blockade of the proteasome prevented GILZ degradation, and this was associated with the ubiquitilation of GILZ. MG-132 prevents degradation of both GILZ monomer and dimer and increased activity of the proteasomal degradation pathway. However, WB analysis does not reveal any significant effects of bafilomycin on the expression of GILZ which indicates that GILZ does not appear to be degraded by lysosomal pathways including autophagy. Lysine 108 of GILZ was predicted to be a target site for ubiquitination and supporting this, when K108 was mutated to arginine, GILZ protein accumulated in excess. Conclusions: GILZ is proteasomally degraded, at least in part via ubiquitination at K108. Understanding the mode of regulation of GILZ degradation may provide new opportunities to inhibit GILZ degradation as a means of enhancing the anti-inflammatory actions of GILZ.

Young Investigator Award Poster presentations

Mr Md Abul Hasnat, SCS

Role of autophagy in autoimmune diseases

Background Autophagy is a ubiquitous cellular mechanism for the lysosomal degradation of cytosolic constituents, including long-live macromolecules, organelles and invading pathogens. Autophagy has been demonstrated to influence inflammation through the regulation of inflammatory molecules, including cytokines and inflammasome components. In this study, we aim to investigate specific molecular pathways of autophagic regulation of cytokines including IL-6 and IL-1 family members. Methods Primary mouse bone marrow-derived macrophages (BMM) and dendritic cells (BMDC) were treated with or without LPS in the presence of 3-MA and Torin-1 and secretion of cytokines was tested by ELISA. Immortalised BMM stably expressing GFP-LC3, an autophagosomal marker, were treated in the presence or absence of LPS, stained with antibodies against different cytokines and examined through confocal microscopy. Result Treatment of cells with the autophagy inducer Torin-1 inhibited the secretion of IL-6 in response to LPS in both BMM and BMDC. In confocal microscopy, LPS induced an increase in autophagy in iBMM over 72 h, with IL-1β sequestered in the autophagosomes throughout. Conclusion Our findings suggest that autophagy can regulate the secretion of multiple cytokines and play a pivotal role in the regulation of inflammatory responses. Further work will explore the interactions between autophagy and other cytokines, including IL-10, IL-1α, IL-18 and B cell activating factor (BAFF).

Mr Aidan Kashyap, The Ritchie Centre, Hudson Institute

The effect of congenital diaphragmatic hernia on the neonatal cardiovascular transition

INTRODUCTION: In congenital diaphragmatic hernia (CDH), the herniating abdominal organs impair normal fetal lung development. The associated pulmonary hypoplasia results in respiratory insufficiency and pulmonary hypertension after birth. We aimed to use an ovine model of CDH to investigate the physiological effects of CDH on the cardiorespiratory transition at birth. METHODS: A diaphragmatic defect (DH) was surgically created at ≈80 days of gestational age (GA; term ≈ 147d; n=10). Controls underwent sham surgery (n=6). At ≈138d GA, all lambs were delivered via caesarean section, with physiological (pulmonary and carotid artery blood flows and pressures; cerebral oxygenation; blood gas status) and ventilatory (tidal volume and airway pressure) parameters monitored during a 2-hour ventilation protocol. Data presented as mean ± SEM and when $p<0.05$ data was considered significant. RESULTS: Diaphragmatic defects were identified in all DH lambs at post-mortem. Compared to Controls, wet lung-to-body-weight ratio was lower in DH lambs (0.02 ± 0.002 vs. 0.03 ± 0.005) and dynamic lung compliance was reduced (0.41 ± 0.14 vs. 1.24 ± 0.15 ml/cmH2O). Increased pulmonary vascular resistance (2.64 ± 0.37 vs. 0.92 ± 0.33 mmHg·min/l) and reduced pulmonary blood flow (24.85 ± 6.92 vs. 60.49 ± 7.81 ml/min/kg) was observed in DH lambs. After 2 hours, cerebral oxygenation was 18% lower in DH lambs compared with Controls (52% ± 3% vs 70% ± 3%). CONCLUSION: We have established an ovine model of CDH with pulmonary hypoplasia, pulmonary hypertension and respiratory insufficiency. Our model enables further investigation of novel antenatal and postnatal therapies for CDH.

Mr Aron Hill, Monash Alfred Psychiatry Research Centre (MAPrc)

Modulation of cortical plasticity and oscillatory activity following network-oriented High-Definition Transcranial Direct Current Stimulation (HD-tDCS)

Transcranial direct current stimulation (tDCS) provides a means of non-invasively altering cortical activity through the delivery of weak electric currents to the brain. Although tDCS has traditionally targeted single brain regions, there is a growing consensus that complex cognitive functions such as working memory (WM) strongly rely on activations across a number of distributed neural networks. Here, we utilised a focal 'high-definition' form of tDCS (HD-tDCS) to modulate two important nodes within the fronto-parietal WM network using a sham-controlled crossover design. Sixteen healthy adults received anodal stimulation (1.5mA, 15min) over either the dorsolateral prefrontal cortex (DLPFC) alone, the DLPFC in combination with the parietal cortex (DLPFC+PC), or sham stimulation. Concurrent transcranial magnetic stimulation and electroencephalography (TMS-EEG) was used to probe cortical reactivity via TMS-evoked potential (TEP) amplitudes both before as well as five and 30 minutes following HD-tDCS in order to investigate short-term changes in cortical plasticity. WM performance was also examined, both before and after stimulation, while oscillatory power was measured using EEG. Results revealed that both the DLPFC and combined DLPFC+PC stimulation conditions potentiated the P60 TEP, while N100 TEP amplitudes were reduced, relative to baseline, following DLPFC+PC stimulation only. Task-related increases in theta and gamma EEG power were also observed following DLPFC+PC stimulation compared to baseline. Interestingly, despite these neurophysiological changes, WM performance remained unaffected at the group level. However, an association was observed between WM performance and N100 amplitude changes. Overall, these findings provide important neurophysiological insight into the effects of a network-oriented approach to HD-tDCS.

Young Investigator Award Poster presentations

Dr Hannah Pearce, ACBD

Re-targeting rAAV6 towards inflamed endothelial cells

Gene therapy holds great potential for cardiovascular diseases, including atherosclerosis, yet available vectors such as recombinant adeno associated virus (rAAV) transduce the vasculature poorly and have high off target transduction. Studies have shown that targeting agents can re-direct vector tropism, increasing efficacy, and an excellent target for atherosclerosis delivery is vascular cell adhesion molecule (VCAM-1), which is upregulated on inflamed endothelial cells. Therefore, a single-chain antibody (scFv) that binds to VCAM-1 was produced, for site specific and covalent conjugation to the exterior of rAAV6. Using flow cytometry, the scFv could be detected binding specifically to VCAM-1 expressed on endothelial SVEC4-10 and MHEC cells, and was functionalised by Sortase A mediated conjugation to allow biorthogonal click chemistry attachment to azide, without affecting function. The AAV6 was separately functionalised with Methylglyoxal-azide (MGO-N3) (MGO forms covalent adducts with capsid arginine residues). MGO functionalisation alone removed native tropism, seen by greatly reduced AAV6-GFP transduction into both SVEC4-10 and MHEC cells, and control CHO and HepG2 cells. Arginine residues make up the heparin binding site of AAV6, and heparin inhibited AAV6-GFP transduction, highlighting an underappreciated role for heparin binding in AAV6 transduction. When the anti VCAM-1 scFv was attached through click chemistry (confirmed with western blotting) endothelial, but not control cell, transduction by AAV6-GFP was greatly enhanced, specifically through VCAM-1 binding. Thus this targeting system could have further application in re-directing AAV6 towards inflamed endothelium for therapeutic use. Overall, as all the components are interchangeable, a highly flexible platform technology for gene transfer was established.

Ms Margaret Murray, SCS

Oral glucose tolerance tests insufficient to diagnose diabetes risk in young, healthy Asian Australians

People of Asian descent living in Western countries experience an increased risk of type 2 diabetes. This research investigated postprandial blood glucose and insulin responses in healthy individuals of Asian and Caucasian heritage. Thirty-eight adults (12 Asian, 26 Caucasian) with normal fasting blood glucose (<5.5 mmol/L) were recruited. Fasting and postprandial capillary blood samples were taken over a two hour period following consumption of white bread (50 g available carbohydrate) to measure blood glucose and plasma insulin. Differences between ethnic groups were assessed using independent t-tests. There were no differences for blood glucose incremental area under the curve (iAUC) or peak concentration (mmol/L). However, Asian participants demonstrated increased iAUC (Asian: 3489 (4061) μU/mL.min; Caucasian: 2545 (2472) μU/mL.min) and peak concentration (Asian: 67.7 (91.8) μU/mL; Caucasian: 46.3 (40.3) μU/mL) for plasma insulin, compared with those of a Caucasian background, p = 0.022 and 0.010, respectively. In a young, healthy population, participants who identified as being of Asian descent had an elevated postprandial insulin response compared with their Caucasian counterparts. These results indicate reduced insulin sensitivity in Asian people, and that glucose tolerance tests alone may be insufficient to diagnose diabetes risk in Asian populations.

Mr Mohamed Saad, Hudson Institute

Oral blocking of ADAM17 Mitigates Kras-induced Lung Adenocarcinoma possibly via inhibition of IL-6 trans-signaling

Lung adenocarcinoma (LAC) accounts for ≈40% of all lung cancers, the leading cause of cancer death worldwide. Oncogenic Kras mutations are a common feature of LAC, although the identity of signaling networks engaging Kras to promote LAC remains ill-defined. In that regard, we have identified a requirement for interleukin-6 (IL-6) in the pathogenesis of Kras-driven LAC. Specifically, this was dependent on the soluble IL-6 receptor (sIL-6R), which is produced by proteolytic cleavage of the membrane -bound IL-6R by a disintegrin and metalloproteinase-17 (ADAM17). Here, we sought to investigate the role of ADAM17 in the pathogenesis of Kras-induced LAC. We coupled the KrasG12D LAC mouse model with Adam17ex/ex mice, which are homozygous for a hypomorphic Adam17 allele resulting in dramatic reduction in ADAM17 expression. Oncogenic KrasG12D was activated using intranasal inhalation of Adenovirus Cre recombinase. Mice were culled 6 weeks following inhalation and LAC was evaluated using histopathology. Immunohistochemical analyses were performed to assess markers for LAC (TTF-1), proliferation (PCNA) and inflammation (CD45). Serum sIL-6R levels were measured using ELISA. qPCR was performed to assess the expression of IL-6 target genes. Following Kras activation, Adam17ex/ex mice showed significant reduction in the area of parenchyma affected by tumor lesions. This was associated with reduced TTF-1 levels and cellular proliferation. Furthermore, reduced ADAM17 expression mitigates the inflammatory response associated with LAC. Serum levels of sIL-6R were significantly reduced in Adam17ex/ex mice, with down-regulation in IL-6 target genes. In conclusion, our data suggests that blocking of ADAM17 may represent an attractive therapeutic target for tackling LAC.

Young Investigator Award Poster presentations

Ms Maria Selvadurai, ACBD

Targeting the platelet internal membrane reveals a novel approach for improved anti-platelet therapies

Background: The class II PI3K, PI3KC2a, is a broadly expressed lipid kinase with emerging biological roles. We have recently shown that PI3KC2a is important in platelet structure and function in mouse - PI3KC2a-deficient mice have dysregulated internal membrane structure and impaired thrombotic function. This suggests that PI3KC2a may be a viable anti-platelet target, however given the lack of PI3KC2a inhibitors, it is unknown whether a similar function exists in human platelets. Aim: To develop novel pharmacological inhibitors of PI3KC2a in order to determine whether PI3KC2a similarly regulates human platelet structure and function. Methods: A rational drug design approach was used to generate first generation PI3KC2a inhibitors. The effects of these on platelet structure was examined using TEM and FIB-SEM, and on prothrombotic function using aggregation of isolated platelets, ex vivo thrombosis in human whole blood, and in vivo thrombosis in mouse models. Results: The compound X151 is a reversible, competitive, active site inhibitor of PI3KC2a. Inhibition of PI3KC2a with X151 reproduces the structural and functional changes seen in PI3KC2a-deficient mouse platelets. X151 dilated the internal membrane system of both mouse and human platelets to a similar extent to that seen in PI3KC2a-deficient mouse platelets. Furthermore, X151 significantly reduced thrombus formation in an ex vivo human whole blood model and two distinct in vivo mouse models. Conclusion: These findings demonstrate that PI3KC2a is involved in the regulation of platelet structure and function via a unique mechanism, and suggest that PI3KC2a may be a suitable target for novel anti-thrombotic drug therapies.

Miss Peta Lee-Tobin, EHCS

Modern sleep rhetoric as self-help practices: Exploring the evidence-base and average user ratings of Android sleep applications

Study objectives: Sleep applications are becoming a popular self-help tool accessible via smartphones for sleep concerns. This study explored the extent of evidence-based content present in sleep apps, and whether the evidence base impacted on average user rating. Method: Sleep apps available in the Google Play store (n=76) were selected after searching using key terms. Content analysis was used to see if the apps contained reference to: (i) sleep literature, (ii) national guidelines, (iii) expert input from clinicians or researchers in sleep medicine, and (iv) general evidence to support the claims made by the app developers. Results: The amount of sleep apps that contained any kind of evidence was limited (approx. one-fifth of the sample). There was a higher average user rating for apps that contained sleep literature compared to those that did not though a difference in user rating was not associated to a sleep app containing multiple sources of evidence. Conclusions: Sleep app users rated apps that contained sleep literature more highly, suggesting that these apps may provide help for the users' sleep concerns, though most apps were not supported by empirical evidence. With app users investing in apps that are not primarily based in empirical evidence, users may self-diagnose and worry about having a sleep disorder based on questionable data.

Dr Jodie Abramovitch, Department of Immunology and Pathology, CCS

Thermal processing enhances IgE but not T cell reactivity of shellfish allergens

BACKGROUND: Shellfish allergy is a major cause of food-induced anaphylaxis. We showed previously that heating increases IgE reactivity of crustacean allergens. Here we investigate the effects of heating of crustacean extracts on cellular immune reactivity. METHODS: IgE reactivity of raw and cooked black tiger prawn, banana prawn, mud crab and blue swimmer crab extracts was assessed by ELISA. PBMC from shellfish-allergic (n=8) and control, non-atopic (n=4) subjects were cultured with the extracts, proliferation assessed by CFSE labelling and effector responses by intracellular IL-4 and IFN-γ. Regulatory T (CD4+CD25+CD127loFoxp3+) cell proportions in cultures were also compared. RESULTS: For each crustacean species, the cooked extract had greater IgE reactivity than the raw (mud crab $p<0.05$, other species $p<0.01$). In contrast, there was a trend for higher PBMC proliferation to raw extracts. In shellfish-stimulated PBMC cultures, dividing CD4+ and CD56+ lymphocytes showed higher IL-4/IFN-γ ratios for shellfish-allergic subjects than for non-atopics ($p<0.001$), but there was no difference between raw and cooked extracts. The percentage IL-4+ of dividing CD4+ cells correlated with total and allergen-specific IgE levels. There was a trend for higher proportions of regulatory T cells in cultures stimulated with raw compared with cooked extracts (mud crab $p<0.001$, banana prawn $p<0.05$). CONCLUSIONS: Our novel findings confirm that raw and cooked shellfish extracts should be included in reliable specific-IgE diagnostic assays, but suggest that raw extracts are suitable for analysis of cellular responses. This has important implications for development of a safe T cell-targeted allergen-specific treatment for shellfish allergy.

Young Investigator Award Poster presentations

Ms Yan Yee Chan, The Richie Centre, Hudson Institute

Isolating effects of the initiation of ventilation on the preterm lamb brain

Background: Initiation of ventilation in the delivery room causes ventilation-induced brain injury (VIBI) in preterm neonates through two major pathways: cerebral inflammation and haemodynamic instability. However, the relative contribution of each pathway on is not known. Methods: Fetal lambs (0.85 gestation) were exteriorised, ventilated with an injurious strategy for 15min either with placental circulation intact to maintain stable haemodynamics (INJINF; n=5) or umbilical cord occluded (INJINF+HAE; n=7), then returned to the uterus. Sham controls were exteriorised but not ventilated (SHAM; n=5) while unoperated controls (UNOP; n=6) did not undergo fetal surgery. At 24h, lambs were delivered and maintained on non-injurious ventilation for up to 1 h during which lambs underwent magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) using a 3T MRI scanner. After MRI, brains were collected; immunohistochemistry and qRT-PCR were used to assess inflammation, cell death, and vascular leakage. One-way ANOVA was used for statistical analysis significance taken at $p<0.05$. Results: At 24h, mRNA expression levels of pro-inflammatory cytokines, tight junction proteins, and markers of cell death were not different between groups. MRS and DTI analyses have detected significant differences between INJ lambs and controls within the internal capsule and frontal white matter. Histological confirmation of injury is currently being undertaken to confirm the detected injury corresponds to pathological injury. Conclusion: Initial investigations suggest that injurious ventilation, irrespective of strategy, increases brain injury. A thorough understanding of the pathways of VIBI can aid development of targeted treatments to improve neurological outcomes of preterm babies.

Ms Elizabeth Thomas, MAPrc

Schizotypy factors reflect symptoms of schizophrenia

It is believed that the personality characteristics and symptoms observed in schizophrenia lie on a continuum, referred to as schizotypy and observed in the non-clinical population. Schizotypy is considered a suitable model for investigating schizophrenia as it mirrors the symptoms, albeit in a more subtle manner. Schizotypy symptoms fall into three main categories: unusual experiences (UnEx) items relate to hallucinations and magical thinking; introvertive anhedonia (InAn) items relate to lack of enjoyment from sources of pleasure and cognitive disorganisation (CogDis) items relate to social anxiety, poor attention and poor decision making. It is theorised that UnEx, InAn and CogDis reflect the positive, negative and cognitive symptoms of schizophrenia respectively. Very few studies have investigated schizotypy across the schizophrenia continuum. 103 patients with schizophrenia/schizoaffective disorder and 258 healthy controls were assessed for schizotypy using the Oxford-Liverpool Inventory of Feelings and Experiences questionnaire. Patients were assessed for positive and negative symptoms using the Positive and Negative Syndrome Scale (PANSS). The MATRICS Consensus Cognitive battery was administered to objectively assess cognition. Schizotypy was observed to lie along a continuum. Significant correlations were found between UnEx and PANSS overall positive score ($p<0.001$) and between InAn and PANSS overall negative score ($p=0.011$). A significant correlation was found between CogDis and Symbol-coding ($p=0.002$) and non-significant trends were found with memory, working memory and fluency tasks. The schizotypy factors reflect the positive, negative and cognitive symptoms of schizophrenia, providing further support for the continuum theory and the use of schizotypy as a model for investigating schizophrenia.

Ms Ms Lakshanie Wickramasinghe, Department of Immunology and Pathology, CCS

Investigating the link between Bronchopulmonary Dysplasia (BPD) and Retinopathy of Prematurity (ROP) in preterm infants

Bronchopulmonary dysplasia (BPD) and Retinopathy of Prematurity (ROP) are two debilitating disorders afflicting preterm infants. The two disorders arise as a consequence of supplemental oxygen exposure used to treat respiratory distress in premature neonates. BPD and ROP can progress into lifelong disabilities such as advanced lung injury, including chronic obstructive pulmonary disease (COPD) and vision loss. While the two disorders share a common initiating factor, the underlying associations between BPD and ROP are not well characterised primarily due to the lack of a robust concurrent animal model of BPD and ROP. In this study, we developed a mouse model of coincident BPD and ROP to advance investigations into the links underlying these two disorders. The supplemental oxygen model was based on the established mouse model of ROP, known as oxygen-induced retinopathy (OIR), which was developed over 20 years ago. As the retinopathy in the OIR model was established, the study largely focused on the development of lung disease. In the early time-points mild histopathology was evident in the lungs with the expected vascular degeneration in the inner retina. In the late time-points, the lesion progressed to severe airspace enlargement and simplification in the lungs, with concurrent thinning in the outer layer of the retina. Inflammation was observed in the lungs in the early and late-stages of the supplemental oxygen model compared to age-matched room air controls. Collectively, the findings indicate that short-term supplemental oxygen therapy has a severe and long-lasting impact on the lungs and the retina. This new model of coincident BPD and ROP provides an opportunity to evaluate the links between the two disorders which may involve inflammatory pathways for the development of future therapeutics which can target both disorders simultaneously.

Young Investigator Award Poster presentations

Dr Edmond Kwan, SCS

Detection of AR-v7 transcripts in whole blood RNA of patients with metastatic castration-resistant prostate cancer (mCRPC)

Background: The expression of AR-v7 in circulating tumour cells (CTCs) of mCRPC patients potentially confers treatment resistance to AR-axis targeting agents, though recent data from the ARMOR3-SV study were conflicting. Due to the barriers of forming a reliable CTC platform, our aim was to develop a rapid and sensitive assay for AR-v7 detection in patient whole blood samples. Method: We created and optimised a sensitive, whole blood quantitative real-time polymerase chain reaction assay to correlate outcomes of patients on AR-axis targeting agents with expression of AR-v7. The expression of AR-v7 mRNA in whole blood from 32 patients with mCRPC was obtained prior to commencing therapy. Each sample was run in triplicate; positivity was defined as at least two replicates reaching cycle threshold within a standard deviation between cycles of ≤ 0.25. Gene expression was correlated with PSA response rate using chi-square test. Results: In our cohort, 7 of 32 patients (22%) were AR-v7+. Of patients commencing abiraterone or enzalutamide (28/32 patients, 88%), we observed similar response rates in the AR-v7+ (3/6) patients, compared to the AR-v7– (14/22) patients (50% vs 63%, P=0.65). AR-v7 was not detected in any of the 13 normal male controls. Conclusion: We developed a sensitive and specific assay for AR-v7 detection in whole blood from mCRPC patients. Similar PSA response rates were seen in AR-v7+ and AR-v7– patients, further questioning the role of AR-v7 as a predictive biomarker for AR-axis targeting agents. Future directions will include cohort expansion and interrogation of other AR variants.

Miss Michelle Flynn, Baker Institute

Hyperglycaemic spikes promote monocytosis and atherosclerosis in an S100A8/A9-RAGE dependent manner

Background: Postprandial hyperglycemic spikes are a major cardiovascular risk factor in diabetes. We have previously shown that hyperglycemia in diabetic mice increases monocytosis and atherosclerosis through S100A8/A9 signalling via the receptor for advanced glycation end-products (RAGE). We aimed to determine whether hyperglycemic spikes alone promote S100A8/A9-RAGE signalling to increase monocytosis and thus atherosclerosis, and if blocking this pathway could reduce this effect. Wildtype C57Bl/6 (WT) and WT mice transplanted with Rage-/- bone marrow (BM) were given 4 intraperitoneal glucose injections (2mg/kg, every 2hrs) to induce hyperglycemic spikes (>15mM) and culled after 1 and 7 days of normoglycemia. To determine if this accelerates atherosclerosis, we induced weekly hyperglycemic spikes for 10 weeks in Apoe-/- mice or Rage-/-Apoe-/- mice, as well as Apoe-/- mice treated with an S100A8/A9 inhibitor, ABR-215757. We found that BM CMPs and GMPs were increased 1 day after glucose spiking and had normalized by 7 days. This translated into increased blood monocyte levels at 7 days. Correspondingly, expression of S100A8/A9 was increased in white blood cells 1 day after glucose spiking. Mice transplanted with Rage-/- BM were protected against monocytosis induced by hyperglycemic spikes. In Apoe-/- mice, hyperglycemic spikes increased atherosclerotic burden 2-fold, which was abolished by RAGE deletion. ABR-215757 intervention inhibited hyperglycemic spike-induced monocytosis, and atherosclerosis, characterized by smaller plaque size, with lower lipid/ macrophage content. These results highlight the potential harm of poor glycemic control by stimulating myelopoiesis and enhancing atherogenesis, dependent on S100A8/A9-RAGE signaling. ABR-215757 treatment inhibiting S100A8/A9-RAGE

Key:

- ACBD : Australian Centre for Blood Diseases
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