TRANSLATIONAL RESEARCH
POSTER COMPETITION

Young Investigator Award Sponsored by:

SANOFI

Judges :

• Professor Jennifer Wilkinson-Berka
• Associate Professor David Curtis
• Dr Sara Prickett

30 Sep 4:30-7:00pm
AMREP Seminar Room, Ground Floor, AMREP Building
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**Abstract**

Traumatic brain injury (TBI) is the leading cause of death and disability in young adults. TBI causes breakdown of the blood brain barrier (BBB) leading to cerebral oedema, elevated intracranial pressure and acute traumatic coagulopathy (ATC). ATC occurs in ~ 30% of severe TBI patients and is a powerful predictor of mortality. Haemostatic changes caused by coagulation dysfunction and excessive fibrinolysis cause ATC. During fibrinolysis, tissue plasminogen activator (tPA) converts plasminogen to plasmin, which degrades fibrin clots. While activation of the fibrinolytic system promotes bleeding, we have shown that tPA and plasmin also promotes BBB disruption following TBI. Paradoxically, we demonstrated that tPA can also worsen BBB damage via formation of complexes with its natural inhibitor, plasminogen activator inhibitor-1 (PAI-1). tPA:PAI-1 complex levels are significantly elevated in cerebrospinal fluid of patients with severe TBI. We have now confirmed this in a separate study where plasma levels of tPA:PAI-1 complex were increased in severe TBI patients. Activation of the fibrinolytic system following TBI therefore promotes both ATC due to plasmin-driven hyperfibrinolysis, and also BBB disruption via active tPA/plasmin and tPA:PAI-1 complex formation. Tranexamic acid (TXA) is a widely used drug that blocks the activation of plasminogen to plasmin and is associated with reduced mortality in TBI patients. Our experimental data showed that TXA administration caused significant reduction in BBB permeability after TBI. Therefore TXA could have added clinical benefit via inhibition of tPA/plasmin-mediated BBB permeability. Agents that block the downstream actions of t-PA:PAI-1 complexes in combination with TXA are likely to improve outcome following TBI.

**Abstract**

TPI deficiency is a rare metabolic disease resulting in severe haemolytic anaemia, neuronal dysfunction, cardiomyopathy, and often results in death in early adolescence. A novel mouse model generated by ENU mutagenesis, labelled RBC19, harbours a homozygous mutation in the glycolytic enzyme triose-phosphate isomerase (TPI) and displays red cell and enzyme abnormalities parallel to that of the human disease. RBC19 homozygotes present with macrocytosis and splenomegaly, with evidence of extramedullary erythropoiesis, and a severely reduced red cell half-life in vivo. Functional assays show the TPI enzyme retains only 28% function of the wildtype enzyme. This ENU mutant provides an ideal model to test the efficacy of a bone marrow transplant to correct the red cell defect and restore enzyme function in the affected animal. Transplantation studies using the RBC19 mouse model would provide fundamental evidence for similar practises to be applied clinically in the treatment of congenital haemolytic anaemias.
Abstract
The immune response following traumatic brain injury (TBI) has been described as a ‘double-edged sword’ as it is important for tissue repair and prevention of invading pathogens however it can be harmful when prolonged or intensified. It is not known why an estimated 60% of people with a sustained TBI experience moderate to severe long-term disability a year later.

Although activated/effectector cytotoxic CD8 T-cells and activated B-cells were increased in the injured brain at this period. Surprisingly, a concomitant elevation of circulating antibodies specific to myelin was observed in TBI mice, a typical feature of demyelinating diseases. These results indicate that there is a significant change in immune cell infiltration up to 32 weeks post-TBI coinciding with neurological deterioration. This is consistent with the hypothesis that there is a causal relationship between the cellular immune response and late-onset neurodegeneration following TBI.

Speaker: Ms Maria Daglas
Thesis title: Is the adaptive immune response detrimental in TBI?
Supervisor(s): Professor Robert Medcalf
Department: Australian Centre for Blood Diseases, Central Clinical School

Abstract
Background and Aim: Reducing the burden of hepatitis C virus (HCV) related liver disease will require treating people who inject drugs (PWID), the group at most risk of infection and transmission. We determine the cost-effectiveness of treating PWID with interferon-free direct-acting antiviral therapy in Australia.

Methods: Using a deterministic model of HCV transmission, treatment and liver disease progression, the expected healthcare costs and quality-adjusted life years (QALYs) of newly HCV-infected PWID were calculated for: no treatment; treatment after initial infection (‘early-treatment’); and treatment prior to developing compensated cirrhosis (‘late-treatment’). Incremental cost-effectiveness ratios (ICERs) were used to compare scenarios.

Results: Compared to no treatment, late-treatment was the most cost-effective option, with a discounted average gain of 2.98 (95%CI 2.68–5.42) QALYs for an additional cost of $15,132 (95%CI $11,372–19,465), giving an ICER of $5,078 (95%CI $2,451–5,349) per QALY gained. Early-treatment gained a discounted average of 5.25 (95%CI 3.28–9.75) QALYs for an additional $53,926 (95%CI $50,853–56,512), giving an ICER of $10,272 (95%CI $3,918–13,750) per QALY gained compared to no treatment. For every 100 newly HCV-infected PWID, there were an estimated 40 (95%CI 38–58) eventual liver related deaths, compared to 7 (95%CI 6–11) and 8 (95%CI 6–13) with early-treatment and late-treatment available respectively.

Conclusions: Treating HCV-infected PWID with new therapies is cost-effective, and could prevent a significant number of liver related deaths. Although late-treatment was more cost-effective than early-treatment, the cost per QALY gained for early-treatment was well below unofficial Australian willingness to pay thresholds.
**Abstract**

**Background & Aims:** Diabetic nephropathy (DN) is a major complication of diabetes leading to end stage renal disease often requiring dialysis and/or transplantation. However, the underlying causes remain unclear. NADPH oxidase (Nox) is a major source of reactive oxygen species (ROS) production in the kidney which contributes to enhanced oxidative stress causing renal damage in diabetes. Among different isoforms of NADPH oxidase, Nox4 appears to be constitutively active in the kidney. The aims of current study were to examine the role of the Nox1 and Nox4 in DN using genetic deletion and pharmacological inhibition approaches in streptozotocin (STZ) induced diabetic mice.

**Methods:** Nox1-/yApoE-/ or Nox4-/yApoE-/ mice and their respective wild type or ApoE-/ mice were rendered diabetic via streptozotocin injection. ApoE-/ non-diabetic and diabetic mice were treated with the specific Nox1/4 inhibitor (GKT137831). Animals were culled after 20 weeks and kidneys were removed for assessment of structural damage, oxidative stress markers, as well as protein expressions extracellular matrix (ECM), pro-fibrotic and pro-inflammatory markers.

**Results:** Deletion of Nox4, but not of Nox1 resulted in renal protection from glomerular injury as evidenced by attenuated albuminuria, preserved renal structure, reduced glomerular accumulation of ECM proteins as well as attenuated glomerular macrophage infiltration. Administration of GKT137831 to diabetic ApoE-/ mice conferred a similar degree of renoprotection as did deletion of Nox4.

**Conclusions:** Collectively, these results identify Nox4 is a key source of ROS responsible for kidney injury in diabetes and provide proof of principle for an innovative small molecule approach to treat and/or prevent DN.

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**Speaker** Mr Christopher Molloy  
**Thesis title** Shear sensitive nano capsules for the specific drug release: Effective anti-thrombotic therapy without bleeding risk  
**Supervisor(s)** Dr Erik Westein  
**Department** BakerDI, Central Clinical School  

**Abstract**

**Aim:** To exploit this feature of thrombosis and achieve site directed therapy using phosphatidyl choline based nano capsules that are prone to release anti-platelet drugs specifically under high shear stress conditions.

**Methods:** We have loaded nano capsules with Cangrelor or Eptifibatide and characterized them in vitro using microfluidic flow channels and in vivo in a range of mouse thrombosis models.

**Results:** Nano capsule delivery of Cangrelor or Eptifibatide inhibited in vitro thrombus formation exclusively under high shear flow conditions. Shear sensitivity of the nano capsules could be accurately tuned by altering the lipid composition allowing controlled release of Cangrelor or Eptifibatide at desired shear stress magnitudes. Occlusive thrombus formation could be prevented in vivo in the carotid artery and mesenteric microcirculation of mice following vessel wall damage. Microscopic analysis revealed normal initial thrombus build-up but an inhibition of platelet aggregation upon reaching full vessel occlusion. Eptifibatide nano capsules reduced fibrin clots 5-fold in a pulmonary embolism model of thrombosis. Importantly, mice infused with shear sensitive anti-platelet nano capsules did not display prolonged bleeding times.

**Conclusion:** Targeted delivery of anti-platelet agents by flow sensitive nano capsules offers a potent, site-specific therapy to prevent atherothrombotic events. The drug is selectively released in areas of pathologic shear stress caused by the formation of near occlusive thrombi without systemically inhibiting platelets or increasing bleeding time. This study is a step towards safer and more potent inhibition of thrombosis with existing anti-platelet drugs while minimising systemic bleeding complications.
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**Abstract**

**Background:** In Australia, ~8% of babies are born preterm. The initiation of ventilation in the delivery room can be inadvertently injurious and cause cerebral inflammation and injury. We aimed to determine whether recombinant human erythropoietin (rhEPO) could mitigate ventilation-induced brain injury.

**Methods:** Preterm lambs (0.85 gestation) were ventilated using an injurious ventilation strategy for 15 minutes (tidal volume targeting 15 mL/kg) and then conventionally ventilated for a subsequent 105 min. At 5 min, lambs were randomly assigned to receive rhEPO (i.v. 5000 IU/kg; Vent+EPO; n=6) or PBS (Vent; n=8). At post mortem, the brains and CSF were collected. Inflammation and vascular leakage were assessed within the periventricular and subcortical white matter (WM) from the frontal and parietal lobes using qPCR and immunohistochemistry.

**Results:** Neuroprotective levels of rhEPO were achieved in the CSF in EPO lambs (292.5±52.2mU/mL). Interleukin (IL)-1β, IL-6 and IL-8 mRNA levels were elevated (p<0.05) in the periventricular WM in ventilated lambs treated with Vent+EPO compared to Vent, while IL-8 was elevated in the subcortical WM (p<0.05). There was a reduction in the areal density of microglia in the subcortical WM within the frontal (p=0.039) and parietal (p=0.002) lobes in Vent+EPO lambs; no difference was observed in the periventricular WM. Vascular leakage was reduced after EPO treatment in the frontal (p=0.108) and parietal lobes (p=0.014), and occludin mRNA levels were increased 6-fold in the periventricular WM after EPO compared to Vent.

**Conclusion:** Prophylactic high-dose rhEPO administration may protect against some aspects of ventilation-induced brain injury in preterm neonates.
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**Abstract**

**Background:** Cerebral Palsy (CP) is the most prevalent cause of chronic disability in children. With limited treatments available, many seek overseas stem cell treatment. However, it remains unknown if such treatments are safe, effective, or the likely mechanism of action. In this study we examined whether adherent umbilical cord blood mononuclear cells (UCB-MNCs), including endothelial progenitor cells (EPCs) and mesenchymal stromal cells (MSCs), could reduce neuronal injury following birth asphyxia; a major risk factor of CP.

**Methods:** UCB-MNCs were isolated from term lamb umbilical cord blood, expanded in culture and characterised. 10x10^6 UCB-MNCs were administered to term lambs 12 or 24 hours following birth asphyxia. MRS was undertaken at 72 hours, lambs were then euthanised, CSF and brains collected.

**Results:** MSCs and EPCs were identified in UCB-MNC cultures. Animals that received UCB-MNC treatment showed reduced inflammatory cell activation in the brain and increased CSF IL-10. MRS analysis in lambs administered cells 12 and 24 hours following asphyxia revealed a trend towards an increase in N-acetyl aspartate in the brain (NAA); a marker of neuronal integrity compared to birth asphyxia alone. The 24 hour cohort also showed a reduction in lactate:NAA ratio (a marker of aerobic metabolism) compared to birth asphyxia alone.

**Conclusion:** Administration of adherent UCB-MNCs, containing EPCs and MSCs, to lambs following birth asphyxia results in improved neuronal integrity and decreased inflammation in the brain. Whilst more research is required, culture expanded UCB-MNCs may represent a useful treatment to prevent the progression of CP following birth asphyxia.
**Speaker**  Ms Caroline Tuck  
**Thesis title**  Adding glucose to fructose reduces breath hydrogen but not symptoms in fructose malabsorbers with a functional bowel disorder  
**Supervisor(s)**  Dr Jane Muir  
**Department**  Department of Gastroenterology, Central Clinical School  

**Abstract**  
**Background/Aims:** Fructose absorption is enhanced by the addition of equal amounts of glucose in healthy volunteers. The success of this strategy in reducing abdominal symptoms when consuming free fructose or fructans in functional bowel disorders (FGID) is unknown. This randomised, double-blind, cross-over trial aimed to address these issues.  
**Methods:** Breath hydrogen and symptom response to sugar solutions- glucose; sucrose; fructose; fructose+glucose; fructo-oligosaccharide (FOS); FOS+glucose – were assessed in patients with fructose malabsorption and a FGID. Following a 24h run-in period where participants consumed a diet low in fermentable carbohydrates (fibre and FODMAPs), participants collected breath samples at baseline and every 20min for 4h after consuming the sugar solution. Breath hydrogen was calculated as area-under-the-curve. Symptom scores were recorded at the end of each day, using a 100mm visual analogue scale.  
**Results:** In 26 participants (3 male, aged 22-65y), breath hydrogen response to 25g fructose (775±904ppm.4h (mean±SD)) reduced following the addition of 25g glucose (84±99;p=0.012, t-test), which was similar to that after glucose alone (133±175). Breath hydrogen response to 10g FOS (3089±1668) was not changed with glucose addition (2166±1320;p=0.559). Overall abdominal symptoms after fructose (median 15mm, IQR 2-46) or FOS (19,2-32) were not changed with glucose addition (5,1-35;p=0.236; 17,2-46,p=0.926, respectively). Glucose addition to fructose worsened nausea (1,0-2vs2,1-10; p=0.018).  
**Conclusions:** These results do not support the addition of glucose to free fructose or fructans as it does not reduce, and potentially worsens symptoms associated with consumption of these sugars in patients with FGID.  
Funding source: None.

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**Speaker**  Ms Marina Iacovou  
**Thesis title**  Dietary modifications of the maternal diet among breastfeeding mothers  
**Supervisor(s)**  Dr Jane Muir, Professor Peter Gibson  
**Department**  Department of Gastroenterology, Central Clinical School  

**Abstract**  
**Background/Aims:** Breastfeeding mothers tend to modify their habitual diet for various reasons. The evidence to support how common this practice is and why, is not clear. This survey aimed to explore common dietary modifications among breastfeeding mothers, the reasons, and if nutritional intake is compromised.  
**Methods:** An on-line survey, using Qualtrics software application, invited anyone who had breastfed to participate.  
**Results:** Of the 1,293 respondents, 98% completed the survey and 77% mothers modified their usual diet. The most common reasons were ‘baby was unsettled’ (31%), ‘baby had lots of wind/gas’ (24%), ‘baby had reflux’ (17%) and ‘baby had colic’ (11%). The most common modifications were avoidance of alcohol (79%), coffee (44%), cow’s milk (24%), milk chocolate (22%), chilli (22%) and cabbage and onion (each 20%). Information was sourced from the internet (44%), maternal and child health nurses (40%), and the Australian Breastfeeding Association (34%). Sourcing information from paediatricians was less common (10%) and 89% of respondents had never seen a dietitian. 33% removed dairy, but did not replace it with other calcium-rich foods nor did they take a calcium supplement. 32% that modified their diet did not take a suggested breastfeeding multi-vitamin for when the nutrition guidelines are difficult to meet.  
**Conclusions:** Three out of four breastfeeding mothers modify their diet, most commonly because of an unsettled baby. Since the majority of information is sourced from the internet and not from experts in nutrition, this group may be at risk of nutritional inadequacies.
Abstract

**Background/Aims:** In patients with irritable bowel syndrome, gas production rate is likely to be an important indicator of tolerance to dietary fibre. However, knowledge of their rates of fermentability by colonic microbiota is crude. Therefore, we aimed to develop and assess a method for evaluating individual fibre supplements in vitro.

**Methods:** Fibre supplements with known fermentability, fructo-oligosaccharides/FOS (Orafti-P95®) and methylcellulose (Citrucel®), were compared against resistant starch (RS) type 4 (Fibresym®) and Sterculia (Normafibe®) in triplicate in a modified ANKOM in vitro gas-measurement system. Pooled faecal inocula from healthy controls (n=3) were incubated with one g fibre substrate, depleted of free sugars, for four hours. Cumulative gas production and hourly pH were measured.

**Results:** Gas production ability was ranked the greatest for FOS followed by RS, Sterculia and least of all, methylcellulose. After adjusting for gas originating from unspiked faecal inocula, mean ± SE gas production was low for Sterculia (1029 ± 665 ml/g) and methylcellulose (-51 ± 85) and moderate for RS (2251±803) compared to FOS (8362 ± 3258). Similarly, pH changes were greater after bacterial fermentation of FOS (mean change -1.6 ± 0.01) compared with methylcellulose (0.01 ± 0.02), Sterculia (-0.13 ± 0.03) and RS (-0.27 ± 0.12).

**Conclusions:** Faecal gas production and pH changes were entirely consistent with known fermentability. Sterculia has a low level and RS, moderate level of fermentation. This system is a simple and rapid way of ranking fibre supplements for fermentability, which may then guide gastrointestinal tolerance of commercially-prescribed fibre supplements.

Funding source(s): N/A

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Speaker  Mrs Judy Moore
Thesis title Women with endometriosis experiencing bowel symptoms benefit from a low FODMAP diet
Supervisor(s) Professor Peter Gibson
Department Department of Gastroenterology , Central Clinical School

Abstract

**Background/Aims:** Endometriosis, a chronic organic condition associated with pelvic pain and bowel symptoms, is frequently misdiagnosed as irritable bowel syndrome (IBS) for some time. While management is often pharmacological or surgical, we hypothesised bowel symptoms might respond to dietary intervention. Aim: to compare the responses to a low FODMAP diet (LFD) of women with both endometriosis and IBS with those with IBS alone.

**Methods:** A consecutive cohort attending a private IBS clinic in Christchurch NZ between 2009 and 2013 prospectively completed a questionnaire on demographics and symptoms. The cohort was grouped into those meeting Rome III criteria for IBS with and without endometriosis. A LFD was taught to all women by a trained Nurse consultant. A positive response to the LFD was determined by the patient reporting a more than 50% improvement in symptoms after 4 weeks of diet.

**Results:** Of 160 women with IBS, 59 (35%) had a concurrent diagnosis of endometriosis. Mean age of those with endometriosis was 28(16-65) where those without was 38(13-84) (P=0.006). A number of demographics and symptoms were more frequently reported in the group with endometriosis. A positive response to the LFD was reported in 75% of those with endometriosis compared with 51% without (P=0.003).

**Conclusions:** The positive response to the LFD suggests this should be an additional management strategy for endometriosis. It is not clear why the response was less in those without endometriosis. Physicians should be alerted to investigate for endometriosis when specific symptoms are reported.
**Speaker**: Dr Rebecca Segrave  
**Thesis title**: Retraining the brain to beat depression: tDCS and cognitive control training  
**Supervisor(s)**: Prof Paul Fitzgerald  
**Department**: Monash Alfred Psychiatry Research Centre, Central Clinical School

### Abstract

**Background**: Major depression is frequency resistant to standard therapeutic approaches. Among the many new treatment avenues being investigated two that have been developed separately, transcranial Direct Current Stimulation (tDCS) and Cognitive Control Training (CCT), may be more efficacious if delivered together. tDCS is a mild non-invasive brain stimulation technique that can modulate excitability within localized regions of the cortex. CCT is a neurobehavioural therapy comprising cognitive tasks specifically developed to also modulate localized cortical excitability. Both techniques aim to enhance activity within the dorsolateral prefrontal cortex (DLPFC) as depression is frequency associated with underactivity in this region, and this is thought to contribute to many of the cognitive and emotional symptoms of the illness. As concurrent cognitive activity can enhance the impact of tDCS, we tested the hypothesis that co-administration of tDCS and CCT would result in greater reduction in depressive severity than administration of either tDCS or CCT alone.

**Methods**: 27 adult participants in the midst of a major depressive episode were randomised into a three-arm sham-controlled between-groups pilot study comparing the efficacy of tDCS + CCT, sham tDCS + CCT and sham CCT + tDCS (5 sessions administered on consecutive working days). Blinded assessments of depression severity and cognitive control were conducted at baseline, end of treatment and three week follow up.

**Results**: All three treatment conditions were associated with an initial reduction in depression severity. However, only administration of tDCS + CCT resulted in sustained antidepressant response at follow up, the magnitude of which was greater than that observed immediately following conclusion of the treatment course. Greater antidepressant response was associated with improved accuracy on a task of DLPFC mediated cognitive control following the first treatment session.

**Conclusions**: The clinical superiority of concurrent tDCS and CCT was apparent even in a small sample and following a relatively short treatment course. This provides encouraging initial evidence for a potential new approach to treating depression.

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**Speaker**: Dr Michelle Yong  
**Thesis title**: Frequency of cytomegalovirus (CMV)-specific CD8+ T Cells distinguishes cmv clinical outcomes following allogeneic allogeneic cell transplant  
**Supervisor(s)**: Professor Sharon Lewin  
**Department**: Department of Infectious Diseases, Central Clinical School

### Abstract

**Introduction**: A simple test to identify recovery of CMV-specific T cell immunity in the post haematopoietic stem cell transplant (HSCT) period could help manage CMV related complications. We assessed CMV-specific CD8+ T cell immunity using a rapid high throughput Quantiferon-CMV assay.

**Methods**: An observational multi-centre prospective study of HSCT recipients was conducted with pre-transplant, 3, 6, 9 and 12 month bloods. CMV-specific immunity was assessed using the Quantiferon-CMV assay and CMV ELISPOT. CMV clinical outcomes were classified as (1) CMV disease (2) treated CMV reactivation (CMV DNA ≥600cp/ml plus antivirals) and (3) spontaneous viral control defined as the resolution of any level of CMV DNA without antivirals.

**Results**: Ninety-four study participants were enrolled. CMV clinical outcomes included CMV disease (n=8), treated CMV reactivation (n=26), spontaneous viral control (n=25) and no detectable CMV DNA (n=31). At 3 months post HSCT, patients with CMV disease had significantly lower CMV IFN-γ responses compared to those with CMV reactivation or spontaneous viral control (median IFN-γ 0.04 vs 0.23 vs 1.86 IU/ml respectively, p=0.001). An indeterminate Quantiferon-CMV result at 3 months was associated with CMV disease (p=0.001) whereas a reactive test was associated with spontaneous viral control (p=0.002).

Twelve month survival was strongly associated with the Quantiferon-CMV result measured 3 months post HSCT being non-reactive, reactive or indeterminate (100% vs 90% vs 61.9% respectively Mantel-Cox Logrank test p=0.002).

**Conclusion**: At 3 months post HSCT, the Quantiferon-CMV assay which measures CMV-specific CD8+ T cell immunity can identify clinically relevant CMV related outcomes including 12 month survival.
**Speaker** Dr Marina Carpinelli  
**Thesis title** Grainyhead-like 2 in craniofacial development  
**Supervisor(s)** Professor Stephen Jane  
**Department** Department of Medicine, Central Clinical School

**Abstract**  
The Grainyhead-like (Grhl) transcription factors control epidermal development. Grhl2 mediates the formation of dorsolateral hinge points during neural tube closure and Grhl2/-/- mice die at embryonic day 11.5 (e11.5) with split face and exencephaly. We are investigating whether Grhl2 is required for later craniofacial development. Primary palate formation occurs between e10.5 and e11.5 and involves fusion of the maxillary prominence of the 1st pharyngeal arch (PA1) with the medial and lateral nasal prominence (MNP, LNP). The Grhl2 null allele contains a lacZ cassette and we have stained Grhl2+/- and Grhl2/-/- mouse embryos for beta-galactosidase. At e9.5 and e10.5, Grhl2 is expressed in the surface ectoderm of PA1 and PA2. By e11.5, expression is confined to the pharyngeal pouches and the nasal pits. In order to identify Grhl2 target genes mediating craniofacial development we performed RNAseq on Grhl2/-/- PA1 at e10.5. Gene ontology analysis of differentially expressed genes revealed a shift from an epithelial gene expression signature towards a mesenchymal signature in Grhl2/-/- mice. QPCR of frontonasal prominence (FNP), MNP and LNP confirmed downregulation of Arhgef19, Cldn4 and Cdhl1 in Grhl2/-/- craniofacial primordia. Arhgef19 encodes an activator of the RhoA GTPase that mediates cell migration and polarisation. In order to identify pathways upstream of Grhl2 we tested a 1.9 kb element 5’ of Grhl2 that is bound by p300 in craniofacial primordia. This sequence drives expression in the pharyngeal pouches at e11.5 and contains a homeobox site that is conserved in mammals, birds, reptiles and frogs.

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**Speaker** Mr Jae Young Lee  
**Thesis title** Overcoming genetic blockade of monocarboxylate transporter 8 (MCT8)-dependent T3 transport to potentiate human oligodendrocyte differentiation and myelination  
**Supervisor(s)** Dr Steven Petratos  
**Department** Department of Medicine, Central Clinical School

**Abstract**  
**Background:** Thyroid hormone (TH) plays a significant role in brain development, regulating oligodendrogenesis and myelination. Transport of TH into neural cells is now identified as an active process involving specific TH transporters, primarily through MCT8. Human slc16a2 gene (encoding for MCT8) mutation results in the X-linked-inherited psychomotor retardation disorder, Allan-Herndon-Dudley syndrome (AHDS), which exhibits a hypomyelinating phenotype.  

**Methods:** A novel method was established deriving pre-myelinating oligodendrocytes from hESC by utilising the Nkx2.1-GFP as reporter. Flow cytometry, immunocytochemistry, qRT-PCR and western blot were used to identify the expression of MCT8 in hESC-derived oligodendrocytes. We downregulated slc16a2 by lentivirus carrying slc16a2-shRNA in pre-oligodendrocytes. We performed a microarray analysis to identify candidate genes governing oligodendrocyte development, along with qRT-PCR and flow cytometry on OPCs treated with and without DITPA. We have treated DITPA in co-cultures of retinal ganglion neurons with hESC-derived oligodendrocytes and compared this with T3 treatment alone. We also administered DITPA in the abovementioned co-cultures following a stable downregulation of slc16a2 in oligodendrocyte.  

**Results:** We demonstrated the MCT8 protein on subsets of precursors to pre-myelinating oligodendrocytes. Knock-down of MCT8 induced significant apoptosis of oligodendrocytes and DITPA administration reversed this apoptosis. Administration of DITPA upregulated oligodendrocyte-specific genes and induced cell-cycle exit. Moreover, DITPA promoted in vitro myelination by hESC-derived oligodendrocytes.  

**Conclusion:** Our results highlight the potential role of MCT8 in TH transport for human oligodendrocyte development and may implicate this TH-transporter as a central co-determinant in the promotion of myelinating oligodendrocytes. In addition, we propose DITPA as a potential therapy to promote myelination in AHDS.
**Abstract**

**Background/Aims:** Malnutrition in healthcare facilities remains an ongoing challenge. Opportunities exist to develop the foodservice system and engage this workforce to improve patient outcomes. The aim was to determine the effect of changing the foodservice system on dietary intake, anthropometry and patients’ satisfaction.

**Methods:** The intervention consisted of a high-energy hospital menu and greater foodservice staff-patient interaction. Sub-acute care patients were allocated to the intervention or usual foodservice system for their length of stay (LOS) in a parallel controlled pilot study. Change in Body Mass Index (BMI) and hand grip strength (HGS) (admission to day 14 or prior if discharge was earlier); dietary intake and; satisfaction with the foodservice were compared between groups.

**Results:** Data were available for 117 participants (n=59 intervention, n=58 control) with a median LOS of 20 days, age 83 years and malnutrition prevalence of 38%. The mean change in BMI (-0.1±0.8 v 0.1±0.7 kg/m2, p=0.343), HGS (2.4±5.4 v 1.4±5.7 kg, p=0.383) and median satisfaction scores (food quality 1.9 v 1.9, p=0.486; meal service 1.7 v 1.7, p=0.805; staff 1.0 v 1.0, p=0.877; environment 1.0 v 1.0, p=0.137) were not different between intervention and control groups, respectively. The intervention group had significantly higher intake of energy (128±50 v 107±37 kJ/kg/day, p=0.018) and protein (1.3±0.6 v 1.1±0.4 g protein/kg/day, p=0.039).

**Conclusions:** There was an improvement in dietary intake (adjusted for weight) and no reduction in patients’ satisfaction with the foodservice. This intervention may be a useful strategy to address malnutrition, through further consideration of clinical outcomes is required.

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**Abstract**

**Objective:** Despite advances in the treatment of people with severe mental illness (SMI), access to work for this community still remains a challenge. Cognitive Remediation (CR) is an intervention that can improve employment outcomes, especially when offered alongside employment support. This pilot study aimed to determine whether CR enhances vocational outcomes for job seekers participating in an innovative vocationally-oriented psycho-educational program implemented in Australia.

**Method:** Fourteen participants with SMI were enrolled in HOPE and attended 20 sessions of CR. Assessments were performed at baseline, post-CR and 6 months follow up. Individuals were assessed on a number of occupational and psychosocial variables (e.g. hours of paid and unpaid work, self-esteem, quality of life, social relationships), in addition to undertaking the MATRICS Consensus Cognitive Battery.

**Results:** There was no increase in hours of paid work for those in employment, but 46% of the group initiated tertiary studies between baseline and 6 month follow up. There was a trend towards a significant increase in number of volunteer hours, with 31% of individuals having initiated a non-paid activity at the end of the CR. As predicted, cognition improved over time as did psychosocial outcomes in the areas of self-esteem, quality of life and social relationships.

**Conclusions:** Consistent with previous studies, CR improved psychosocial and cognitive functioning. While employment benefits were not found, promising outcomes were reported on volunteering and educational participation. This pilot is highly relevant as it suggests there may be potential for combining CR with HOPE to enhance vocation-related participation and potential employability of jobseekers with SMI in Australia. Thus, a randomised controlled trial is required to validate the effectiveness of HOPE+CR within a larger sample.
**RESULTS:**

**Methods:**
349 adults (144 patients with schizophrenia, 40 first-degree relatives and 165 healthy controls) were assessed for schizotypy factors using the Oxford-Liverpool Inventory of Feelings and Experience. Of those, 191 adults were genotyped for NRG1 SNPs rs35753505 and rs6994992. MANOVAs exploring the effects of the NRG1 SNPs on schizotypy factor scores were conducted in the non-clinical group only (n=101). Age, ethnicity and gender were controlled for as covariates.

**Results:** Confirming previous findings, schizotypy scores for all factors were significantly higher in the patient group as compared to controls (p<0.001). A significant interaction was observed between rs35753505 and rs6994992 in the non-clinical population for the cognitive disorganisation factor of schizotypy (p=0.004).

**Conclusion:** This is the first study to demonstrate an association between NRG1 and the cognitive disorganisation factor of schizotypy in a non-clinical population. From this, it can be inferred that NRG1 may contribute to cognitive deficits in the clinical population, which is consistent with previous findings. This finding also supports the use of schizotypy as a model for schizophrenia.

**Speaker** Dr Chris Karayiannis  
**Thesis title** MRI markers of Intracerebral haemorrhage in stroke patients with atrial fibrillation  
**Supervisor(s)** Associate Professor Velandai Srikanth  
**Department** Department of Medicine, School of Clinical Sciences

**Abstract**

**Background and Aims:** Atrial fibrillation (AF) is a risk factor for stroke requiring anticoagulation. Cerebral microbleeds (CMBs), cortical siderosis (SS), white matter lesions (WML) and cerebral atrophy are common MRI abnormalities in older people, and may signify greater bleeding risk. We investigated their prevalence and associations with stroke type in patients with AF.

**Methods:** Cross-sectional study of patients with AF admitted to a stroke ward between 2010-2013, who underwent brain MRI. MRI markers were rated using standardized methods. Logistic regression was used to study their associations with stroke type adjusting for age and sex.

**Results:** 170 patients, mean age 78 years (SD 9.8), 155 (91.2%) ischaemic stroke, 15 (8.8%) ICH. Prevalence of markers were: any CMB 50%, multiple (≥2) CMBs 30%, severe atrophy 37.7%, confluent WML 18.8%, SS 8.9%, ≥1 coexistent severe abnormalities 1.8% to 12.4%. SS was strongly associated with multiple CMBs (mCMBs) (Odds Ratio, OR 8.14, p<0.001). Compared with ischaemic stroke patients, those with ICH were significantly more likely to have SS (OR 4.69, p=0.02), but not WML (OR 1.12, p=0.86) or severe atrophy (OR 0.51, p=0.83). There was an association of ICH with CMBs that strengthened as the burden of CMBs increased. OR for ICH was 1.90 (95% CI 0.62-5.87, p=0.26) in those with ≥2 CMBs, OR 3.16 (0.90-11.09, p=0.073) in those with ≥5 CMBs, and OR 5.94 (CI 1.57-22.55 p=0.009) in those with ≥10 CMBs.

**Conclusions:** SS and multiple CMBs may be markers of bleeding risk while considering anticoagulation for AF. Large prospective studies are required.
Abstract: Abdominal aortic calcification (AAC) has prognostic value for adverse cardiovascular outcomes. Altered bone and mineral metabolism during ageing is well understood to contribute to increased AAC. Loss of skeletal muscle mass also occurs with age and may precipitate bone demineralisation. We aimed to determine the association between low relative muscle mass and AAC in community-dwelling older Australians.

Methods: Cross-sectional study of 327 participants. Appendicular lean mass (ALM) was determined by dual energy x-ray absorptiometry. AAC was determined by thoraco-lumbar radiography. Aortic calcification score (ACS; range 0-24) was calculated visually as the extent of calcification on the aortic walls between the L1-L4 vertebrae, and compared across sex specific tertiles of ALM normalised to body mass index (ALM/BMI).

Results: Mean age=70.6±5.5years; mean BMI=28.2±5.2kg/m2; females n=199 (61.9%). Prevalence of any AAC was highest in patients in the bottom tertile of ALM/BMI [n=77(74.8%)] compared to middle [60(65.2%)] and upper [72(54.5%)] tertiles; (p=0.006). Median ACS was highest in the bottom tertile of ALM/BMI [4(0-12.5)] [median and (IQR)] compared to middle [2(0-5) and upper [1(0-4)] tertiles; (p=0.005). In multivariable logistic regression, the upper tertile for ALM/BMI had decreased odds (B=-0.734; Odds=0.480; 95% confidence interval: 0.250-0.920; p=0.027) of having any AAC compared to the lowest tertile independent of traditional risk factors of age, sex, body fat, smoking, hypertension and elevated total cholesterol.

Conclusion: AAC is more prevalent and severe in community-dwelling older adults with low relative ALM. Prospective studies are required to determine whether low muscle mass predicts development and progression of aortic calcification.

Abstract: Turner Syndrome (TS), the most common female chromosomal abnormality, is characterised by short stature and gonadal failure. TS is associated with osteoporosis and increased fracture rates. Diagnosing low bone mass is challenging in TS as short stature underestimates bone mineral density (BMD).

Aim: To investigate risk factors for low BMD in an Australian TS cohort. Method: Retrospective cross-sectional audit of 79 TS patients who underwent Dual X-ray Absorptiometry (DXA) at Monash Health. Data collection included BMD, calculated bone mineral apparent density (BMAD) (to adjust for smaller bone size in TS1,2), biochemistry and medical history. Data analysis included multivariate regression statistics to adjust for confounding.

Results: Median (range) age at TS diagnosis was 12(0-65)years. Primary amenorrhoea was common (81%). Median age of commencing oestrogen was 16(11-46)years. Median (range) age, height and body mass index at DXA was 29(14-66)years, 148.5(127.8-170.0)cm, and 25.6(12.4-49.5)kg/m2 respectively. Bone-related biochemistry was normal at time of DXA. Spine and femoral neck Z-scores<−2.0 were observed in 26.4% and 7.7%, respectively, and, at the spine, lower Z-scores were associated with a later age of oestrogen commencement (p=0.045). After adjusting for confounding, spine and hip BMD/BMAD were inversely associated with age at commencing oestrogen and years of oestrogen deficiency, and growth hormone therapy was not associated with BMD/BMAD.

Conclusion: This study, involving the largest Australian adult TS cohort, indicates that low bone mass is common. Delay in commencing oestrogen is an independent risk factor for reduced spinal bone mass. Avoiding oestrogen deficiency is important in optimising bone health in TS.