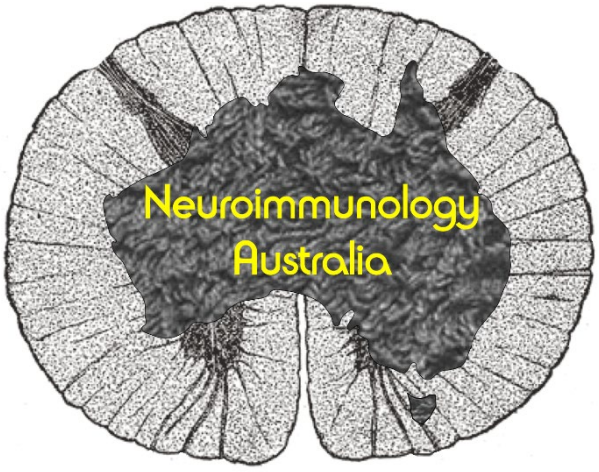
ISSN 1838-904X

# PROCEEDINGS OF NEUROIMMUNOLOGY AUSTRALIA




VOLUME 12 JUNE 2026

**Thank you to our workshop sponsors:**

Gold sponsor:


Silver sponsor:


Bronze sponsors:



Contributor:

**Oral Session Abstracts:**

**SESSION 1**

**Chair: Fabienne Brilot**



**SESSION 2**

**Chair: Jacqueline Orian**

**SESSION 3**

**Chair: Markus Hofer**



**Panel Discussion**

**Chairs: Aakanksha Dixit & Barney Viengkhou**

Panel discussion on:

"The independent PI roadmap: Carving your research in a collaborative field"

**Poster Session abstracts**

**Microglial gp130 activation mitigates acute and chronic neuronal deficits following ischemia-reperfusion injury in mice**

Maryanne Melanie Gonzales Carazas, Seung Jae Kim, Yi Xu, Jana Vukovic
School of Biomedical Sciences, The University of Queensland, Brisbane, QLD, Australia
Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia
uqmgonz7@uq.edu.au

Timely reperfusion is critical to reduce brain tissue damage after ischemic stroke. However, its restoration can initiate pathological cascades, including inflammatory activation, that drive secondary damage and functional decline. Therefore, therapeutic strategies oriented to modulate inflammatory mechanisms following ischemia-reperfusion injury may prevent secondary damage and improve post-stroke outcomes. Our lab has shown that microglial activation of gp130, the central signal transducer of interleukin-6 family, alters microglial phenotype and promotes neuroprotection after traumatic brain injury. Hence, this project aims to investigate the effects of microglial gp130 activation during the acute (1-4 days) and chronic (6 months) phases after ischemia-reperfusion injury in mice. Sustained microglial gp130 activation was induced in a genetic mouse model CX3CR1CreERT2 x Lgp130fl/+, via tamoxifen gavage prior to 60-min middle cerebral artery occlusion (MCAo) and reperfusion. Acutely, microglial gp130 activation prevented the post-reperfusion decline in cortical blood flow observed in vehicle treated mice ($p=0.032$), as assessed by laser speckle imaging. Moreover, microglial gp130 activation acutely promoted faster recovery of exploratory motor behaviour in the open field ($p<0.0001$). In the chronic phase, microglial gp130 activation improved spatial memory in the active place avoidance test ($p=0.033$) and prevented motor impairments observed in vehicle treated mice, including ipsilateral rotational bias ($p=0.004$) and increased exploratory activity ($p=0.043$). In addition, chronic motor coordination deficits were improved, as indicated by increased latency to fall on the rotarod ($p = 0.0007$). Overall, microglial gp130 activation improves outcomes following ischemia-reperfusion injury by acutely enhancing cerebral perfusion and motor function, and its sustained activation appears critical for chronic motor and cognitive recovery.

**Dissecting the Role of CD169+ Macrophages in Traumatic Spinal Cord Injury Using a Multi-Omics Approach**

Capucine Bianciotto

School of Biomedical Sciences, The University of Queensland, Brisbane, QLD, Australia
c.bianciotto@uq.edu.au

Traumatic spinal cord injury (SCI) triggers a complex inflammatory response that mediates both tissue damage and repair. Diverse myeloid immune cell populations dominate the spinal cord lesion site, but their individual role(s) remain poorly characterised. Here, we investigated the origin and dynamics of a subset infiltrating macrophages using a multi-modal approach.

We first generated a single-cell RNA sequencing (scRNAseq) atlas of CD45+ immune cells isolated from the injured mouse spinal cord, with or without immune-modulatory therapy (IVIG). Subclustering identified 42 immune cell types, 38% of which showed significant changes in abundance in response to IVIG. Of these, CD169+ macrophages were amongst the most strongly affected, exhibiting pronounced shifts in both cell subtype abundance and gene expression.

Using flow cytometry, we show that CD169+ cells are mobilised into the blood after SCI, with their numbers peaking at 1 day during the (sub)acute phase (day 0-7). Immunofluorescent staining at 1, 3, and 7 dpi further demonstrated recruitment of CD169+ macrophages to both the lesion core and penumbra regions. These results are consistent with the spatial distribution of CD169+ macrophages observed in our Visium spatial transcriptomics data. Transcriptomics data further showed that CD169+ macrophages adopt a pro-inflammatory profile and express genes associated with neuroinflammation and synaptic pruning.

Together, our findings provide the first detailed characterization of CD169+ macrophages in SCI, and our ongoing experiments are now focused on delineating their functional contribution to neuroinflammation and synaptic remodeling."

**Multi-omic profiling identifies reversible immune–epigenetic dysfunction in autistic regression**

Shrujna Patel[1#], Hiroya Nishida[1#], Velda X Han[1,2,3#,] Brooke A Keating[1], Katherine G Zyner[4], Jessica P Hayes[1], Brian Gloss[5], Nader Aryamanesh[6,7], Pinki Dey[8], Lee L Marshall[6], Erica Tsang[1], Sarah Alshammery[1], Xianzhong Lau[9], Ruwani Dissanayake[10], Shekeeb Mohammad[1,11], Mark Graham[12], Shrujna Patel[1,11^], Russell C Dale[1,11,13^*] Joint first author[#] Joint senior author[^]

[1] Kids Neuroscience Centre, The Children's Hospital at Westmead, Faculty of Medicine and Health, University of Sydney
[2] Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore, Singapore
[3] Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[4] Computational Systems Biology Unit, Children's Medical Research Institute, Faculty of Medicine and Health, University of Sydney
[5] Westmead Research Hub, Westmead Institute for Medical Research, Westmead
[6] Bioinformatics Group, Children's Medical Research Institute, University of Sydney, Westmead
[7] Faculty of Medicine and Health, Sydney Medical School, University of Sydney, Camperdown
[8] School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney
[9] Australian Genome Research Facility Ltd, Melbourne, VIC
[10] Australian Genome Research Facility Ltd, Westmead, NSW
[11] The Children's Hospital at Westmead Clinical School, Faculty of Medicine and Health, University of Sydney, Sydney
[12] Biomedical Proteomics, Children's Medical Research Institute, The University of Sydney
[13] The University of Sydney, School of Medical Sciences and Discipline of Child and Adolescent Health, Sydney

shrujna.patel@sydney.edu.au

Autistic regression, characterised by the loss of previously acquired developmental skills, affects up to 30% of children with autism spectrum disorder, yet its underlying biology remains poorly understood. There are currently no disease-modifying treatments or established clinical pathways for affected children. Increasing evidence implicates immune and epigenetic dysfunction in neurodevelopmental disorders, although integrated mechanistic studies of regression are lacking.

We performed integrated transcriptomic, proteomic, and chromatin accessibility profiling in children with autistic regression and healthy controls, including bulk RNA sequencing, single-cell RNA sequencing, proteomics, phosphoproteomics, and ATAC sequencing. To our knowledge, this represents the first integrated multi-omic characterisation of autistic regression.

Despite marked clinical heterogeneity, we identified convergent molecular abnormalities across patients. Transcriptomic analyses demonstrated coordinated dysregulation of immune and epigenetic pathways, including chromatin remodelling, histone modification, and transcriptional regulatory networks. ATAC sequencing demonstrated widespread disruption of chromatin accessibility and a shift toward a closed chromatin state, accompanied by downstream immune and translational dysfunction across multiple datasets.

To determine whether these abnormalities were biologically reversible, patient-derived peripheral blood mononuclear cells were treated in vitro with the histone deacetylase inhibitor Givinostat, followed by single-cell RNA sequencing. Givinostat reversed dysregulated translational signatures and downregulated inflammatory immune pathways in patient immune cells.

Together, these findings identify convergent immune–epigenetic abnormalities in autistic regression and support a model in which altered chromatin accessibility contributes to downstream immune dysfunction. The reversibility of these molecular signatures in patient-derived cells highlights the therapeutic potential of epigenetic modulation and positions immune–epigenetic dysfunction as a tractable biological mechanism in autistic regression and related neurodevelopmental disorders.

**Insights into neurological immune-related adverse events associated with immune checkpoint inhibitor cancer therapy**

Magdalena Lerch, Suzanne Culican, David Brown, Ming-Wei Lin, David McDonald, Markus Reindl, Sarosh Irani, Matthew Cook, Martin Stockler, Sudarshini Ramanathan on behalf of the AUTOCHECK Collaboration

ML: Translational Neuroimmunology Group, ANZAC Research Institute and Kids Neuroscience Centre, Sydney Medical School, Faculty of Medicine and Health, University of Sydney, Sydney, Australia;
SC, DB, MWL, DM: NSW Health Pathology-ICPMR, Centre for Immunology and Allergy Research, Westmead Institute for Medical Research, University of Sydney, Sydney, Australia;
MR: Clinical Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria;
SI: Mayo Autoimmune Neurology Group, Department of Neurosciences, Mayo Clinic, Jacksonville, Florida;
MC: Division of Immunology and Infectious Diseases, John Curtin School of Medical Research, Australian National University and Canberra Clinical Genomics, Canberra, Australia; Cambridge Institute of Therapeutic Immunology and Infectious Disease, Department of Medicine, University of Cambridge, Cambridge, United Kingdom;
MS: Department of Medical Oncology, Concord Cancer Centre, Concord Hospital; Department of Medical Oncology, Chris O'Brien Lifehouse, Sydney, Australia
MS: Department of Neurology, Concord Hospital, Sydney, Australia;
SR: Translational Neuroimmunology Group, ANZAC Research Institute and Kids Neuroscience Centre, Sydney Medical School, Faculty of Medicine and Health, University of Sydney, Sydney, Australia; Department of Neurology, Concord Hospital, Sydney

magdalena.lerch@health.nsw.gov.au

The development of immune checkpoint inhibitors (ICI) has revolutionised cancer therapy. However, the use of ICIs may lead to the development of immune-related adverse events (irAEs), resulting in severe disability, interruption of cancer therapy, and even death. Neurological irAEs occur in 1-10% of ICI-treated patients and can be associated with antibodies (Abs) binding to neuronal or glial antigens. We studied the presence of immunoglobulin G (IgG) and IgM Abs targeting different neuroglial antigens in the serum of 169 cancer patients prior to and after ICI treatment. We found IgG Abs targeting neuronal proteins in 21/169 (12%) of our patient cohort post ICI treatment compared to 1/59 (1.7%, p=0.019) of controls. Out of the Ab positive patient samples, 48% were attributed to Abs recognising cell surface proteins and 52% had Abs binding to intracellular targets. Importantly, 58% of patients that were Ab positive after ICI therapy already had Abs targeting the same protein prior to ICI initiation. 23% of patients developed de novo Abs after ICI treatment and 15% presented with Abs only before ICI therapy. The high proportion of patients with specific neuronal IgG prior to and after ICI administration raises implications for undertaking screening of patients before receiving ICIs to develop a more personalised risk profile. Correlation with clinical manifestations, evaluation of IgM positivity, and defining functional effects of IgGs in comparison to their idiopathic counterparts are underway. Understanding the underlying immunobiology will contribute to predicting complications from ICIs, enabling personalised treatment to improve patient survival and quality of life.

**Mechanisms of neutrophil-mediated inflammatory T cell priming in autoimmune neuroinflammation**

Oliver Wilkinson, Caleb Wong Han, Ervin Kara, Shaun McColl, Iain Comerford

The Chemokine Biology Laboratory, School of Biological Sciences, Adelaide University.
oliver.wilkinson@adelaide.edu.au

Background: The functional impact of neutrophil responses in multiple sclerosis (MS) pathogenesis remains poorly understood despite their strong associations with MS onset, severity, and relapse risk. We have previously identified a pathogenic neutrophil subset characterised by expression of CD49d that directly promotes priming of inflammatory GM-CSF/IL-17A-secreting CD4+ T cells, a pro-inflammatory T cell population clearly implicated in CNS autoimmunity. We have demonstrated that neutrophil-driven T cell polarisation occurs through distinct cell-contact dependent mechanisms and via soluble mediators. However, the specific molecular mechanisms through which neutrophils drive inflammatory T cell priming are unknown.

Methods/Results: RNA sequencing of CD49d+ neutrophils isolated from spleens of mice with experimental autoimmune encephalomyelitis (EAE) revealed enrichment of gene modules related to T cell-costimulatory molecule expression and pro-inflammatory cytokine production, including IL-1β, compared to CD49d- neutrophils. In addition, analysis of a blood neutrophil transcriptomic dataset identified enrichment of antimicrobial peptide pathways in neutrophils from people with MS relative to healthy controls. Using these findings to guide targeted investigation of molecular mechanisms controlling neutrophil-driven pathogenic Th17 cell priming, we identified roles for IL-1β and the antimicrobial peptides LCN2 and CAMP, as blockade of these mediators in neutrophil-T cell co-cultures significantly reduced GM-CSF secretion by T cells.

Conclusion: These findings identify IL-1 and antimicrobial peptides as previously unrecognised molecular pathways used by pathogenic neutrophils to promote inflammatory T cell responses. This increases understanding of pathological crosstalk between innate and adaptive arms of the immune system in CNS autoimmunity and may present novel therapeutic targets for MS and related inflammatory autoimmune diseases.

Funded by MS Australia Incubator Grant IGR2-0307"

**Nanoplastics activate innate immunity in microglia and exacerbate α-synuclein–induced neurotoxicity**

Eduardo Albornoz Balmaceda[1], Cassandra Rauert[2,3], Elvis D. Okoffo[2], Yufei Pan[2], Giovanni Pietrogrande[4], Selin Pars[4], Ernst Wolvetang[4], Kevin V. Thomas[2,3] and Trent M. Woodruff[1]

[1]School of Biomedical Sciences, Faculty of Health, Medicine and Behavioural Sciences, The University of Queensland; [2]Queensland Alliance for Environmental Health Sciences (QAEHS), The University of Queensland; [3]Minderoo Centre, Plastics and Human Health; [4]Australian Institute for Bioengineering and Nanotechnology, The University of Queensland

e.albornoz@uq.edu.au

The increasing accumulation of plastic waste in the environment has led to the emergence of micro- and nanoplastics (NPs) as novel contaminants with potential health impacts. While their effects on peripheral tissues are increasingly recognised, the consequences of NP exposure on the human brain and its resident immune cells remain poorly understood. Here, we investigated the neuroimmune response to environmentally relevant nanoplastics using human induced pluripotent stem cell (hiPSC)-derived brain organoids containing microglia, as well as human monocyte-derived microglia-like cells (MDMi). We examined the effects of a panel of polystyrene (PS)-based NPs, fluorescently labelled or unlabelled, with sizes ranging from 25-50 nm, across a range of doses and time points.

Exposure to all NP types induced a dose- and time-dependent activation of microglia, characterised by upregulation of proinflammatory mediators and morphological changes indicative of reactive states. Functionalised particles (COOH-PS and $NH_2$-PS) elicited stronger activation than non-functionalised PS, suggesting that surface chemistry modulates their immunogenicity. Notably, the presence of α-synuclein aggregates, key pathological drivers in Parkinson's disease, potentiated NP-induced microglial activation, amplifying inflammasome-related and cytokine responses. In human midbrain organoids containing microglia, combined exposure to NPs and α-synuclein aggregates resulted in pronounced microglial activation and dopaminergic neuronal loss, recapitulating early neurodegenerative features.

These findings identify nanoplastics as novel environmental neurotoxicants capable of eliciting innate immune activation in human microglia, particularly under conditions of protein aggregation stress. Our data provide mechanistic insight into how chronic exposure to nanoscale plastic contaminants may synergise with pathogenic proteins to accelerate neurodegenerative processes. Future studies will assess the neurotoxicity of environmentally derived nanoplastics in vitro and in vivo to better evaluate the neurological risks of plastic pollution and develop strategies to mitigate its long-term impact on brain health.

*Invited Plenary Speaker*

**A quick update on the 2024 McDonald Criteria for MS.**

**Professor Anneke van der Walt**

Prof Anneke van der Walt is an academic Neurologist with subspecialty training in multiple sclerosis, neuroimmunology and neuro-ophthalmology. She leads the MS and Neuro-ophthalmology Research Group at the School of Translational Medicine, Monash University, and serves as Director of the MS, Neuroimmunology and Neuro-ophthalmology Unit at Bayside Health/Alfred Care Group.

Prof. Van der Walt's research program spans five interconnected areas: ageing in MS, digital and neuroimaging biomarkers, women's health in MS, real-world evidence from disease-modifying therapies, and neuro-ophthalmology. She co-developed MSReactor, a digital cognitive monitoring platform and leads Australia's only multidisciplinary Idiopathic Intracranial Hypertension clinic.

Prof van der Walt completed her undergraduate training in South Africa before relocating to Australia, where she completed specialist training in Neurology and a PhD in Neuroscience under the supervision of Professors Trevor Kilpatrick and Helmut Butzkueven at the University of Melbourne. This was followed by postdoctoral training at the Melbourne Brain Centre, UoM (2013 to 2017).

Prof van der Walt is Chief Operating Officer of the MSBase Foundation, overseeing a registry of over 140,000 patient records across 40 countries, and serves on the executive committee of the BigMS collaboration (>300,000 records). She holds editorial roles at the Multiple Sclerosis Journal (Q1, IF 5.2) and serves as a Lead Correspondent for the ECTRIMS Controversies Podcast.

She has received substantial competitive fellowship and grant funding totalling over $34 million, with $17 million secured as CIA/CI from competitive bodies including two NHMRC fellowships.

**Stage-dependent autoimmune-like proteomic profiles in multiple sclerosis**

Marie Amigo, David A Mahns, James S Dunn

M.Amigo@westernsydney.edu.au

Background: Multiple sclerosis (MS) is an immune-mediated disease, but the extent to which its circulating proteomic profile resembles systemic autoimmune diseases remains unclear. We aimed to define a proteomic signature of systemic autoimmunity using type 1 diabetes (T1D, n=20), rheumatoid arthritis (RA, n=16), and systemic lupus erythematosus (SLE, n=21), and to test whether autoimmune-like molecular profiles are detectable across MS disease forms.

Methods: Cross-sectional serum and plasma proteomic data were analysed to identify proteins associated with systemic autoimmune disease and to derive an autoimmune signature using robust multivariate/projection-based approaches. This signature was then applied to MS samples, including relapsing-remitting MS (RRMS, n=49) and progressive MS (PMS; SPMS/PPMS, n=27), as well as fibromyalgia (FM, n=10) as a non-classical autoimmune comparator. Autoimmune-likeness, disease-axis composition, pathway enrichment, and exploratory clinical associations were assessed.

Results: The autoimmune signature showed good discrimination between autoimmune diseases and controls and was enriched for immune effector processes, inflammatory response, complement/coagulation, and plasma lipoprotein remodelling. When projected onto MS, 37% of samples were classified as autoimmune-like and 32% as intermediate. RRMS showed 35% autoimmune-like and 24% intermediate profiles, whereas PMS showed 30% autoimmune-like and 59% intermediate profiles. FM samples were mostly control-like, with 20% classified as intermediate. Disease-axis analyses suggested that RRMS profiles were more frequently SLE-like, while PMS showed a more mixed RA/SLE-like composition. Proteins contributing to autoimmune-like classification in RRMS and PMS partially overlapped, suggesting that similar scores may arise from partly distinct biological mechanisms. Exploratory analyses also identified associations between the autoimmune score and clinical or self-reported measures, including pain-related symptoms, treatment exposure, and relapse-related variables.

Conclusion: MS does not uniformly reproduce a systemic autoimmune proteomic profile, but instead displays heterogeneous autoimmune-like molecular states that may differ between relapsing and progressive disease. Interpretation remains limited by treatment heterogeneity, serum/plasma differences, subgroup size, and observational design."

**Serum cytokine levels in MOGAD disease stages: the search for a biomarker predicting relapse**

Elisha Siwan[1,2,3], Ganesha Liyanage[1,2,3], Magdalena Lerch[1,2,3,4], Vera Merheb[1], Fiona X Z Lee[1], Russell Dale[1,2,3], Sudarshini Ramanathan[1,2,3,4], Fabienne Brilot[1,2,3] on behalf of the Australasian MOGAD study group
[1]Kids Neuroscience Centre, the Children's Hospital at Westmead, Sydney.
[2]The University of Sydney, Faculty of Medicine and Health, Sydney
[3]The University of Sydney, Brain and Mind Centre, Sydney
[4]Department of Neurology, Concord Repatriation General Hospital, University of Sydney, Sydney
elisha.siwan@sydney.edu.au

Background: MOGAD is an inflammatory demyelinating disease presenting with a monophasic or relapsing disease course. Relapses occur in 50% of patients and can increase to 70% within five years of follow-up. Recurrent demyelinating episodes can be associated with a higher degree of disability, thus making the prediction of relapses a high priority. We recently published that the non-P42 epitope is associated with a relapsing course, however this feature alone cannot predict an oncoming relapse. Herein we investigated a panel of inflammatory cytokines in the sera of control and MOGAD patients at different disease stages.

Methods: Sera was collected from healthy controls (HC) (n= 9) and other neurologic disease (OND) controls (n=7) as well as MOGAD patients (n=61), which were stratified according to monophasic (n=13) and relapsing (n=48) disease course at sample collection; and according to disease stage: onset, relapse and remission. The serum concentration of inflammatory cytokines: IL-33, IL-23, IL-18, IL-17α, IL-12p70, IL-10, IL-8, IL-6, MCP-1, TNF-α and IFN-ɣ were measured and concentration determined.

Results: Serum cytokine levels were not statistically different between MOGAD patients (n=61) and combined OND and HC controls (n=16). However, when stratified by disease course; IL-18 levels were 3.2-fold higher in monophasic (n=12) patients compared to OND Controls (n= 7) (P=0.01). No significant differences were found across disease stages in cytokine levels except MCP-1, which was different across onset, remission and relapse (P=0.0007). Compared to onset, MCP-1 was 2.12-fold higher in remission (P=0.002). MCP-1 was slightly decreased during relapse compared to remission (n.s) although levels at relapse were 2.09-fold higher than at onset (P=0.002).

Conclusions: MCP-1 levels fluctuate with MOGAD disease activity. Though not significant, the decrease in MCP-1 from remission to relapse suggests the monitoring of MCP-1 may help to predict an oncoming relapse episode. Future investigations are warranted with larger sample sizes."

**Neuropathological Alterations in the Cerebellum at P10 in Growth-Restricted Piglets**

Bhuvaneswari Harishankar[1], Kirat Chand[1], Paul Colditz[1,2], Julie Wixey [1]

[1] Frazer Institute, Faculty of Health, Medicine and Behavioural Sciences, The University of Queensland
[2] Royal Brisbane Women's Hospital

b.harishankar@student.uq.edu.au

Background
Fetal growth restriction (FGR) affects 5–10% of pregnancies worldwide. It is a major pregnancy complication commonly caused by placental insufficiency. FGR is associated with an increased risk of perinatal morbidity and mortality, with long-term adverse neurodevelopmental outcomes, including motor dysfunction and cerebral palsy. This study aimed to investigate the effects of FGR on cerebellar neuropathology at postnatal day 10 (P10).
Methods
Newborn piglets with spontaneous fetal growth restriction (FGR; birth weight <10th percentile) and normally grown (NG) littermates were studied from postnatal day 1 (P1) to postnatal day 10 (P10) (FGR = 8; NG = 7). Hematoxylin and eosin (H&E) staining and immunohistochemistry were performed to assess neuropathological alterations using the neuronal markers microtubule-associated protein 2 (MAP2) and neuronal nuclei (NeuN). White matter markers were myelin-binding protein (MBP), neurofilament (NF), and pan-oligodendrocytes (Olig2+). Apoptosis was labelled using caspase-3 (Casp3).
Results
At P10, FGR piglets demonstrated a significant decrease in cerebellar width in the anterior lobe, but not in the posterior lobe, compared with NG piglets. Immunohistochemistry revealed a significant decrease in neuronal cell numbers and structural integrity in both the posterior and anterior lobes of FGR piglets. White matter analysis demonstrated hypomyelination (MBP and NF) in the anterior and posterior lobes, associated with reduced numbers of oligodendrocytes in FGR piglets. In addition, significantly increased apoptosis was observed in the grey matter of the anterior lobe but not the posterior in FGR piglets compared with NG piglets.
Conclusion
These findings demonstrate that FGR is associated with significant neuropathological alterations in the cerebellum at P10, including impaired white matter maturation, altered neuronal integrity, and increased apoptosis, which was more prevalent in the anterior lobe. These cellular and regional changes may contribute to long-term neurodevelopmental deficits in FGR infants."

*Invited Plenary Speaker*

**AI in MS and Other CNS Neurological Diseases: Where Are We Now, and Where Are We Headed?**

**Associate Professor Tim Wang**

A/Prof Tim Wang is a Principal Research Fellow at the University of Sydney's Faculty of Medicine and Health, and Co-Lead of the Computational Neuroimaging Group at the Brain and Mind Centre. Trained in electronics engineering and neuroscience, his research sits at the intersection of brain science and artificial intelligence, with a focus on translating advanced AI and neuroimaging methods into measurable real-world impact across multiple sclerosis, dementia and Alzheimer's disease, movement disorders and many others.

His work develops imaging biomarkers, large machine learning models for clinical neurology and neuroscience, and integrated agentic systems for clinicians and scientists. As Co-Founder of the Sydney Neuroimaging Analysis Centre (SNAC), Tim has also co-led the journey from conceptualisation to commercialisation of TGA- and FDA-cleared neuroimaging AI tools now embedded in routine clinical care. He has secured more than AUD $12 million in competitive and industry research funding — including major MRFF, MS Australia, and Commonwealth grants — and has authored more than 70 peer-reviewed publications in leading journals including npj Digital Medicine, Brain, Neurology, JNNP, and Medical Image Analysis. He is the inaugural Nerve Research Foundation Fellow and an MS Australia Fellow.

**Insufficient Brain Engagement Limits Baricitinib Efficacy in Cerebral Interferonopathies**

Barney Viengkhou, Nicholas B Gallo; Markus J Hofer

1 School of Life and Environmental Sciences and the Charles Perkins Centre, The University of Sydney, Sydney, NSW 2006, Australia
2 Biogen Inc, Cambridge, MA 02142, USA
3 School of Medical Sciences and the Charles Perkins Centre, The University of Sydney, Sydney, NSW 2006, Australia"

barney.viengkhou@sydney.edu.au

Aicardi-Goutières syndrome (AGS) is a prototypical but severe cerebral interferonopathy driven by chronic type I interferon (IFN-I) signalling and progressive neuroinflammation. Janus kinase inhibitors, like baricitinib, suppress peripheral IFN-I activity, yet neurological responses remain inconsistent, suggesting that effective therapy requires a critical threshold of IFN-I suppression within the brain. Whether limited brain drug exposure constrains this threshold remains undefined. We therefore investigated the brain pharmacology and therapeutic efficacy of baricitinib in a mouse model of AGS (transgenic IFN-I expression in the brain), alongside targeted reduction of IFN-I signalling via genetic ablation of the IFN-I receptor, Ifnar1.

Following oral dosing, baricitinib concentrations were quantified and pharmacodynamic responses assessed via interferon-stimulated gene (ISG) expression. Long-term efficacy was evaluated using behavioural, molecular, and neuropathological analyses. Oral baricitinib achieved robust systemic exposure but limited brain penetration, with brain concentrations reaching ~8% of plasma levels. After 14 weeks of treatment, brain interferon activity showed only a modest, non-significant reduction (interferon score: 100 to 80). Treatment partially improved cerebrovascular integrity and reduced immune cell infiltration, gliosis, and neurodegeneration, but did not improve motor function or significantly extend survival (median increase of 2.5 weeks). In parallel, reduction of IFN-I signalling via heterozygous loss of Ifnar1 in vascular cells had minimal impact, whereas homozygous deletion halted disease progression with no neuropathology and improved survival (8-week increase in survival), defining a threshold requirement for pathway suppression.

These findings demonstrate that restricted brain exposure limits the neurological efficacy of baricitinib in AGS. Limited IFN-I inhibition within the brain, even with vascular effects, is insufficient for therapeutic benefit. In contrast to genetic ablation of Ifnar1, baricitinib exposure is likely inadequate to achieve effective vascular target engagement. This pharmacokinetic–pharmacodynamic dissociation identifies insufficient brain delivery as a primary barrier and underscores the need for brain-penetrant strategies in interferon-driven neuroinflammatory disease."

**Rare Genetic Interferonopathy Reveals Gut–Brain Metabolic Crosstalk**

Jinni Yan, Markus J Hofer, Madysen Elbourne, Velda X Han, Michelle A Farrar, Russell C Dale

Faculty of Science, School of Mathematical and Physical Sciences University of Technology Sydney Ultimo NSW Australia.
Faculty of Science, School of Life and Environmental Sciences, Charles Perkins Centre The University of Sydney Sydney NSW Australia.
Department of Paediatrics, Yong Loo Lin School of Medicine National University of Singapore Singapore Singapore.
Discipline of Paediatrics and Child Health, School of Clinical Medicine UNSW Medicine and Health, University of New South Wales Sydney NSW Australia.
Faculty of Medicine and Health, Clinical School, The Children's Hospital at Westmead University of Sydney Sydney NSW Australia.

jingya.yan@uts.edu.au

Aicardi-Goutières syndrome (AGS) is a rare genetic interferonopathy because of aberrant DNA or RNA metabolism with secondary host anti-viral (interferon) activation. This metabolomics study aimed to improve the biological understanding of AGS and explore potential biomarkers.

We performed untargeted cerebrospinal fluid (CSF) metabolomics using a UPLC-Q-Exactive-HFx Mass Spectrometry of 10 genetically confirmed AGS patients (8 males, mean 4.8 years, range 0.2-16.5) and age-sex matched controls. Metabolites were then quantified and validated using UHPLC-QqQ-MS/MS in CSF and serum.

We identified expected elevated inflammatory metabolites (neopterin and kynurenine) and unexpected elevated gut microbe metabolites in CSF samples: Indole, p-Cresol, γ-Butyrobetaine and N-Butyryl-L-homoserine lactone (all p FDR $< 0.05$). Using a targeted assay, we confirmed elevation of these metabolites in CSF, and also in the serum of patients with AGS (all $p < 0.01$).

Our findings suggest gut microbe metabolite leakage traversing the gut-blood-brain barrier in AGS, potentially because of endothelial dysfunction.

**A novel human iPSC-platform to assess immune-modulating therapeutics**

Rovin Verdillo  Cesar L Moreno, Russel C Dale, Markus J Hofer

School of Life and Environmental Sciences, Faculty of Science, The University of Sydney, NSW
Charles Perkins Centre, The University of Sydney, NSW
Kids Neuroscience Centre, The Children's Hospital at Westmead, Faculty of Medicine and Health, University of Sydney, NSW
The Children's Hospital at Westmead Clinical School, Faculty of Medicine and Health, University of Sydney, NSW

rovin.verdillo@sydney.edu.au

Aicardi–Goutières syndrome (AGS) is a monogenic interferonopathy characterised by progressive neurological decline. Pathogenic mutations in AGS drive chronic activation of innate immune pathways, including cyclic GMP-AMP synthase (cGAS) and type I interferon (IFN) signalling. Although current therapeutics reduce peripheral IFN responses, they have limited efficacy in reducing central symptoms due to their limited blood-brain barrier penetrance. Our lab recently identified the brain microvasculature as a highly IFN-responsive interface in AGS, highlighting a promising therapeutic target that overcomes the need for blood-brain barrier penetrance. Here, we establish a human induced pluripotent stem cell (iPSC)-based platform to model brain microvascular dysfunction in AGS and evaluate current and emerging therapeutics.

Our iPSC cohort comprises a healthy control and three TREX1-associated AGS cell lines: a CRISPR/Cas9 knockout, and two patient-derived homozygous variants (c.602T>A, p.V201D; c.341G>A, p.R114H). iPSCs were differentiated into brain endothelial cells and pericytes, the key cellular components of the brain microvasculature. We evaluated three immune-modulating therapeutics: JAK inhibitor ruxolitinib, small-molecule cGAS inhibitor (IMSB301), and antisense oligonucleotides targeting the human IFNAR1. Therapeutic efficacy was assessed by the suppression of chronic innate immune signalling pathways and restoration of vascular integrity in cerebrovascular organoids.

Together, this work establishes a patient-specific human iPSC platform to assess current and next-generation immune-modulating therapeutics in AGS and provides a translational framework for targeting IFN-mediated neurological disease.

**Patient-Derived cells and In Vitro therapeutics can define novel Biomarkers and Disease-Modifying therapies for Neurodevelopmental Disorders**

Jessica Hayes, Brooke A. Keating, Hiroya Nishida, Erica Tsang, Markus J Hofer, Peter Valtchev, Shekeeb S Mohammad , Shrujna Patel, Russell C Dale

jessica.hayes4@health.nsw.gov.au

Neurodevelopmental disorders (NDDs) arise from complex interactions between genetic and environmental factors, leading to gene dysregulation and ongoing immune-brain crosstalk. Single-cell RNA sequencing (scRNA-seq) provides an unprecedented opportunity for characterisation of these processes at the cellular level in individual children with NDDs. This technology enables transcriptional profiling of tens of thousands of individual cells per patient, comparison with controls, and precise evaluation of candidate therapeutics through pre- and post-treatment analyses.

We have established a streamlined translational pipeline to accelerate the identification of disease-modifying therapies for NDDs. Candidate drugs are first assessed in vitro using patient-derived peripheral blood mononuclear cells (PBMCs). PBMCs are incubated with candidate drugs or vehicle control for 24 hours, after which cells are loaded into HIVE™ devices (Honeycomb Technologies) for scRNA-seq analysis to assess drug-induced transcriptional changes.

Across multiple NDD cohorts, we identified a transcriptional signature characterised by downregulation of ribosomal pathways and dysregulation of immune-related pathways compared with healthy controls. We hypothesise that drugs with gene regulatory and anti-inflammatory effects represent promising therapeutic candidates. For example, sodium butyrate normalised dysregulation at both gene and pathway levels in vitro.

To complement this model, drugs demonstrating anti-inflammatory efficacy are translated into clinical care and assessed ex vivo. Whole blood samples collected before and after treatment are analysed using the same scRNA-seq workflow. For example, intravenous immunoglobulin reversed baseline immune and ribosomal pathway abnormalities and downregulated histone modification pathways.

This integrated pipeline enables individualised assessment of therapeutic responses and supports the identification of biomarkers and disease-modifying treatments for NDDs.

**Poster Abstracts**

## High-Dimensional Full Spectrum Flow Cytometric Analysis of Peripheral Blood Mononuclear Cells from Spinal Cord Injury Patients

Shoshana Chandra, Trisha Jogia1, Laura F. Grice1, James Walsham2 & Marc J. Ruitenberg 1,3
[1]School of Biomedical Sciences, Faculty of Health, Medicine & Behavioural Sciences, The University of Queensland, Australia
[2] Princess Alexandra Hospital (Queensland Health), Brisbane, Australia
[3] Mater Research Institute - The University of Queensland, Translational Research Institute, Brisbane, Australia

shoshana.chandra@uq.edu.au

Background: Traumatic spinal cord injury (SCI) is a debilitating condition that also has a profound systemic impact at the immunological level. To combat the dysfunctional immune response associated with SCI, we introduced Intravenous Immunoglobulin (IVIG) as an immunomodulatory therapy in an open-label phase I/IIa trial (ACTRN12616001385437). The purpose of this study was to compare and contrast peripheral blood mononuclear cell profiles in SCI patients with and without IVIG therapy.

Methods: We developed a 25-marker high-dimensional spectral flow cytometry panel to identify and phenotype immune cells, including monocytes, lymphocytes, and dendritic cells, and to distinguish specific subtypes and rare subpopulations. High-dimensional visualisation and clustering methods were used to group immune cell populations based on marker expression.

Findings & Interpretations: Following SCI, CD3+ lymphocyte dynamics were markedly altered, with early shifts characterised by transient expansion of NKT cells and reductions in CD4+ T cells within the first week post-injury. IVIG treatment attenuated acute NKT cell depletion observed at 1 and 3 days post-injury, maintaining proportions comparable to uninjured controls and distinct from untreated SCI patients. In contrast, CD3+ regulatory T cells were consistently elevated across all post-injury timepoints in IVIG-treated individuals, suggesting enhanced immunoregulatory activity. Changes were also evident within CD3− populations, where monocyte and dendritic cell frequencies increased at 1 and 7 days post-injury relative to naïve controls. IVIG-treated patients exhibited persistently higher proportions of myeloid dendritic cells across all examined timepoints, indicating a potential shift toward antigen-presenting phenotypes. Functional marker analysis further revealed increased expression of HLA-DR and CD38 across multiple immune subsets, including NK cells, monocytes, and CD8+ T cells, consistent with heightened activation and maturation states. Collectively, these findings demonstrate that IVIG modulates lymphocyte and monocyte activity, unlocking avenues for further investigations into how specific immune cell subsets and/or states influence the outcome from CNS injury.

**Spatial mapping of microglia and astrocyte subtypes in experimental autoimmune encephalomyelitis**

Hamish Hay

QIMR Berghofer Institute, Brisbane

hamish.hay9@gmail.com

MS is a chronic inflammatory disease of the CNS characterised by immune-mediated demyelination, glial activation, and progressive neuroaxonal injury. Although microglia and astrocytes are increasingly recognised as central regulators of neuroinflammation, their regional and stage-specific roles during disease progression remain incompletely understood. This project uses the EAE mouse model to examine how T cell infiltration, microglial activation, astrocyte reactivity, and neuronal-myelin integrity change across disease stages. On day 0, female C57Bl/6J mice were immunised subcutaneously with MOG35-55 in Complete Freund's Adjuvant containing heat-killed Mycobacterium tuberculosis, and pertussis toxin. Control mice received vehicle. All mice received an intraperitoneal injection of pertussis toxin on day 2. Mice were perfused at either day 13 (n=10/group) or day 15 (n=10/group) post-immunisation; brains were then collected and processed for cryotomy. Free-floating 40 μm brain sections were used to optimise immunofluorescent staining panels using antibodies targeting the following cell types: microglia (Iba-1, Tmem119, MHC class II, CD68), astrocytes (GFAP, C3, S11a10), neurons (NeuN, NF200, beta III tubulin, myelin basic protein) and T cells (CD3). Ongoing work for this project will involve multiplex immunofluorescence staining to assess inflammatory and neurodegenerative markers in the cerebral cortex, hippocampus and cerebellum. Confocal imaging will be performed to determine whether distinct spatiotemporal patterns of microglia and astrocyte reactivity are associated with regional differences in T cell infiltration and tissue injury. By characterising the spatial relationship between activated microglia and astrocytes, T cell infiltration, and neuronal-myelin disruption, this study aims to clarify how local neuroimmune environments contribute to EAE pathology. These findings may provide insight into region-specific mechanisms of CNS inflammation and identify cellular patterns relevant to MS disease progression.