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MOTOR NEURON DISEASE RESEARCH CENTRE

The 7th Annual Macquarie Neurodegeneration Meeting

19 SEPTEMBER 2024

An event for Australian neuroscientists to showcase their research and to stimulate conversation and foster collaboration to develop treatments for diseases including motor neuron disease, Alzheimer's disease, frontotemporal dementia, Parkinson's disease and other degenerative brain disorders.

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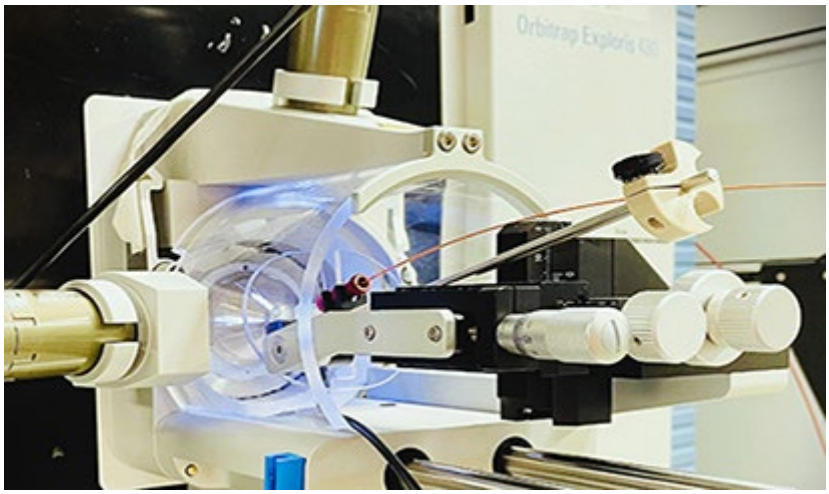

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Committee

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The Macquarie Neurodegeneration Meeting is an annual event hosted by the Macquarie University Motor Neuron Disease Research Centre. The aim of this event is for Australian neuroscientists to showcase their research and to stimulate conversation and foster collaboration to better understand and develop treatments for diseases including motor neuron disease, Alzheimer's disease, frontal temporal dementia, Parkinson's disease and other degenerative brain disorders.

We welcome your involvement and hope the day provides inspiration and assists in fostering collaboration and connections in the neurodegeneration research community.

Yours Sincerely,
The Conference Organising Committee

COMMITTEE MEMBERS	
Professor Julie Atkin	Co-Director
Professor Ian Blair	Co-Director
Christina Cassidy	Centre Administrator
Flora Cheng	Research Assistant
Dr Pradeep Cholan	Postdoctoral Research Fellow
Dr Sandrine Kim Kiow Chan Moi Fat	Postdoctoral Research Fellow
Dr Sina Shadfar	Postdoctoral Research Fellow
Dr Sharlynn Wu	Postdoctoral Research Fellow

Program

Conference Opening	
9:00 am -9:30 am	**Registration**
9:30 am – 9:35 am	**Welcome Remarks by Professor Julie Atkin** Co-Director Motor Neuron Disease Research Centre Macquarie Medical School Macquarie University
Session 1	**Chairs – Professor Ian Blair & Dr Alison Hogan**
9:35 am – 10:05 am	**Prof Gareth Miles** Assistant Vice Principal, Dean of Science and Professor of Neuroscience at the University of St Andrews, Scotland, UK. *Investigating the role of astrocytes in the pathophysiology of Amyotrophic Lateral Sclerosis* ***(30 min)***
10:05 am- 10:20 am	**Dr Sina Shadfar** Motor Neuron Disease Research Centre, Macquarie University *Restoring Genomic Integrity: A Novel Strategy Against DNA Damage and Age-Related Diseases* ***(15 min)***
10:20 am -10:35 am	**Dr Nirma Perera** Florey Institute of Neuroscience and Mental Health, University of Melbourne *A Blood-Based Biomarker for Autophagy - the Cell's Waste Clearance and Recycling Pathway* ***(15 min)***
10:35 pm -10:50 pm	**Dr Magdalena Przybyla** Dementia Research Centre, Macquarie University *Tau spreading in Alzheimer's disease models is facilitated by the amyloid-β precursor protein* ***(15 min)***
Break	
10:50 am - 11:20 am	**Join us for morning, trade display and posters.**
Session 2	**Chairs – Professor Gareth Miles & Dr Grant Richter**

Program

11:20am – 11:50am	**Professor Bradley Turner** Head of the Motor Neuron Disease Group and Research Lead of the Brain Health and Repair Mission. The Florey Institute, University of Melbourne *Harnessing patient iPSCs as a drug screening platform for sporadic ALS* ***(30 min)***
11:50am –12:05pm	**Dr Rossana Rosa Porto** School of Medicine, Western Sydney University *Could heat therapy be utilised as a novel treatment for Alzheimer's disease? Insights from a pilot study in mice.* ***(15 min)***
12:05pm –12:20pm	**Dr Rose Chesworth** Western Sydney University *Combining tauopathy and neuroinflammation exacerbates spatial learning impairments in a new double transgenic mouse model for Alzheimer's disease* ***(15 min)***
12:20pm – 12:35pm	**Dr Sarah El-Wahsh and Ms Katrina Byrne** Faculty of Medicine and Health, The University of Sydney *Speech Pathologists' confidence levels and professional development needs in motor neurone disease (MND): An Australian Survey* ***(15 min)***
Lunch	
12:35 pm – 1:50 pm	**Lunch, Poster Session and Trade Displays**

Program

Session 3	Chairs – Professor Bradley Turner & Dr Sonam Parakh
1:50 pm – 2:20 pm	**Professor Simon Lewis** Consultant Neurologist, an NHMRC Leadership Fellow and Professor of Cognitive Neurology. Macquarie Medical School, Macquarie University *Parkinson's Disease - Where are we now?* ***(30 min)***
2:20 pm – 2:35 pm	**Dr Kathryn Laloli** NeuRA *Clinical Diagnostic Accuracy in the Sydney Brain Bank* ***(15 min)***
2:35 pm –2:50 pm	**Associate Professor Cath Suter** Sydney Local Health District *Spatially resolved transcriptomics of human cortex reveals unique disease signatures and potential biomarkers for chronic traumatic encephalopathy* ***(15 min)***
2:50 pm – 3:20 pm	**Prof Kim Hemsley (zoom)** Head, Childhood Dementia Research Group Flinders Health and Medical Research Institute, College of Medicine and Public Health, Flinders University *Children get dementia too - and they urgently need treatment options!* ***(30 min)***
Break	
3:20 pm – 3:55 pm	**Please join us in the foyer for afternoon tea, posters and trade displays**
Session 4	**Chairs - Professor Julie Atkin & Dr Shu Yang**
3.55 pm –4:25 pm	**Professor Roger Chung** Pro Vice-Chancellor, Academic Health Strategy, Faculty of Medicine, Health and Human Science Group Leader, Motor Neuron Disease Research Centre, Macquarie University *Developing novel AAV gene therapies for ALS* ***(30 min)***

Program

4:25 pm –4:30 pm	**Dr Andrew Affleck** RPA Hospital, Sydney Local Health District *Chronic traumatic encephalopathy and other neurodegenerative comorbidities seen in the Australian Sports Brain Bank* ***(5 min)***
4:30 pm – 4:35 pm	**Dr Hannah Suddull** Dementia Research Centre, Macquarie University *How Does the 3' UTR Sequence of mRNA Regulate Tau Expression?* ***(5 min)***
4:35 pm –4:40 pm	**Ms Sushmitha Somanahalli Purushotham** School of Medicine, Western Sydney University *Evaluation of anti-inflammatory molecule in restoring K+ homeostasis during neurodegeneration* ***(5 min)***
4:40 pm – 4:45 pm	**Miss Anastasiya Potapenko** Motor Neuron Disease Research Centre, Macquarie University *The contribution of ataxin-3's deubiquitinase function to the pathophysiology of neurodegenerative diseases including Machado-Joseph disease* ***(5 min)***
4:45 pm – 4:50 pm	**Ms Sara Assar Kashani** Motor Neuron Disease Research Centre, Macquarie University *Actin dysregulation in transgenic FUS animal models and its novel isoform EC-FUS* ***(5 min)***
4:50 pm – 4.55 pm	**Miss Vanessa Alexandre da Silva (zoom)** Federal University of São Carlos (Brazil), Western Sydney University *Exploratory analysis of ADAM10 isoforms levels and activity in neuron-like cell fractions.* ***(5 min)***
4.55 pm – 5.00 pm	**Dr Ignacio Simo**

Program

	Motor Neuron Disease Research Centre, Macquarie University *Mitochondrial dysfunction as a cause of MJD* ***(5min)***
5:00 pm – 5:30 pm	**Dr Jenna Gregory (via Zoom)** Senior Clinical Lecturer & Consultant Pathologist & Clinical Lead NHS Grampian Tissue Biorepository Institute of Medical Sciences School of Medicine, Medical Sciences & Nutrition University of Aberdeen *Presymptomatic pathological TDP-43 aggregation is a common feature in peripheral, non-central nervous system tissues in people with ALS.* ***(30 min)***
Close of Presentations	
5:30 pm – 5:35 pm	**Closing remarks by Professor Roger Chung** Pro Vice-Chancellor, Academic Health Strategy Faculty of Medicine, Health & Human Science Macquarie University
5:35 pm – 5:45 pm	**Prize Presentation**

Invited Speakers

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Professor Roger Chung

Neurobiology & Molecular Therapeutics Group, Macquarie University Motor Neuron Disease Research Centre

Professor of Neurobiology & Neurochemistry, Macquarie Medical School

Pro Vice-Chancellor, Academic Health Strategy

Macquarie University

I am the Professor of Neurobiology and Neurochemistry, and Pro Vice-Chancellor, Academic Health Strategy in the Faculty of Medicine, Health & Human Sciences. I lead the Neurochemistry & Molecular Therapeutics Group within the Macquarie University Centre for Motor Neuron Disease Research.

My main areas of research interest involve a multi-disciplinary approach to understanding the biochemical, molecular and cellular mechanisms that underpin how neurons respond to injury or neurodegenerative disease, and how non-neuronal cells (glia) are involved in modulating this process. More recently, we have taken our understanding of disease mechanisms to develop molecular therapies for Motor Neuron Disease (MND, also known as amyotrophic lateral sclerosis or ALS). We have developed gene therapies for MND/ALS, which have been licensed to Celosia Therapeutics. I am the co-Founder and Chief Scientific Officer of CelosiaTX.

I completed my PhD in molecular biology in 2003, and have since led a research team at the University of Tasmania (2004-2013) and at Macquarie University since 2013.

Research interests

In 2013, I co-led the creation of the Centre for Motor Neuron Disease Research at Macquarie University. This Research Centre takes a multidisciplinary approach to unravelling the molecular origins of MND through identifying the genetic and epigenetic causes of MND, biochemical and proteomic evaluation of protein defects in MND, cell biology and animal models of disease, and patient biomarker studies and clinical trials. My current research program involves a multidisciplinary approach including proteomics, molecular and cellular biology, synthetic biology and molecular bioengineering, neuropathology and neuroimaging, and animal models of MND/neurodegeneration. I work closely with valued collaborators Dr Albert Lee and A/Professor Marco Morsch. Several of my current research projects are described briefly below:

https://researchers.mq.edu.au/en/persons/roger-chung

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Professor Kim Hemsley

College of Medicine and Public Health

Flinders University

Professor Kim Hemsley is a neuroscientist who leads the Childhood Dementia Research Group in the Flinders Health and Medical Research Institute at Flinders University, South Australia. The Group moved to Flinders from SAHMRI in 2019.

Kim's interest in neuroscience began in 1993 when she joined the Neuropharmacology Laboratory of Emeritus Professor Ann Crocker at Flinders University as a Research Assistant. Some years later, encouraged and mentored by Ann, she undertook a PhD investigating the mechanisms and brain regions involved in mediating the extrapyramidal side effects caused by antipsychotic drugs.

In 2002 Kim took up a post-doctoral position in the Lysosomal Diseases Research Unit at the Women's and Children's Hospital in Adelaide, South Australia and began to establish the Childhood Dementia Research Group, whose goal was to better understand how and why degeneration of brain structure and function occurs in a childhood-onset form of dementia called Sanfilippo syndrome. A second even more important aim of the group is to develop and test potential treatments for this (currently) untreatable disorder. Evaluation of potential blood-borne biomarkers and establishment of prognostic tests for newborns diagnosed with Sanfilippo and other similar disorders are current areas of focus.

She is also involved in studies examining brain-related changes in other childhood dementias including Gaucher disease, Niemann-Pick C, Hunter syndrome, GM1 gangliosidosis and Zellweger Spectrum Disorder, and is interested more broadly in the effect of lysosomal insufficiency on biological processes.

Kim is a member of the Scientific Advisory Boards of the Sanfilippo Children's Foundation and Childhood Dementia Initiative (both Australia) and is currently Chair, of the Scientific Advisory Board of the National MPS Society (USA).

Finally, Kim is passionate about achieving and celebrating equity, diversity and inclusion in medical science & more broadly. She currently Co-Convenes the Gender, Inclusion, Diversity and Equity Committee in the College of Medicine and Public Health at Flinders University.

https://www.flinders.edu.au/people/kim.hemsley

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Professor Simon Lewis

Professor of Cognitive Neurology & Consultant Neurologist

Macquarie University

Simon Lewis is a Consultant Neurologist, an NHMRC Leadership Fellow and Professor of Cognitive Neurology at Macquarie University. He has published over 300 peer review papers, 2 books and 8 book chapters and has helped to attract over $40 Million in funding from various sources including the NHMRC, MRFF, ARC and Michael J Fox Foundation to support his research targeting Parkinson's Disease, Dementia with Lewy Bodies and related conditions.

https://www.profsimonlewis.com/

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Professor Bradley Turner

Head of the Motor Neuron Disease Group and Research Lead of the Brain Health and Repair Mission.

The Florey Institute, University of Melbourne

Bradley Turner is a Professor of Neuroscience at the University of Melbourne with an international reputation in determining the molecular basis of MND. He leads the Brain Health & Repair Mission and MND Laboratory at the Florey Institute. Brad obtained his PhD in biochemistry at the University of Melbourne, followed by postdoctoral positions at the University of Oxford and Florey Institute in mouse functional genetics. His research team implement the largest MND patient-induced pluripotent stem cell library in Australia, neural organoids and mouse models for disease modelling and drug screening with 5 drug candidates advanced to clinical trials in MND.

https://florey.edu.au/researcher/bradley-turner/

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Professor Jenna Gregory

Senior Clinical Lecturer & Consultant Pathologist
& Clinical Lead NHS Grampian Tissue Biorepository
Institute of Medical Sciences
School of Medicine, Medical Sciences & Nutrition

University of Aberdeen
Scotland, United Kingdom

Jenna studied preclinical medicine at St Andrews University before completing her clinical training and undertaking her PhD as part of the prestigious MD PhD programme at Cambridge University. Following this she moved to the University of Edinburgh to train as a pathologist and was appointed as a SCREDS Clinical Lecturer in 2018, recently moving to Aberdeen in March 2022 to take up a Senior Clinical Lecturer post in the Institute of Medical Sciences. Jenna also holds posts as the co-lead for the Academic Training Pathway (supporting clinical academics from medical students to lecturers) and the Clinical Lead for the NHS Grampian tissue bank. She also works as an NHS pathologist, specialising in gut pathology.

Her research focuses on the molecular mechanisms underlying neurodegenerative diseases with a particular focus on motor neuron disease (MND). Her research vision is to learn from the clinical success of other diseases, such as cancer, to improve translational success in MND. Recent successes have been in (i) developing tools for early and accurate disease detection (Zacco et al 2022; Spence et al 2024) (ii) exploring readily accessible sites for diagnostic tissue biopsy (Pattle et al 2023), and defining distinct molecular signatures of disease to improve precision medicine approaches (Rifai et al 2022; Rifai et al 2023).

https://www.abdn.ac.uk/people/jenna.gregory

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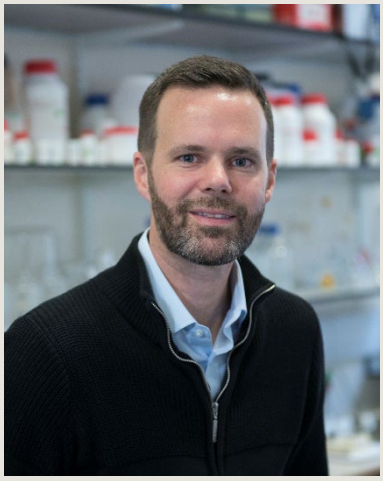
Professor Gareth Miles

Assistant Vice Principal, Dean of Science and Professor of Neuroscience

University of St Andrews
Scotland, United Kingdom



Prof Gareth Miles is currently Assistant Vice Principal, Dean of Science and a Professor of Neuroscience at the University of St Andrews, Scotland, UK. He leads a research laboratory that examines the physiology and pathophysiology of neural circuits that control movement. Prof Miles' laboratory focusses on circuits within the brainstem and spinal cord that control rhythmic movements such as breathing and locomotion. His translational work aims to decipher disease mechanisms and reveal novel therapeutic targets for Amyotrophic Lateral Sclerosis (ALS/MND). Prof Miles's research extends from the level of ion channels on individual neurons to whole neural networks. His laboratory utilises a combination of electrophysiological, live cell imaging, molecular genetic, and anatomical labelling techniques; typically applied to *ex vivo* rodent preparations and human stem cell-based models. Prior to establishing his laboratory at St Andrews in 2007, Prof Miles completed his PhD in the laboratory of Prof Greg Funk (University of Auckland, New Zealand; 1999-2003) and undertook postdoctoral training in the lab of Prof Rob Brownstone (Dalhousie University, Canada; 2003-2006). Prof Miles has been appointed to the research panels of several ALS/MND-related charities, including the 'Motor Neuron Disease Association UK Biomedical Research Advisory Panel' and the 'My Name'5 Doddie Foundation's Independent Research Review Committee'. Prof Miles was awarded the 7th International Paulo Gontijo Award in Medicine (2015) in recognition of outstanding ALS-related research.

https://ncm.wp.st-andrews.ac.uk/

Abstract Lists

Invited Speaker Abstracts

Abstract Lists

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15 Minutes Abstracts		
Dr Rose Chesworth Western Sydney University	*Combining tauopathy and neuroinflammation exacerbates spatial learning impairments in a new double transgenic mouse model for Alzheimer's disease*	33
Dr Sarah El-Wahsh and Ms Katrina Byrne Faculty of Medicine and Health, The University of Sydney	*Speech Pathologists' confidence levels and professional development needs in motor neurone disease (MND): An Australian Survey*	34
Dr Kathryn Laloli NeuRA	*Clinical Diagnostic Accuracy in the Sydney Brain Bank*	37
Dr Nirma Perera Florey Institute of Neuroscience and Mental Health, University of Melbourne	*A Blood-Based Biomarker for Autophagy - the Cell's Waste Clearance and Recycling Pathway*	38
Dr Magdalena Przybyla Dementia Research Centre, Macquarie University	*Tau spreading in Alzheimer's disease models is facilitated by the amyloid-β precursor protein*	39
Dr Rossana Rosa Porto School of Medicine, Western Sydney University	*Could heat therapy be utilised as a novel treatment for Alzheimer's disease? Insights from a pilot study in mice.*	40
Dr Sina Shadfar Motor Neuron Disease Research Centre, Macquarie University	*Restoring Genomic Integrity: A Novel Strategy Against DNA Damage and Age-Related Diseases*	42
Associate Professor Cath Suter Sydney Local Health District	*Spatially resolved transcriptomics of human cortex reveals unique disease signatures and potential biomarkers for chronic traumatic encephalopathy*	43

Abstract Lists

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5 Minute Abstracts		
Dr Andrew Affleck RPA Hospital, Sydney Local Health District	*Chronic traumatic encephalopathy and other neurodegenerative comorbidities seen in the Australian Sports Brain Bank*	45
Miss Vanessa Alexandre da Silva Federal University of São Carlos (Brazil), Western Sydney University	*Exploratory analysis of ADAM10 isoforms levels and activity in neuron-like cell fractions.*	46
Ms Sara Assar Kashani Motor Neuron Disease Research Centre, Macquarie University	*Actin dysregulation in transgenic FUS animal models and its novel isoform EC-FUS*	47
Miss Anastasiya Potapenko Motor Neuron Disease Research Centre, Macquarie University	*The contribution of ataxin-3's deubiquitinase function to the pathophysiology of neurodegenerative diseases including Machado-Joseph disease*	49
Dr Ignacio Simo Motor Neuron Disease Research Centre, Macquarie University	*Mitochondrial dysfunction as a cause of MJD*	50
Ms Sushmitha Somanahalli Purushotham School of Medicine, Western Sydney University	*Evaluation of anti-inflammatory molecule in restoring K+ homeostasis during neurodegeneration*	51
Dr Hannah Suddull Dementia Research Centre, Macquarie University	*How Does the 3' UTR Sequence of mRNA Regulate Tau Expression?*	52

Abstract Lists

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Posters		
Dr Leila Akbari Dementia Research Centre, Macquarie University	*Analysis of Extracellular Tau Dynamics in Tau58 Mice*	54
Ms Marie Amigo Western Sydney University	*The role of the immune system in Multiple Sclerosis and Fibromyalgia: Novel Perspectives on disease pathogenesis*	55
Miss Anushka Chatterjee School of Medicine, Western Sydney University	*The impact of phytosomal curcumin diet on glial activation and neuroinflammatory markers on a mouse model of chronic neuroinflammation*	56
Miss Eleanor Clifton-Bligh The Australian Sports Brain Bank, The University of Sydney	*Tau filament structures associated with repetitive head injury and chronic traumatic encephalopathy (CTE)*	58
Ms Andrea Kuriakose Motor Neuron Disease Research Centre, Macquarie University	*Investigating the role of the microbiome-gut-brain axis within a mouse model of Machado-Joseph disease*	60
Miss Joanna New The Australian Sports Brain Bank. The University of Sydney	*Exploiting tau amyloid polymorphism for diagnosis of Chronic Traumatic Encephalopathy (CTE)*	61
Mr Daniel O'Shaughnessy Motor Neuron Disease Research Centre, Macquarie University	*MM-BWAP: Macquarie university Motor neuron – Bioinformatics Whole genome*	63
Ms Valeria Perales-Salinas Western Sydney University	*Evaluation of an Anti-Inflammatory in Restoring K+ Homeostasis during Neurodegeneration in Alzheimer's Disease*	64
Miss Zoe Zussa Motor Neuron Disease Research Centre, Macquarie University	*Integration is the foundation for discovery: Macquarie Neurodegenerative Diseases Biobank*	65

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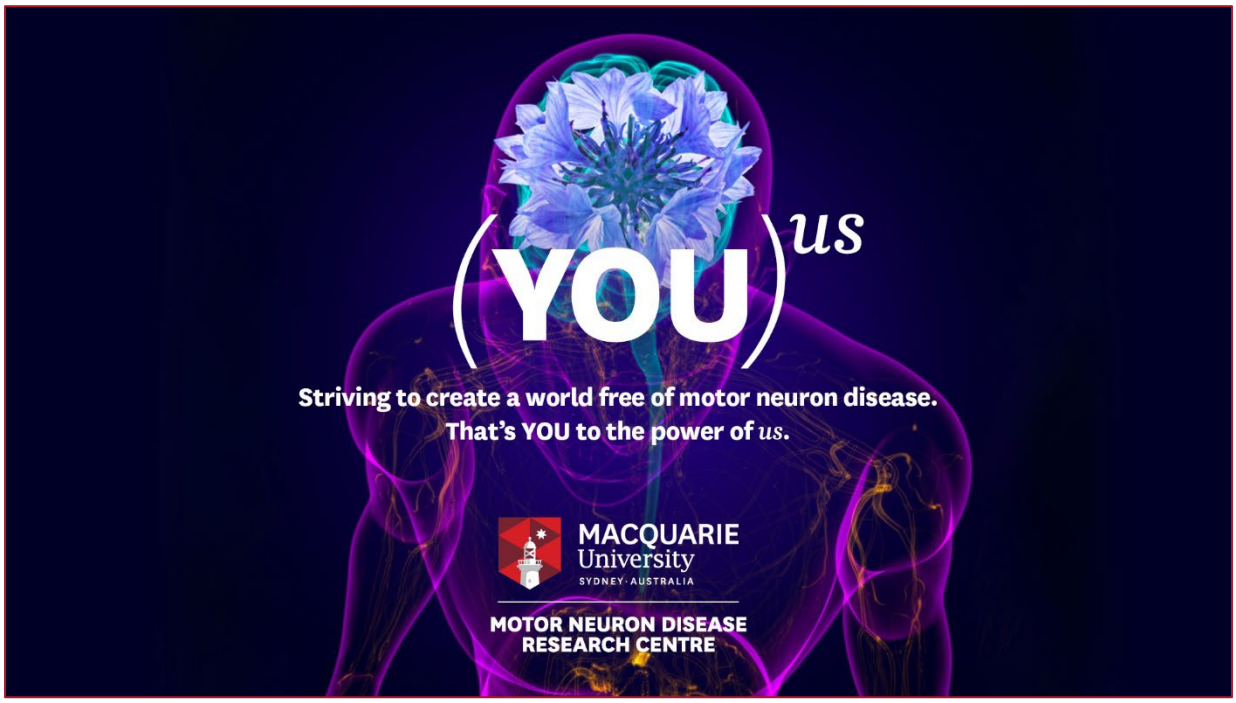
MOTOR NEURON DISEASE RESEARCH CENTRE

INVITED SPEAKER ABSTRACTS



PROFESSOR ROGER CHUNG

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Developing novel AAV gene therapies for ALS

We have previously discovered pathogenic mutations in the *CCNF* gene (encodes the CyclinF protein) in ALS patients, and subsequently determined that a physiological function of Cyclin F is to bind TDP-43 and facilitate its degradation via the ubiquitin-proteasome system. We have subsequently demonstrated that experimental overexpression of Cyclin F reduces TDP-43 levels incell culture and mouse studies. In this presentation, I will provide an overview of our commercialisation journey towards developing a Cyclin F-AAV gene therapy. This technology has been patented and licensed to Celosia Therapeutics, a Macquarie University spin-out company launched in late 2022.

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Presymptomatic pathological TDP-43 aggregation is a common feature in peripheral, non-central nervous system tissues in people with ALS.

*Fergal M. Waldron1, Tatiana Langerová1, Kristine Roberts1, Jenna M. Gregory*1*

Background

A recently developed TDP-43 RNA aptamer (TDP-43APT) with greater sensitivity and specificity for detecting pathological TDP-43, compared to currently available antibodies, has revealed novel pathologies in ALS, including early nuclear aggregation preceding disease symptoms. Also, whilst ALS has traditionally been considered a disease of the central nervous system and associated cell types, non-CNS manifestations of disease are gaining increasing awareness.

Methods

Using TDP-43APT to identify pathological TDP-43, and Stathmin-2 cryptic exon probes to demonstrate concurrent loss of TDP-43 function, we examined non-central nervous system tissues in a cohort of ante-mortem tissue taken from people who, years later, went on to develop ALS.

Results

Amongst organs with evidence of pathological TDP-43 aggregation, and loss-of-function, were colon, skin, muscle, blood vessels, gallbladder, and lymph node, with pathological TDP-43 aggregation present long before motor symptom onset. Amongst the seven people who went on to develop ALS for whom skin biopsies were taken prior to disease diagnosis, all seven were positive for pathological TDP-43. In one case of note, an individual with a C9orf72 mutation had two temporally distinct biopsies from the same skin site. We observed no pathological TDP-43 in the biopsy taken 24-months prior to ALS diagnosis but florid TDP-43 pathology in the same year as diagnosis but still prior to symptom onset, identifying a phenoconversion time-window within which skin TDP-43 pathology emerged.

Discussion

We report that pathological TDP-43 aggregation is a common feature in a number of organ systems prior to motor symptom onset in ALS. Cell types affected include peripheral neuronal cells, dendritic cells, chondrocytes, and other cells with a shared cell linage from the neural crest, implying a neurodevelopmentally defined cell-type specific predisposition to TDP-43 pathology, that may help us to guide peripheral biopsy and biomarker development. In line with this, skin and gut perhaps provide promising potential for ease of biopsy.

PROFESSOR KIM HEMSLEY

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Children get dementia too - and they urgently need treatment options!

The incidence of childhood dementia is 1 in 29001 – not too dissimilar to the number of people affected by cystic fibrosis. Childhood dementia is caused by > 170 individually rare genetically inherited disorders. Few have treatments available, and half of children with dementia die before the age of 10 years1. Patients experience global cognitive impairment that is progressive. In this presentation Kim will introduce you to childhood dementia and its impacts on children, families and communities. She will also describe the collaborative research being undertaken by her group at Flinders University, that is examining a variety of potential treatment approaches for patients with childhood dementia caused by Sanfilippo syndrome.

Elvidge et al (2023) Brain 146: 4446-4455. https://doi.org/10.1093/brain/awad242

PROFESSOR SIMON LEWIS

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Parkinson's Disease - Where are we now?

Parkinson's Disease is the fastest growing neurodegenerative disease in the world and has no cure. Patients progressively deteriorate across motor and non-motor domains with a significant incidence of institutional care. However, many potential pathophysiological targets have been identified and there is a recognised prodromal phase, which in combination with novel biological markers might allow the use of neuroprotective strategies at the earliest stages of disease. This presentation will focus on our current disease modifying strategies and also cover how we might find novel approaches for symptoms that lead to the loss of independence.

Abstracts

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Investigating the role of astrocytes in the pathophysiology of Amyotrophic Lateral Sclerosis

A growing body of evidence implicates non-cell autonomous disease mechanisms, including those involving glial cells and interneurons, in the pathogenesis of the devastating motor neuron disease Amyotrophic Lateral Sclerosis (ALS). We have therefore investigated the potential contribution of astrocytes to motoneuron pathophysiology in ALS. This has been achieved by utilising a combination of electrophysiological and anatomical techniques, applied to human iPSC-derived models, transgenic mice and human postmortem tissue. We have found that human iPSC-derived astrocytes harbouring ALS mutations cause dysfunction of human iPSC-derived motoneurons. This dysfunction, which occurs prior to any overt signs of motoneuron pathology or loss, is characterised by loss of action potential output and a reduction in the magnitude of voltage-gated sodium and potassium currents. More recent analysis of locomotor-related motoneuron output, recorded from ex vivo spinal cord preparations obtained from ALS model mice, has revealed dysfunction in the pathways by which astrocytes normally regulate motoneuron output. Finally, given that astrocytes interact with neurons at synaptic junctions, forming tripartite synapses, we have assessed the fate of tripartite synapses in ALS. Analyses of synapses in mouse models and human postmortem tissue has revealed a selective vulnerability of tripartite synapses throughout the spinal cord. Taken together, our findings suggest that aberrant signalling between astrocytes and spinal neurons, potentially at tripartite synapses, contributes to ALS pathogenesis and that therapeutic strategies which aim to re-establish normal astrocyte to neuron signalling may be beneficial towards the treatment of ALS.

Abstracts

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Harnessing patient iPSCs as a drug screening platform for sporadic ALS

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Modeling heterogeneous and largely sporadic neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), remains a notorious challenge to the discovery of effective treatments. Patient induced pluripotent stem cell (iPSC) technology holds enormous promise to model these diseases, however no studies to date have recapitulated neurodegeneration in sporadic neurodegenerative disease using large patient cohorts. To address this gap, we generated a rigorously validated large-scale iPSC library containing over 100 sporadic ALS (SALS) patients and developed a robust phenotypic screen interrogating motor neuron health and survival. In a population-wide screen, SALS patient-derived motor neurons undergo spontaneous degeneration recapitulating in-life clinical phenotypes of donors. Transcriptional profiles of SALS patient-derived motor neurons correlate with ALS post-mortem tissue, and SALS patient-derived motor neurons replicate the efficacy of riluzole, the only approved drug that prolongs life in ALS. In a focused drug screen, we re-evaluated over 100 drugs tested in clinical trials in ALS over the last 30 years and identified drugs superior to riluzole using this system. Recapitulation of key ALS pathology, in-life clinical phenotypes and riluzole efficacy validates the use of patient-derived neurons in SALS and neurodegeneration research, and paves the way for a new generation of ALS disease modeling and therapeutic development.

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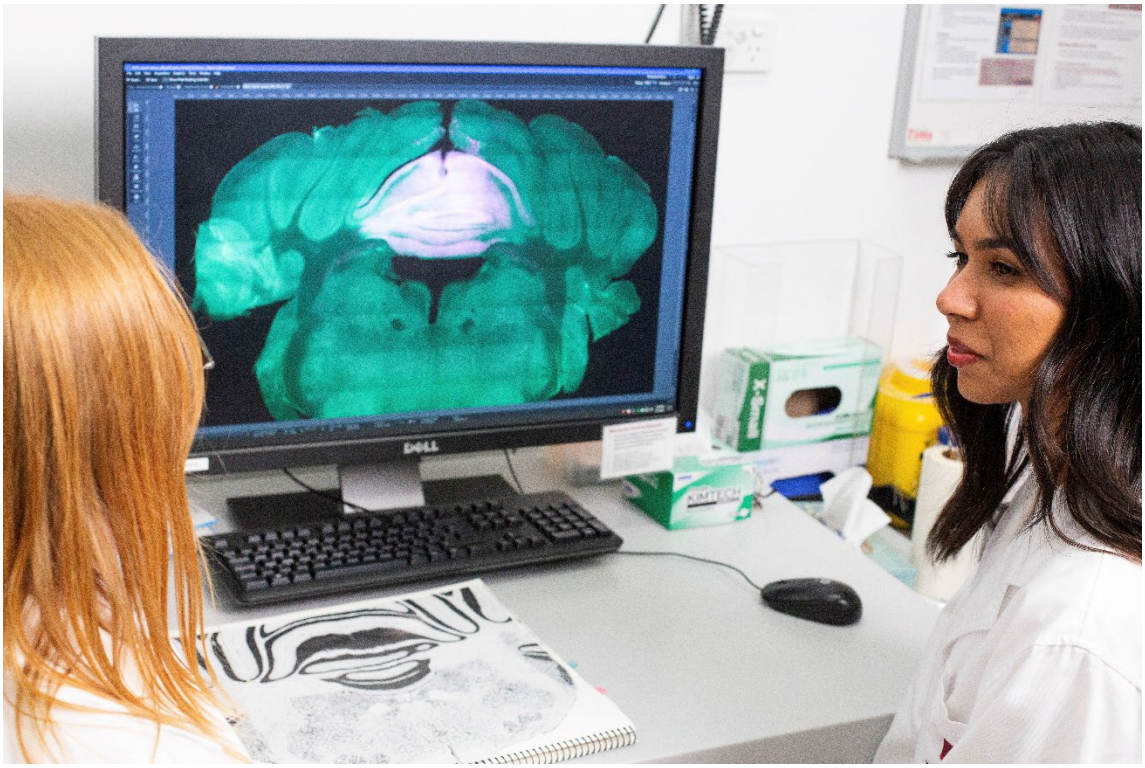
15-MINUTE SPEAKER ABSTRACTS



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Combining tauopathy and neuroinflammation exacerbates spatial learning impairments in a new double transgenic mouse model for Alzheimer's disease

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Background: Tau pathology and neuroinflammation are two key pathological features of Alzheimer's disease, but we do not fully understand how these features interact. To address this, we created a double transgenic mouse model (i.e. IL6-TAU) of chronic neuroinflammation combined with tauopathy, by crossing heterozygous glial fibrillary acid protein interleukin 6 (GFAP-IL6) mice with heterozygous TAU58/2 (expressing mutant human P301S) mice. We hypothesised that double transgenic mice would exhibit an accelerated and/or more severe motor and cognitive phenotype compared to GFAP-IL6 or TAU58/2 mice.

Methods: 6 and 12-month-old male and female IL6-TAU, GFAP-IL6, TAU58/2 and control littermates were assessed in behavioural domains including spatial memory (y-maze: 6 months, cheeseboard: 12 months), motor function (rotarod, pole test), sensorimotor gating (prepulse inhibition) and social recognition memory (social preference test).

Results: Spatial learning in the cheeseboard at 12 months was slower in IL6-TAU mice compared to all other groups, suggesting combined neuroinflammation and tauopathy impairs acquisition of spatial learning. This was not observed at 6 months in the y-maze, suggesting spatial learning deficits in IL6-TAU mice may only occur at a later age. Significant motor and sensorimotor gating impairments were observed in TAU58/2 and IL6-TAU mice at 6 and 12 months; these phenotypes were not exacerbated in IL6-TAU mice. Mice of all genotypes showed intact sociability and social recognition memory.

Conclusion: These experiments showed that neuroinflammation and tauopathy can interact, thereby worsening spatial learning in an age-dependent manner. This supports targeting both tauopathy and neuroinflammation for the treatment of cognitive impairments in Alzheimer's disease.

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Speech Pathologists' confidence levels and professional development needs in motor neurone disease (MND): An Australian Survey

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Abstract:

Clinician confidence is crucial for effective patient-professional relationships. Limited research explores confidence levels of allied health professionals, specifically speech pathologists (SPs), when supporting people with motor neurone disease (PwMND). This study investigated SPs' confidence levels across key practice areas: swallowing, oral secretions, oral hygiene, airway management, and communication. It also investigated associated demographic/background variables, facilitators/barriers affecting confidence development, and professional development needs.

Seventy-two SPs from Australia completed an online questionnaire. Quantitative data were analysed using descriptive statistics and association analysis, while content analysis was applied to open-ended responses.

Participants reported varied confidence levels, with higher confidence with general interventions like diet/fluid modification and clear speech strategies, but lower confidence in MND-specific interventions like voice preservation, secretion management, and electronic alternative and augmentative communication. Factors including years of experience, MND caseload proportion, multidisciplinary team structure, and clinician age were significantly associated with confidence. Participants identified facilitators/barriers to confidence development, categorised into four themes. Participants shared insights from their

experience supporting PwMND, informing development of practical tips for new clinicians.

The findings highlight the complex factors affecting SPs' confidence when supporting PwMND. A set of recommendations has been developed to advance multidisciplinary research and clinical practice in this area. Enhancing allied health workforce confidence can improve clinician satisfaction and patient care.

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Clinical Diagnostic Accuracy in the Sydney Brain Bank

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Diagnosing complex neurological disorders presents significant challenges, and inaccuracies in diagnosis can undermine patient care. Brain banks play a crucial role in assessing the accuracy of clinical diagnoses, providing valuable insights for enhancing diagnostic precision and patient outcomes. We conducted a prospective study of all autopsies performed at the Sydney Brain Bank, involving cases collected across Australia and New Zealand between 2004 and 2023. We evaluated the diagnostic accuracy for ten neurological disorders: Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, motor neurone disease, Huntington's disease, cerebrovascular disease, frontotemporal dementia, corticobasal degeneration, and progressive supranuclear palsy. Of the 822 cases analysed, 712 were clinically diagnosed with one of these disorders. Remarkably, 22% of patients had at least one incorrect diagnosis, and 15% had no correct clinical diagnoses. Diagnostic accuracy varied considerably, ranging from 100% for Huntington's disease to 13.5% for corticobasal degeneration. Moreover, there were significant differences in diagnostic accuracy between males and females for the diagnoses of Parkinson's disease. We summarised the autopsy-confirmed diagnoses of false positives to provide clinicians with alternative diagnoses to consider. These findings underscore the need for improved diagnostic methods and highlight the crucial role of brain banks in enhancing diagnostic accuracy and patient care.

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A Blood-Based Biomarker for Autophagy - the Cell's Waste Clearance and Recycling Pathway.

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Autophagy, the recycling of cytoplasmic waste, is essential for cellular health and metabolism. Autophagy dysfunction is linked to neurodegenerative diseases, including motor neuron disease (MND). However, the development of autophagy-targeted therapies has been stalled by the lack methods to measure human autophagy. We aimed to address this by identifying a blood-based biomarker to distinguish normal from impaired autophagy.

We hypothesized that autophagy impairment will result in metabolite changes detectable in blood. Global deletion of the essential autophagy gene Atg7 was induced in adult transgenic mice. After one month of autophagy deletion, tissue and serum were collected for western blotting and mass spectrometry for lipids and polar metabolite (sugars, amino acids) analyses.

A 50% reduction in Atg7 and 2-fold rise in p62 proteins confirmed autophagy deletion. Principal component analysis revealed control and autophagy-deficient mice clustering into separate groups indicating autophagy deletion gives rise to a unique metabolite signature. From volcano plots, 11 polar metabolites and 20 lipids were identified as significantly changing with autophagy deletion (fold changes ≥1.5).

To validate human translational relevance, metabolomic profiles of autophagy-deficient mice were compared with a plasma lipidomic study distinguishing MND patients (n=103) from healthy controls (n=30). Remarkably, 13 lipids were consistently altered in both the autophagy-deficient mice and MND patients, emphasizing the role of autophagy dysfunction in MND. With further validation, this biomarker could revolutionize development of autophagy targeted therapies and fill a critical gap in clinical practice by offering a measurable endpoint for autophagy interventions—ultimately improving the management of autophagy impacted diseases.

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Tau spreading in Alzheimer's disease models is facilitated by the amyloid-β precursor protein

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Alzheimer's disease (AD) is characterised by the aggregation of two proteins within the brain- amyloid-β which results from aberrant cleavage of the Amyloid Precursor Protein (APP) and deposits in extracellular plaques and the tau protein which forms neurofibrillary tangles. However, it is tau spreading that best correlates with clinical symptoms in AD, whilst the mechanisms that potentially drive tau spreading remain still unknown. More recently a study has demonstrated that binding of tau fibrils to the extracellular region of the Amyloid Precursor Protein led to the uptake of tau into cells, suggesting that APP may function as a tau fibril receptor during the spreading of tau, thereby contributing to disease progression. To address this and investigate whether APP modulates tau pathology spreading *in vivo*, we combined Alzheimer's disease mouse models with recently developed AAV- based reporter constructs, brain slice stimulations and microfluid chambers. This approach allowed us to stepwise uncover underlying molecular pathways of tau release/uptake/and spreading *in vivo,* and further decipher a novel role of APP in tau pathology spreading. More specifically, our data shows that APP facilitates the induction of tau pathology and promotes neuronal release and spreading of tau in *vivo*. Further our finding demonstrate that this process is amplified by pathogenic *APP* mutations as well as increased levels of APP. Accordingly, depletion of *APP* significantly reduced this effect, resulting in less seeding and spreading of tau. In summary, our data points to APP as being an integral part of tau pathology spreading and further delineates a novel role for pathogenic APP mutations in AD.

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Could heat therapy be utilised as a novel treatment for Alzheimer's disease? Insights from a pilot study in mice.

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Current treatments for Alzheimer's disease (AD) have severe side effects without pronounced beneficial impact on disease progression. Heat treatment (HT) induces heat shock proteins of 70 kDa (HSP70)1 and has therapeutic properties in chronic diseases such as cardiovascular disease2, diabetes3 and depression4. There is an inverse correlation between sauna frequency and risk of AD in humans5. We aimed to develop a HT protocol that has minimal welfare impacts (i.e. no anaesthesia required) and is clinically relevant, to be applied in mouse models of AD.

Adult C57BL/6 males were exposed to either 1) acute HT, at 40.8±0.2°C for 20 or 30 minutes, or 42±0.2°C for 20 minutes or 2) chronic HT 2 times per week for 4 weeks. We evaluated a range of behaviours and recorded body temperature every minute during HT. Bodyweight and health parameters were also recorded intermittently, until tissue was collected.

When incubator temperature was 42±0.2°C, significant HSP70 levels were detectable 4 h after acute (induced) or 72 h after (baseline) the last session of chronic HT in the hippocampus and prefrontal cortex, brain regions relevant to AD. Exploration behaviour was decreased while immobility time was increased in HT animals when compared to control mice.

Thus, our new sauna-like protocol is a valid model to increase levels of HSP70 in tissues relevant to AD and could be easily translated to clinical trials with no severe side effects. The model will now be applied in AD transgenic mice models to evaluate its ability to prevent or limit disease progression.

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Restoring Genomic Integrity: A Novel Strategy Against DNA Damage and Age- Related Diseases

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Abstract:
DNA damage is a serious threat to cellular viability, and it is implicated as the major cause of normal ageing[1, 2]. Hence, targeting DNA damage therapeutically may counteract age-related cellular dysfunction and disease, such as neurodegenerative conditions. Identifying novel DNA repair mechanisms therefore reveals new therapeutic interventions for multiple human diseases. Double-stranded breaks (DSBs) are the most deleterious type of DNA damage, which are repaired by either homologous recombination or non-homologous end-joining (NHEJ). In neurons, NHEJ is the only mechanism available, which is much more error prone. DSB damage is implicated widely in neurodegenerative diseases[1]. However, there are no therapeutic interventions to enhance DNA repair. Protein disulphide isomerase (PDI) participates in many diseases but its roles in these conditions remain poorly defined. Whilst PDI primarily localised in the endoplasmic reticulum (ER), it has also been detected in the nucleus, where its role also remains unclear. We describe here a novel role for PDI in DNA DSB repair following at least two types of DNA damage. PDI functions in NHEJ, and following damage it relocates to the nucleus, where it co-localises at DNA damage foci with critical DSB repair proteins. The redox activity of PDI mediates DNA repair, highlighting these cysteines as targets for therapeutic intervention. The therapeutic potential of PDI was also confirmed by its protective activity in a whole organism, against DNA damage induced in vivo in zebrafish. Hence, harnessing the redox function of PDI has potential as a novel therapeutic target against DSB DNA damage relevant to several human diseases.

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Spatially resolved transcriptomics of human cortex reveals unique disease signatures and potential biomarkers for chronic traumatic encephalopathy

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Chronic traumatic encephalopathy (CTE) is an environmental tauopathy found almost exclusively in individuals with a history of repeated exposure to mild head trauma. The disease is poorly described clinically, and at present CTE can only be diagnosed by post-mortem examination of the brain. There is a pressing need to understand the pathophysiology of this disease, and to identify biomarkers for diagnosis during life. CTE lesions first appear in the cortex and are randomly distributed, often requiring extensive sampling to find the pathognomonic pattern of perivascular hyperphosphorylated tau at the depths of cortical sulci. This renders molecular characterisation of lesions complicated and often confounded, particularly when fresh tissue is examined. We have addressed this by performing spatially resolved transcriptomics within and around known CTE lesions in human prefrontal cortex using the Visium platform. Within tau-positive CTE lesions we observed altered expression of hundreds of genes across multiple lesions; overexpression of four genes (GFAP, APNLR, AQP1, TNC) was universal. Together the alterations signify a complex long-term molecular response to brain trauma, including heightened astrocytic activity, neuroinflammation, altered blood-brain barrier function, and extracellular matrix remodelling. We also observed expansion of the first cortical layer in CTE cases, and concomitant elevated expression of RELN and NDNF, which may indicate a compensatory response to neuronal loss that is unique to CTE. Together these gene expression signatures provide the first glimpse into the intricate molecular dynamics underlying CTE lesions *in situ*, and provide candidate molecules to explore for the development of in-life diagnostics.

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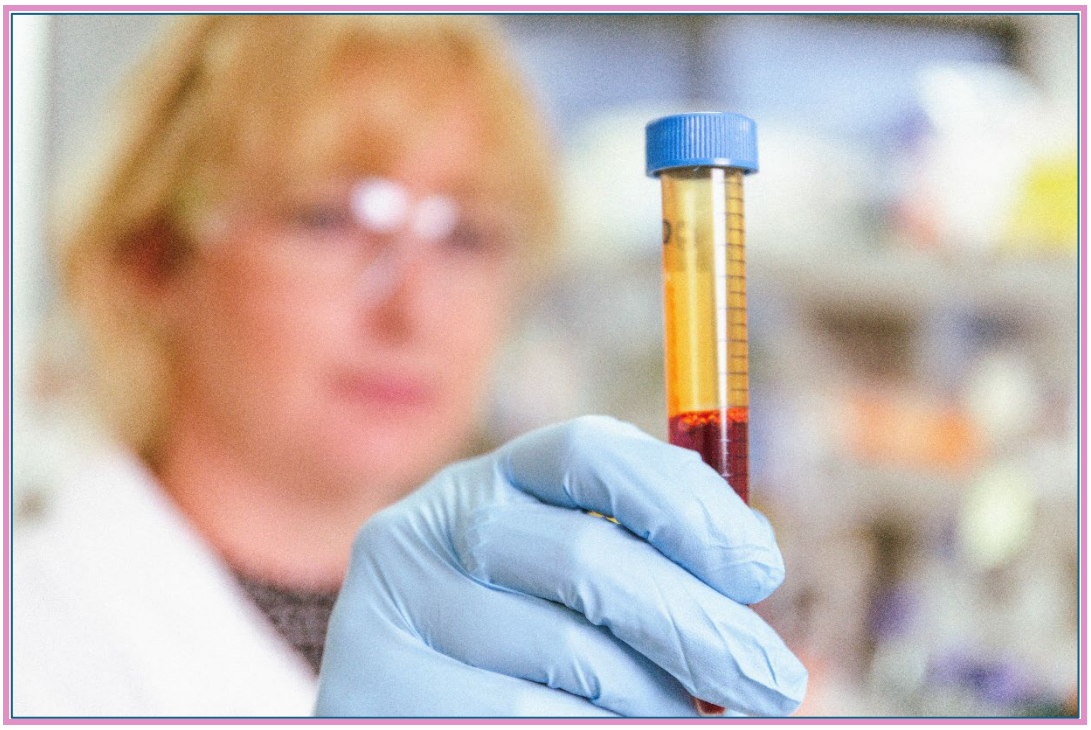
5-MINUTE SPEAKER ABSTRACTS



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Chronic traumatic encephalopathy and other neurodegenerative comorbidities seen in the Australian Sports Brain Bank

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Chronic traumatic encephalopathy (CTE) is a degenerative brain disease that can only be detected after post-mortem examination of the brain. CTE is characterised by the abnormal aggregation of hyperphosphorylated tau in neurons seen around blood vessels at the sulcal depths of the cerebral cortex. The Australian Sports Brain Bank (ASBB) was established in 2018 to identify the prevalence of CTE in at risk Australians and to support research to understand CTE further. So far, ninety-nine cases have been reported through the ASBB, with forty-eight (49%) of those being found to have CTE. When excluding other proteinopathies (such as TDP-43, beta-amyloid and alpha-synuclein) the most common neuropathological comorbidities seen in the CTE group included small vessel disease and ageing-related tau astrogliopathy. While repetitive head injuries were common to all CTE cases, these comorbid pathological findings in a relatively “pure” and younger cohort of CTE cases reinforces the concept that dysfunctional astroglia, particularly at the blood brain barrier, are likely involved in the underlying pathophysiology of CTE. This knowledge together with other data may assist future studies in targeting novel mechanism to detect CTE lesions during life.

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Exploratory analysis of ADAM10 isoforms levels and activity in neuron-like cell fractions.

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Introduction: Alzheimer's disease (AD) pathology involves the accumulation of amyloid-beta (Aβ) peptides into senile plaques generated by Amyloid Precursor Protein (APP) cleavage by β- secretases. When APP is cleaved by ADAM10 instead, neuroprotective fragments are released. ADAM10 possesses three isoforms: a zymogen (proADAM10), a proteolytically active mature (mADAM10), and a soluble (sADAM10) isoform. Our group has shown that sADAM10 levels and activity are altered in the plasma of persons with AD. Thus, we aimed to investigate the levels and activity of ADAM10 isoforms in neuron-like cells to understand their central functioning.

Methods: SH-SY5Y cells were differentiated into neuron-like cells using retinoic acid. The media was collected, and the cells were fractionated into cytoplasmic, membrane-bound, and nuclear protein-rich portions. Western blotting (WB) experiments were performed on each fraction to detect ADAM10 isoforms and assess fraction purity using anti-GAPDH (cytoplasm), anti-VDAC (membranes), and anti-Lamin A/C (nuclei) antibodies. Antibodies targeting the N-terminal and C- terminal regions of ADAM10 were used to detect the soluble and membrane-bound isoforms, respectively. Additionally, enzymatic activity assays were conducted.

Results: The characterization of the fractioning process and preliminary results of the activity assays show feeble sADAM10 activity in the cell medium, compared to mADAM10 in the membrane and cytoplasm fractions and recombinant ADAM10 ($p < 0.001$).

Conclusion: These preliminary results show that sADAM10 has feeble activity in neuron-like cells, which agrees with our previous findings, validating the potential use of plasma ADAM10 as a blood-based AD biomarker.

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Actin dysregulation in transgenic FUS animal models and its novel isoform EC-FUS

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Abstract:

Objectives: FUS is an RNA/DNA binding proteins that mislocalized to the cytoplasm and causes a severe form of Amyotrophic Lateral Sclerosis (ALS) (1,2,3). A novel isoform of FUS, which we have termed extracellular FUS (EC-FUS) is the only extracellular pathological protein linked to ALS. Rapid assembly and disassembly of actin filaments, involving the polymerisation from monomeric G-actin to polymeric F-actin, regulates many vital responses in neurons and this is mediated by actin binding proteins (5,6). However, the interplay between actin dynamics and FUS and EC-FUS pathology has not been characterized yet.

Methods and Materials: Three homozygous (FUS (+/+)) and three non-transgenic (NTg) brain mice were used in this study. G-actin and F-actin in vivo assay and western blotting for anti pCofilin/Cofilin, pLIMK/LIMK and profilin-1 used to measure actin dysregulation. We also used two days zebra fish lysates in three groups: EGFP-FUS, EGFP-WT and NTg. By using HA-stable HEK cells expressing EC-FUS and their concentrated conditioned media, we also monitored actin dysregulation in this cell line.

Key Findings: More F-actin (Filament actin) and less G-actin (monomeric actin) were present in animal models. We also investigated more pCofilin/Cofilin in these models. Also increased phosphorylation of LIMK1/2 and profilin-1 were also detected, providing mechanistic insights into these observations in FUS mice brain. FUS mislocalisation, inclusion formation and stress granule formation resulted after pharmacological actin polymerization, linking dysregulation of actin dynamics to FUS pathology in ALS. These findings explain actin dynamic dysregulation as a novel mechanism leading to FUS and EC-FUS pathology in ALS.

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The contribution of ataxin-3's deubiquitinase function to the pathophysiology of neurodegenerative diseases including Machado-Joseph disease

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Abstract:

Machado-Joseph disease (MJD) is an incurable neurodegenerative disease characterised by progressive ataxia, wheelchair dependence, and the requirement of full-time care. The cause of MJD is mutation of the *ATXN3* gene, which causes the ataxin-3 protein to contain an abnormally long chain of the amino acid glutamine, termed polyglutamine (polyQ) expansion. PolyQ-expanded ataxin-3 misfolds, aggregates, and forms neurotoxic inclusions. The attachment of ubiquitin to proteins is termed ubiquitination and is known to impact the abundance, subcellular localisation, and function of proteins. Ataxin-3 functions as a deubiquitinase (DUB) enzyme, meaning it removes ubiquitin from proteins. Increasing evidence suggests that polyQ expansion alters ataxin-3's DUB function, however, how ataxin-3's DUB function is altered by polyQ expansion and how this contributes to MJD pathology is unclear.

We have explored how the DUB function of ataxin-3 is altered by polyglutamine expansion and how this contributes to MJD. We have identified that matrin-3, a protein implicated in amyotrophic lateral sclerosis (ALS), is differentially K48-ubiquitinated in cells expressing polyglutamine-expanded compared to wild-type human ataxin-3. We have subsequently identified that: 1) protein levels of matrin-3 are increased in the cerebellum and cerebrum of MJD mice; 2) ataxin-3 and matrin-3 co-localise and co-interact in cells; 3) matrin-3 is degraded predominantly by autophagy. Collectively, this evidence suggests a potential role for ataxin-3 in regulating matrin-3 homeostasis. We are continuing to investigate whether ataxin-3's DUB function may be involved in the regulation of matrin-3, and whether this contributes to MJD and ALS to hopefully identify novel treatment avenues for both diseases.

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Mitochondrial dysfunction as a cause of MJD

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Machado Joseph disease (MJD) is a progressive neurodegenerative disease characterised by devasting motor impairments in patients. MJD is caused by the inheritance of an expanded CAG trinucleotide repeat region within the ATNX3 gene, leading to an expanded polyglutamine (polyQ) tract within the ataxin-3 protein, causing neurodegeneration within the brain and spinal cord.

Within this study, we explored mitochondrial function in cell culture, zebrafish and rodent models of MJD to gain an understanding of mitochondrial function in the disease, and possible mechanisms of dysfunction. Proteomics analysis of MJD and WT brain samples revealed that the oxidative phosphorylation pathway, including most of the proteins acting in the electron transport chain within the mitochondrial inner membrane, were downregulated in both male and female MJD mice in comparison to WT mice. Moreover, mitochondrial analysis from primary culture neurons extracted from MJD mice showed a significant decrease in the number of branches, the number of branch junctions per mitochondria and the mean form factor (which provides information about mitochondrial morphological complexity). Finally, we observed a greater effect of rotenone on zebrafish expressing human h*ATXN3* with 84Q compared to zebrafish carrying h*ATXN3* with 23Q, which is consistent with lower levels of SDHA observed by western blot in these mutant fish. Additionally, succinate levels were higher in all MJD zebrafish, primary cell and brain samples from transgenic mice. Considering these findings, we concluded that *ATNX3* mutations influence mitochondrial ETC activity and that further investigation is warranted to identify potential targets for disease treatment.

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Evaluation of anti-inflammatory molecule in restoring K^+ homeostasis during neurodegeneration

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Background - Neuroinflammation and glial cell dysfunction are associated with neurodegenerative diseases and are central to disease pathology. Amyotrophic lateral Sclerosis (ALS) is a neurodegenerative disease associated with a specific loss of motor neurons (MNs) leading to motor dysfunctions. $SOD1^{G93A}$ mice model of ALS is accompanied by increased levels of neuroinflammation, reactive astrocytes and an impaired ability of astrocytes to maintain K^+ homeostasis. This study aims to evaluate the therapeutic effect of phytosomal Curcumin, a cytokine suppressive anti-inflammatory drug in ameliorating ALS disease progression and motor symptoms in $SOD1^{G93A}$ mice.

Methods – In this study, we used various behavioural tests, extracellular electrophysiological recordings and imagining techniques to assess motor functions, dysregulation of K^+ ion homeostasis, and neuroinflammation levels.

Key findings – Through extracellular electrophysiological recordings we observed a significant reduction in the astrocytic K^+ clearance rate in layer 2/3 of the primary motor cortex of aged $SOD1^{G93A}$ mice fed with a normal diet. This decrease was accompanied by signs of astrocytic cellular hypertrophy and increased reactivity. Additionally, our preliminary behaviour results indicate significant motor deficits in $SOD1^{G93A}$ mice that were fed with a normal diet in the open field test and accelerod test. However, $SOD1^{G93A}$ mice fed with curcumin diet did not improve motor functions.

Conclusions – So far, our findings indicate a limited effect of curcumin in rescuing motor deficits in $SOD1^{G93A}$ mice. However, we are exploring the ability of curcumin in reducing levels of neuroinflammation and restoration of K^+ homeostasis in $SOD1^{G93A}$ mice.

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How Does the 3' UTR Sequence of mRNA Regulate Tau Expression?

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Abstract

The majority of Tau-focused research has concentrated on the protein; however, regulation of tau mRNA and the potential RNA Binding Proteins (RBPs) of this transcript have been under-studied. The regulation of mRNA stability is crucial for controlling mRNA, and subsequent protein expression levels in neuronal cells. Specific mRNA half-lives are dependent on sequences located within their 3' Untranslated Region (3'-UTR), which are recognized by RBPs. The 3'-UTR of the tau-encoding gene MAPT mRNA has been recognized as critical in providing its stability and tau protein expression. However, RBPs that interact with the MAPT mRNA are yet to be identified.

Here, we utilised a newly established mouse line, Tau.3U/MS2, that expresses an introduced MS2 RNA tag sequence before the 3'-UTR of *MAPT*. The MS2 tag forms RNA loops that are recognised by the MS2-tag binding protein (MCP) conjugated to a biotin-labelling protein (APEX2). This allows for the study of MAPT mRNA in vivo, to identify 3'-UTR interacting proteins, using Label Free Quantitation Mass Spectrometry (LFQ-MS).

LFQ-MS analysis identified 2124 proteins. Applying statistical and STRING analysis, 8 proteins were identified to be involved in mRNA 3'-UTR binding, along with other potential molecular functions including 5'-UTR mRNA binding, rRNA binding, and pre-RNA binding. Proximity labelling has proven to be a valuable method for the identification of RNA–protein interactions. Here we present preliminary data for potential mRNA Tau-binding proteins. Illuminating the importance of understanding RBPs that are essential for molecular neuronal function and the relevance of the 3'-UTR for neuronal development and physiology.

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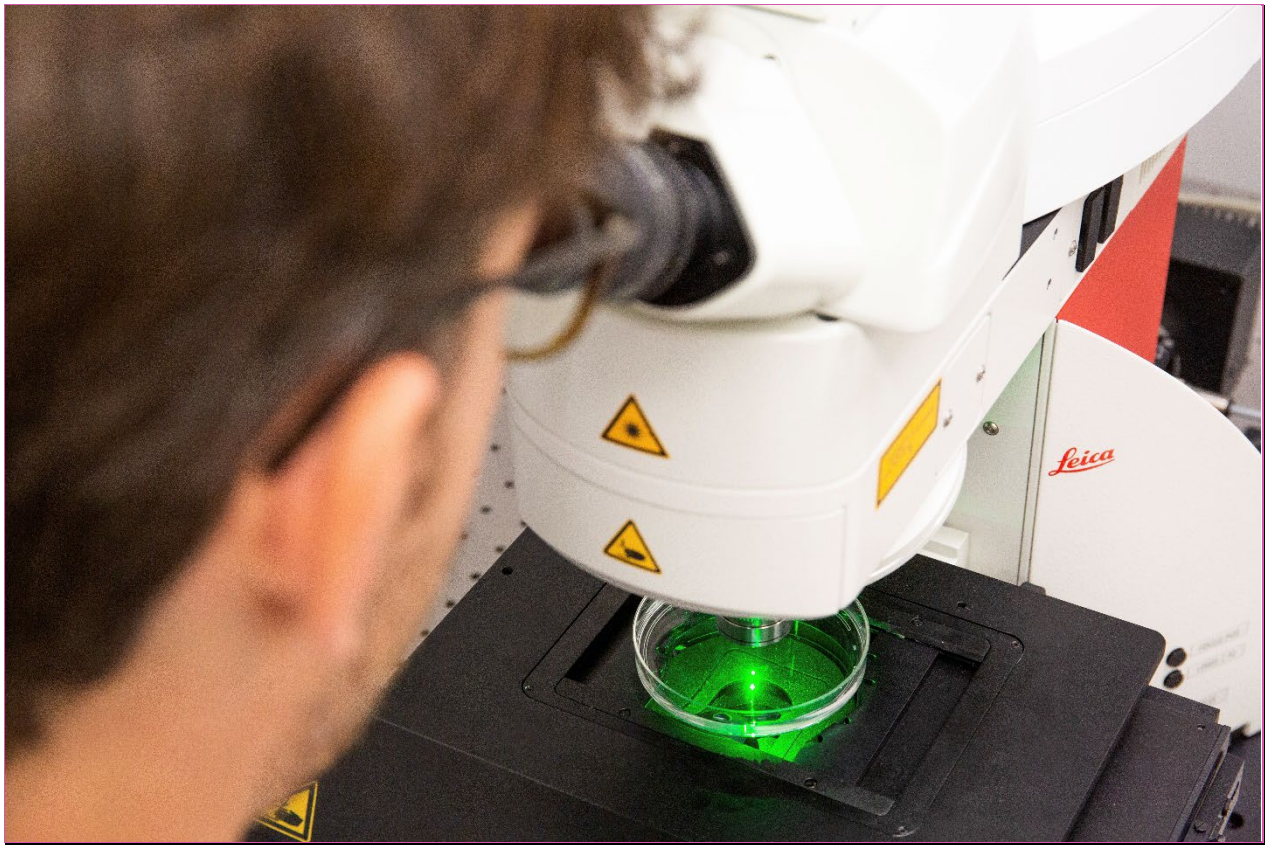
POSTER PRESENTER ABSTRACTS



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Analysis of Extracellular Tau Dynamics in Tau58 Mice

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Aim: Use microdialysis to analyse extracellular tau levels in a dementia mouse model.

Background: Tau accumulation is a hallmark of Frontotemporal Dementia (FTD) and Alzheimer's Disease (AD). In these diseases, tau becomes hyperphosphorylated and forms tangles that disrupt brain function and contribute to cognitive decline. Tau spreads throughout the brain via a "prion-like" mechanism, propagating pathological tau across neurons. Understanding tau propagation is key to developing targeted therapies for AD and FTD. This project utilized an established microdialysis technique to study extracellular tau in a mouse model of Frontotemporal Dementia (Tau58 mouse strain). Microdialysis allows continuous sampling and analysis of extracellular fluid, offering valuable insights into dynamic changes in analyte concentrations over time.

Methods: Wild-type and transgenic Tau58 mice, which express human tau carrying the P301S pathogenic mutation, ranging in age from 3 to 7 months (both genders) were utilised for this study. Mice were surgically implanted with a microdialysis probe (2MDa cut-off) and then samples were collected over a 48-hour period. Samples were analysed with ELISA to determine levels of human tau in the collected interstitial fluid.

Results: We observed an increase in extracellular tau levels following neuronal stimulation (via application of KCl) compared to baseline.

Conclusion: With this study, we characterised the levels of extracellular tau present in the brains of Tau58 mice. Having established the baseline levels of extracellular tau, we next aim to identify the molecular mechanisms that contribute to this process and identify factors that can modulate tau propagation.

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The role of the immune system in Multiple Sclerosis and Fibromyalgia: Novel Perspectives on disease pathogenesis.

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Background: Multiple Sclerosis (MS) is a common non-traumatic disabling disease affecting young adults and characterised by chronic inflammation and demyelination. While MS is commonly classified as an autoimmune disease, the precise mechanisms responsible for the immune system's recognition of self-proteins as antigenic targets remain elusive.

Objective: We aim to analyse the MS-associated immunological characteristics to identify the spectrum of autoantigens that potentially contribute to the onset and progression of the disease. Therefore, we could gain a better understanding of the disease's aetiology and a more precise diagnosis during its early stages.

Methods: We used mass spectrometry-based proteomics to compare the proteome signature of plasma from individuals with MS, Fibromyalgia and control, and identified significant changes in protein expression functional pathways. In parallel, we assessed the antigen auto-recognition with IgG immunoprecipitated derived from each individual with dot blot assays and SDS-PAGE separations. In-gel digestion has been performed on the antigens pulled down with IgG.

Results: Across MS and Fibromyalgia samples, plasma-based proteomic analysis specifically identified a host of immune-related proteins and provided insight into immunological characteristics in the later stages of both diseases. The co-immunoprecipitation of IgGs and bound antigens showed proteins expressed selectively in some participants. Lastly, the dot blot assays revealed variable cross-reactivity across the samples and conditions.

Conclusion: MS and fibromyalgia exhibit various post-pathogenic changes commonly observed in various brain disorders. However, in-depth studies examining the immune cross-reactivity involving host and foreign antigens are needed to distinguish MS- and fibromyalgia-specific alterations and unravel crucial insights into the disease's pathogenesis.

Keywords: Multiple Sclerosis, Fibromyalgia, Neuroimmunology, Autoimmunity, Mass spectrometry.

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The impact of phytosomal curcumin diet on glial activation and neuroinflammatory markers on a mouse model of chronic neuroinflammation

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Chronic neuroinflammation is a pathological hallmark for neurodegenerative disorders triggered by internal or external stimuli leading to altered central nervous system (CNS) homeostasis, production of proinflammatory cytokines, chronic glial activation, overexpression of neuroinflammatory markers and protein misfolding. This multifaceted nature of neurodegenerative disorders demands therapeutic strategies which will have an impact on the cellular and molecular phenotype without causing deleterious effects. Therefore, in this study, we explored a highly bioavailable phytosomal curcumin formulation in a mouse model of chronic neuroinflammation (GFAP-IL6).

A comprehensive approach combining transcriptomic analysis of the cerebellum, hippocampus, amygdala and prefrontal cortex and immunohistochemistry along with stereology was employed to investigate the effect of curcumin supplementation on neuroinflammatory markers and glial activation on mice at 9 months age.

Phytosomal curcumin feeding was able to interfere with the neuroinflammatory pathways by downregulating the mRNA levels of pro-inflammatory markers *P2rx7* and *Nfkb1* in the hippocampus as compared to the animals on control diet. In female GFAP-IL6 mice, the amygdala was the region that curcumin feeding had the greatest impact with genes such as *Aif1, C3, Nfkb1, S100a10, Tmem119* being downregulated. Curcumin diet also had a positive impact on the glial activation with lower microglial numbers in the cerebellum along with lower microglial and astrocyte numbers in the hippocampus as compared the mice on control diet.

Our study on phytosomal curcumin supplementation in GFAP-IL6 mice mostly showed positive effects on neuroinflammatory markers and glial cells therefore making it a therapeutic potential against chronic neuroinflammation either by reversing or slowing down the neuroinflammatory process.

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Tau filament structures associated with repetitive head injury and chronic traumatic encephalopathy (CTE)

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Abstract:

Chronic traumatic encephalopathy (CTE) is a neurodegenerative tauopathy uniquely associated with prior exposure to repeated head injury such as that sustained during contact sport or military service.[1,2] Diagnosis of CTE is made post-mortem by identifying a pathognomonic lesion defined by the abnormal deposition of hyperphosphorylated tau (p-tau) protein in neurons around small blood vessels at the depth of cortical sulci.[2] Whilst p-tau deposition also occurs in Alzheimer's disease (AD), the spatial and temporal pattern and molecular structural configuration differs from CTE.[3] The current diagnostic method employs an anti-p-tau antibody to detect the distinct deposition patterns.[4] However, aside from p-tau, very little is known about CTE pathophysiology and the absence of CTE-specific biomarkers impedes clinical detection or monitoring during life. Moreover, anti-p-tau antibodies cannot discriminate AD and CTE tau deposits which presents challenges for diagnosing comorbid CTE/AD pathology.

This study reports on differences in proteome profiles and tau structure between CTE and AD. Using the Sequential Window Acquisition of All Theoretical Mass Spectra (SWATH-MS) method, we compared the brain proteomes of CTE, AD and control samples to discover protein biomarkers and gain insights into CTE pathogenesis. Tau structural differences were investigated using immunohistochemistry. We compared MC1, an antibody reportedly selective for the tau conformation in AD,[4] to an anti-p-tau antibody on CTE, AD and comorbid CTE/AD samples. This approach will assess whether MC1 can differentiate CTE and AD tau deposits. Identifying CTE-specific biomarkers and differentiating CTE tau from AD tau are important steps towards diagnosis and treatment of CTE during life.

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Investigating the role of the microbiome-gut-brain axis within a mouse model of Machado-Joseph disease

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Abstract:

Machado-Joseph disease (MJD) is a progressive neurodegenerative disease characterised by devastating motor impairments in patients. MJD is caused by the inheritance of an expanded CAG trinucleotide repeat region within the *ATXN3* gene, leading to an expanded polyglutamine (polyQ) tract within the ataxin-3 protein. Production of polyQ expanded mutant ataxin-3 leads to the formation of toxic aggregates and neurodegeneration within the brain and spinal cord.

Growing evidence has highlighted the role of the microbiome-gut-brain axis in the pathogenesis and progression of several neurodegenerative diseases. As such, previous work from our group has identified pre-symptomatic microbial shifts prior to the onset of motor symptoms within the CMVMJD135 mouse model of MJD. Additionally, these shifts were found to correlate with the severity of disease at later stages[1]. Within a separate study, we found that alongside microbiota changes, MJD mice exhibit a faster gut transit time in comparison to WT mice[2]. Thus, we aimed to explore the possible mechanisms causing these changes within the microbiome-gut-brain axis, and whether this preceded or followed central neurodegeneration. Therefore, this present study focused on quantifying the formation of ataxin-3 aggregates within the brain relative to proteinopathy and morphological changes within the gut of pre- and early symptomatic MJD mice. Interestingly, we observed aggregates in the brains of pre-symptomatic MJD mice at an earlier timepoint than previously reported, at a similar timepoint to which we observed changes within the microbiota. However, we observed no aggregates, changes in enteric neuron populations or morphology within the gut.

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2. Unpublished data.

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Exploiting tau amyloid polymorphism for diagnosis of Chronic Traumatic Encephalopathy (CTE).

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Abstract

Tauopathies are a heterogenous group of neurodegenerative diseases characterised by intracellular deposition of abnormal misfolded tau protein with hallmark amyloid structure. A lack of reliable biomarkers with broad and often overlapping clinical syndromes makes accurate diagnosis of tauopathies a pressing, unmet need[1]. Chronic Traumatic Encephalopathy (CTE) is a clinical tauopathy associated with common and prolonged exposure to repetitive head impacts, such as those sustained through contact sports, military engagements or interpersonal violence[7-8]. Neuropathological lesions of tau in CTE are well characterised, but currently only accurately identified with postmortem examination[6].

High resolution cryo-electron microscopy reveals that the tau-amyloid ultrastructure is extremely diverse across tauopathies including CTE and Alzheimer's disease (AD), a phenomenon known as polymorphism[2-5]. Moreover, advances in conformation-based detection arrays show promise towards the development of highly specific small molecule binders for disease-associated tau polymorphs[9]. This work reports on an *in vitro* system for recombinantly producing tau amyloid fibrils comprising both CTE and AD polymorphs. Fibrils produced are screened against a suite of fluorescent amyloid-binding probes and complete excitation/emission spectral information utilised to identify unique profiles for polymorphs of interest. *In vitro* results will be compared and validated with *ex vivo* fibrils ascertained from CTE and AD patients within serial sections from fixed human cortex tissue provided by a collaboration with The Australian Sports Brain Bank. These findings may facilitate the discovery of a binder capable of discerning tau-polymorphs such those implicated in CTE and AD and may guide research towards improved diagnosis and management of CTE during life.

Abstracts

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MM-BWAP: Macquarie university **M**otor neuron – **B**ioinformatics **W**hole genome **A**nalysis **P**ipeline

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Abstract:
Motor neuron disease (MND) is a progressive neurodegenerative disease leading to muscle weakness, paralysis, and death, on average, 27 months after symptom onset. MND is genetically heterogenous, and heritability evidence suggests that there is a genetic component underlying both inherited and sporadic MND cases. Large-scale genomics offers valuable insights into MND, yet the bioinformatic processing, management and updating of these large datasets can be complex and prohibitive. Our continual development of the MMBWAP pipeline aims to support the Macquarie University MND Research Centre through streamlining computational analysis and providing additional annotated resources to support interpretation for both researchers and clinicians.

MM-BWAP is designed in a highly modular fashion using the *nextflow* workflow language, for both short-read WGS and RNA sequencing data. Carried out in according to clinical best practice, the pipeline also provides detailed quality metrics to ensure high quality outputs. MM-BWAP is structured with a core workflow for alignment, phasing, variant calling, and variant aggregation via genomicsDB, with multiple automated annotated analysis branches dependant on researcher questions: comparative genomics, clinical genomics, genotyping known disease-causing genetic variation (single nucleotide variants, indels, short tandem repeats), polygenic/oligogenic inheritance, dual de novo short tandem repeat identification, and known and cryptic alternative splicing events.

We have utilised an extensive cohort of genomic datasets and sample-matched clinical data, including matched WGS, RNA (blood & brain), pedigrees (where available) and biobank/clinic patient data to identify sequence variation linked to disease, and to investigate potential MND biomarkers. Integrating this data with the MM-BWAP pipeline has significantly improved our analytical throughput and quality.

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Evaluation of an Anti-Inflammatory in Restoring K+ Homeostasis during Neurodegeneration in Alzheimer's Disease

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Abstract:

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder characterized by the accumulation of amyloid-beta plaques, tau tangles, and chronic neuroinflammation, leading to synaptic dysfunction and neuronal death. Recent research highlighted the role of disrupted potassium (K^+) homeostasis in AD, with astrocytes playing a crucial part in maintaining this balance. This disruption is associated with increased level of neuroinflammation, which has been shown to contribute to neuronal hyperexcitability and accelerate neurodegeneration. The aim of our study is to investigate the potential of phytosomal curcumin, a highly bioavailable form of curcumin, as a therapeutic agent to mitigate neuroinflammation and restore K^+ homeostasis.

Using two complementary mouse models: the 5xFAD model, which mimics AD pathology, and the GFAP-IL6 model, which simulates chronic neuroinflammation, we aim to explore the effects of long-term dietary supplementation with curcumin. We hypothesize that curcumin will reduce neuroinflammatory markers, enhance K^+ clearance rate, and modulate key signalling pathways involved in astrocytic activation and neuroinflammation. To achieve this, we measure K^+ clearance rates in acute brain slices using K^+-selective microelectrodes, assess glial reactivity through immunohistochemistry, and analyse molecular pathway activation via qPCR and Western Blot.

Preliminary results from the GFAP-IL6 mouse model indicate trends suggesting that chronic neuroinflammation may impact astrocytic K^+ clearance rates. Although the data is not yet statistically significant, early observations show a possible reduction in K^+ clearance in the GFAP-IL6 mice compared to controls, with some improvement following curcumin supplementation. These findings will be further investigated to clarify the role of curcumin in modulating K^+ homeostasis and its potential to counteract neuroinflammatory processes in AD.

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Integration is the foundation for discovery: Macquarie Neurodegenerative Diseases Biobank

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Around 140,000 new cases of motor neuron disease (MND) are diagnosed globally each year, with ~2,000 Australians currently suffering from this fatal neurodegenerative disease. The progressive degeneration of motor neurons leads to muscle weakness, paralysis, and death within 2-5 years of symptom onset. MND is biologically complex, with gene mutations as the only proven cause.

The Macquarie Neurodegenerative Diseases Biobank (MQND Biobank) was established in 2013 as a research-clinical interface between the MND Research Centre and MQ Health Neurology Clinic. The MQND Biobank aims to provide resources for MND researchers to perform integrative research, coupling clinical and demographic information with derivative omics data obtained from longitudinal biospecimen collections.

MQND Biobank has recruited 1,117 participants, 522 MND patients (39.5%F, average age 65±12.3 years) and 593 control participants (62.2%F, average age 58±15.3 years). Every 3-6 months, clinical data and biospecimens including DNA, RNA, plasma, serum, urine, and hair are collected. A subset of participants have cerebrospinal fluid (CSF), fibroblasts, post-mortem brain and spinal cord available. The MQND Biobank currently holds 74,000 biospecimens with MND cases and control participants having an average of 3.9 and 2.9 longitudinal collections, respectively.

We have generated over 5,400 derivative datasets for MND patients and controls from the MQND Biobank and historical DNA collections including whole-genomes (blood- and brain-derived, n=1,088), whole-exomes (n=135), transcriptomes (blood-derived n=210, brain-derived n=165), methylation arrays (n=1,677) and SNP microarrays (n=2,343). Three-quarters of participants have 2 or more different datasets available.

We have established the largest MND biobank in Australia, which holds biospecimen-derived data and time-point matched clinical data. This comprehensive resource has been integrated to identify MND genetic causes and risk alleles, disease-specific gene expression profiles and biomarkers, and will be invaluable for future investigations of personalised medicine in MND.

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