

The 6th Annual Macquarie Neurodegeneration Meeting

14 SEPTEMBER 2023

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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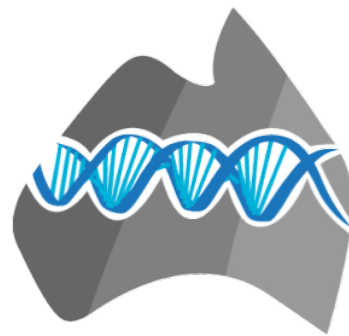
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Welcome



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	
<u>Professor Julie Atkin</u>	Co-Director
<u>Professor Ian Blair</u>	Co-Director
Christina Cassidy	Centre Administrator
<u>Flora Cheng</u>	Research Assistant
<u>Dr Pradeep Cholan</u>	Research Assistant
<u>Dr Lyndal Henden</u>	Postdoctoral Research Fellow Research
Fabiha Farzana	PhD Candidate
<u>Dr Jenn Fifita</u>	Research Fellow
<u>Dr Jia Li</u>	Macquarie University Research Fellow
<u>Dr Sina Shadfar</u>	Postdoctoral Research Fellow
<u>Associate Professor Bingyang Shi</u>	Macquarie Medical School
<u>Dr Dean Southwood</u>	Postdoctoral Research Fellow
<u>Dr Sharlynn Wu</u>	Postdoctoral Research Fellow

Program

Conference Opening	
9:00 am -9:30 am	Registration
9:30 am – 9:35 am	Welcome Remarks by Professor Ian Blair Co-Director Motor Neuron Disease Research Centre Macquarie Medical School Macquarie University
Session 1 Associate Professor Bingyang Shi & Dr Jennilee Davidson	
9:35 am – 10:05 am	Associate Professor Xiaobo Mao Institute for Cell Engineering, Department of Neurology Johns Hopkins University School of Medicine Institute for NanoBioTechnology, Department of Material Science and Engineering Johns Hopkins Whiting School of Engineering <i>Prion-like Transmission and Therapy in Neurodegenerative Disease</i> (30 min via Zoom)
10:05 am – 10:20 am	Dr Cyril Jones Jagaraj Motor Neuron Disease Research Centre Macquarie Medical School Macquarie University <i>Dysregulation of actin dynamics in ALS</i> (15 min)
10:20 am – 10:35 am	Dr Fiona Bright Dementia Research Centre Macquarie Medical School Macquarie University <i>Complement cascade and TDP-43 pathology in MND</i> (15 min)
10:35 pm – 10:50 pm	Dr Sophia Luikinga The Florey Institute of Neuroscience and Mental Health <i>Lipids as a novel MND specific blood-based biomarker</i> (15 min via Zoom)
Break	
10:50 am – 11:20 am	Join us for morning, trade display and posters. Foyer

Program

Session 2		Chairs – Professor Julie Atkin and Dr Jia Li	
11:20 am – 11:40 pm	Associate Professor Angela Laird Motor Neuron Disease Research Centre Macquarie Medical School Faculty of Medicine, Health and Human Sciences Macquarie University	<i>Studying ataxin-3 function and modulation to treat neurodegenerative disease</i> (20 min)	
11:40 am – 11:55 am	Dr Sian Genoud Dementia Research Centre Macquarie Medical School Macquarie University	<i>The physiological role of tropomyosins in the healthy brain</i> (15 min)	
11:55 am – 12:10 pm	Dr Renate Thienel College of Health, Medicine, and Wellbeing The University of Newcastle	<i>Can an online battery match in-person cognitive testing in predicting age-related cortical changes?</i> (15 min)	
12:10 pm – 12:40pm	Professor Melinda Fitzgerald John Curtin Distinguished Professor Deputy Vice Chancellor, Research (Interim) Curtin University	<i>Personalising care following Traumatic Brain Injury: the AUS-TBI and AUS-mTBI initiatives</i> (30 min via Zoom)	
Lunch			
12:40 pm – 1:50 pm	Lunch, Poster Session and Trade Displays		

Program

Session 3		Chairs – Dr Luan Luu and Anastasiya Potapenko	
1:50 pm – 2:20 pm	<p>Professor Sue Fletcher Centre for Molecular Medicine and Innovative Therapeutics Murdoch University</p> <p><i>Antisense oligomer mediated modulation of C9ORF72 repeat expansion transcripts</i> (30 min via Zoom)</p>		
2:20 pm – 2:35 pm	<p>Dr Amr Abdeen Brain and Mind Centre, School of Medical Sciences (Neuroscience) Faculty of Medicine and Health University of Sydney</p> <p><i>Copper supplementation rescues impaired motor phenotype in a novel mouse model of SOD1 proteinopathy</i> (15min)</p>		
2:35 pm – 2:50 pm	<p>Dr Georgia Watt Western Sydney University</p> <p><i>Novel mouse model combining neuroinflammation and tauopathy demonstrates reduced anxiety and impaired motor and sensorimotor gating function</i> (15min)</p>		
2:50 pm – 3:20 pm	<p>Professor Elizabeth Coulson Head of School, School of Biomedical Sciences Faculty of Medicine Professor of Neuroscience, Queensland Brain Institute, Clem Jones Centre for Ageing Dementia Research The University of Queensland</p> <p><i>Central and peripheral cholinergic neuron degeneration can be prevented by p75 neurotrophin receptor inhibitors</i> (30 min via Zoom)</p>		
Break			
3:20 pm – 3:50 pm	<p>Please join us in the foyer for afternoon tea, posters and trade displays</p>		

Program

Session 4	
Chairs - Professor Ian Blair and Dr Sonam Parakh	
3:50 pm – 4:20 pm	<p>Professor Lachlan Thompson Professor of Neural Repair The University of Sydney Faculty of Medicine and Health Charles Perkins Centre Sydney School of Medical Sciences The University of Sydney</p> <p><i>Cell therapy for Parkinson’s disease. Past, present and future (30 min Zoom)</i></p>
4:20 pm – 4:25 pm	<p>Ms Derya Dik Neuroscience Research Australia University of New South Wales</p> <p><i>String vessel formation regionally increases in long duration Parkinson’s disease (5 min)</i></p>
4:25 pm – 4:30 pm	<p>Miss Jan Cheng Wicking Dementia Research and Education Centre University of Tasmania</p> <p><i>Using iPSCs to explore SARM1-dependent neurodegeneration (5 min via Zoom)</i></p>
4:30 pm – 4:35 pm	<p>Ms Caroline Faucher University of Newcastle</p> <p><i>The relationship between sleep duration and cortical sulcal width in midlife and older adults (5 min)</i></p>
4:35 pm – 4:40 pm	<p>Dr Ole Tietz Macquarie Medical School Macquarie University</p> <p><i>Trapping the Tau - PSD95 Protein-Protein Complex (5 min)</i></p>

Program

4:40 pm – 4:45 pm	<p>Mrs Evgeniia Samokhina Western Sydney University</p> <p><i>Region-specific alterations of astrocytic K⁺ clearance in a mouse model for Alzheimer’s disease</i> (5 min via Zoom)</p>
4:45 pm – 4:50 pm	<p>Dr Alison Hogan Motor Neuron Disease Research Centre Macquarie Medical School Macquarie University</p> <p><i>Zebrafish models to investigate dysregulation of the TDP-43 protein in Motor Neuron Disease</i> (5 min)</p>
4:50 pm – 4:55 pm	<p>Ms Fariha Kabir Wicking Dementia Research and Education Centre University of Tasmania</p> <p><i>Effects of HDAC6 Inhibition in ALS mouse models</i> (5 min)</p>
4:55 pm – 5:25 pm	<p>Professor Pietro Fratta Professor of Cellular and Molecular Neuroscience Department of Neuromuscular Diseases UCL Queen Square Institute of Neurology Faculty of Brain Sciences University College London</p> <p><i>Cryptic splicing: from foe to friend in tackling amyotrophic lateral sclerosis</i> (30 min via Zoom)</p>
Close of Presentations	
5:25 pm – 5:30 pm	<p>Closing remarks by Professor Clement Loy Head of School and Dean of Medicine Macquarie Medical Macquarie University</p>
5:30 pm – 5:40 pm	<p>Prize Presentation</p>

Invited Speakers

Professor Elizabeth Coulson

Head of School, School of Biomedical Sciences, Faculty of Medicine

Professor of Neuroscience, Queensland Brain Institute, Clem Jones Centre for Ageing Dementia Research

The University of Queensland



Professor Elizabeth (Lizzie) Coulson did her undergraduate Honours degree at the University of Melbourne, majoring in Genetics and Biochemistry. Her PhD (1997) in the Department of Pathology, University of Melbourne, with Professor Colin Masters, was on the normal function of the amyloid precursor protein of Alzheimer's disease. Following a year at the ZMBH, University of Heidelberg, Germany, she pursued postdoctoral work studying neuronal cell death in neurodegeneration and development at the Walter and Eliza Hall Institute with Professor Perry Bartlett before being recruited in 2003 to the University of Queensland as a founding member of the Queensland Brain Institute. She was appointed Professor in 2015, joining the School of Biomedical Sciences and becoming Deputy Head in 2019 and Head in 2020. She maintains a 20% Queensland Brain Institutes appointment and is a member of the Clem Jones Centre for Ageing Dementia Research.

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Invited Speakers

Distinguished Professor Melinda (Lindy) Fitzgerald

John Curtin Distinguished Professor
Deputy Vice-Chancellor, Research (Interim)

Curtin University



Professor Fitzgerald leads a team of researchers and post-graduate students in nationally coordinated research focused around understanding and preventing the loss of function that occurs following neurotrauma. She leads the MRFF funded AUS-TBI and AUS-mTBI national consortia, each of 100 researchers and up to 50 partner organisations, designing informatics approaches in moderate to severe and in mild traumatic brain injury.

Lindy also founded and is the CEO of Connectivity: Traumatic Brain Injury Australia, a not-for-profit that links people with lived experience, carers, researchers, clinicians and health care providers to improve outcomes for people following TBI of all severities.

Invited Speakers

Professor Pietro Fratta

Professor of Cellular and Molecular Neuroscience

Department of Neuromuscular Diseases

UCL Queen Square Institute of Neurology

Faculty of Brain Sciences

University College London

Professor Pietro Fratta is a Consultant Neurologist and Professor of Cellular and Molecular Neuroscience at UCL. His clinical and research interests center on motor neuron diseases (MND) and RNA biology. He has been leading an independent research team since 2015 in University College London, and since 2023 has a Satellite lab at the Francis Crick Institute.

He practices at the National Hospital for Neurology and Neurosurgery, where he established in 2015 the only Kennedy's Disease-dedicated clinic in the UK and an MND Genetics clinic. He previously trained at the University of Milan, University of Southern California and San Raffaele Scientific Institute.

<https://iris.ucl.ac.uk/iris/browse/profile?upi=PFRAT57>

Invited Speakers

Associate Professor Angela Laird

Motor Neuron Disease Research Centre
Macquarie Medical School
Faculty of Medicine, Health and Human Sciences

Macquarie University



A/Prof Angela Laird completed a PhD in Neuroscience in 2008, studying spinal cord injury at UNSW, Sydney. She then went on to undertake a postdoctoral position at KU Leuven in Belgium, using zebrafish to study motor neuron disease.

Today, Angela leads the Neurodegeneration Treatment Team within the Centre for Motor Neuron Disease Research, Macquarie University. The team have been successful in producing and characterising the world's first transgenic zebrafish model of spinocerebellar ataxia type-3 (also known as Machado Joseph Disease, MJD). They are currently testing the effect of various treatments on their zebrafish models of MJD and motor neuron disease, together with their cellular and rodent models, with the aim of identifying disease treatments and cures.

In addition to her research, Angela is currently the Deputy Chair of the Australian Academy of Science's Early and Mid-Career Researcher (EMCR) Forum Executive Committee. Within that role she works to ensure that EMCR viewpoints are considered in funding and award guidelines, policy changes and research opportunities.

<https://researchers.mq.edu.au/en/persons/angela-laird>

Invited Speakers

Associate Professor Xiaobo Mao

Institute for Cell Engineering, Department of Neurology
Johns Hopkins University School of Medicine
Institute for NanoBioTechnology, Department of Material Science and Engineering
Johns Hopkins Whiting School of Engineering

John Hopkins University



Dr. Mao received his PhD (Physical Chemistry) at the National Center for Nanoscience and Technology, Chinese Academy of Sciences in 2010. He then worked as postdoc in the labs of Profs. Drs. Ted and Valina Dawson at the Institute for Cell Engineering, Department of Neurology, Johns Hopkins School of Medicine (JHSOM) during 2010-2016. After postdoctoral fellowship, he worked as Assistant Professor in 2017 and became Associate Professor in 2021 at JHSOM.

He has published more than 50 research articles in many high-impact journals (*Science, Nature, Nature Medicine, PNAS, Nature Comm, Nano Today*) focusing on pathogenic protein cell-to-cell spreading.

<https://scholar.google.com/citations?user=xwAtsGEAAAAJ&hl=en>

Invited Speakers

Professor Lachlan Thompson

Professor of Neural Repair

The University of Sydney Faculty of Medicine and Health

Charles Perkins Centre

Sydney School of Medical Sciences

The University of Sydney



Professor Lachlan Thompson completed a PhD in Neuropharmacology at the University of Melbourne in 2002. He currently holds appointments as Professor of Neural Repair at the University of Sydney and Honorary Professor of Neuroscience at the University of Melbourne. His research program over the last 20 years has been dedicated to understanding the potential for replacement of neural circuitry in the damaged central nervous system, including through endogenous neurogenesis, but predominately through neural transplantation.

Professor Thompson contributed some of the first studies to utilise cells expressing fluorescent reporters in order to characterise anatomical connectivity of neural grafts. He is an international board member for the Network of CNS Transplantation and Regeneration and is the inaugural co-president of the Asia-Pacific Association for Neural Repair.

<https://www.thompson-lab.com/>

Invited Speaker Abstracts

<p>Professor Elizabeth Coulson</p> <p>Head of School, School of Biomedical Sciences, Faculty of Medicine Professor of Neuroscience, Queensland Brain Institute, Clem Jones Centre for Ageing Dementia Research The University of Queensland</p>	<p>Central and peripheral cholinergic neuron degeneration can be prevented by p75 neurotrophin receptor inhibitors</p>	<p>22</p>
<p>Professor Melinda Fitzgerald</p> <p>John Curtin Distinguished Professor Deputy Vice Chancellor, Research (Interim) Curtin University</p>	<p>Personalising care following Traumatic Brain Injury: the AUS-TBI and AUS-mTBI initiatives</p>	<p>23</p>
<p>Professor Sue Fletcher</p> <p>Centre for Molecular Medicine and Innovative Therapeutics Murdoch University</p>	<p>Antisense oligomer mediated modulation of C9ORF72γ repeat expansion transcripts</p>	<p>24</p>
<p>Professor Pietro Fratta</p> <p>Professor of Cellular and Molecular Neuroscience Department of Neuromuscular Diseases UCL Queen Square Institute of Neurology Faculty of Brain Sciences University College London</p>	<p>Cryptic splicing: from foe to friend in tackling amyotrophic lateral sclerosis</p>	<p>25</p>
<p>Associate Professor Angela Laird</p> <p>Macquarie University Motor Neuron Disease Research Centre Macquarie Medical School Faculty of Medicine, Health, and Human Sciences Macquarie University</p>		<p>26</p>

Abstract Lists

<p>Associate Professor Xiaobo Mao</p> <p>Institute for Cell Engineering, Department of Neurology Johns Hopkins University School of Medicine Institute for NanoBioTechnology, Department of Material Science and Engineering Johns Hopkins Whiting School of Engineering</p>	<p>Prion-like Transmission and Therapy in Neurodegenerative Disease</p>	<p>27</p>
<p>Professor Lachlan Thompson</p> <p>Professor of Neural Repair The University of Sydney Faculty of Medicine and Health Charles Perkins Centre Sydney School of Medical Sciences The University of Sydney</p>	<p>Cell therapy for Parkinson's disease. Past, present and future</p>	<p>28</p>

15 Minutes Abstracts

<p>Dr Amr Abdeen Brain and Mind Centre, School of Medical Sciences (Neuroscience) Faculty of Medicine and Health University of Sydney</p>	<p>Copper supplementation rescues impaired motor phenotype in a novel mouse model of SOD1 proteinopathy</p>	<p>30</p>
<p>Dr Fiona Bright Dementia Research Centre Macquarie Medical School Macquarie University</p>	<p>Complement cascade and TDP-43 pathology in MND</p>	<p>32</p>
<p>Dr Sian Genoud Dementia Research Centre Macquarie Medical School Macquarie University</p>	<p>The physiological role of tropomyosins in the healthy brain</p>	<p>34</p>
<p>Dr Cyril Jones Jagaraj Motor Neuron Disease Research Centre Macquarie Medical School Macquarie University</p>	<p>Dysregulation of actin dynamics in ALS</p>	<p>35</p>
<p>Dr Sophia Luikinga The Florey Institute of Neuroscience and Mental Health</p>	<p>Lipids as a novel MND specific blood-based biomarker.</p>	<p>36</p>
<p>Dr Renate Thienel College of Health, Medicine, and Wellbeing The University of Newcastle</p>	<p>Can an online battery match in-person cognitive testing in predicting age-related cortical changes?</p>	<p>37</p>
<p>Dr Georgia Watt Western Sydney University</p>	<p>Novel mouse model combining neuroinflammation and tauopathy demonstrates reduced anxiety and impaired motor and sensorimotor gating function.</p>	<p>38</p>

5 Minute Abstracts

<p>Miss Jan Cheng Wicking Dementia Research and Education Centre University of Tasmania</p>	<p>Using iPSCs to explore SARM1-dependent neurodegeneration</p>	<p>41</p>
<p>Ms Derya Dik Neuroscience Research Australia University of New South Wales</p>	<p>String vessel formation regionally increases in long duration Parkinson's disease</p>	<p>42</p>
<p>Ms Caroline Faucher University of Newcastle</p>	<p>The relationship between sleep duration and cortical sulcal width in midlife and older adults</p>	<p>43</p>
<p>Dr Alison Hogan Motor Neuron Disease Research Centre Macquarie Medical School Macquarie University</p>	<p>Zebrafish models to investigate dysregulation of the TDP-43 protein in Motor Neuron Disease</p>	<p>44</p>
<p>Ms Fariha Kabir Wicking Dementia Research and Education Centre University of Tasmania</p>	<p>Effects of HDAC6 Inhibition in ALS mouse models</p>	<p>45</p>
<p>Mrs Evgeniia Samokhina Western Sydney University</p>	<p>Region-specific alterations of astrocytic K⁺ clearance in a mouse model for Alzheimer's disease</p>	<p>47</p>
<p>Dr Ole Tietz Macquarie Medical School Macquarie University</p>	<p>Trapping the Tau - PSD95 Protein-Protein Complex</p>	<p>48</p>

Posters

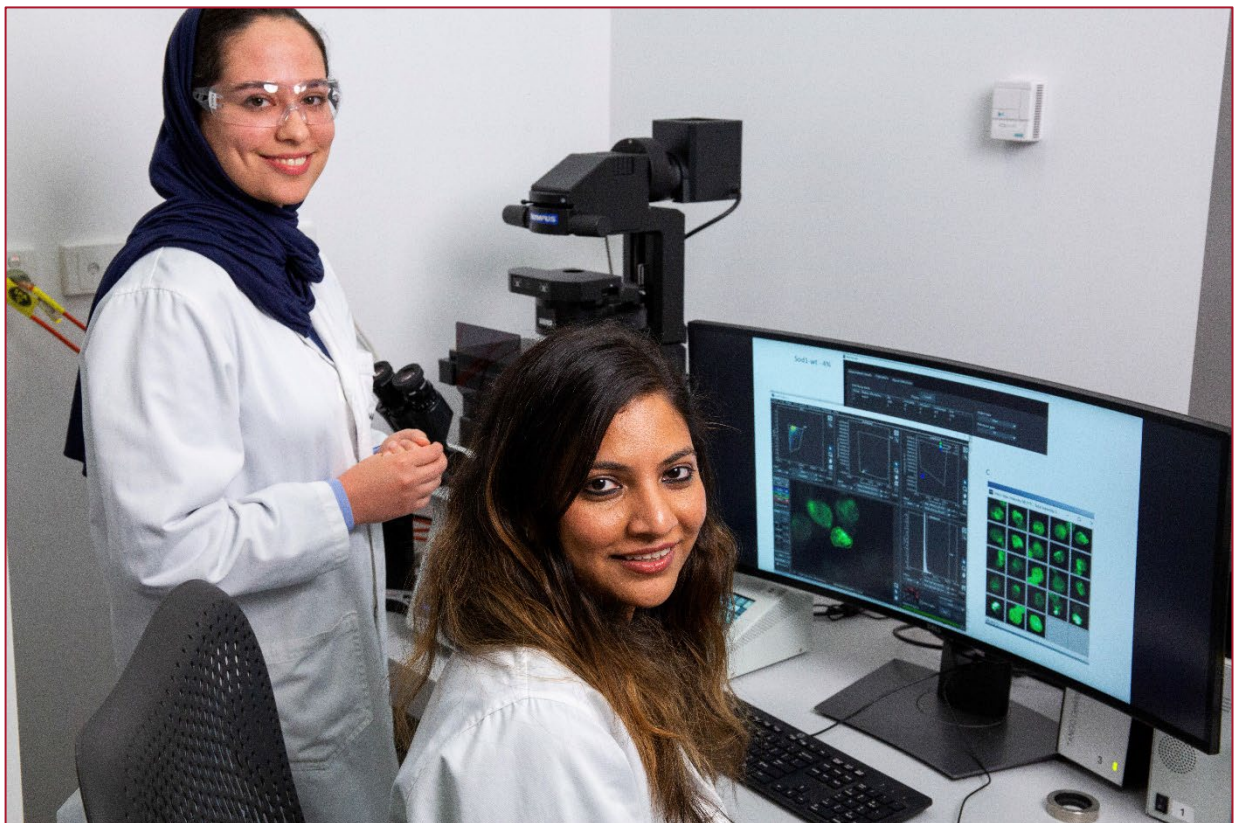
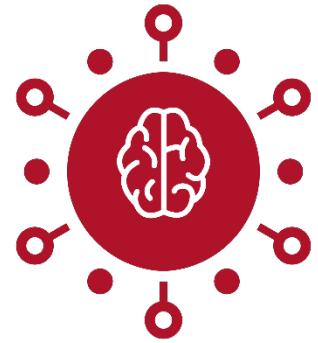
<p>Miss Yvonne Aguirre Candia Faculty of Medical Science University of Sydney</p>	<p>TREM2 protein expression on microglia and macrophages in acute MS lesions</p>	<p>50</p>
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<p>Natalie Grima Motor Neuron Disease Research Centre Macquarie Medical School Macquarie University</p>	<p>RNA sequencing of amyotrophic lateral sclerosis peripheral blood reveals distinct molecular subtypes</p>	<p>56</p>
<p>Mr Justin Houx University of New South Wales</p>	<p>Single molecule detection of TDP-43 CTD Liquid Liquid Phase Separation</p>	<p>57</p>
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<p>Miss Elizabeth Kalotay University of New South Wales</p>	<p>Testing DARS1 gene replacement therapy in mouse models of the leukodystrophy HBSL</p>	<p>60</p>
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Abstract Lists

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<p>Mr Jackson McPartland Karl Lab, Western Sydney University School of Medicine (Master of Research Student) Bowen Lab, University of Sydney Brain and Mind Centre (Research Assistant)</p>	<p>Evaluation of the therapeutic effectiveness of a novel cannabis formulation (i.e., Eve strain extract) in Alzheimer's disease transgenic mice</p>	<p>63</p>
<p>Pranav Pancham Neuroimmunology Laboratory, School of Medicine Western Sydney University</p>	<p>Neuroimmunology Laboratory, School of Medicine, Western Sydney University, Campbelltown Campus, Australia</p>	<p>64</p>
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<p>Miss Chelsea Rowley Charles Perkins Centre University of Sydney</p>	<p>The Effect of Gpr109a and Sex in Cuprizone Induced Demyelination and Remyelination</p>	<p>66</p>
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<p>Ms Feifei Su University of New South Wales</p>	<p>Neuronal growth regulator 1 (NEGR1) promotes α-synuclein oligomer clearance</p>	<p>70</p>
<p>Ms Sharlynn Wu Macquarie Medical School Macquarie University</p>	<p>Developing a molecular platform for the rapid functional study of novel oligogenic ALS candidate genes</p>	<p>71</p>

Abstracts

INVITED SPEAKER ABSTRACTS



Abstracts

PROFESSOR ELIZABETH COULSON

Head of School, School of Biomedical Sciences Faculty of Medicine
Professor of Neuroscience, Queensland Brain Institute, Clem Jones Centre for Ageing Dementia Research

The University of Queensland

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Central and peripheral cholinergic neuron degeneration can be prevented by p75 neurotrophin receptor inhibitors

Abstracts

PROFESSOR MELINDA FITZGERALD

John Curtin Distinguished Professor
Deputy Vice Chancellor, Research (Interim)

Curtin University

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Personalising care following Traumatic Brain Injury: the AUS-TBI and AUS-mTBI initiatives

Traumatic brain injury (TBI) is a physical injury to the brain that can occur from a range of causes including road traffic crashes, falls, during sports, and from violence. Each year in Australia, 190,000–200,000 TBI occur, of which ~180,000 are mild TBI, including concussion. Moderate to severe TBI can be devastating for those affected. Even mild TBI can have long-lasting negative impacts on individuals, their families, and society.

The neurodegenerative disease processes in TBI are complex and variable depending on the nature of the injury and the characteristics of the individual and their pre-existing health. Consequently, management of people with TBI is hindered by poor prediction of those at risk of delayed recovery and the inability to personalise care at the level of the individual.

The AUS-mTBI consortium is building sustainable digital platforms to facilitate collection of mild TBI data from across Australia. We are leveraging and substantially expanding the HeadCheck application (app) into multi-faceted online platforms (apps and computer based website) to collect potentially predictive data elements. These will be used to determine predictors of optimal outcomes, which will be used to develop online personalisation of care to be validated and trialled to determine effects on outcome.

The AUS-TBI consortium are designing an approach to collect potentially predictive indicators of long term outcomes in moderate to severe TBI, in the domains of social, health, biological, clinical and intervention data. Data management systems are being designed to facilitate secure data collection, linkage, storage, management and analysis, to facilitate personalisation of care at the level of the individual and ultimately improve outcomes for people with more severe TBI.

Abstracts

PROFESSOR SUE FLETCHER

Centre for Molecular Medicine and Innovative Therapeutics

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Antisense oligomer mediated modulation of C9ORF72 repeat expansion transcripts

Leon M Larcher¹, Rakesh N Veedu^{1,2}, Ianthe L Pitout¹ and Sue Fletcher¹

¹Murdoch University and ²Syngenis, Perth, WA

Approximately 10-20% of motor neuron disease (MND) cases are caused by mutations in one of >45 different genes. The most common pathogenic mutation in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) is the expansion of a GGGGCC (G₄C₂) repeat sequence in intron 1 of the *C9ORF72* gene. The proposed mechanisms by which the *C9ORF72* repeat expansion induces neurodegeneration are (i) RNA toxic gain-of-function from accumulation of RNA foci and sequestration of RNA binding proteins (RBP); (ii) gain-of-function through the accumulation of toxic dipeptide repeat proteins produced through non-ATG translation of the hexanucleotide repeat region and (iii) haploinsufficiency of *C9ORF72*. The *C9ORF72* pre-mRNA undergoes alternative splicing to produce three transcript variants that encode two different proteins, the functions of which are becoming evident.

Antisense oligonucleotides are single-stranded nucleic acid analogues that can be used to modulate gene expression by several different mechanisms. We have developed both direct and indirect antisense oligomer strategies to modulate the repeat expansion-containing *C9ORF72* mRNA (transcript variant 3). Treatment of MND patient-derived cell models with our compound PMO-C9 reduced *C9ORF72* variant 3 while maintaining total *C9ORF72* mRNA levels in patient derived cell models. In an alternative approach, DNazymes designed to cleave repeat expansion containing transcripts also reduced the levels of *C9ORF72* variant 3.

While nucleic acid therapeutics hold unique promise, achieving safe and efficient delivery of these drugs to deep target tissues, including the central nervous system, remains a significant obstacle to clinical application. Evolving oligonucleotide chemistries, conjugates and delivery modalities are addressing these challenges and delivering safer and more effective molecules. However, we are working in an environment beset by recent failures in the clinic, and a poor appetite for biotech. Despite this currently unfavourable ecosystem, opportunities exist to deliver patient impact and demonstrate the utility of oligonucleotide drugs.

Abstracts

PROFESSOR PIETRO FRATTA

Professor of Cellular and Molecular Neuroscience
Department of Neuromuscular Diseases
UCL Queen Square Institute of Neurology
Faculty of Brain Sciences

University College London

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Cryptic splicing: from foe to friend in tackling amyotrophic lateral sclerosis

Cryptic splicing has emerged as an important consequence of TDP-43 loss and found to be common in ALS and FTD brains. Specific cryptic events have been identified as important in disease pathogenesis and are being targeted by novel therapeutic approaches. We have developed a way to harness cryptic splicing in order to drive the expression of therapeutics in a cell-specific manner.

Abstracts

ASSOCIATE PROFESSOR ANGELA LAIRD

Motor Neuron Disease Research Centre
Macquarie Medical School
Faculty of Medicine, Health and Human Sciences

Macquarie University

Angela.laird@mq.edu.au

Studying ataxin-3 function and modulation to treat neurodegenerative disease

Motor Neuron Disease Research Centre, Macquarie Medical School, Faculty of Medicine, Health, and Human Sciences, Macquarie University; angela.laird@mq.edu.au

Machado Joseph disease (MJD), also known as spinocerebellar ataxia Type-3, is a neurodegenerative disease that causes a loss of balance and co-ordination, leading to paralysis and unfortunately death. MJD is caused by inheritance of an expanded trinucleotide repeat region within the ATXN3 gene, which results in an ataxin-3 protein containing an expanded polyglutamine repeat sequence.

Within this study we are focusing on the normal function of ataxin-3, whether that function is impaired in MJD, and screening for treatments that modify ataxin-3 abundance. Here I will focus on the role of ataxin-3 as a deubiquitinating enzyme (DUB) and exploring whether the presence of the disease-causing expanded polyglutamine tract within the protein, increases or decreases this DUB function.

Expanding on that, I will also present the findings of our study to identify therapeutic candidates that modulate the abundance of human ataxin-3, in the hope that use of identified candidates can provide insights into the effect of increasing and decreasing ataxin-3 abundance, both within MJD and other neurodegenerative diseases.

Abstracts

ASSOCIATE PROFESSOR XIAOBO MAO

Institute for Cell Engineering, Department of Neurology
Johns Hopkins University School of Medicine
Institute for NanoBioTechnology, Department of Material Science and Engineering
Johns Hopkins Whiting School of Engineering

John Hopkins University

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Prion-like Transmission and Therapy in Neurodegenerative Disease

α -Synucleinopathies is characterized with accumulation of misfolded α -synuclein (α -syn), including Parkinson's disease (PD), Dementia with Lewy Bodies (DLB), and Multiple System Atrophy (MSA). Braak's prion-like theory fundamentally subverts the understanding of PD and related α -synucleinopathies. Emerging evidence shows that pathologic α -syn is a prion-like protein that spreads from one region to another in PD brain, which is an essential driver to the pathogenesis of PD. **(1)** In the cell-to-cell transmission of pathogenic α -syn, we identified that lymphocyte-activation gene 3 (LAG3) is an essential receptor that mediates the internalization of α -syn preformed fibrils (PFF) (*Science 2016*)¹ ([link](#)). Deletion and inhibition of LAG3 significantly impede α -syn pathology spread. We have provided the mechanistic understanding on the spread of pathological proteins and provides structural information for the therapeutic targeting of pathological α -syn spread (*PNAS 2021*)² ([link](#)).

We further determined that LAG3 antibody (i.p.) can significantly inhibit the α -synucleinopathy. **(2)** Pathogenic α -syn can cause neurodegeneration via PARP1 activation. Depletion and inhibition of PARP1 can significantly inhibit α -syn induced neurotoxicity and PAR-PFF strain spreading (*Science 2018*)³ ([link](#)). **(3)** Because pathogenic α -syn seeds can drive the disease progression, it is important to target the intracellular α -syn aggregates. However, traditional antibodies fail to penetrate into plasma membrane, which cannot efficiently inhibit the propagation of α -synuclein. We developed a nanobody library and screened several nanobodies that bind to α -syn fibrils. By AAV-transduction, the nanobody can significantly inhibit the pathogenic α -syn spreading (*Nature Comm 2022*)⁴ ([link](#)). These studies provide the new insights of therapeutic development of α -syn-related pathogenesis. **(4)** Pathogenic α -syn and ROS (reactive oxidative species) can form a feed-forward loop driving disease. Inhibition of the ROS can significantly inhibit cell-to-cell transmission of pathogenic α -syn (*Nano Today 2021*)⁵ ([link](#)).

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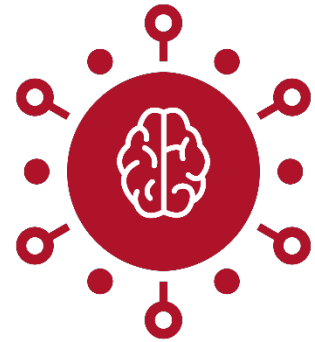
Cell therapy for Parkinson's disease. Past, present and future

Midbrain dopamine (mDA) neurons can be replaced in patients with Parkinson's disease (PD) in order to provide long-term improvement in motor functions. The limited capacity for long-distance axonal growth in the adult brain means that cells are transplanted ectopically, into the striatal target. As a consequence, several mDA pathways are not re-instated, which may underlie the incomplete restoration of motor function in patients. Here, we show that viral delivery of GDNF to the striatum, in conjunction with homotopic transplantation of human pluripotent stem-cell-derived mDA neurons, recapitulates brain-wide mDA target innervation. The grafts provided re-instatement of striatal dopamine levels and correction of motor function and also connectivity with additional mDA target nuclei not well innervated by ectopic grafts.

These results demonstrate the remarkable capacity for achieving functional and anatomically precise reconstruction of long-distance circuitry in the adult brain by matching appropriate growth-factor signalling to grafting of specific cell types.

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15-MINUTE SPEAKER ABSTRACTS



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Copper supplementation rescues impaired motor phenotype in a novel mouse model of SOD1 proteinopathy

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Misfolding and abnormal deposition of the cuproenzyme superoxide dismutase 1 (SOD1) is a pathological feature of the Parkinson's disease substantia nigra pars compacta (SNc) where its accumulation is associated with decreased regional copper levels. We posited that SOD1 proteinopathy contributes to dopamine neuron loss, and thus developed a novel murine model ($hSOD1^{WT}/Ctr1^{+/-}$) which combines high levels of wildtype human SOD1 and brain copper deficiency to test this hypothesis. Immunofluorescent dual-labelling of misfolded SOD1 and tyrosine hydroxylase (TH) demonstrated a marked increase in aggregated SOD1 protein in TH⁺-dopamine neurons within the SNc $hSOD1^{WT}/Ctr1^{+/-}$ mice compared with control mice. Three-dimensional reconstruction of these images demonstrates that the preponderance of SOD1 aggregates is outside TH⁺-neuron cell bodies, suggesting the accumulation of SOD1 in neuronal processes and glia, or their release into the extracellular space. Quantitative stereology revealed that the density of TH⁺-dopamine neurons in the SNc was significantly reduced in $hSOD1^{WT}/Ctr1^{+/-}$ mice compared with all mouse strains ($p < 0.05$). These data support our hypothesis that wildtype SOD1 is prone to misfolding in a cellular environment of copper deficiency and that resultant SOD1 proteinopathy is associated with SNc dopamine neuron death in an age-related manner. Behavioural assessment of our mouse model at 5-months demonstrated impaired grip strength ($p < 0.001$) and balance beam performance ($p < 0.001$). Copper supplementation using the blood-brain barrier permeable copper delivery agent CuATSM (15 mg/kg daily for 3 months) resulted in a 3.4-fold increase in midbrain

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copper levels in five-month-old $hSOD1^{WT}/Ctr1^{+/-}$ mice. CuATSM treatment did not modify grip strength in $hSOD1^{WT}/Ctr1^{+/-}$ mice but dramatically improved balance beam performance (reduced number of paw slips, $p < 0.001$; reduced latency, $p < 0.05$). Our findings have implications for Parkinson's disease and ALS where aggregated wild-type SOD1 is a pathological feature, and support ongoing clinical trials of CuATSM treatment in Parkinson's disease and ALS patients (ClinicalTrials.gov Identifier: NCT03204929; NCT02870634).

Abstracts

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Complement cascade and TDP-43 pathology in MND

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Abnormal TDP-43 pathology within the central nervous system (CNS) is a feature of 97% of motor neuron disease (MND) and 50% of frontotemporal dementia (FTD) patients. Neuroinflammation is also a hallmark of neurodegeneration¹, and a critical factor of the inflammatory response in neurodegeneration is aberrant activation of the complement cascade (CC)²⁻⁴. Previously, we showed significantly altered expression of key CC components in serum of human FTD and MND patients⁴. Consistent with these findings, bulk RNA-sequencing of CNS tissue extracted from a genetically modified (GM) TDP-43 mouse model showed significant dysregulation of the same components. To further explore this, the expression of various CC's across all three pathways were individually knocked-down (KD) using shRNA-mediated adeno associated virus (AAV) injected into the CNS in four GM mouse models of human TDP-43 pathology in addition to two GM mouse models of other non-TDP43 proteinopathies. Mice underwent physiological testing and post-mortem analysis of neuropathology and gliosis within the CNS. Physiological testing showed significantly advanced pathological phenotypes including motor deficits, tremor, hind limb paralysis, gait abnormalities and premature death upon AAV mediated depletion of CC, compared to those administered a control AAV. Importantly, pathological phenotypes were restricted only to models of mutant TDP-43 and not wild type TDP-43 or other proteinopathies. To further explore this, 3D human brain organoids derived from human embryonic stem cells (hESCs) expressing mutant and wild type TDP-43 respectively were treated with AAV's to KD the same panel of CC components. Consistent with mutant TDP-43 mouse models, detrimental phenotypes were observed in mutant TDP-43 3D human brain organoids but not wild-type TDP-43. Collectively this work indicates an important, specific relationship between the CC and mutant TDP-43 mediated neurodegeneration in MND/FTD.

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The physiological role of tropomyosins in the healthy brain

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Abstract:

The actin cytoskeleton is an essential structural component of all mammalian cells, and involves the constant dynamic cycling of actin filaments, a process mediated by numerous actin-associated proteins^[1]. Tropomyosins are actin binding proteins that form co-polymers with actin filaments, and have isoform specific properties in the brain^[2]. Here, we report the expression, localisation and physiological function of various tropomyosin isoforms (and by proxy, their actin filaments) in mouse primary neurons, astrocytes and microglia – with a focus on the post-synaptic isoform in neurons. Behavioural analysis was conducted on tropomyosin knock-out mouse models and identified behavioural alterations in a sex dependent manner. Using live calcium imaging in primary mouse tropomyosin knock-out primary neurons compared with wild-type, we identified a significant reduction in single cell amplitude, increase in rise and fall time ($P < 0.001$), suggesting a reduction in synaptic strength and a role of tropomyosin in fast spontaneous neuronal firing. Interestingly however, we report a significant increase in neuronal connectivity and neuronal network ensembles ($p < 0.0001$) – attributed to the observed increase in dendritic field of tropomyosin knock-out neurons. Tropomyosin knock-out neurons also exhibit significant reductions in receptor internalisation (63% reduction, $P < 0.05$) suggesting a role of tropomyosins in endocytosis.

To investigate this further, we identify that tropomyosins mediate pathological tau uptake in primary neurons – a processes driving tau-related dementia progression. Identifying and targeting this pathway can therefore have significant implications for the development of disease modifying therapies to slow or halt pathological tau spread throughout the brain in tau-related dementias such as Alzheimer's disease.

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Dysregulation of actin dynamics in ALS

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ALS pathology is characterised by abnormal accumulation of post translationally modified, wildtype TDP-43 (~97%) in the cytoplasm (1). Understanding the underlying pathological mechanisms of TDP-43 and motor neuron degeneration will help design effective therapy for ALS/MND patients. Actin is a highly abundant protein and exists as either monomeric G-actin or polymeric F-actin in dynamic equilibrium (2). Abnormal bundling, actin rods and accumulation of F-actin are features of tau-induced neurodegeneration in AD and other neurodegenerative diseases (2). However, the role of actin dynamics remains largely unexplored in ALS. The main aim of this study is to determine whether actin dynamics and actin binding proteins are dysregulated in ALS patients, and mice models of ALS. Our results show actin dynamics is dysregulated by TDP-43 pathology in sporadic ALS. We found actin dynamics was dysregulated in cells expressing cytoplasmic TDP-43, TDP-43 rNLS mice and in sporadic ALS patient spinal cords. Dysregulated actin-binding proteins (increased phosphorylated cofilin, tropomyosin, LIMK1/2, Rac1) were also detected in sporadic ALS patients and disease models. Our results also demonstrate TDP-43 interacts actin and more insoluble actin was produced in cells expressing cytoplasmic TDP-43. Moreover, pharmacological induction of actin polymerisation induced features of TDP-43 pathology such as mis-localisation of TDP-43 and formation of stress granules. This is the first study to demonstrate that dysregulation of actin dynamics and the LIMK1/2-cofilin pathway are associated with TDP-43 pathology in ALS/MND. This study should prompt a paradigm shift in our view of the pathological processes involving TDP-43 in ALS/MND.

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Acknowledgments

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Lipids as a novel MND specific blood-based biomarker

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Abstract:

Lipid dysregulation has been associated with disease severity, progression and survival in MND patients. We recently discovered extensive lipid dysregulation in spinal cord and skeletal muscle of the clinically relevant mutant TDP-43^{Q331K} mouse [1]. Here, we aimed to validate the utility of lipids as blood-based biomarkers using multiple preclinical mouse models. We collected blood from SOD1^{G93A}, C9ORF500, TDP-43^{Q331K} mice at pre-symptomatic, mid and end stage timepoints and performed targeted lipidomics. We performed analysis on pre-symptomatic plasma of SOD1^{G93A}, C9ORF500, TDP-43^{Q331K} mutant mice compared to their WT littermates. Receiver operating characteristics (ROC) analysis with area under curve (AUC) cut-off of 0.83 and $p < 0.05$ identified 50 lipids in TDP-43, 107 in C9 and 51 in the SOD1 dataset. We then tested lipid combinations in sets of 3, which were validated on a dataset of human plasma samples consisting of 103 MND, 39 Parkinson's disease (PD) and 30 control samples. A random number of samples in these datasets were blinded, and we instructed machine learning program to assign samples to either MND or control, MND or PD and PD or control based on the ROC of 3 lipids. Excitingly, we identified at least 1 panel of lipids that could accurately assign MND from control and MND from PD, but unable to distinguish PD from control, indicating this panel is specific to MND. We expect that this panel of lipid biomarkers could be an excellent candidate for early diagnosis of MND, a tool that is of high demand in the clinic.

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Can an online battery match in-person cognitive testing in predicting age-related cortical changes?

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Introduction:

Studies into cognitive changes typically employ detailed in person cognitive testing, which is not always feasible. Therefore, we compared the relationship between brain morphology (sulcal width) and cognitive functioning, using an online and an in-person modality and disentangled the influence of age, sex, β -Amyloid (A β) and APOE-status.

Methods:

141 healthy participants (mean age 60, range 46-71 years, 75% female) assessed with structural MRI; cognitive batteries both, face-to-face and online (Cambridge Brain Systems), A β status (Fluorine-18 florbetaben-PET scan) and APOE genotype (Lupton et al., 2021);

Canonical Partial Least Square method to compare cognitive modalities and Sulcal width (SW; Morphologist pipeline-BrainVISA toolbox; Borne et al., 2020). Age effects tested with two-sided Wald Test. Analysis of covariance to test age and sex-interactions, amyloid and APOE status, sex-effects (controlling for age), A β , and APOE (controlling for age and sex).

Results:

The single robust mode for brain (SW) - behaviour (cognition) covariation loaded most strongly onto memory and executive functions for both the onsite (1st mode, $p=0.013$, $cov=3.55$, $z-cov=2.93$, $R^2=0.18$, $z-R^2=0.95$; 2nd mode, $p>0.99$), and the online battery (1st mode, $p<0.001$, $cov=2.76$, $z-cov=4.71$, $R^2=0.14$, $z-R^2=1.15$; 2nd mode, $p=0.99$) (Fig. 1).

Cognition-related SW showed a regional pattern similar for online and in person cognitive appraisal. Significant effect of sex on SW projections in both the online and onsite conditions with larger sulcal width for men ($p<0.001$) and a similar effect on onsite cognitive projections with lower performance for men ($p<0.001$) (Fig. 2a). Cognitive performance - both online ($p=0.03$) and in-person ($p<0.01$) - showed a significantly steeper decline with age for A β -positive participants

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(Fig. 2b). Variance explained for the online cognitive assay ($R^2=0.15$) was only slightly less than for the in-person testing ($R^2=0.18$). Brain-behaviour z-transformed covariance was likewise comparable across modalities.

Conclusion:

Similar sulcal width brain projections for both cognitive modalities, with memory and executive domains showing the strongest loadings. A β -aggregation associated with a steeper cognitive projection slope for both batteries, suggesting that in our preclinical sample the early stages of A β accumulation accelerate cognitive ageing potentially before translation into structural brain changes. Adequate sensitivity of online cognitive tests for studying age-related neurobiology of cognition is suggested.

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Abstracts

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Novel mouse model combining neuroinflammation and tauopathy demonstrates reduced anxiety and impaired motor and sensorimotor gating function

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Background: Tau pathology and neuroinflammation are two key features of Alzheimer's disease (AD). However, few preclinical models have been developed to investigate interactions between tauopathy and neuroinflammation. Thus, we have created a mouse model of chronic neuroinflammation combined with tauopathy by crossing heterozygous glial fibrillary acid protein interleukin 6 (GFAP-IL6) transgenic mice with heterozygous TAU58/2 (expressing mutant human *P301S*) transgenic mice. We hypothesised GFAP-IL6-TAU58/2 (IL6-TAU) would present with an accelerated and more severe motor and cognitive phenotype compared to GFAP-IL6 or TAU58/2 mice.

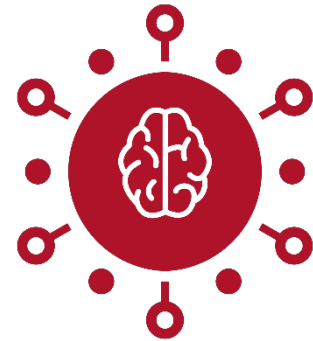
Methods: 6-month-old male and female IL6-TAU, GFAP-IL6, TAU58/2 and WT controls were assessed in behavioural domains including anxiety, motor function, cognition, and sensorimotor gating. At the conclusion of behavioural testing brain tissue was collected for immunohistochemistry analysis.

Results: IL6-TAU mice demonstrated an anxiolytic phenotype, motor impairments and sensorimotor gating impairments compared to WT controls and GFAP-IL6 mice. Social recognition memory was impaired in all transgenic mice compared to WT controls. Critically, the combination of tauopathy and neuroinflammation did not exacerbate any behavioural phenotypes in IL6-TAU mice compared to TAU58/2. There was no effect of the combination of tauopathy and neuroinflammation on spatial learning and memory.

Conclusions: 6-month-old IL6-TAU mice demonstrated accelerated and more severe deficits in motor function and sensorimotor gating compared to the GFAP-IL6 mice as well as an anxiolytic phenotype. However, there was no behavioural differences between the IL6-TAU and TAU58/2 transgenic mice. No cognitive differences were noted at this age.

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5-MINUTE SPEAKER ABSTRACTS



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Using iPSCs to explore SARM1-dependent neurodegeneration

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Excitotoxicity is a pathological feature shared by many neurodegenerative diseases, such as Alzheimer's disease, amyotrophic lateral sclerosis, and Batten disease. SARM1 promotes neurodegeneration resulting from distinct causes such as vincristine-induced peripheral neuropathy and axonal injury, however its role in excitotoxicity-induced neurodegeneration is unknown. We have used human induced pluripotent stem cell (hiPSC)-derived neurons to explore the role of SARM1-dependent neurodegeneration pathways following excitotoxicity.

Using CRISPR/Cas technology, we introduced MYC-tagged human SARM1 variants into hiPSCs derived from a single donor, namely MYC-hSARM1 and MYC-hSARM1-K193R, a dominant-negative SARM1 that inhibits endogenous SARM1 function. hiPSCs from both lines expressed undifferentiated cell markers OCT4, SSEA4, NANOG, and TRA-1-81, and embryoid bodies cultured from these cell lines demonstrated each line retained pluripotency. DNA sequencing confirmed that no edits had occurred at potential off-target sites, and virtual karyotyping indicated no evidence of chromosomal instability in either cell line. Image analysis showed that the MYC-tagged hSARM1 variants colocalised with mitochondria in hiPSC-derived neural stem cells, reflecting the localisation of endogenous SARM1.

Using neurons differentiated from these hiPSC lines, and a small molecular inhibitor of SARM1, we will study the effects of SARM1 inhibition in neurodegeneration with a particular focus on excitotoxicity through exposure to kainic acid, a glutamate analogue. Preliminary results show kainic acid reduced cell viability (ATP and NAD⁺ assays) and caused neurite beading and fragmentation in unedited hiPSC-derived neurons. We are extending these studies to other neurotoxins, genetic models of neurodegenerative disease, and will employ 'omics studies to identify pathways downstream of SARM1 in neurodegeneration.

Abstracts

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String vessel formation regionally increases in long duration Parkinson's disease

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Parkinson's disease (PD) is characterised by α -synuclein deposition in the form of Lewy pathology in the substantia nigra (SN). Cerebral hypoperfusion of the visual cortex has been reported in PD and associates with visual hallucinations, although the cellular mechanism/s have not been identified. We investigated regional changes in the vasculature in PD cases with variable disease durations. Specifically, we assessed the presence of string vessels, which are non-functional thin tissue fragments composed of collapsed basement membrane.

We performed collagen IV immunohistochemistry on 10 μ m formalin-fixed, paraffin-embedded tissue sections from the SN, visual cortex and hippocampus of long (n=10) and short disease duration (n=8) PD cases compared to controls (n=7). Both total capillary length and percentage of string vessels were quantified using Image J.

No difference in age at death, post-mortem delay or capillary length was seen between groups ($p > 0.05$). Increased string vessel formation was observed in the SN of all PD cases ($p < 0.001$). String vessels were increased in the visual cortex despite an absence of Lewy pathology in long ($p = 0.01$) (Braak IV-VI) but not short disease duration cases ($p > 0.05$) (Braak IV-V). Interestingly, no changes in string vessel formation were observed in the hippocampus in any group.

Our data demonstrates regional variations in string vessel formation in PD. String vessel formation in the visual cortex is present in cases with advanced disease stage, when visual hallucinations are common, and may underlie cortical hypoperfusion. Our findings suggest a significant vascular component to the pathogenesis of PD, which may be amenable to therapeutic intervention.

Abstracts

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The relationship between sleep duration and cortical sulcal width in midlife and older adults

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Abstract:

Evidence suggests poor sleep is associated with worse cognitive and brain health, and increased dementia risk. This study investigated the influence of sleep duration, napping, depression and APOE ϵ 4 on the cognition-brain relationship in older adults, using sulcal width (SW).

137 cognitively normal adults (aged 46-72) from the Prospective Imaging Study of Ageing participated. Demographics, sleep duration, depressive symptoms were collected via online questionnaires. Cognition was assessed using Creyos. APOE genotype was determined from blood-extracted DNA. Imaging was acquired using a 3T Siemens PRISMA scanner. SW was extracted using Morphologist pipeline.

Canonical Partial Least Squares were used to obtain latent variables of cognition and SW. ANCOVAs measured the effect of sleep duration categories (7-7.5 hours versus {<7 or \geq 8 hours}), with sex and age as covariates. Depression likelihood was added as a covariate of interest. The effect of napping, and APOE ϵ 4 on these same components were measured by ANCOVAs, with sex and age as covariates.

We observed a significant effect of sleep duration on SW ($F(1,133)=4.17$, $p=0.043$). This effect remained significant ($F(1,132)=4.89$, $p=0.029$) after including depression as a covariate, which was also significant in the model ($F(1,132)=4.62$, $p=0.034$). A significant interaction between APOE ϵ 4 status and age ($p=0.050$) on SW was observed.

Results add weight to studies suggesting that not too much or too little sleep is needed to maintain brain health in later life. Depression was also associated with poorer brain health. At approximately 60, a positive APOE ϵ 4 status was associated with increasing age-related brain atrophy.

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Zebrafish models to investigate dysregulation of the TDP-43 protein in Motor Neuron Disease

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Motor Neuron Disease (MND) is a highly heterogeneous disease with respect to genetic contributors to disease onset, clinical presentation and pathologies. One of the rare pathological features common to the vast majority (~95%) of patients is cytoplasmic mislocalisation and aggregation of TDP-43. To investigate the contribution of this TDP-43 dysregulation to disease progression, we have established multiple transgenic zebrafish lines which overexpress TDP-43 selectively within motor neurons. One line carries a familial TDP-43 mutation (TDP-43^{G294V}) and another carries TDP-43 with a disrupted nuclear localisation sequence (TDP-43^{dNLS}) to reflect cytoplasmic mislocalisation pathology. These zebrafish show no developmental abnormalities and normal motor function at 2 days post fertilisation (nervous system fully developed at this stage). However, by 6 days, TDP-43^{G294V} is associated with increased susceptibility to stress and TDP-43^{dNLS} is associated with motor deficits and anxiety-associated behaviour. At the adult stage, both TDP-43^{G294V} and TDP-43^{dNLS} fish demonstrate a reduced lifespan from approximately 12 months of age, reduced number of mature spinal cord motor neurons and reduced muscle mass. These MND-relevant phenotypes support the suitability of the TDP-43 transgenic zebrafish to study disease processes. The optical transparency of zebrafish in the early stages of development present an opportunity to study these processes at the molecular level in a living model in real time, including the dynamics of TDP-43 phase separation, protein-protein interactions and axonal transport.

Abstracts

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Effects of HDAC6 Inhibition in ALS mouse models

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Abstract:

Altered microtubule acetylation and impaired axonal transport are proposed as key pathological mechanisms for developing amyotrophic lateral sclerosis (ALS). The histone deacetylase 6 (HDAC6) enzyme is known for regulating the acetylation of α -tubulin, one of the subunits of microtubules. ACY-738, a novel HDAC6-specific inhibitor, has shown promising results for slowing neuron degeneration in Alzheimer's disease and fused in sarcoma-ALS models by increasing α -tubulin acetylation [1, 2]. Nevertheless, the effect of HDAC6 inhibition by ACY-738 in other models of ALS, and the potential protective effect on vulnerable axons, is still unknown.

This study utilises three transgenic (tg) ALS mouse models for modelling both TDP-43 and SOD1 pathology: TDP-43^{Q331K}, NEFH-hTDP-43 ^{Δ NLS}, and mSOD1^{G93A}. Our goal is to evaluate the therapeutic potential of ACY-738 with and without the current therapeutic drug, riluzole, in these ALS models.

For grip strength and body weight data, there were no statistically significant differences among the groups, across the three models. The biochemical assays showed, across the 3 models, ACY-738 (+/- riluzole) significantly increased ($p < 0.05$; $n = 3-6$) tubulin acetylation in spinal cord tissue compared to untreated tg mice. There were no significant differences in lower motor neuron (LMN) counts among treatment groups in ($n = 10$) TDP-43^{Q331K} mice. Female NEFH-hTDP-43 ^{Δ NLS} mice treated with riluzole had significantly higher ($p < 0.05$; $n = 5-9$) LMN counts and female mSOD1^{G93A} had significantly higher ($p < 0.05$; $n = 6-9$) LMN counts when treated with riluzole or ACY-738 individually compared to untreated. Furthermore, combined treatment with ACY-738 and riluzole significantly ($p < 0.05$; $n = 6-9$) restored the axon size in mSOD1^{G93A} mice, irrespective of sex.

Abstracts

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Abstracts

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Region-specific alterations of astrocytic K⁺ clearance in a mouse model for Alzheimer's disease

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Aims: Alzheimer's disease (AD) is an age-dependent neurodegenerative disorder characterised by neuronal loss and neuronal hyperexcitability, which emerges during the initial stages of the disease. Previous studies indicate that astrocytes, which are responsible for K⁺ homeostasis, can affect the excitability profile of neurons via alterations in their K⁺ clearance properties. Hence, this study aims to assess the astrocytic K⁺ clearance rate in the hippocampus and somatosensory cortex in a mouse model of AD during disease progression.

Methods: Simultaneous extracellular recordings of the K⁺ clearance rate and astrocytic inward currents in acute brain slices containing the somatosensory cortex and hippocampus. All recordings were taken from a mouse model for AD (5xFAD) and their littermate controls.

Results: We found that following transient local application of KCl, the K⁺ clearance rate in the hippocampus of aged 5xFAD mice was significantly lower than in WT littermates. This decrease was accompanied by a reduction of astrocytic inward currents in the hippocampus but not the somatosensory cortex. Moreover, selective inhibition of Kir4.1 channels indicated significant differences between the clearance mechanisms at the hippocampus and the somatosensory cortices of 5xFAD mice, which was correlated with a significant decrease in the number of primary connected astrocytes.

Conclusions: Our results indicate a region-specific dysfunction of astrocytes in 5xFAD mice, which affects their ability to clear K⁺ from the extracellular milieu. These findings indicate that the supportive function of astrocytes to neurons is diminished during disease progression and provide a potential explanation for the increased vulnerability of neurons during neurodegeneration.

Abstracts

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Trapping the Tau - PSD95 Protein-Protein Complex

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Abstract:

Tau is an intrinsically disordered protein that stabilizes microtubules in neurons. Misfolded tau protein is a hallmark of Alzheimer's Disease (AD) and variety of other neurodegenerative diseases. The pathway by which disordered, healthy tau forms disease defining misfolded protein aggregates is unknown; moreover, the structure of tau in complex with known interacting proteins has not been resolved. Post-synaptic density protein 95 (PSD95) is an important interaction partner of tau in disease progression, where binding of tau protein to PSD95 interferes with synapse organization and stabilization.¹

Here we use site-specific, scar-less, post-translational modification of human tau protein to enable the covalent trapping of the tau-PSD95 complex by Protein Interface Catalysed Capture (PICC).² We introduced dehydroalanine (Dha) into the specific positions on both recombinant 2N4R human tau and synthetic tau fragments and further modified these with light-driven radical Chemistry to introduce halo-alkyl groups to tau proteins and peptides. These groups act as alkylating agents at the protein-protein interface to allow the covalent trapping of protein-protein complexes.

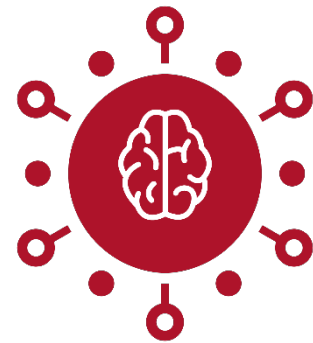
Tryptic digest of tau-PSD95 complexes followed by mass spectrometry identified specific interacting residues on PSD95 in complex with tau and allowed *in silico* reconstruction of the tau-PSD95 complex. Here we present the first folded structure of tau in complex with an interacting protein. These results will aid drug discovery programs and enable the identification of tau protein-protein inhibitors as a novel class of therapeutics.

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Abstracts

POSTER PRESENTER ABSTRACTS



Abstracts

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TREM2 protein expression on microglia and macrophages in acute MS lesions

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Keywords:

Neurodegeneration, demyelination, neuroinflammation, microglia

Abstract:

Triggering receptor expressed on myeloid cells-2 (TREM2) is hypothesized to regulate microglial functions and be involved in multiple sclerosis (MS) pathogenesis [1]. Most studies to date have predominantly evaluated TREM2 in animal models [2, 3]. Further understanding of TREM2 expression and functionality in the injured human central nervous system (CNS) is required. We aim to examine cell type-specific distribution and the expression level of TREM2 protein in acute MS lesions and peri-lesion white matter (PWM).

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MS Research Australia Brain Bank provided post-mortem human CNS tissue for triple immunolabelling with TREM2, IBA1 (pan-microglial marker), CD163 (perivascular macrophage marker) or TMEM119 (microglial marker) and CD68 (lysosomal marker). Nikon C2 confocal microscope was used to image 3 regions of interest (ROI) from the lesion centre and 3 ROI from the PWM (same slide). Using ImageJ we: 1. counted single, double and triple-labelled cells in the ROI and 2. measured the mean pixel intensity x the area of triple-labelled cells (n=60 cells inside and n=60 cells outside the lesion). Statistical data were analysed and displayed using GraphPadPrism.

Acute lesions can be either microglia-rich or macrophage-rich determined by CD163 and IBA1/TMEM119 expression and cell morphology. Observational and statistical data from the acute centre revealed an increase in the total number of cells expressing TREM2 compared to PWM yet TREM2 expression per cell remains stable. TREM2 expression on macrophages tends to be membranous whereas it is perinuclear in microglia. The majority of the cells in the lesion centre also express CD68.

At the site of injury, there is increased TREM2⁺ microglia and macrophages. However, TREM2 is only upregulated in terms of the number of cells and not expression per cell. This same population appears to be phagocytosing myelin debris which allows remyelination.

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Abstracts

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Cellular changes in the Subthalamic Nucleus in Parkinson's Disease

Parkinson's disease is a complicated degenerative disorder affecting millions worldwide, causing motor and non-motor symptoms. The pathophysiology of Parkinson's disease involves cellular changes, which are crucial to understanding effective treatment strategies.

Studying cellular changes may lead to interventions that slow down the progression of the disease.

A small structure called the subthalamic nucleus (STN) is found deep inside the brain, next to the basal ganglia and beneath the thalamus. The STN regulates movement, thought, and emotion and gets inputs from the cortex, striatum, and globus pallidus, among other areas of the brain. The substantia nigra and the globus pallidus, which are crucial for regulating motor activity, get outputs from the STN as well.

Reduced inhibition of the STN occurs as a result of the loss of dopamine-producing neurons in the substantia nigra in Parkinson's disease (PD). This causes the STN to become more active, which in turn leads to an overactive motor cortex and thalamus.

In our study we are specifically looking at cellular markers (nNOS and FOX-P2) and their organisation in the Subthalamic nucleus to understand the implications of cellular changes in human post-mortem brain tissue in PD cases. Our hypothesis is based on the presentation of neurons in the subthalamic nucleus, that has been divided into 6 subregions as the STN has shown inter regional differences with respect to its function. We aim to be able to differentiate, compare and reason the cellular representation in the STN with respect to functional and non-motor symptom changes in Parkinson's Disease.

Abstracts

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Regulation of Sequestosome-1/p62 is impaired by ALS-linked cyclin F

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Abstract:

The protein sequestosome-1/p62 has been implicated in several types of genetic and sporadic ALS. Emerging evidence indicates that the biochemical properties of p62 regulate p62 foci formation as a preceding step to protein clearance, and suggests that p62 has an intermediary role leading to pathological protein aggregation[1-2].

ALS-linked cyclin F causes defects to the protein clearance pathways and causes TDP-43 aggregation in neurons and neuronal death[3-4]. We recently demonstrated that p62's ubiquitylation, solubility and foci formation were dysregulated by the ALS mutant SCF cyclin F complex in neuronal-like cells[2]. To investigate the downstream effects of the dysregulated protein interaction in human ALS models, we investigated the cyclin F-linked ALS model in patient derived cells and tissue.

Consistent with cell studies, we found that cyclin F patient-derived fibroblasts and induced pluripotent stem cells also had dysregulated p62 solubility. We found that p62 was hyper-ubiquitylated in cyclin F patient post-mortem spinal cord motor neurons (p.S621G and p.S195R). We also performed protein interaction network analysis to determine whether the dysregulated mutant cyclin F-p62 protein interaction caused further dysregulation to downstream p62-protein interactors. Here we found that the interaction network of p62 was markedly different in mutant cyclin F expressing cells.

Our data suggest that selective ubiquitylation of p62 facilitates biochemical properties required to regulate p62 solubility and foci formation leading up to protein clearance. We suggest that differential ubiquitylation of p62 disrupts its solubility as a pathogenic mechanism of ALS. We conclude that further investigation of the dysregulated downstream p62-protein network is warranted.

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Abstracts

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Investigating the protective role of Protein Disulphide Isomerase against DNA damage in Amyotrophic Lateral Sclerosis

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Background

The DNA damage response is vital for genomic stability and its relevance in neurodegenerative diseases like ALS is growing. Our prior research underscored the protective role of protein disulphide isomerase (PDI), a unique chaperone with oxidoreductase activity, against various ALS-related pathologies. However, PDI's protective potential against DNA damage in ALS remains unexplored. Our aim is to investigate the protective roles of PDI in DNA repair.

Methods

Neuro-2A (N2A) cell lines were used with different PDI expression levels - overexpression or siRNA knockdown. DNA damage was induced using etoposide and hydrogen peroxide. Fluorescence microscopy captured images, and DNA damage foci were analyzed using ZEN blue or ImageJ software.

Results

Etoposide or hydrogen peroxide-induced DNA damage was mitigated with PDI overexpression. Conversely, examining DNA damage induction in PDI-depleted cells highlighted PDI's protective effect. PDI translocated to the nucleus upon etoposide-induced DNA damage, suggesting a direct role. The study also determined that PDI's redox is protective against DNA damage.

Conclusions

These findings indicate PDI's redox activity shields against DNA damage, a function disrupted in ALS. Understanding these mechanisms may pave the way for future ALS therapeutics based on PDI, aimed at preventing DNA damage.

Abstracts

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RNA sequencing of amyotrophic lateral sclerosis peripheral blood reveals distinct molecular subtypes

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Amyotrophic lateral sclerosis (ALS) is a heterogeneous neurodegenerative disease with limited therapeutic options. A key factor limiting the development of effective therapeutics is the lack of disease biomarkers. We sought to assess whether biomarkers for diagnosis, prognosis or cohort stratification could be identified by RNA sequencing (RNA-seq) of ALS patient peripheral blood.

Whole blood RNA-seq data were generated for 96 sporadic ALS (sALS) cases and 48 healthy controls. Differences in sALS-control gene expression, transcript usage and predicted leukocyte proportions were assessed, with pathway analysis used to predict the activity state of biological processes. Weighted Gene Co-expression Network Analysis and machine learning algorithms were applied to search for diagnostic and prognostic gene expression patterns. Unsupervised clustering analysis was employed to determine whether sALS patient subgroups could be detected.

245 (1.9%) genes were identified to be significantly differentially expressed in sALS patients relative to controls, with enrichment of immune, metabolic and stress related pathways. sALS patients also demonstrated switches in proportional transcript usage across a small set of genes. We established a classification model that distinguished sALS from controls with an accuracy of 78% (sensitivity: 79%, specificity: 75%) using the expression of 20 genes however, machine learning algorithms could not accurately predict survival from gene expression profiles. Finally, clustering analysis identified four patient subgroups with gene expression signatures and immune cell proportions reflective of distinct peripheral effects.

Our findings suggest that peripheral blood RNA-seq can identify diagnostic biomarkers and distinguish molecular subtypes of sALS patients however, its prognostic value requires further investigation.

Abstracts

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Single molecule detection of TDP-43 CTD Liquid Liquid Phase Separation

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Abstract:

In this study the phase transition between homogenous protein solutions of TDP-43 monomers to protein condensates was investigated using single molecule spectroscopy. Single molecule spectroscopy measures the number of proteins in complexes and the physical size (diffusion) of the complex, directly in solution. We hypothesized that it could be used in heterogenous mixtures to quantify liquid-liquid phase transitions and protein aggregation.

First, we established the phase transition diagram for TDP-43 CTD, at the single molecule level, and observed that droplets form extremely rapidly (within seconds) upon changes in protein concentrations. While macroscopic droplets form over 24h at high protein concentrations (20 micromolar), we show that TDP-43 nuclei and nanodroplets form readily at sub-micromolar physiological concentrations.

The formation of liquid condensates was enhanced in the presence of a chemical chaperone, trimethylamine N-oxide (TMAO). Our single molecule data mapped the entire phase diagram, and revealed the different steps of nucleation and growth of the condensates. Additionally, more biologically relevant environments such as cell lysate were used to demonstrate formation of condensates in pseudo cellular environments, in the absence of TMAO, and at very low concentrations of TDP-43. We explored in detail the kinetics of these transitions, determined the reversibility of transitions between different phases and determined when condensates become ThT positive.

Furthermore, the effect of several partner proteins such as α -synuclein and FUS was investigated. We will demonstrate the co-phase separation of Synuclein and TDP-43 and the specificity of these interactions. The study paves the way for further studies on protein condensates and protein co-aggregation at the single molecule level.

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Abstracts

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What is the role of SARM1 in axonal connectivity?

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Axon degeneration is a hallmark of traumatic brain injury and neurodegenerative disease and is a significant cause of death and disability worldwide. Sterile Alpha and TIR motif-containing protein 1 (SARM1) is emerging as a key player in modulating axon degeneration. Following an injury, SARM1 is activated, which results in rapid depletion of NAD⁺ and energy stores in the axon, which accompanies signalling cascades that lead to axon degeneration. SARM1 activation appears to hasten the process of axonal degeneration leading to neuronal connectivity disruption but does SARM1 have any role in maintaining axonal connectivity in the cerebral cortex in the absence of injury?

Using cranial windows and *in vivo* multiphoton imaging, we directly visualize excitatory axons in the cortex of Thy1-GFP-M transgenic mice, crossed with SARM1 null mutants. Based on synapse type, we classify and image three different subpopulations of axons, and compare morphology, synaptic density, and synaptic turnover in the presence and absence of SARM1 (n=45 axons), prior to laser-mediated axotomy to induce Wallerian degeneration of distal segment (disconnected) as well as analysis the proximal segment (connected). Each axon is imaged at least four times at 48-hour intervals prior to and after the lesion to determine the synaptic density (synapses/unit length) and turnover (a measure of how dynamic the synapses are). Preliminary analysis indicates that axon morphology, synaptic density, and turnover are comparable in the young adult brain in the presence or absence of SARM1. Finally, the absence of SARM1 does not appear to alter the onset time of degeneration.

Abstracts

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Testing *DARS1* gene replacement therapy in mouse models of the leukodystrophy HBSL

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Abstract:

Leukodystrophies are a diverse group of genetic disorders that affect myelination within the central nervous system (CNS), almost all of which are currently incurable. Biallelic mutations in the *DARS1* gene, which encodes the cytoplasmic aspartyl-tRNA synthetase (AspRS), cause a leukodystrophy known as Hypomyelination with Brainstem and Spinal cord involvement and Leg spasticity (HBSL). In mice, while complete knockout of *Dars1* is embryonically lethal, heterozygous *Dars1* knockout mice are phenotypically normal. This suggests that even partial restoration of AspRS function through *DARS1* gene replacement may yield substantial therapeutic benefits for HBSL patients. Recently, our group has generated two mouse models of HBSL pathology, where *Dars1* expression is conditionally knocked out in either neurons (*Dars1^{NeuroKO}*) or oligodendrocytes (*Dars1^{OligoKO}*). Both models exhibit pronounced neurological dysfunction, and further characterisation of these mice will provide valuable insights into the contribution of the individual cell populations to the overall HBSL pathophysiology. Additionally, our group has developed recombinant adeno-associated viral vectors (rAAVs) for CNS-targeted gene delivery of an optimised human *DARS1* coding sequence. Encouragingly, rAAV-mediated *DARS1* delivery has shown great efficacy in rescuing the phenotype of our most severe *Dars1^{NeuroKO}* model, providing an initial proof-of-concept for HBSL gene replacement therapy.

Abstracts

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In Vivo Validation of an Inducible Microglial Cannabinoid Receptor 2 Knockout Mouse

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Abstract:

Chronic neuroinflammation, characterized by sustained pro-inflammatory activation of microglia, is a hallmark of neurodegenerative disease. The endocannabinoid system has been identified as a potential therapeutic target to modulate neuroinflammation. Using an in vivo model of L-dopa induced dyskinesia (LID), we previously demonstrated that cannabinoid receptor 2 (CB2) agonists can reduce neuroinflammation and LID severity¹. We hypothesize that these beneficial are due to stimulation of microglial CB2 specifically.

To test this, we engineered a novel mouse line using cre-lox technology to create a tamoxifen-inducible and microglia-specific CB2 knockout. Reporter genes were introduced for histological analysis of CB2 expression. CB2 agonist reduced LID severity in all mouse lines, regardless of genotype. Tamoxifen or vehicle administration did not produce significant differences. Histological analysis confirmed the high efficiency and specificity of CB2 knockout.

Our findings indicate that the genetic modifications did not affect CB2 function and tamoxifen did not impact dyskinesia. This allows us to proceed with tamoxifen induced CB2 knockout to determine the role of microglial CB2 in the beneficial effects of CB2 agonists. This microglia-specific conditional CB2 knockout mouse line is a valuable tool for cannabinoid research and can be used to analyse CB2 expression and develop cell/tissue-specific CB2 knockout lines. Although further validation is needed, these results provide important insights and a valuable tool for the field of field of cannabinoid research.

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Abstracts

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Limbic-predominant age-related TDP-43 encephalopathy (LATE) in FTLD-tau cases from the Sydney Brain Bank

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Abstract:

Limbic-predominant age-related TDP-43 encephalopathy (LATE) is an age-related neuropathology consisting of phosphorylated TDP-43 deposition in a 3-stage progression (1). LATE may be the sole causative factor for cognitive decline or may accelerate decline in the presence of co-pathologies (1,2). To date, few studies have described LATE in FTLD-tau (3).

We have assessed all FTLD-tau cases (n=106) in the Sydney Brain Bank for the presence of LATE, including progressive supranuclear palsy, corticobasal degeneration, Pick's disease and globular glial tauopathy subtypes. An Alzheimer's disease (AD) group was added for comparison (n=142). We assessed the associations between neuropathological diagnosis, age, presence of LATE, LATE stage and presence of other coexisting pathologies.

There was no difference in age at death between any of the groups ($p > 0.05$), however disease duration was significantly lower in the FTLD-tau group ($p = 0.002$). LATE was found in 24% of FTLD-tau and 42% of AD cases. Globular glial tauopathy cases were more likely to have LATE than other FTLD-tau subtypes (47% versus <32% in other FTLD-tau subtypes). 86% of all cases with LATE were stage 2 or greater. The majority of all cases had two or more coexisting pathologies, with 63-73% of FTLD-tau subtypes and 84% of end-stage AD showing more than a single pathology.

We conclude that LATE occurs as a coexisting pathology in approximately 25% of FTLD-tau cases and contributes to the multiple pathologies that have been reported in FTLD-tau cases of all ages (3). As such, FTLD-tau cases with coexisting pathologies, including LATE, should be considered representative of this disease population.

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Abstracts

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Evaluation of the therapeutic effectiveness of a novel cannabis formulation (i.e., Eve strain extract) in Alzheimer's disease transgenic mice

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Alzheimer's disease (AD) is the most common form of dementia. This disease is characterised by amyloid-beta ($A\beta$) plaque deposition and tau hyperphosphorylation that causes neurofibrillary tangles (NFT). Neurodegeneration, neuroinflammation and oxidative stress are also evident. These brain pathologies result in cognitive and behavioural impairments. Currently, no treatment options exist that cure the disease or stop or reverse disease progression. Preclinical mouse models of AD, such as the *APP/PS1* transgenic mice, mirror aspects of AD-specific neuropathological, cognitive, and behavioural changes. Thus, this model can provide insights into the potential validity of novel therapeutic interventions. Current preclinical mostly *in vitro* evidence suggests that cannabis extracts may lessen AD-related $A\beta$ plaque deposition and NFT formation, thus improving cognitive and behavioural outcomes through the combined synergistic activity of multiple cannabinoids, terpenes and flavonoids, called the 'entourage effect'. Thus, we sought to evaluate the effectiveness of 125 mg/kg cannabidiol (CBD)-rich cannabis extract (Eve) in treating AD-related behaviours in *APP/PS1* transgenic mice. AD mice exhibited hypolocomotion, reduced social interaction, and a moderate spatial learning impairment. Importantly, Eve increased explorative behaviours in the elevated plus maze, suggesting a beneficial effect of Eve on anxiety-related behaviours. However, Eve did not reverse behavioural deficits present in *APP/PS1* mice. Future research concerning cannabis extract therapy in AD may need to consider other Eve dosing or the use of cannabis extracts with a different cannabinoid profile.

Abstracts

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Investigating the Role of C99 Polypeptide in Alzheimer's Disease Progression: Insights from MC65 Cell Line Studies

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Abstract:

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder characterized by the accumulation of amyloid beta ($A\beta$) peptides. Despite extensive research, many aspects of AD pathology and progression remain enigmatic. Various in vitro models have been developed to replicate the sequential enzymatic cleavage of amyloid precursor protein (APP), leading to $A\beta$ accumulation.

The stable genetic modification of the human neuroblastoma cell line MC65 derived from SK-N-MC allows for the conditional production of the C99 polypeptide, bypassing the need for β -secretase cleavage from APP. Subsequent γ -secretase activity results in the production of neurotoxic $A\beta$ peptides implicated in neuronal damage.

While MC65 models have been extensively used, there remains a gap in our understanding of the mechanisms underlying neuronal dysfunction, particularly regarding the effects of conditionally expressed C99 on endogenous APP. To address this gap, we conducted comprehensive studies, including time course experiments conducted over four days at four-hour intervals. Our investigations focused on measuring APP fragments, $A\beta$ peptides, C99 polypeptide, BACE1, and Presenilin 1 and 2 levels.

Our findings revealed a progressive increase in C99 concentration in MC65 cells over time, correlating with elevated levels of $A\beta_{40}$ and $A\beta_{42}$ peptides, as well as γ -secretase activity. Notably, β -secretase exhibited a substantial increase even in the absence of APP accumulation. This study elucidates a direct relationship between C99 production and β -secretase activity, shedding light on a mechanism that negatively impacts APP.

Conclusion:

In summary, our study provides valuable insights into the intricate processes involved in Alzheimer's disease pathogenesis. By establishing a link between C99 production and β -secretase activity, we highlight a potential avenue for further exploration in understanding AD progression and potential therapeutic interventions. Further investigations into this relationship may unveil novel targets for the development of effective treatments for Alzheimer's disease.

Abstracts

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Ataxin-3 as a deubiquitinating enzyme: is its deubiquitinating function altered in Machado-Joseph disease?

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Abstract:

Dysfunction of the ubiquitin-proteasome system has been linked to the pathogenesis of various neurodegenerative diseases, with ubiquitin-positive inclusions observed in Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, and prion diseases. Machado-Joseph disease (MJD) is a genetic neurodegenerative disease characterised by progressive loss of muscle control, balance, coordination, and movement. The typical age of onset of MJD is around 40 years, and as it stands there is no treatment beyond symptomatic management. MJD is caused by mutation of the ATXN3 gene, causing the resultant ataxin-3 protein to have an expanded polyglutamine repeat region. Ataxin-3 functions as a deubiquitinating enzyme, and increasing evidence suggests that polyglutamine expansion may alter ataxin-3's deubiquitinating function. However, whether polyglutamine expansion results in a gain or loss of deubiquitinating function of ataxin-3, and the downstream consequences of this on its substrates, has not been fully elucidated.

We have explored how the levels of K48- and K63-ubiquitinated proteins are altered in cellular, zebrafish, and mouse models of MJD. We have also used a proteomic approach to identify K48-ubiquitinated proteins that differ in abundance when polyglutamine-expanded ataxin-3 is present, compared to wild-type ataxin-3 or the absence of human ataxin-3. To gain insight into the downstream consequences of this altered K48-ubiquitination, we are investigating whether abundance and subcellular localisation of these proteins is altered in cellular, zebrafish, and mouse models of MJD, using western blotting, co-immunoprecipitation, and immunofluorescence analysis. Understanding how the deubiquitinating function of ataxin-3 is altered in MJD is crucial to identifying new avenues of treatment for MJD.

Abstracts

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The Effect of Gpr109a and Sex in Cuprizone Induced Demyelination and Remyelination

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Background:

Multiple sclerosis (MS) is a neuroinflammatory demyelinating disease which currently has no treatments that facilitate remyelination to halt disease progression. A receptor expressed on microglia, Gpr109a, has emerged as a novel therapeutic target to increase phagocytosis by microglia¹, which is essential for clearance of myelin debris to facilitate remyelination².

Methods:

In this study, we induced demyelination by feeding transgenic Gpr109a knock-out mice a 0.2% cuprizone diet for 5 weeks followed by withdrawal of cuprizone for 3 days to allow for partial remyelination. Behavioural tests using a walking beam and walking ladder were conducted to assess fine motor function following demyelination and remyelination. Histological analysis will be conducted to quantify myelin and glial cell populations in the corpus callosum, a white matter tract affected by demyelination in this model.

Results:

Across both behavioural tests, there was a trend that knock-out mice had less foot slips compared to wild-type mice after 5 weeks of cuprizone treatment. Further to this, there was a trend that wild-type mice had a reduction in foot slips following partial remyelination. This trend was not seen in knock-out mice. Female mice had less foot slips after 5 weeks of cuprizone treatment compared to males. However, males saw a reduction in the number of foot slips following partial remyelination. This was not observed in female mice.

Conclusion:

These results suggest that lack of Gpr109a beneficially impacts fine motor function following demyelination but not remyelination. Additionally, there are sex differences in the ability to remyelinate, highlighting the importance of further investigating the role of Gpr109a as a potential therapeutic target for remyelination.

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Abstracts

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

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Abstract:

Neuroinflammation and glial cell dysfunction are associated with neurodegenerative diseases and are central to disease pathology^{1,2,4}. Amyotrophic lateral Sclerosis (ALS) is a neurodegenerative disease associated with a specific loss of motor neurons (MNs) leading to motor dysfunctions. In the SOD1^{G93A} mice model of ALS, the ability of astrocytes to maintain K⁺ homeostasis is impaired in the primary motor cortex, which can affect the excitability of MNs and is accompanied by reactive astrocytes and increased levels of neuroinflammation^{7,5, 3,6}. In this study, we aim to evaluate the therapeutic effect of phytosomal Curcumin, a cytokine suppressive anti-inflammatory drug in ameliorating ALS disease progression, specifically the dysregulation of K⁺ ion homeostasis by astrocytes, neuroinflammation level, MN hyperexcitability, and death by employing behavioural tests, electrophysiological recordings, imaging, and molecular biology techniques. We provided a curcumin-enriched diet to SOD1^{G93A} and WT mice from PND30 and assessed their motor and anxiety levels via behavioural tests including an open field test, accelerod test, and beam walking test from PND111 to PND119. Preliminary results indicate significant motor deficits between genotypes, as SOD1^{G93A} mice that were fed with a normal diet had significant motor deficits compared to WT mice. Moreover, mice that were fed with a Curcumin-enriched diet exhibited an increase in latency to fall and lesser time to traverse the beam in comparison to SOD1^{G93A} fed with a normal diet, suggesting a limited effect on motor deficits.

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Abstracts

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Neuronal growth regulator 1 (NEGR1) promotes α -synuclein oligomer clearance

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Brains of patients with Parkinson's disease (PD) are characterized by abnormal accumulation of α -synuclein oligomers which form aggregates in cell bodies, dendrites, and axons of neurons. These aggregates cause neuronal toxicity and ultimately death. The mechanisms causing α -synuclein accumulation are incompletely understood. We demonstrate that the levels of α -synuclein and its oligomers are increased in brains of mice deficient in a synaptic cell adhesion molecule neuronal growth regulator 1 (NEGR1). We show that α -synuclein oligomers similarly accumulate in synapses of NEGR1-expressing and NEGR1-deficient cultured hippocampal neurons. α -Synuclein oligomers are also found extrasynaptically, and the levels of these oligomers are increased in NEGR1-deficient neurons. NEGR1 reduces the levels of α -synuclein and its oligomers in transfected Chinese hamster ovary (CHO) cells. The NEGR1-dependent degradation of α -synuclein is blocked in CHO cells treated with the proteasome inhibitor MG132, but not in cells treated with the lysosome inhibitor bafilomycin. The NEGR1-dependent degradation of α -synuclein and its oligomers is reduced in cells expressing familial PD-causing α -synucleinA30P and α -synucleinE46K mutants. The NEGR1-dependent degradation of α -synuclein is blocked in cells expressing α -synuclein with mutated sites involved in binding to the plasma membrane. Our data indicate that NEGR1 promotes clearance of non-synaptic α -synuclein oligomers most likely via their proteasomal degradation, and suggest that this mechanism is dysregulated in PD.

Abstracts

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Developing a molecular platform for the rapid functional study of novel oligogenic ALS candidate genes

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Amyotrophic lateral sclerosis, a deadly neurodegenerative disease, is monogenic in 70% of Australian ALS families. The remaining unsolved 30% do not exhibit classical Mendelian inheritance patterns and are thus challenging to solve via traditional genetic analyses. We applied a gene discovery strategy to an ALS family (MQ1) negative for known ALS-causative gene mutations, revealing five candidate variants, of which two exhibited strong potential for pathogenicity. New bioinformatics tools also allowed us to assess short tandem repeat (STR) expansions in next-generation sequencing data. This revealed an intermediately expanded *ataxin-2* (*ATXN2*) STR—known to increase ALS risk—in affected MQ1 patients. The close genomic proximity suggests co-inheritance of all 3 candidate variants, further supporting oligogenic disease effects in MQ1.

To enable the continued use of our rapid *in vitro* functional pipeline, which relies on a transient overexpression paradigm, and overcome low co-expression, we developed a novel molecular multicistronic platform, which increased co-expression of candidates A and B in HEK293T cells by 10-fold. Using this platform, efficient co-expression of *ATXN2* with candidate variants A and B was also achieved. Confocal microscopy revealed no differences in cellular morphology between wildtype and MQ1-specific expanded *ATXN2*. Additionally, cytoplasmic inclusions were positive for candidate variants A and B, but not *ATXN2* regardless of STR size.

We have developed a promising molecular platform to examine oligogenic effects in ALS and optimized a pipeline that enables functional study of multiple genes simultaneously and rapidly.



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