A Tribute to Euan MacDonald

Academic Symposium

incorporating public event

Celebrating Euan's Legacy

Weds 8th – Thurs 9th October 2025

Euan's Guide

EUAN MACDONALD CENTRE

Vital research into motor neuron disease

SpeakUnique

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Academic Programme

A Tribute to Euan MacDonald

8th-9th October 2025, John McIntyre Centre, Edinburgh

Weds 8th October

09.00-10.00	Registration and coffee	
	Chair: Prof Siddharthan Chandran	
10.00	Prof Siddharthan Chandran, MacDonald Professor of Neurology; Director of the Euan MacDonald Centre and UK Dementia Research Institute	Welcome
10.10	Prof Richard Ribchester, Emeritus Professor of Cellular Neuroscience, University of Edinburgh	A brief history of EMC time: from beginnings to big bang
10.20	Prof Sabine Liebscher, Director, Institute of Systems Neuroscience, Medical University of Innsbruck, Austria	The complexity of circuit dysfunction: reframing ALS/FTD pathophysiology
10.50	Prof Tom Gillingwater, Professor of Anatomy, University of Edinburgh	Targeting bioenergetic pathways in motor neuron disease
11.20-11.40	Refreshment break	
	Chair: Prof Gareth Miles	
11.40	Dr Matthew Livesey, Senior Lecturer, Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield	Targeting network inhibition for therapeutic rescue in MND
12.10	**Early-career researcher flashtalks**	
	Alyssa Corbett, Euan MacDonald Centre PhD student, University of St Andrews	Communication between neurons and astrocytes is dysfunctional in presymptomatic ALS mice
	Hannah Crick, Euan MacDonald Centre PhD student, University of Edinburgh	A novel mouse model of X-linked spinal muscular atrophy offers a platform for preclinical development of UBA1 targeting therapeutics
	Dr Johnny Tam, MRC Clinical PhD Fellow, University of Edinburgh	Deep learning digital speech biomarkers of dysarthria in MND
	Dr Áine Heffernan, Postdoctoral Research Assistant, University of Edinburgh	Neuronal TDP-43 pathology drives alterations in oligodendrocyte lineage dynamics in ALS
12.40	Dr Owen Gwydion James, Wellcome Early Career Research Fellow, UK Dementia Research Institute at King's College London	Investigating the role of disease modifiers for protein-RNA pathogenesis in ALS
13.10-14.10	Lunch and posters; Poster presentations #1-11, 13.40-14.10	
14.10-17.00	**Celebrating Euan's Legacy public session** – see separate programme Poster presentations #12-22, 15.20-16.00	
17.00-18.30	Wine reception	

Thurs 9th October

08.00-09.00	Registration and coffee	
	Chair: Dr Bhuvaneish Selvaraj Thangaraj	
09.00	Prof Christopher E Shaw, Professor of Neurology and Neurogenetics, King's College London & University of Auckland, New Zealand	Gene therapy for ALS and FTD: are we there yet?
09.30	Dr Andrea Serio, Reader in Neural Tissue Engineering, King's College London; Principal Investigator, UK DRI; Group Leader, The Francis Crick Institute	Engineering connections: combining stem cells, neurobiology & bioengineering to understand human neurodegenerative diseases
10.00	**Emerging leaders**	
	Dr Matthew Broadhead, Postdoctoral Researcher/Co-Principal Investigator, University of St Andrews	Synaptic diversity and vulnerability in amyotrophic lateral sclerosis
	Dr Helena Chaytow, Research Fellow, University of Edinburgh	The CCL2-CCR2 axis drives neuromuscular denervation in ALS
	Dr Caroline McHutchison, Lecturer in Psychology, University of Stirling	Mild cognitive impairment in presymptomatic MND
	Dr Maria Stavrou, Senior Clinical Research Fellow, University of Edinburgh	Astrocytes as drivers of axonal transport in ALS
11.00-11.30	Refreshment break; poster presentations #23-34	
	Chair: Dr Chris Sibley	
11.30	Prof Sharon Abrahams, Professor of Neuropsychology, University of Edinburgh	Cognitive assessment in MND: why and how?
12.00	**Early-career researcher flashtalks**	
	Dr Laura Comley, Postdoctoral Research Fellow, University of Edinburgh	Early loss of intramuscular motor axons limits capacity for recovery following Smn up-regulating therapy in a mouse model of SMA
	Dr Shreya Parthadas Sharma, Postdoctoral Research Fellow, University of Edinburgh	Mechanisms of glutamate-mediated excitotoxicity in ALS
	Dr Daniel Jutzi, Postdoctoral Research Associate, University of Edinburgh	The structured RNA-binding domains and condensation capacity of FUS shape its RNA-binding landscape and function
12.30	Prof Mahesh (Max) Parmar, Professor of Medical Statistics and Epidemiology, Director MRC Clinical Trials Unit at UCL and Institute of Clinical Trials and Methodology, University College London	Improving health by improving trials
13.00	Prof Siddharthan Chandran, MacDonald Professor of Neurology; Director of the Euan MacDonald Centre and UK Dementia Research Institute	Poster prizes and close
13.15	'Grab and go' lunch	

Celebrating Euan's Legacy

14.00	**Arrivals**	
14.10	Welcome	Prof Siddharthan Chandran
14.20	**Euan's legacies**	Chaired by Chloe Kippen
	Euan's Guide: Real reviews. Real voices.	Kiki MacDonald, Joe Logue and Antonia Lee-Bapty
	SpeakUnique: The future of voice technology for health	Olivia Szczerbakiewicz and Dr Oliver Watts
15.00	**Euan MacDonald Centre research snapshots**	Chaired by Prof Siddharthan Chandran
	Spot the Difference – Finding changes to protein production in MND	Dr Hannah Smith
	Why do some people with MND survive longer than others?	Jade Lucas
	Finding the missing pieces and solving the puzzle: blood biomarkers in MND	Dr Hatice Bozkurt
15.20	**Refreshment break**	**Browse information stands and academic posters**
16.00	**Public lecture**	Introduced by Prof David Argyle
	The Euan MacDonald Centre: Making a difference	Prof Siddharthan Chandran, Prof Suvankar Pal and Bruce Virgo
17.00	**Wine reception**	**Browse information stands and academic posters**
18.30	**Close**	

Posters

Poster competition judges: Dr Helena Chaytow, Dr Matthew Broadhead, Dr Rachel Kline

Session 1: Weds 8th October 13:40-14:10
Discovery Science

#	Title	Presenting author
1	Investigating Tripartite Synapse Pathology in ALS Utilizing a hiPSC-derived Organoid Model	Ahmad Jibai
2	Gliotransmission is Dysfunctional in Spinal Motor Networks of Presymptomatic SOD1 Mice	Alyssa Corbett
3	In depth multi-omic analysis of axonal homeostasis across scale using a bioengineered platform and IPSC-derived human motor neurons	Cathleen Hagemann
4	Long-term persistent defects at the neuromuscular junction following pharmacological SMN upregulation in mouse models of SMA	Charles Nyasa
5	Optimising Models to allow testing of Bioelectric Modulators to Drive Motor Axon Regeneration in Mouse Models	Ernie Ho
6	Capacity of a synthetic retinoic acid receptor agonist to reduce oxidative stress, stress granule production and TDP-43 mislocalization	Francesco Moramarco
7	Comparison of the motor neuron translatome in mouse models of ALS and SMA reveals defects specific to protein translation.	Hannah Smith
8	Characterization of the human cortical synaptome in ALS-FTD	Hidefumi Suzuki
9	Facilitating Neuromuscular Junction Recovery After Treatment in in Mouse Models of Spinal Muscular Atrophy	Inga Partlova
10	Assessing the Cellular and Pathological Determinants of Disease Duration in ALS using Multiparametric Imaging Mass Cytometry analysis	Jade Lucas
11	Early loss of intramuscular motor axons limits capacity for recovery following Smn up-regulating therapy in a mouse model of spinal muscular atrophy	Laura Comley

Session 2: Weds 8th October 15:20-16:00
Discovery – Translational Science

#	Title	Presenting author
12	Investigating the role of TDP-43 mis-splicing events in motor neuron disease pathogenesis	Maja Matoga
13	Towards novel biomarker discovery for motor neuron disease: Ultra-sensitive mass spectrometry-based proteomic approach	Krishna Bhavsar
14	High-Throughput Transcriptomics (DRUG-seq) for ALS Drug Discovery	Mungo Harvey
15	Human cell screening platforms to accelerate translation from bench to clinic	Rod Carter

16	Transcriptomic analysis of protein misfolding enteropathy – a pathological entity predicting neurodegenerative disease and life-limiting prognosis	Tatiana Langerová
17	Matrin-3 Cellular Expression in Motor Neuron Disease Models	Molly Roberts
18	Deconstructing the roles of Oligodendrocytes and Neurons in mediating TDP-43-related neurodegeneration	Marcus Keatinge
19	Loss of TDP-43 causes AMPAR current dysfunction in iPSC derived motor neuron	Shreya Das Sharma
20	Exploring the interplay between axonal metabolic alterations and degeneration in ALS	Sofia Fredin
21	Human Models of Oligodendrocytes, and Oligodendrocyte-Neuron crosstalk	Sophie Hawkins
22	Whole-brain single-synapse mapping of MAGUK complex organisation at nanoscale resolution reveals synapse diversity shaped by age and disease-associated mutation	Takeshi Kaizuka

Session 3: Thurs 9th October 11:00-11:30
Translational – Clinical Science

#	Title	Presenting author
23	Identifying and Validating Blood-based Biomarkers in Motor Neuron Disease using Nucleic Acid-Linked Immuno-Sandwich Assay	Hatice Bozkurt
24	EMG4MND: High-Density EMG At Home Unassisted for PLWMND	Adrien Rapeaux
25	MND-SMART – A collaborative, expeditious, and definitive clinical trials platform for ALS	Amy Stenson
26	Patient and public involvement and engagement (PPIE) in MND-SMART	Sindy Golgota
27	Acoustic speech analysis and machine learning in the diagnosis and monitoring of neurodegenerative disorders	Christine Weaver
28	Ante-mortem consenting for brain and spinal cord donation –a quality improvement exercise evaluating experiences of people with MND	Isaac Chau
29	A 10-year retrospective analysis of epidemiology and survival within the Scottish MND population	Isaac Chau
30	The predictive and diagnostic value of motor screening in a neurodegenerative clinic	Kuba Olszak
31	Retinal Imaging in Motor Neuron Disease – Amyotrophic Lateral Sclerosis: A Systematic Review	Miracle Ozzoude
32	Influences of Specialist Palliative Care Team Input, Advance Care Planning, Non-Invasive Ventilation and Gastrostomy Status on Unscheduled Hospital Admissions and Place of Death for People with Motor Neuron Disease: A Retrospective Cohort Analysis	Nathaniel Quail
33	The MND diary project - Exploring factors which help people to feel able to cope following a diagnosis of motor neurone disease	Nicola Glennie
34	High-throughput drug screening reveals everolimus confers neuroprotection in ALS through mTOR pathway Inhibition	Abby O'Sullivan

Speaker Biographies

Weds 8th October 10.00-13.10

Prof Siddharthan Chandran, MacDonald Professor of Neurology; Director of the Euan MacDonald Centre and UK Dementia Research Institute

Siddharthan Chandran is Director of the Euan MacDonald Centre for MND Research and Director of the UK MRC Dementia Research Institute. He graduated from Southampton Medical School, trained in neurology at Queens Square, UCL and Cambridge where he also undertook a PhD in developmental neurobiology. He holds the MacDonald Chair of Neurology, at the University of Edinburgh, is Professor of Neurology at University College London, and Visiting Faculty at the Centre for Brain Research, Indian Institute of Science, India.

Siddharthan is best known for his work in motor neuron disease and multiple sclerosis. His work encompasses the use of human induced pluripotent stem cells to identify cellular phenotypes of neurodegenerative diseases as well as pioneering innovation in multi-arm, multi-stage platform trials.

He is a Fellow of the Royal Society of Edinburgh and the Academy of Medical Sciences.

Prof Richard Ribchester, Emeritus Professor of Cellular Neuroscience, University of Edinburgh

Richard is Emeritus Professor of Cellular Neuroscience at the University of Edinburgh, a position he adopted when he formally retired from his Personal Chair in 2020, after 40 years on the University's academic staff. Richard's research career was focused on the structure and function of motor neurons and neuromuscular junctions in health and disease. Working in collaboration with Michael Coleman's group in Cambridge, Richard's team studied long-lasting protection from axotomy-induced synaptic degeneration in the WldS mouse variant, including its age-dependence and sensitivity to use and disuse. He also devised ways to combine optical and electrophysiological tools for monitoring synaptic degeneration in situ, for which he was awarded the 2015 Delsys Prize for Innovation in Electromyography.

Richard was a founding member and Convener of "EdMoND" (the Edinburgh Motor Neuron Disease Research Group) in 2006, which led in 2007 to establishment of the Euan MacDonald Centre.

Prof Sabine Liebscher, Director, Institute of Systems Neuroscience, Medical University of Innsbruck, Austria

Sabine Liebscher is a physician and neuroscientist, currently serving as Professor of Systems Neurobiology and Director of the Institute of Systems Neuroscience at the Medical University of Innsbruck since February 2025. Prior to this, she held a W2 Professorship in Cellular Neurophysiology at the Faculty of Medicine, University of Cologne, and led a Clinician Scientist research group and was a resident in Neurology at the Institute of Clinical Neuroimmunology at Ludwig Maximilians University (LMU) Munich.

Sabine studied medicine at the Technical University of Dresden, where she also completed her MD thesis. She then completed my PhD with distinction at the Max Planck Institute of Neurobiology and LMU Munich. In 2014, she established an independent junior research group funded through the prestigious Emmy Noether Programme of the German Research Foundation (DFG).

Sabine's scientific work focuses on the pathophysiology of neurodegenerative diseases, especially amyotrophic lateral sclerosis (ALS), where she aims to understand how neural circuits and individual circuit elements are affected to give rise to typical symptoms of the disease and to further fuel the degenerative process. Her research bridges clinical questions and experimental neuroscience, utilizing in vivo two-photon imaging**,** single-cell transcriptomics, and virus-based circuit manipulation to address disease-induced alterations in neuronal networks.

Prof Tom Gillingwater, Professor of Anatomy, University of Edinburgh

Tom graduated in Human Biology [Anatomy] from the University of Leeds before moving to the University of Edinburgh, graduating with a PhD in Neuroscience in 2001. Following a period of postdoctoral research, he was appointed to a Lectureship in Anatomy at the University of Edinburgh in 2004, promoted to a personal chair in 2010, and became the 15th Professor of Anatomy at the University of Edinburgh in 2015. Tom graduated from Edinburgh University Business School with an MBA in 2006, is an elected Fellow of the Royal Society of Edinburgh (FRSE), Royal Society of Biology (FRSB), and Royal Microscopical Society (FRMS), and an Honorary Fellow of the Anatomical Society (HonFAS).

Tom leads an active research team that has published more than 190 papers in a variety of leading international journals. He has supervised or co-supervised more than 40 PhD and MSc research students. Tom has board-level experience from several national and international organisations (including Association Française Contre les Myopathies, the SMA Trust, SMA Europe, Muscular Dystrophy UK, and the Anatomical Society) and sits on the editorial boards of international journals: he was Editor-in-Chief at the Journal of Anatomy from 2011 to 2022 and has been Associate Editor at the Journal of Neuromuscular Diseases since 2013. He has served as an external examiner for the University of Glasgow, University of Oxford, RCSI, UCL and NUI Galway, and is an Intercollegiate MRCS Examiner for the Royal College of Surgeons.

Dr Matthew Livesey, Senior Lecturer, Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield

Dr Matthew Livesey is a Senior Lecturer at the Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield, where he leads research into the mechanisms driving neurophysiological impairments in motor neurone disease (MND) and related dementias. After completing his PhD at the University of Dundee, he held a Royal Society of Edinburgh research fellowship at the University of Edinburgh, working with Professors Siddharthan Chandran, Giles Hardingham and David Wyllie. His laboratory, influenced by his time working in the Euan MacDonald Centre, combines electrophysiology, patient-derived stem cell models and animal models to investigate why motor neurons lose their function and how patient-specific electrical signatures can guide personalised treatments. Over the last 5 years, work has been funded by the MRC, MND Accelerator, MND Association, Alzheimer's Research UK, Alzheimer's Society and the Royal Society.

Alyssa Corbett, Euan MacDonald Centre PhD student, University of St Andrews

Alyssa Corbett is a PhD student at the University of St Andrews, funded by the Euan MacDonald Centre. She researches how supporting cells in the spinal cord, called astrocytes, stop working properly in ALS. She also serves as Co-Chair of the Clinical Trials Team at I AM ALS and sits on the Scientific Review Committee at Hop On A Cure, working to advance research and improve the ALS clinical trial landscape.

Hannah Crick, Euan MacDonald Centre PhD student, University of Edinburgh

Hannah is a Euan MacDonald Centre-funded PhD student in the Gillingwater group at the University of Edinburgh. An undergraduate degree in neuroscience led her to MND research, and her work is now focussed on a rare, genetic form of MND.

Dr Johnny Tam, MRC Clinical PhD Fellow, University of Edinburgh

Johnny Tam is an MRC clinical research training fellow and final year PhD student at the Anne Rowling Regenerative Neurology Clinic and the Centre for Clinical Brain Sciences. His thesis, which is the title of this talk, is supervised by Professors Suvankar Pal, Siddharthan Chandran, and Dr Oliver Watts from SpeakUnique.

Dr Áine Heffernan, Postdoctoral Research Assistant, University of Edinburgh

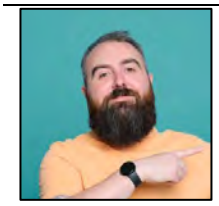
Áine is a postdoctoral researcher in Prof Siddharthan Chandran's lab based at the UK DRI in the University of Edinburgh. Her primary research interest is understanding altered neuro-glial interactions in neurodegenerative conditions, which represents an underexplored avenue for therapeutic discovery.

Dr Owen Gwydion James, Wellcome Early Career Research Fellow, UK Dementia Research Institute at King's College London

Dr Owen Gwydion James is a Wellcome Early Career Research Fellow in the UK Dementia Research Institute at King's College London, working in the lab of Professor Jernej Ule. Originally from Cardiff, Owen obtained his BSc at Newcastle University and his Master's at the University of Edinburgh. His PhD in the lab of Prof. Siddharthan Chandran at the University of Edinburgh focussed on developing a human stem cell-derived model of myelination and was funded by the Euan MacDonald Centre. He moved to King's College London and the lab of Jernej Ule to pursue a postdoctoral position and obtained an Early Career Award from Wellcome to investigate genetic modifiers of RNA regulation in ALS and FTD. His research background spans advanced stem cell modelling, phenotypic drug discovery, protein-RNA interactions, and computational biology.

Weds 8th October 14.10-17.00
Celebrating Euan's Legacy public session

Kiki MacDonald is Co-Founder of Euan's Guide



Joe Logue is Community Manager of Euan's Guide

Antonia Lee-Bapty is CEO of Euan's Guide

Olivia Szczerbakiewicz is Customer Support & Experience Executive, SpeakUnique

Dr Oliver Watts is Chief Technology Officer, SpeakUnique

Hannah Smith, postdoctoral research fellow, University of Edinburgh

Hannah Smith is a postdoctoral research fellow in the lab of Professor Tom Gillingwater. Her current research focuses on identifying early changes in motor neurons which may contribute to disease progression. She will be presenting her MND Scotland-funded project, which investigated the changes caused by disruption to protein synthesis in MND.

Jade Lucas, PhD student, University of Edinburgh

Jade Lucas is a 3rd year PhD student Chandran/Selvaraj lab at the University of Edinburgh researching why some people with motor neuron disease (MND) live for many years while others survive only a short time. She is passionate about public engagement, raising awareness of MND and facilitating 'Bench to Bedside' research. Jade graduated with a first-class MSci degree in Neuroscience from University College London (UCL).

Dr Hatice Bozkurt, Clinical PhD Fellow and Rowling Scholar, University of Edinburgh

Hatice Bozkurt is a medically trained second-year PhD student and Rowling Scholar at the University of Edinburgh, and a member of the UK Dementia Research Institute and Euan MacDonald Centre. Her research focuses on identifying and validating blood biomarkers to improve early diagnosis, monitoring, and prognosis in MND to advance clinical care and research.

Prof Suvankar Pal, Professor of Neurodegenerative Disorders and Clinical Trials, University of Edinburgh

Suvankar Pal is Professor of Neurodegenerative Disorders and Clinical Trials and Honorary Consultant Neurologist. He is co-lead investigator of the UK wide innovative multi-arm multi-stage MND SMART trial, the Scottish Motor Neuron Disease Register (CARE-MND), a Deputy Director at the Anne Rowling Clinic, Co-Investigator of the UK Dementia Research Institute, and Clinical Lead for Neurology at NHS Forth Valley. His clinical and research interests are focused on improving outcomes for people with neurodegenerative disorders, including accelerating early and accurate diagnoses, evaluating atypical presentations, leading population-based disease registries for longitudinal deep clinical phenotyping, digital and wet lab biomarker development/reverse translation, and delivery of innovative clinical trials.

Bruce Virgo, Member of MND-SMART patient advisory group

Bruce Virgo is a retired maritime solicitor and MND/ALS Advocate. He is a member of the MND-SMART Patient Advisory Group; the Patient and Carers Advisory Council at the International Alliance of ALS/MND Associations, and various other MND bodies.

Thursday 9th October 09.00-13.15

Prof Christopher E Shaw, Professor of Neurology and Neurogenetics, King's College London & University of Auckland, New Zealand

Professor Chris Shaw is Director of the Maurice Wohl Clinical Neurosciences Institute and a Group leader in the UK Dementia Research Institute. For 30 years he led a motor neuron disorders clinic at King's College Hospital which underpinned his research exploring the genetics, molecular and cellular pathobiology of MND and Frontotemporal Dementia (FTD). His team have led the discovery of many MND and FTD genes and developed stem cell and transgenic mouse models of disease. These revealed important insights into disease mechanisms, identified novel drug targets, and run clinical trials of antisense oligonucleotide therapies. In 2020 he co-founded AviadoBio, a Gene Therapy company spinout from his laboratory, which is developing genetic therapies for neurodegenerative disorders using viral vectors.

Dr Andrea Serio, Reader in Neural Tissue Engineering, King's College London; Principal Investigator, UK DRI; Group Leader, The Francis Crick Institute

Andrea studied biotechnology and medical biotechnology in Italy before moving to Edinburgh to pursue a PhD in stem cell modelling for neurodegeneration. With the support of the Euan MacDonald Centre, he developed novel human stem cell-based models of motor neuron diseases, as well as several different new protocols of analysis and imaging tools. He then specialised in Tissue Engineering with a Postdoc at Imperial College London, before establishing his own lab in 2017 at King's College London. In 2019 he also became a Group Leader at the Francis Crick Institute, where he has a seconded lab. Finally in 2023 he joined the UKDRI as a Principal Investigator.

Dr Matthew Broadhead, Postdoctoral Researcher/Co-Principal Investigator, University of St Andrews

Matthew Broadhead is an Early Career Neuroscientist pursuing my independent research into synaptic diversity in health and disease. His primary focus is to investigate the synaptic communication junctions between neurons in the nervous system. He also investigates how non-neuronal cells interact with the synapses, and how these interactions may be affected in Amyotrophic Lateral Sclerosis (ALS). He uses advanced fluorescence microscopy techniques alongside other methods to reveal novel insights into how disease mechanisms selectively impact certain types of synapses.

Dr Helena Chaytow, Research Fellow, University of Edinburgh

Helena completed her PhD with Dr Philip Chen at Royal Holloway University, working on developing antisense therapies for MND, before moving up to Edinburgh to begin her postdoc with Tom Gillingwater. Helena has now worked in the Gillingwater lab for 8 years, developing a pipeline of preclinical MND models that she uses to understand the mechanisms driving MND pathology and developing new therapies against it.

Dr Caroline McHutchison, Lecturer in Psychology, University of Stirling

Caroline McHutchison is a lecturer in psychology at the University of Stirling who studies the cognitive and behavioural changes that occur in MND. Her work aims to understand when these symptoms first appear, how they develop over time, and what factors might put people at a higher risk of developing them.

Dr Maria Stavrou, Senior Clinical Research Fellow, University of Edinburgh

Maria Stavrou is a consultant neurologist and clinical postdoctoral research fellow at the University of Edinburgh, where I co-lead the MND service. After completing neurology training in 2024, I was awarded a prestigious two-year College of Medicine bridging fellowship to combine clinical leadership with translational research.

Maria's MRC-funded PhD uncovered a novel mechanism by which C9ORF72-mutant astrocytes disrupt axonal transport, demonstrating that targeting astrocyte metabolism can rescue neuronal dysfunction (Stavrou et al., in third revision, Nature Neuroscience). Building on this, my research now focuses on defining how astrocyte–neuronal metabolic crosstalk shapes axonal transport and bioenergetics in ALS.
Alongside research, I lead multidisciplinary MND care in Edinburgh and contribute to MND-SMART, the UK's first adaptive, multi-arm, multi-centre trial of repurposed drugs for MND. My involvement spans drug evaluation, protocol development, and trial delivery across the national network.

Prof Sharon Abrahams, Professor of Neuropsychology, University of Edinburgh

Sharon Abrahams, Ph.D, D.Clin.Psy is a Professor of Neuropsychology and a Clinical Neuropsychologist at the University of Edinburgh. She has worked in the field of MND for over 30 years. She qualified as a clinical neuropsychologist in 1998, and specialises in the assessment of adults with dementia and neurodegenerative disease.

Sharon moved to the University of Edinburgh in 2004 and is one of the founding members of the Euan MacDonald Centre. In 2015 she was awarded a personal chair in neuropsychology. She has over 150 research journal publications. Together with colleagues in Edinburgh she developed The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) a brief assessment designed to detect changes in cognition and behaviour in MND and which is now routinely used internationally, translated into 28 languages and incorporated as an outcome measure in clinical trials.

Sharon is Associate Editor of the journal Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration and was awarded the Freda Newcombe Prize in 2022 by the British Neuropsychological Society as a distinguished scientist for her pivotal work on cognitive and behaviour changes in MND and frontotemporal dementia.

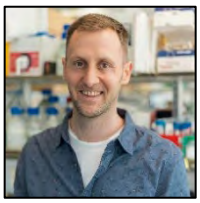
Dr Laura Comley, Postdoctoral Research Fellow, University of Edinburgh

Dr Laura Comley is a postdoctoral researcher in Dr Lyndsay Murray's lab at the University of Edinburgh, where she uses mouse models to investigate the neuromuscular system in spinal muscular atrophy (SMA). Her research explores how early changes in intramuscular axons may affect disease progression and the potential for recovery following treatment.

Dr Shreya Das Sharma, Postdoctoral Research Fellow, University of Edinburgh

Shreya is a postdoc in Dr Selvaraj and Prof Chandran's lab at the university of Edinburgh. Her passion lies in studying how the physiology of neurons is altered during neurodegeneration. Her current postdoctoral work explores the mechanisms underpinning glutamate-mediated excitotoxicity in ALS to develop targeted therapeutics.

Dr Daniel Jutzi, Postdoctoral Research Associate, University of Edinburgh



Daniel trained as an RNA molecular biologist at the University of Bern, where he became interested in understanding how RNA-binding proteins contribute to diseases such as motor neuron disease and frontotemporal dementia. Following a postdoctoral position in Marc-David Ruepp's lab at King's College London, he recently moved to Edinburgh to join Chris Sibley's team, where he will be supported by an Alzheimer's Research UK fellowship.

Prof Mahesh (Max) Parmar, Professor of Medical Statistics and Epidemiology, Director MRC Clinical Trials Unit at UCL and Institute of Clinical Trials and Methodology, University College London

Mahesh (Max) Parmar is Professor of Medical Statistics and Epidemiology and Director of both the MRC Clinical Trials Unit at UCL and the Institute of Clinical Trials and Methodology at UCL.

Since joining the MRC in 1987, Max has published over 450 peer-reviewed papers. His clinical work has influenced policy and improved patient outcomes, while his methodological contributions—such as multi-arm, multi-stage in platform trials, flexible parametric models, and meta-analyses—have shaped research practice.

Under his leadership since 2010, the MRC Clinical Trials Unit has led globally significant studies, especially in cancer, infectious, and neurodegenerative diseases, combining innovative trial designs with methodological advances to accelerate patient impact.

He was Associate Director of the National Cancer Research Network for over a decade, helping double patient participation in cancer trials across England. Max was awarded an OBE in 2019 and the Royal Statistical Society's Bradford Hill Medal in 2024.

Poster Abstracts

1

Investigating Tripartite Synapse Pathology in ALS Utilizing a hiPSC-derived Organoid Model

Ahmad Jibai[1], Matthew Broadhead[1], Neela Murti[1], Channa Jakobs[2], Astrid Van Der Geest[2], Jeroen Pasterkamp[2], Gareth Miles[1]

1 School of Psychology and Neuroscience, University of St Andrews, St Andrews, UK
2 Department of Neuroscience, UMC Utrecht, Utrecht, Netherlands
Euan MacDonald Centre for MND Research

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder characterized by motor neuron (MN) degeneration in the brain and spinal cord. Early-stage synaptic changes and glial dysfunction are though to contribute to MN degeneration. The involvement of tripartite synapses, consisting of presynaptic neurons, postsynaptic neurons, and astrocytes (a major type of glial cell), remains underexplored. Recent work by our lab identified selective vulnerability of tripartite synapses in ALS mouse model spinal cords and human post-mortem tissue. It is hypothesized that tripartite synapse pathology may represent a conserved hallmark of the early stages of ALS. Our goal is to investigate the role of tripartite synapses in ALS using human iPSC-derived organoids. Using immunohistochemistry in cortical organoids we have validated synaptic and astrocytic labelling. Using high-resolution and super-resolution microscopy, and quantitative image analysis, we demonstrate bona fide synapse and tripartite synapse structures in cortical organoids and evidence of synaptic maturation between 60 and 120 days in vitro. From analysis of human iPSC-derived cortical organoid harbouring C9ORF72 mutations (C9) and gene-corrected controls (C9Δ), we find no change in the number of synapses ($p = 0.5895$), and no change in the percentage of synapses contacted by the astrocytic marker, Ezrin ($p=0.8791$), indicating no selective loss of tripartite synapses. However, we observed a significant difference in postsynaptic structure between C9 and C9Δ lines ($p=0.01846$), irrespective of whether the synapses were tripartite or non-tripartite. Contrary to our hypothesis, our findings indicate no such selective tripartite synapse pathology, despite structural synaptic changes in ALS neurons. We are currently developing a protocol to grow spinal organoids from human iPSCs to investigate structural and functional changes in synapses and astrocytes in ALS.

2

Gliotransmission is Dysfunctional in Spinal Motor Networks of Presymptomatic SOD1 Mice

Alyssa Corbett[1], Molly Roberts[1], Carlotta Löer[1], Dr. Matthew Broadhead[1] & Prof. Gareth Miles[1]

1School of Psychology and Neuroscience, University of St Andrews, Fife, UK
Euan MacDonald Centre for MND Research

ALS is a fatal neurodegenerative disease characterized by the progressive loss of upper and lower motor neurons (MNs). Excitotoxicity is a hallmark of ALS pathology; MN death occurs from excessive excitatory synaptic transmission. Astrocytes can communicate with and regulate the activity of neurons: a function known as 'gliotransmission'. Normally, astrocytes prevent excessive excitatory neuronal transmission via a protective negative feedback loop. In ALS, astrocytes show dysfunction prior to MN loss. Thus, I aimed to investigate gliotransmission function in presymptomatic P7-10 SOD1 mice and wildtype (WT) littermates, as identifying and targeting areas of dysfunction could prevent later neurodegeneration. To begin, ex-vivo electrophysiological recordings of spinal motor network output revealed hyperactivity in the SOD1 mice. Furthermore, astrocytic stimulation was able to reduce motor network output in WT mice but failed to do so in the SOD1 mice. Targeting the gliotransmission negative feedback loop indicated that this pathway is overactive in SOD1 mice and may thus be unable to respond to additional stimulation. At a cellular level, whole-cell patch clamping revealed that SOD1 ventral lumbar interneurons (INs) have a divergent response to astrocytic stimulation, failing to hyperpolarize like WT INs. Immunolabelling revealed increased expression of mGluR5 in SOD1 astrocytes: the receptor involved in the gliotransmission pathway. Overall, these findings reveal that a key gliotransmission pathway is dysfunctional in SOD1 mice by just the second post-natal week. This may be contributing to the identified spinal motor network hyperactivity as well as later excitotoxicity. This makes this pathway an exciting target for early therapeutic intervention.

3

In depth multi-omic analysis of axonal homeostasis across scale using a bioengineered platform and IPSC-derived human motor neurons

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Motor neurons are among the largest cells in the human body, with their axons spanning up to 1m in length. Despite their size, the majority of resources are located in the cell body. Managing the fundamental components of the cell—RNA, proteins, and lipids—becomes crucial for maintaining axonal integrity and connecting to the motor neuron target in the periphery. Previously, we developed a novel bioengineered platform that allowed us to demonstrate how axons adapt their biological processes based on their length. This adaptation is evident in changes to mitochondria, localized protein synthesis, and the positioning of RNA binding proteins. However, our understanding of molecular synergies has been limited by examining isolated phenotypes. To address this, we integrated different omics approaches to identify connections and understand synergistic pathways. We have further enhanced our bioengineered platform, enabling us to isolate significant amounts of material from distinct fractions of axons. Additionally, we validate our findings using imaging-based approaches. Our study offers unprecedented insight into axonal biology and homeostasis across varying axonal lengths. Moreover, it correlates molecular phenotypes with length-dependent axonal characteristics for the first time.

4

Long-term persistent defects at the neuromuscular junction following pharmacological SMN upregulation in mouse models of SMA

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Introduction Spinal muscular atrophy (SMA) is a genetic neuromuscular disease characterised by SMN protein deficiency and affects neuromuscular junctions (NMJs). Although current SMN upregulating therapies have shown efficacy in preserving neuromuscular connections and prolonging survival, the long-term structural integrity at the NMJ following onset of SMN upregulating therapy is not clearly understood. Here, were report a detailed morphological study of differentially susceptible cranial muscles in 49-days-old high-dose and 63-days-old low-high dose SMN-C3 (small molecule SMN2 splicing modifier) treated SMA mice [Smn−/−; SMN2+/+; SMNΔ7+/+ model, herein referred to as SMND7] to represent early and delayed treatment-onset models of SMN upregulation, respectively. Results At P49, high-dose treated SMNΔ7 mice showed modest but statistically significant decline in innervation status in the severely susceptible LALc and the moderately susceptible AAL muscles comparing with WT. The relatively resistant LALr was unaffected. Assessment of postsynaptic parameters revealed significant reduction in endplate number and size in the LALc but not in the other muscles. Analysis of the low-high treated SMND7 mice showed even higher denervation in all tested muscles including the resistant LALr, reflecting worse pathology comparing with the high-dose treated cohort. Moreover, there was significant decrease in endplate number and size coupled with increased endplate fragmentation in all three muscles in the low-high treated cohort. Conclusion This study shows worse remnant pathology in low-high than in high-dose treated SMA mice, suggesting that when SMN upregulating treatment is delayed, many aspects of the NMJ cannot be recovered, even when on therapy for the same length of time.

5

Optimising Models to allow testing of Bioelectric Modulators to Drive Motor Axon Regeneration in Mouse Models

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Recent studies suggest bioelectric modulators can facilitate axon regeneration, but this has not been tested in manmals or MND models. This project investigates whether bioelectric modulators promote axon regeneration and NMJ recovery following peripheral nerve injury and in a regulatable ALS mouse model. We first optimized time points for the interventional experiments. We validated tibial and sciatic nerve crush injury using Thy1-YFP mice (expressing YFP in projection neurons). In the tibial model, all lumbrical muscle endplates lost pre-synaptic innervation by 3 days post-injury, remained denervated at day 8, and were fully reinnervated by 13 days, suggesting a narrow recovery window which is unsuitable for drug testing. In contrast, different leg muscles were at different stages of regeneration at 11 days post sciatic nerve crush, providing a model of dynamic recovery phase for drug testing. For the ALS model, we characterised NMJ loss in the rNLS mice, where the expression of the human TDP43 protein with a defective localisation signal (NLS) can be suppressed by doxycycline. Mice were conceived on doxycycline diet until 5 weeks old, followed by taking off doxycycline for either 3 or 5 weeks. After 3 weeks off doxycycline, tibialis anterior (TA) and extensor digitorum longus (EDL) showed 12% and 9% vacant endplates respectively. After 5 weeks, these increased to 43% and 23%, suggesting that TA is more vulnerable in this model. Together, we validated two models with distal axon degeneration which can be used for evaluating pro-regenerative drug efficacy.

6

Capacity of a synthetic retinoic acid receptor agonist to reduce oxidative stress, stress granule production and TDP-43 mislocalization

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Motor neuron disease (MND) is a degenerative disease characterized by loss of motor neurons, resulting in muscle weakness, atrophy and respiratory failure. The production of stress granules (SGs) and the phosphorylation and mislocalization of TDP-43 have been intimately linked to the disease. These two pathological phenotypes contribute to neuronal death and degeneration. Retinoic acid (RA), the active metabolite of vitamin A, has emerged as an anti-inflammatory, anti-apoptotic and regenerative compound, with potential therapeutic implications during neurodegeneration. Based on this evidence, this study aimed to model MND pathological phenotypes and identify the capacity of retinoic acid receptor (RAR) agonist to reverse ALS neurodegeneration hallmarks such as stress clearance, pathological SG disassembly and aberrant TDP-43 dynamics. NSC-34, HEK293 and SHSY5Y cell lines together with mouse cortical primary neurons were exposed to sodium arsenite to induce stress and toxicity and subsequently treated with the RAR agonist DC645. The impact of DC645 on ALS hallmarks was determined using MTT, immunocytochemistry, oxidative stress assays as well as western blotting. Results showed (i) a significant improvement in cell viability when cells under oxidative stress were treated with DC645, (ii) a reduction in SG clusters under the same condition and (iii) a reduction of mislocalised TDP-43 aggregates. These results suggest a role for RAR agonists in reversing the detrimental action of stress and restoring normal cellular physiology after the induction of several MND hallmarks. We would like to thank the Cunningham Trust for funding this project.

7

Comparison of the motor neuron translatome in mouse models of ALS and SMA reveals defects specific to protein translation

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Although highly dissimilar in onset age and genetic cause, the motor neuron diseases Amyotrophic Lateral Sclerosis (ALS) and Spinal Muscular Atrophy (SMA) share a common pathology of dysregulated protein translation. Elucidating the downstream cascade of pathways affected by this disruption therefore offers an important avenue to gain mechanistic insights and develop effective therapies. Using TRAP-seq, we profiled the motor neuron translatome of two mouse models for ALS and SMA, normalised against the bulk transcriptome to focus on translation-specific differential expression. Comparison between both disease models offered the potential to uncover universal neurodegenerative pathways specifically focused on disrupted protein translation, using early phenotypic timepoints to determine candidates contributing to pathology at a therapeutically advantageous stage of disease. At early symptomatic timepoints, we found 447 translation-enriched DEGs in the ALS dataset and 1382 in SMA. This confirms that both models exhibit mRNA translation alterations as an early phenotype. However, only 19 DEGs were shared in both datasets, with the majority unique to either the ALS or SMA data. Interestingly, the shared DEGs associate with increased cell stress and DNA repair responses, and downregulated chemokine signalling and cell motility. This indicates a cellular response to motor neuron dysfunction but before widespread cell death in both models. These shared DEGs could represent potential candidates for targeting disease-agnostic pathways underlying motor neuron degeneration.

8

Characterization of the human cortical synaptome in ALS-FTD

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Synaptic impairment, together with the formation of TDP-43 aggregates and neurodegeneration, is a pathological hallmark of ALS-FTD. Its correlation with the severity of neurological symptoms suggests that it represents an essential disease mechanism. Although recent studies have highlighted the considerable diversity of synapses, it remains largely unknown which synapses, defined by their anatomical location and specific molecular constituents, are selectively affected in ALS-FTD. We have previously developed a method termed synaptome mapping, which combines a high-content imaging system capable of acquiring comprehensive morphological images at single-synapse resolution with large-scale image analysis using artificial intelligence (AI). In the present study, we applied this approach to post-mortem brains from ALS-FTD patients to characterize disease-specific features of synaptic pathology. The study cohort consisted of post-mortem Brodmann area 4 tissue from 20 ALS-FTD patients registered in the UK Biobank and 24 age-matched neurologically healthy controls. Synaptic proteins, including PSD95, PSD93, and GLUN1, were visualized as puncta using fluorescence immunohistochemistry. Quantitative analyses were performed for each cortical layer (L1-L6), assessing puncta density, size and intensity, as well as synapses subtypes classified by AI-based analysis. As a result, distinct patterns of synaptic impairment were observed for each synaptic protein. Moreover, these patterns differed from those observed in the brains of patients with Alzheimer's disease, another neurodegenerative disorder, suggesting that they are specific to ALS-FTD. These findings provide new insight into the molecular and structural basis of synaptic pathology in ALS-FTD and may facilitate the identification of novel therapeutic targets.

9

Facilitating Neuromuscular Junction Recovery After Treatment in in Mouse Models of Spinal Muscular Atrophy

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Despite the availability of therapeutic options for spinal muscular atrophy (SMA), significant neuromuscular deficits persist even after pre-symptomatic treatment. A key hallmark of SMA pathology involves motor neuron loss and neuromuscular junction (NMJ) disruption. In this study, we evaluated whether a dual therapy approach—combining Nusinersen with an additional SMN-enhancing therapeutic—could improve motor unit and NMJ recovery in the SMNΔ7 mouse model of SMA. We administered Nusinersen early (postnatal day 2) and analyzed NMJ recovery in cranial muscles, which vary in vulnerability and allow for whole-mount analysis. Assessments were performed at P6, P12, and P18. The dual therapy enabled evaluation of potential synergistic effects on motor unit structure and stability. Nusinersen treatment alone significantly improved endplate innervation across all time points, even in highly vulnerable muscles. Most endplates were fully occupied post-treatment, suggesting enhanced NMJ integrity. However, from P6 onwards, a reduction in intramuscular axon numbers was observed in these same muscles. This reduction, paired with stabilized endplate occupancy, resulted in a marked increase in motor unit size—an adaptation that could affect long-term axonal health. Importantly, the dual therapy approach further improved outcomes. In one of the more vulnerable cranial muscles, axon number increased significantly when Nusinersen was combined with the second SMN therapeutic, suggesting an additive benefit. Together, these results indicate that while Nusinersen alone improves NMJ function, combining it with additional SMN-targeted therapies may offer enhanced motor unit recovery, addressing persistent deficits more effectively in SMA.

10

Assessing the Cellular and Pathological Determinants of Disease Duration in ALS using Multiparametric Imaging Mass Cytometry analysis

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There is a marked, but underappreciated, heterogeneity in ALS disease duration. Despite the median survival of 3 years from symptom onset, 10 – 20% of people with ALS survive longer than 8 years (long survivors) and 10% of people live for less than two years (short survivors). Whilst clinical factors such as younger age-of-onset and bulbar site-of-onset are associated with long and short survival, respectively, the cellular and pathological factors determining the rate of disease progression remain poorly understood. Here, we have successfully established an Imaging Mass Cytometry (IMC) antibody panel of >30 markers enabling quantitative and spatially resolved analysis of the neurogliovascular unit and disease pathology in spinal cord and BA4 post-mortem tissue. Utilising this high-dimensional profiling technique on post-mortem tissue from 7 short sALS survivors, 6 long sALS survivors and 6 healthy controls, we have identified cellular and pathological features associated with disease duration in ALS. Preliminary analysis has highlighted a lower percentage of ChAT-positive cells in long survivors, suggesting that overall neuronal density may not correlate directly with survival. Additionally, we have identified alterations in other cell types, pointing towards glial or inflammatory contributions. Ongoing analysis using spatial and neighbourhood profiling will further elucidate the cellular interactions and microenvironments that distinguish long from short
survivors. Combined with complementary snRNA-seq and bulk proteomics analysis, these insights may aid in identifying mechanisms of resilience and open new avenues for therapeutic intervention and prognostication.

11

Early loss of intramuscular motor axons limits capacity for recovery following Smn up-regulating therapy in a mouse model of spinal muscular atrophy

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Although treatments for spinal muscular atrophy (SMA) have dramatically changed the prognosis for patients, clinical response remains variable. Our objective is to identify posttreatment deficits which will inspire the next generation of therapies. Here we have used the cranial muscles from the SmnΔ7 mouse model of SMA to profile motor unit pathology in differentially vulnerable muscles.
We show that distal motor unit pathology is progressive in all muscles analysed and that loss of intramuscular motor axons precedes muscle denervation. Motor axon loss was evident by P1 in the most vulnerable muscles (40% of axons lost) with progressive loss of up to 77% byP12. Electron microscopy of intramuscular axons confirms the loss of motor axons andreveals a trend towards the selective loss of the more immature axons.
We next administered SMN-inducing therapies to mice at P2 and profiled axon number at P12. Following treatment, all muscles appeared fully innervated, but motor axon loss was still evident in the most vulnerable muscles. Importantly, a delay in treatment by 1 day increased the proportion of muscles with persistent loss of motor axons. Administration of dual Smn-upregulating therapy was unable to offer further protection to motor axons. Collectively this data demonstrates that Smn up-regulating therapy can inhibit motor axon loss, but the capacity is limited
by the number of intramuscular axons which remain at the time of treatment onset. This work highlights the importance of developing complementary therapies which can promote motor axon regeneration to act in synergy with Smn upregulating compounds.

12

Investigating the role of TDP-43 mis-splicing events in motor neuron disease pathogenesis

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Transactive response DNA-binding protein 43 (TDP-43), a regulator of RNA metabolism, forms cytoplasmic inclusions in several neurodegenerative diseases, most notably in Amyotrophic Lateral Sclerosis (ALS). Its nuclear depletion leads to cryptic exon (CE) inclusion in ATG4B and RANBP1, potentially resulting in transcript degradation by nonsense-mediated decay (NMD). Here, we explore these mis-splicing events and their impact on the autophagy and nucleocytoplasmic transport (NCT) pathways respectively, in a cell model depleted of TDP-43. Specifically, we analyse the effect of RANBP1 protein decrease on NCT by analysis of mass spectrometry data of fractionated cell lysates and the effect of ATG4B protein decrease on LC3-I/II processing in autophagy. We also re-analyse published RNA-seq datasets from patients or models of TDP-43 loss of RNA regulatory function, showing CE inclusion in ATG4B and RANBP1.

13

Towards novel biomarker discovery for motor neuron disease: Ultra-sensitive mass spectrometry-based proteomic approach

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There is an unmet need for simple and scalable diagnostic, prognostic and stratification biomarkers for motor neuron disease. TAR DNA-binding protein 43 (TDP-43) pathology is a defining feature in most cases of amyotrophic lateral sclerosis (ALS) and related motor neuron diseases (MNDs). Yet, despite its central role, we still lack reliable biomarkers that directly reflect TDP-43 dysfunction in MND. TDP-43 dysfunction leads to accumulation several short fragments of transcripts and peptides termed “Cryptic exons/Cryptic peptides”, this project is designed to identify and quantify cryptic peptides generated by TDP-43 pathology in blood samples by employing state-of-the-art Ultra-sensitive mass spectrometry and bioinformatic approaches with a longer-term goal of testing their value as biomarkers for MND. We have established TDP-43 loss of function models in human peripheral macrophages. Our comprehensive proteomic approaches enabled us in identifying MND specific cryptic peptides in peripheral macrophages from people living with MND (pwMND) samples. We will next develop highly sensitive and multiplexed quantitative Parallel Reaction Monitoring mass spectrometry (PRM-MS) assays to detect and quantify specific levels of cryptic peptides in peripheral macrophages and serum/plasma of deeply phenotyped and genotyped pwMND samples obtained through MND-SMART and CARE-MND. By combining innovative proteomics with clinical resources, we aim to establish cryptic peptides as a novel class of blood-based biomarkers for ALS and MND, with potential to support earlier diagnosis and more precise monitoring of disease progression and therapy.

14

High-Throughput Transcriptomics (DRUG-seq) for ALS Drug Discovery

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Amyotrophic lateral sclerosis (ALS) remains a devastating neurodegenerative disease with extremely limited therapeutic options. Despite extensive clinical investigation, over 40 compounds have failed in randomised trials, with riluzole remaining the sole approved treatment offering modest survival benefit. ALS pathogenesis involves complex mechanisms including neuroinflammation, mitochondrial dysfunction, and critically, TDP43-driven pathology affecting RNA processing, which occurs in over 95% of cases regardless of genetic background. We have applied DRUG-Seq, a novel high-throughput transcriptomics platform, adapted for drug discovery in iPSC-derived motor neurons. This methodology enables systematic screening of compound effects on the transcriptome of TDP43 knockout motor neurons, providing unprecedented throughput for identifying therapeutics that reverse disease-associated transcriptomic signatures. We established that suitable numbers of technical repeats required for high-throughput screening: four technical repeats per compound at approximately two million reads per well ensures robust detection of differentially expressed genes whilst maintaining experimental feasibility. Validation studies demonstrate that DRUG-Seq successfully recapitulates known TDP43-mediated transcriptomic changes, including alterations in Stathmin2 and Unc13A, with strong correlation to established RNA-sequencing technologies. Furthermore, we have conducted further studies to compare to Full-Length DRUGseq technologies to evaluate the effects of compounds on RNA and splicing changes observed in TDP43 loss of function models. This has been scaled this platform to screen approximately 1,800 repurposed compounds, comprising CNS-penetrant drugs and the FDA-approved compounds. Analysis of this comprehensive dataset is ongoing to identify compounds that effectively reverse TDP43 loss-of-function signatures. This approach demonstrates transcriptome-guided drug repurposing for ALS for identifying novel single-agent or combination therapeutics.

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Human cell screening platforms to accelerate translation from bench to clinic

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ALS/MND is driven by the loss of function of motor neurons in the brain and spinal cord. This loss of function is driven by various cellular dysfunctions in the brain including; proteinopathy (TDP43) inside motor neurons, hyper excitability of neurons, and chronic glial inflammation driven by microglia and astrocytes. We showcase the use of high throughput human cell platforms for identification of drug candidates for the treatment of ALS. DrugSeq (Digital RNA with perturbation of Genes), uses high throughput transcriptomics to identify compounds capable of reversing TDP43 loss of function gene signatures in human motor neurons. Immunohistochemistry and high throughput imaging and analysis, is used to identify compounds that can inhibit inflammation in astrocytes (IL1a induced MX1) and microglia (LPS induced CD38). Similar high throughout methodology can identify compounds that protect motor neurons from excitotoxic insult (AMPA). We have used these assays to screen compounds with known safety profiles (FDA and EMA approved), for rapid repurposing into ALS trials (MND-SMART). More exploratory screening is performed on novel compounds, designed for brain penetrance, low toxicity and physiochemical diversity.

16

Transcriptomic analysis of protein misfolding enteropathy – a pathological entity predicting neurodegenerative disease and life-limiting prognosis

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Background: Significant neuronal damage has occurred by the time patients with ALSFTSD present with symptoms. Thus, there is an urgent need for early intervention strategies using paired, minimally invasive predictive or target-engagement biomarkers. A hallmark pathology of neurodegenerative diseases – protein misfolding – is challenging to detect in central nervous system in patients in vivo. Contrary to this, the gastrointestinal (GI) tract is readily available for a biopsy, and ALSFTSD patients display digestive symptoms and GI tract localised protein pathology before the onset of neurological symptoms. Moreover, a large Swedish cohort study showed an increased risk of ALSFTSD in a cohort of individuals with a gut biopsy without a definitive histological diagnosis. Aim: We aim to assess pathological protein aggregation in GI tract biopsies and determine whether they could provide an early, minimally invasive target for predictive biomarker development. Methods: We used immunohistochemistry to identify TDP-43, FUS, SOD1, tau, and alpha-synuclein pathologies in archival biopsies from 196 individuals with unexplained GI symptoms (2010-2011), with over 10 years of clinical follow-up. Moreover, spatial transcriptomic analysis of this tissue is ongoing. Results: We found that 60% of our cohort displayed at least one type of protein pathology in their GI tissue. 38% of the cohort was diagnosed with a neurological disorder. Furthermore, the presence of two or more proteinopathy markers indicated a dose-dependent, life-limiting prognosis over the 10-year follow-up period. Implications: These data imply that we are overlooking significant neurodegenerative disease-associated life-limiting proteinopathy in individuals with histologically unexplained GI symptoms.

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Matrin-3 Cellular Expression in Motor Neuron Disease Models

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Previous research has postulated a shared pathway for two motor neuron diseases, amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA), involving the ALS-associated proteins TDP-43 and FUS and the SMA-associated protein Survival of Motor Neuron (SMN). During the formation of nuclear gems, these proteins can interact in an RNA-dependent manner and thus the involvement of the RNAPII/U1snRNP complex represents a potentially conserved mechanistic site to investigate. One component is Matrin-3, an RNA binding protein known to interact with both TDP-43 and FUS (Chaudhary et al., 2022) and mutations of which have been associated with familial ALS (Johnson et al., 2014). We hypothesised that pathological changes in the cellular expression of Matrin-3 could be a shared element of motor neuron diseases. Immunohistochemical techniques were used to investigate Matrin-3 protein expression in neurons and astrocytes in the lumbar spinal cord of TDP43-ΔNLS mice and ALS patient iPSC-derived cortical organoids (carriers of the C9orf72 expansion mutation). Matrin-3 shows significantly greater nuclear than cytoplasmic expression across cell types, and neurons had higher expression than astrocytes across cell compartments. However, genotype had no significant effect in either TDP43-ΔNLS mice compared to controls ($F(1,4) = 0.031$, $p = 0.870$) or ALS patient organoids compared to gene-corrected controls ($F(1,4) = 2.349$, $p = 0.200$). Thus, Matrin-3 localisation is unaffected in ALS models. Ongoing research is comparing Matrin-3 expression in models of SMA.

18

Deconstructing the roles of Oligodendrocytes and Neurons in mediating TDP-43-related neurodegeneration

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A key feature of amyotrophic lateral sclerosis (ALS) is the cytoplasmic aggregation of TDP43 in neurons and glia. While neuronal death is central to ALS, oligodendrocytes—which support and myelinate axons—are also affected and are believed to contribute to disease progression. To investigate the cell-specific impact of TDP43 pathology, we generated novel zebrafish models expressing a human TDP43 Δnls mutant, inducing cytoplasmic aggregation either ubiquitously (TDP43Δubi), or restricted to neurons (TDP43Δneuro) or oligodendrocytes (TDP43Δoligo). Ubiquitous expression caused early neuronal and glial dysfunction, with lethality by ~10 days post-fertilisation (dpf). At 5 dpf, motor neurons exhibited axon thinning and distal swellings, leading to degeneration. TDP43Δubi fish showed ~30% oligodendrocyte loss and ~60% reduction in myelin, alongside an ~80% decrease in spontaneous movement. Cell-restricted models revealed that neuronal TDP43 pathology alone was sufficient to cause behavioural deficits and motor neuron degeneration. Interestingly, myelin reduction occurred in both TDP43Δneuro and TDP43Δoligo lines without changes in oligodendrocyte number, indicating both cell-autonomous and non-autonomous effects. Notably, myelin loss in TDP43Δneuro fish preceded axonal degeneration, suggesting neuronal dysfunction drives oligodendrocyte impairment and forms a pathological feedback loop. These findings underscore the reciprocal role of neurons and oligodendrocytes in ALS progression and highlight the utility of zebrafish models in dissecting cell-type-specific contributions to neurodegeneration.

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Loss of TDP-43 causes AMPAR current dysfunction in iPSC derived motor neuron

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Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disorder, characterized by loss of motor neurons (MNs) in the motor cortex, brainstem and spinal cord. A key mechanism underlying MN vulnerability in ALS is glutamate-mediated excitotoxicity mediated by dysfunctional AMPA receptors (AMPA-R), which are ligand-gated ion channels. Here, we used iPSC-derived MNs from sporadic ALS patients – comprises 90% of ALS cases – to further understand AMPAR-mediated excitotoxicity and its implications in sporadic ALS. Using electrophysiology, we found that sALS MNs displayed increased calcium-permeable AMPA-Rs. A key pathology observed in ALS- both genetic and sporadic forms, is the presence of cytoplasmic TDP43 aggregates, leading to TDP43 nuclear loss-of-function. Our pilot data shows that the aberrant calcium-permeable AMPA-R expression was due to TDP43 loss-of-function in the MNs, and this phenotype was reversed after TDP43 re-expression, suggestive of a reversible mechanism. Additionally, unbiased proteo-transcriptomic assays on TDP43 KO MNs showed downregulation of DPP6 gene - auxiliary subunit of the A-type potassium channels - due to mis-splicing of DPP6. Interestingly, in sALS MNs showing AMPA-R dysfunction, DPP6 expression was downregulated. Crucially, overexpressing DPP6 in TDP43 KO MNs reversed the AMPA-R dysfunction. In conclusion, we show DPP6 can be a potential therapeutic target for reversing excitotoxicity in ALS.

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Exploring the interplay between axonal metabolic alterations and degeneration in ALS

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Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease marked by the degeneration and death of motor neurons, leading to paralysis and death. Despite decades of research, no effective cure or treatment exists, highlighting the urgent need for therapeutic advances. Motor neurons, the primary cells affected in ALS, are especially vulnerable due to their unique structure and function. Some peripheral motor neurons have axons up to a meter long, creating high metabolic demands to sustain neurotransmission and other essential activities. Mitochondria, which generate about 90% of cellular ATP, are critical for meeting these demands, making motor neurons highly dependent on mitochondrial function. However, ALS-associated mutations disrupt mitochondria, causing energy deficits and triggering Wallerian-like degeneration. This follows a "dying-back" pattern, with axonal degeneration beginning at the distal end and progressing toward the soma. The key regulator of Wallerian degeneration is the pro-degeneration enzyme Sterile Alpha and TIR Domain Containing 1 (SARM1). Evidence links ALS-related mitochondrial dysfunction to SARM1 activation, suggesting a reciprocal relationship that accelerates disease progression. Targeting SARM1 is therefore a promising therapeutic strategy, as its inhibition protects against axonal degeneration and offers a mutation-independent approach to ALS treatment. This research aims to characterise the links between SARM1-driven degeneration and length-dependent axonal metabolic alterations. Using a bioengineered human stem cell platform with motor neurons carrying ATP sensors, this work will map the metabolic landscape, reveal degeneration mechanisms, and assess SARM1 as a therapeutic target.

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Human Models of Oligodendrocytes, and Oligodendrocyte-Neuron crosstalk

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The contribution of glial cells to disease progression in neurodegenerative diseases is comparatively understudied compared to the neuron. Of the three major glia classes, the oligodendrocyte (OL) is the most overlooked, perhaps due to the difficulties in modelling this particular cell type in a laboratory setting. There is strong evidence of oligodendrocyte involvement in ALS. In post-mortem tissue, we observe down-regulation of myelin genes and cytoplasmic aggregation of TDP-43: a major pathogenic protein in this disease. We also observe genetic risk factors in the form of single nucleotide polymorphisms (SNPs) in OL-specific genes. Oligodendrocytes provide key structural, metabolic and trophic support to neurons, alongside their well-regarded function of enabling saltatory conduction. We aim to generate reliable, human OL and OL-neuron models in order to understand the OL contribution to disease pathology and progression. Recently, we have established a genetically inducible system for fast and reproducible OL-lineage cell generation from human iPSCs. We observe MBP+ cells within four days of induction, increasing to ~80% MBP+ cells after 14 days. Using this system, we are now exploring the role of TDP-43 and other relevant disease-associated proteins in oligodendrocytes.

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Whole-brain single-synapse mapping of MAGUK complex organisation at nanoscale resolution reveals synapse diversity shaped by age and disease-associated mutation

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Membrane-associated guanylate kinases (MAGUKs) are scaffolding proteins that organise signalling complexes linking glutamate receptors, ion channels, intracellular signalling proteins, and trans-synaptic adhesion molecules. These MAGUK-containing complexes regulate synaptic transmission and plasticity, playing critical roles in both innate and learned behaviours. Although MAGUKs are well-established as abundant components of the postsynaptic density (PSD), the nanoscale spatial organisation and packing density of MAGUK complexes within the PSD remain poorly characterised. Here, we present a method for quantifying inter-complex distances between MAGUK assemblies within individual synapses by Förster resonance energy transfer (FRET). We integrate this with synaptome mapping technology to analyse synapses across the mouse brain throughout the lifespan. Moreover, applying this approach to a genetic model of neuropsychiatric disorders, we visualise how synaptic protein complex packing is affected by disease. These findings uncover a previously unrecognised molecular architecture of synapses, revealing how synaptic structure is dynamically modulated by age and disease-associated mutations, with region-specific effects across the brain. This method is also applicable to investigating synaptic abnormalities in motor neurone disease.

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Identifying and Validating Blood-based Biomarkers in Motor Neuron Disease using Nucleic Acid-Linked Immuno-Sandwich Assay

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Motor Neuron Disease (MND) is clinically heterogeneous, diagnostically challenging, with poor prognosis, and limited therapeutic options. The absence of accessible blood-based biomarkers has held back progress towards precision medicine for MND. However, the recent emergence of highly sensitive immunoassays offers considerable promise in identification of blood-based biomarkers that will inform on underlying pathophysiology and enable accurate diagnosis and disease status monitoring. Here, we report on findings of parallel use of the ultra-sensitive multiplexed NUcleic Acid-Linked Immuno-Sandwich Assay (NULISA) and Single molecule array (Simoa), to interrogate serum from people with MND (pwMND). Serum samples of 48 pwMND linked to the Scottish MND Register (CARE-MND), and 38 controls were analysed using the 120-Plex NULISAseq CNS Disease Panel and a Simoa Neurology 2-Plex B duplex assay. Results showed that NfL, NfH, pTau-181, pTau-217, pTau-231, total tau, FABP3, Aβ38, and Aβ40 levels were significantly elevated in MND

compared to controls ($p < 0.05$). In addition, Simoa and NULISAseq assays demonstrated strong correlations for both serum NfL and GFAP (Spearman's Rank Coefficient $R > 0.90$; $p < 0.05$). In conclusion, use of the multiplexed NULISAseq panel has confirmed a previously well-established elevation in NfL and NfH in individuals with MND, and replication of elevation in total tau, pTau-217, pTau-181, pTau-231, Aβ38, Aβ40, and FABP3. Findings provide more confidence in validity and reproducibility of the biomarkers identified using NULISAseq assay, offer more insights into the underlying pathophysiology and heterogeneity of MND, suggest that pTau-181 might be potential motor neuron neurodegeneration markers as a readout in clinical trials of disease-modifying drugs in MND; and warrant further validation studies to correlate with disease trajectory, phenotype, and presence of co-pathologies.

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EMG4MND: High-Density EMG At Home Unassisted for PLWMND

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MND/ALS is a fatal neurodegenerative condition causing progressive muscle weakness, with no known cure. As disease progresses the patient burden of attending clinical appointments for care and research increases, as people living with MND (PLWMND) often require the use of wheelchairs limiting mobility and independence. To provide a means for PLWMND to track disease progression at home, this work presents the design process for a high-density EMG-recording device making use of cost-effective, 3D printed parts and commercial off-the-shelf (COTS) electronics. An ideal outcome would be to enable PLWMND to carry out these measures at home unassisted, improving their independence, providing high quality data for tracking disease, and enabling the scaling of remote clinical trials for therapies and care research. The design process will integrate a future PPIE workshop involving PLWMND, their carers, relevant clinicians and laypeople to refine the design from a set of starting candidates, presented in this work.

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MND-SMART – A collaborative, expeditious, and definitive clinical trials platform for ALS

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Aim: There is an urgent need for innovation in trial design to encourage participation and accelerate definitive testing of treatments for people with motor neuron disease (pwMND). MND is rapidly progressive and fatal; 1 in 3 pwMND die within a year of diagnosis, and there is only one licensed medicine, riluzole, that extends life by 2-4 months. Historically <5% of pwMND in the UK have participated in a clinical trial.

Methods: MND SMART is a multi-arm, multi-stage (MAMS), adaptive, multi-centre, randomised, seamless Phase 2-3 platform trial that is co-produced alongside pwMND. Co-led design with world-leading medical statisticians ensures the trial meets all assumptions from underlying power calculations and is sensitive to definitively detect any neuroprotective effect of drugs tested. MND SMART delivers (i) simultaneous evaluation of multiple treatment arms against a single contemporaneously randomised control group, (ii) early cessation of drugs that show no activity through multiple staged analyses, and (iii) addition of new arms in a 'continuous' trial platform. These features deliver substantial efficiencies in time, cost, and sample size requirements compared

with conventional serial two-arm studies. Drug selection for MND SMART includes state-of-the art high-throughput phenotypic screens focussing on disease relevant human based model systems, initially for screening repurposed drugs. Each cycle of MND SMART is conducted in four stages with progression of any given intervention contingent on satisfying predefined criteria at each stage. MND-SMART is designed and delivered from inception to dissemination alongside our PPIE group (established 2018), with innovation supporting decentralised trial delivery (telehealth and community appointments, e-consenting, electronic diaries, home delivery of drugs, use of clinical results), drug selection , and co-authorship in outputs.

Results: Following launch in 2020, c.1000 participants have been randomised across 22 sites in all 4 UK nations and conclusive results reported for the first two drugs (memantine and trazodone) within 3.5 years of launch. Amantadine was launched in April 2024, and tacrolimus, in February 2025. Combinatorial drugs will also be evaluated. MND-SMART has delivered a highly curated randomised longitudinal bioresource comprising DNA, plasma, serum, post-mortem brain/spinal cord/CSF providing a powerful platform for reverse translation and mechanistic studies.

Conclusion: MND-SMART is the largest ever trial ever MND in the UK and has transformed the research landscape delivering expeditious and definitive results and supportive reverse translation.

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Patient and public involvement and engagement (PPIE) in MND-SMART

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MND-SMART is an innovative multi-arm multi-stage UK-wide platform trial aiming to improve outcomes for people with MND (pwMND). Historically, MND trials have suffered from narrow inclusion criteria, low recruitment, and high attrition rates (up to 30%) (1). MND-SMART has embedded patient and public involvement and engagement (PPIE) in its design since inception, recognising the importance of co-production with pwMND in addressing these challenges. PPIE activity in MND-SMART was evaluated through a structured review of all interactions with the trial's patient advisory group (PAG) since 2018. PPIE has visibly shaped MND-SMART's innovative design and delivery. Co-production with patients has informed several of the trial's distinguishing features, including broad inclusion criteria, home delivery of trial drugs, remote clinical assessments and compliance monitoring, and routinely performed NHS tests as outcome measures to minimise participant burden. PPIE group members have also consistently contributed to review of participant-facing documentation, funding applications, public communications and scientific publications. The impacts of PPIE have resulted in a generalisable participant population and an attrition rate of less than 10%. A defining element of MND-SMART's strategy for co-production is the emphasis on building close partnerships between researchers and pwMND. Despite challenges posed by rapid disease progression and high attrition in the MND population (1), several PPIE group members have actively contributed to the trial's development since its conception in 2018. Collaborative working has accelerated delivery of innovation in pursuit of testing more ambitious treatments, also creating a sense of hope and optimism among participants.

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Acoustic speech analysis and machine learning in the diagnosis and monitoring of neurodegenerative disorders

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Aim: There is an urgent need for scalable, non-invasive and quantifiable biomarkers in neurodegenerative disorders (NDDs) including dementia. Speech is an attractive candidate, with potential for remote and cost-effective assessments. Development of robust models is currently limited by a lack of high quality clinically annotated speech data. We aim to develop novel speech processing and machine learning (ML) approaches by interrogating a large prospective longitudinal speech cohort including people with cognitive disorders, motor neuron disease (MND), Parkinson's disease (PD), and multiple sclerosis (MS). Methods: People living with NDDs and healthy individuals recorded longitudinal standardised recording tasks on an App co-produced with patients, aligned to contemporaneous deep clinical phenotyping (clinical rating scales, cognitive tests and blood-based biomarkers). We used state-of-the-art ML models to classify individuals in the MND and cognitive disorder groups. Conventional and deep learning features were extracted for inputs to random forest classifiers. To assess confounding effect, data was matched and balanced by age and sex, and performance on non-speech segments of recordings were also reported. Results: 800 participants provided 5665 recordings over 1000 assessments. Classifiers discriminating between disease and healthy individuals demonstrated promising test ROC-AUC of ~0.85 in both groups. Conversely, non-speech segment models performed at or near random chance levels, demonstrating limited bias from recording quality or environment. Conclusions: We show that ML with both conventional and deep learning acoustic features demonstrate potential diagnostic and monitoring utility in NDDs. We also demonstrate that large scale and frequent speech data collection is possible in this population. Ongoing work includes scaling data acquisition and analysis across larger more diverse populations and refining ML algorithms.

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Ante-mortem consenting for brain and spinal cord donation –a quality improvement exercise evaluating experiences of people with MND

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Background: The Edinburgh Brain Bank (EBB) is one of the largest global resources of brain and spinal cord tissue, driven by a rich culture of pre-mortem consent by the Scottish clinical specialist nurses and the Scottish national MND register, CARE-MND. Aims and Objectives: To explore the factors that influence pre-mortem consent among people with MND (pwMND) using a cross-sectional survey co-produced with patients and clinicians to improve the quality of the consent process and research equity across Scotland. Methods: A survey was distributed via email and post to all pwMND on CARE-MND who had consented to research contact. Quantitative data were analysed using descriptive statistics, and free-text responses were analysed thematically using NVivo. Results: 64 responses were received from across the whole of Scotland. Respondents were mostly male (62.5%) with lower limb onset (51.6%). Median age at symptom onset and diagnosis was 60 and 63, respectively. Median disease duration was 23 months. Altruism and hope motivated donors, while concerns about family perceptions, adequate information, and impact of funeral arrangements were primary reasons for declining. Conclusions and future directions Results from our survey have identified a generalisable population of people participate in consenting for autopsy. Hope and altruism were positive themes driving this decision. Results will be disseminated to nurses, patients, and the brain bank nurse team. Future direction aim to narrow the information gap through creating patient facing material and summarise studies that the brain bank has contributed to, and addressing concerns that currently lead to people declining autopsy.

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A 10-year retrospective analysis of epidemiology and survival within the Scottish MND population

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Introduction: The Scottish MND Register was launched in 1989 as the first national population based register globally. It was re-launched in 2007 coinciding with rapid expansion of clinical research anchored at the Euan MacDonald Centre, and again in 2015 as a digital platform CARE-MND, delivering seamless and harmonised care for people with MND (pwMND) across Scotland, aligned to a doubling of nurses in Scotland and appointment of a National Nurse Consultant. CARE-MND acts as a research interest register for observational and interventional trials and also as a powerful platform for studying changes in the epidemiology of MND in Scotland, guiding allocation of resources to optimise patient outcomes. Capture-recapture methodology has previously demonstrated >99% case ascertainment of MND in Scotland. This study aims to evaluate the incidence, prevalence, and survival of pwMND in Scotland over the decade since launch of the digital CARE-MND platform in January 2015.

Methods: Data was interrogated from the Scottish MND register (Scotland A REC 15/SS/0216) for all individuals diagnosed with MND from 1st January 2015 to 31st December 2024. Detailed clinical characteristics, epidemiological, and survival data were extracted from CARE-MND. Statistical analyses included descriptive statistics, epidemiological measures, and Kaplan-Meier survival curves.

Results: 2491 pwMND were identified during the 10 year study period (male, 58%; female, 42%). Median disease duration from date of diagnosis and symptom onset to death was 11.89 months (4.94-24.59) and 25.82 months (14.82-46.99), respectively. Median diagnostic latency was 12.71 months (7.62-24.31). The average annual prevalence rate and incidence rate per 100,000 over the 10 year period was 7.28 and 3.88, respectively. Cox proportional hazards model demonstrated that females, people with MND- Frontemporal Dementia (MND-FTD), bulbar onset, and a diagnosis of 80 years old or older have worse survival than other subtypes of MND. Riluzole use was found to have a greater benefit in people with Amyotrophic Lateral Sclerosis (ALS) subtype. Gastrostomy had greater benefit in ALS patients aged 70-79, female, and with bulbar and multifocal onset.

Conclusions and Future Direction: Results from this study of over 2400 pwMND in Scotland over a 10 year period from 2015 to 2024 provide insights into the epidemiology and determinants of survival that are generalisable to wider international populations. Future work will include evaluating the age- and sex- standardised prevalence and incidence, changes in incidence over the last 3 decades, and survival analyses per health board.

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The predictive and diagnostic value of motor screening in a neurodegenerative clinic

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Background: Motor decline is increasingly recognized as a key feature of various neurodegenerative disorders. The Edinburgh Motor Assessment Scale (EMAS) is a brief screening tool designed to identify both the pattern (e.g., amyotrophic) and distribution (e.g., lower limb) of motor symptoms. This exploratory study aims to evaluate the predictive value of motor screening using the EMAS at the Anne Rowling Regenerative Neurology Clinic.

Methods: A retrospective review of medical records of 156 patients (mean age 61.81 ± 8.08 years) was conducted. Data on mortality, diagnostic status and EMAS scores collected from January 2013 to December 2016 were extracted from the NeuroCARE database. The cohort was dichotomised based on the motor function at the beginning of follow-up.

Results: The mean follow-up period was 111.65 (±39.30) months. 32.69% patients had no motor impairment (NMI) and 67.31% had motor impairment (MI) at the beginning of follow-up. Despite no significant difference in the mean age (p=0.084), the mortality at follow-up was significantly higher in the MI group (90.2% vs 75.2%, p=0.033). Lower limb impairment posed a significant mortality risk (HR=1.58, 95% confidence interval 1.09-2.30, p=0.016). For the 99 patients diagnosed with mild cognitive impairment at the beginning of follow-up, overall EMAS score (p=0.021) and extrapyramidal signs (OR=2.28, 95% confidence interval 1.04-5.04, p=0.041) were associated with progression to dementia. Impaired eye movements were associated with progression to frontotemporal vs Alzheimer's dementia (OR=1.77, 95% confidence interval 1.743-1836.40, p=0.023).

Conclusions: Even a brief motor assessment of patients presenting with cognitive symptoms can provide relevant prognostic information.

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Retinal Imaging in Motor Neuron Disease – Amyotrophic Lateral Sclerosis: A Systematic Review

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Motor neuron disease (MND) is a group of neurodegenerative disorders affecting the motor neurons. Amyotrophic lateral sclerosis (ALS) accounts for 80–90% of MND cases and is characterised by the progressive loss of upper and lower motor neurons, leading to severe muscle denervation with high morbidity and mortality rate(1). Recent studies suggest subtle retinal abnormalities may also occur in MND(2). We reviewed the existing literature to investigate whether retinal imaging might have utility as a tool for studying ongoing neurodegeneration in MND. Databases such as Embase (Ovid), PubMed, Scopus, Web of Science and CINAHL+ were searched for English-language studies of participants with MND or ALS (age ³ 18 years) imaged with optical coherence tomography (OCT), scanning laser ophthalmoscope, and/or OCT angiography. Eighteen met the criteria. Findings were heterogenous: three studies reported no evidence of significant differences in retinal measures between MND and healthy controls (HC), whilst twelve found thinner retinal fibre layer (peripapillary and macular RNFL), inner and outer nuclear layers and choroid in MND. Conversely, three studies observed thicker pRNFL and choroids in MND, and two studies showed increased outer vessel wall thickness and sparser vessel branching in MND compared to HC. Nine studies also reported associations between retinal measures and disease severity or duration. Although these findings indicate retinal abnormalities in MND, suggesting neurodegeneration beyond the motor system, results remain inconclusive due to disease and study heterogeneity. Future longitudinal retinal imaging studies are needed to further evaluate the usefulness of these techniques for revealing information about MND.

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Influences of Specialist Palliative Care Team Input, Advance Care Planning, Non-Invasive Ventilation and Gastrostomy Status on Unscheduled Hospital Admissions and Place of Death for People with Motor Neuron Disease: A Retrospective Cohort Analysis

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Objective: Motor neuron disease is a rapidly progressing neurological condition. People with life-limiting conditions generally prefer to die at home and avoid hospital admissions, with Specialist Palliative Care Team involvement often pivotal. Our aim was to investigate the role of advance care planning, Specialist Palliative Care Team input and other relevant variables on place of death and unscheduled hospital admissions in a Scottish population of people with motor neuron disease.

Methods: National CARE-MND audit data, primary and secondary care data, and local Palliative Care records were interrogated. Chi-square, point-biserial correlation and binary logistic regression analysed associations ($p < 0.05$ statistically significant). Participants (188) were deceased, having a verified motor neuron disease diagnosis between 2015-2017, diagnosis occurring ≥28 days before death.

Results: Advance care planning and Specialist Palliative Care Team input of ≥28 days were associated with increased odds of dying outside hospital (BLR:OR 3.937, CI 1.558-9.948, $p = 0.004$ and OR 2.657, CI 1.135-6.222, $p = 0.024$ respectively). Non-invasive ventilation decreased the odds of dying outside hospital (BLR:OR 0.311, CI 0.124-0.781, $p = 0.013$). Having a gastrostomy increased odds of ≥1 admissions in the last year of life (BLR:OR 5.142, CI 1.715-15.417, $p = 0.003$). Statistical significance was retained with removal of gastrostomy-related complications.

Conclusion: Early Specialist Palliative Care input and advance care planning may increase the likelihood of death outside of hospital for persons with motor neuron disease. Further research is warranted into barriers of facilitating death outside of hospital with home non-invasive ventilation use and the association between gastrostomy status and unscheduled admissions.

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The MND diary project - Exploring factors which help people to feel able to cope following a diagnosis of motor neurone disease

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We know that coping with MND can be hard, but we don't know the best ways of helping people to cope. The MND Diary project, collected 22 hours of interviews and 150 pages of diaries documenting 3 - 6 months of everyday experiences of 13 people, across the UK, living with MND. Additional interviews with 5 family members and 2 focus groups with healthcare professionals helped to provide rich insight into what helped and what did not help people feel that they were coping well and living a good life. By analysing the stories people told me I found people felt able to cope when they could tell a story about themselves and their life that was acceptable to them. Support from families was crucial in helping people do this but many families were providing 24-hour care for their loved one while working full-time, putting them under severe stress. Well-funded, caring and timely provision of health and social care, along with input from MND charities and organisations such as Euan's Guide could aid people in being able to feel they were living well. However, people also reported that the provision of health and social care could be poor, complicated to navigate, underfunded and could increase stress in people's lives. Some people felt unsupported by their healthcare providers and tensions could arise when healthcare providers foregrounded a story of disease progression and physical decline which some people preferred to keep in the background of the stories they told about their life.

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High-throughput drug screening reveals everolimus confers neuroprotection in ALS through mTOR pathway Inhibition

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Amyotrophic lateral sclerosis (ALS) involves multi-cellular dysfunction with several inter-dependent pathomechanisms, including but not limited to, TDP43 mis-accumulation, increased astrocyte reactivity and microglial inflammation. There is a need for identifying therapeutics that target multiple dysfunctional cellular mechanisms associated with ALS pathobiology. Here, we tested >4500 repurposed drugs on two independent high-throughput phenotypic screens to identify drugs that ameliorate both human TDP43 aggregation and astrocyte reactivity, which revealed that inhibition of the mTOR pathway is beneficial for these dysregulated processes. Particularly, we identified everolimus, an mTOR inhibitor, which ameliorated TDP43 aggregation, astrocyte reactivity and microglial inflammation in both in vitro human stem cell models and in vivo TDP43 DNLS mouse model. In vivo studies also confirmed everolimus target engagement in CNS tissues and, crucially, increased survival of motor neurons in spinal-cord and motor-cortex. Thus, everolimus is a well-tolerated CNS-penetrant repurposed drug that targets multiple ALS pathomechanisms and confers neuroprotection, warranting testing in clinical trials.

Delegate List (for academic symposium)

Sharon Abrahams	Professor of Neuropsychology, University of Edinburgh
Haya Alabduljader	PhD Student, University of Edinburgh
Riana Ali	Research Practitioner, University of Edinburgh
Hazel Allardyce	Postdoctoral Research Fellow, University of Aberdeen
Georgia Andreopoulou	Academic Physiotherapist, University of Edinburgh
Joanne Astbury	College Advancement Officer, University of Edinburgh
Thomas Bak	Professor of Cognitive Science and Multilinguism, University of Edinburgh
Paul Baxter	Postdoctoral Researcher, UK DRI at the University of Edinburgh
Paula Beltran Lobo	Postdoctoral Research Fellow, UK DRI at the University of Edinburgh
Guy Bewick	Senior Lecturer, University of Aberdeen
Jamie Bhagwan	Scientific Group Lead, Axol Bioscience
Krishna Bhavsar	Postdoctoral Researcher, University of Dundee
Jenea Bin	Research Fellow, University of Edinburgh
Hatice Bozkurt	Clinical PhD Fellow (Rowling Scholar), University of Edinburgh
Matthew Broadhead	Postdoctoral Researcher, University of St Andrews
Tom Burley	Regional Business Manager, Alamar Biosciences
Tia Cainer	Research Practitioner, University of Edinburgh
James Carpenter	Professor of Medical Statistics, London School of Hygiene & Tropical Medicine
Neil Carragher	Chair of Drug Discovery and Director of Science Edinburgh Cancer Research, University of Edinburgh
Roderick Carter	Post Doctoral Researcher, UK DRI at the University of Edinburgh
Laoise Casserly	PhD Student, UK DRI at the University of Edinburgh
Mario Cecchini	Postdoctoral Research Assistant, University of Edinburgh
Kevin Chalmers	Senior Account Manager (Scotland), Miltenyi Biotec Ltd
Siddharthan Chandran	Director of the Euan MacDonald Centre, University of Edinburgh
Helena Chaytow	Senior Postdoctoral Researcher, University of Edinburgh
Theresa Chiwera	Senior ALS Clinical Trials Manager/ PhD Researcher, King's College London

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Laura Comley	Postdoctoral Researcher, University of Edinburgh
Sandra Constantinou Juhasz	Research Assistant, University of Edinburgh
James Cooper	Senior Research Technician/Part-time PhD, UK DRI at the University of Edinburgh
Alyssa Corbett	Euan MacDonald Centre PhD Student, University of St Andrews
Chris Cox	Vice-Principal Philanthropy and Advancement, University of Edinburgh
Jane Craik	Trustee, Alan Davidson Foundation
Hannah Crick	Euan MacDonald Centre PhD Student, University of Edinburgh
Melanie Cross	Clinical Director - Respiratory Medicine, NHS Lothian
Paolo Cucurachi	Assistant Research and Trials Manager, University of Edinburgh
Sophie Cuthbertson	PhD Student, University of St Andrews
Owen Dando	Bioinformatician, University of Edinburgh
Shreya Das Sharma	Postdoctoral researcher, University of Edinburgh
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Rebecca Devon	Anne Rowling Clinic Deputy Director Science & Strategy, University of Edinburgh
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Brian Dickie	Chief Scientist, MND Association
Kosala Dissanayake	Lecturer in Veterinary Biomedical Science, University of Edinburgh
Amelia Edmondson-Stait	Software Developer, SpeakUnique
Catherine Elton	Chief Business Officer, Axol Bioscience
Kiterie Faller	MRC Clinician Scientist, University of Edinburgh
Rizwan Farrukh	PhD Student, University of Edinburgh
Chris Fleming	Software Engineer, SpeakUnique
Sofia Fredin	PhD Student, King's College London
Lizzie Freestone	Customer Support and Experience Executive, SpeakUnique
Steven Fyfe	Senior Channel Sales Manager, Azenta

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Federica Genovese	PhD Student, University of Edinburgh
Jessica Gill	Assistant Clinical Database Manager, University of Edinburgh
Tom Gillingwater	Professor of Anatomy, University of Edinburgh
Nicola Glennie	Post Graduate Researcher, University of Stirling
Francesco Gobbo	Postdoctoral Researcher, UK DRI at the University of Edinburgh
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Xin He	Bioinformatician, UK DRI at the University of Edinburgh
Caite Healy	Trustee, Alan Davidson Foundation
Áine Heffernan	Postdoctoral Researcher, UK DRI at the University of Edinburgh
Cameron Henn	Research Technician, UK DRI at the University of Edinburgh
Ernie Ho	PhD Student, University of Edinburgh
Samantha Ho	Postdoctoral Researcher, UK DRI at the University of Edinburgh

Mathew Horrocks	Professor of Biophysics, University of Edinburgh
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Amarachi Ihenacho	Assistant Research and Trials Manager, University of Edinburgh
Mandy Jackson	Senior Lecturer, University of Edinburgh
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