



# 2022 MNDRA Funded Research



# What research is MND Research Australia funding in 2022?

*In 2022, MNDRA awarded four different types of research grants to 26 talented researchers around Australia. We are thrilled to have invested more than \$3.1 million to support the best MND research in Australia in 2022.*

**The Betty and John Laidlaw MND Research Prize** aims to reward an outstanding mid-career researcher with a demonstrated background of excellence in neuroscience research. The Prize is a grant of up to \$200,000 for an innovative and collaborative two-year project to advance the understanding, treatment and care of classical MND.

**The four MND Postdoctoral research Fellowships** awarded in 2022 span three years and aim to encourage young researchers to focus their interest on ALS/MND. Funds of \$350,000 are provided to cover the salary of a full time research fellow. Postdoctoral scientists with a track record in areas of neuroscience related to MND and no more than three years postdoctoral research experience were invited to apply. One of the fellowships awarded in 2022 is the Scott Sullivan MND Postdoctoral Fellowship, which is largely funded by MND&ME with a contribution from MNDRA.

**MNDRA Innovator Grants** provide funding for research that is innovative and has a clear relationship to the causes, treatments or cures of MND or the support of people living with MND. Innovator Grants support research for one year commencing in the calendar year 2022, and were awarded to 17 Australian researchers. The prestigious Charcot Prize is awarded to the highest ranked Innovator Grant.

**The MNDRA PhD Scholarship Top-up Grants** are awarded as an incentive to an outstanding PhD student. The grant provides a \$5,000 per annum stipend for a PhD candidate. PhD students who have been awarded a full PhD scholarship for biomedical or public health research in motor neurone disease are encouraged to apply. In 2022, four of these top-up grants were awarded.



# MNDRA Betty and John Laidlaw MND Research Prize 2022-2023

<b>BETTY AND JOHN LAIDLAW MND RESEARCH PRIZE 2022</b>	
Lead Investigator	Associate Professor Parvathi Menon
Institution	University of Sydney
Title	Improved Understanding of Brain Excitability in ALS/MND
<p>Cortical hyperexcitability, is an important mechanism underlying MND which contributes to nerve degeneration and consequent muscle wasting, varying MND types, adverse prognosis, and disease progression. Mechanisms underlying cortical hyperexcitability in MND are partially understood and their limitation or reversal may be vital in MND management. Loss of inhibitory interneurons has been proposed as a mechanism for cortical hyperexcitability in mouse models. This research project will help prospectively interrogate the function of distinct cortical interneuron populations in sporadic MND patients using unique cortical stimulation techniques to improve understanding of this key pathogenic mechanism.</p>	

*The Betty Laidlaw MND Research Prize was first awarded in 2015 and has been funded every year since. Betty Laidlaw lived with primary lateral sclerosis for over 30 before her death in early 2020. Her husband, John Laidlaw, was her primary carer. John died in late 2019, after which time the award was renamed to the Betty and John MND Research Prize, to acknowledge the incredible generosity of both John and Betty, who supported the Betty Laidlaw MND Research Prize from the time of its inception in 2016.*

## MNDRA Postdoctoral Fellowships 2022-2024

Bill Gole MND Postdoctoral Fellowship (2022 – 2024)	
Lead Investigator	Dr Fiona Bright
Institution	Macquarie University
Title	Exploring undefined regions & novel functions of the TDP-43 protein - The molecular pursuit to uncover the cause and ultimately find a cure for MND
<p>In 95% of MND patients, abnormal protein deposits of TDP-43 are present within cells of the brain, and spinal cord. The molecular mechanisms underlying TDP-43 pathology in MND remains unknown. The structural parts of TDP-43 containing disease-causing mutations have undergone detailed studies, yet the remaining part is significantly understudied. Importantly, this part contains TDP-43's transport and protein binding machinery with ample opportunity to learn about its physiological movement within the brain and spinal cord. Novel regulators of TDP-43 transport, and other functions awaits discovery. This project will explore undefined regions and molecular pathways of TDP-43 which holds the key to understanding what goes wrong in MND.</p>	

*Bill Gole died from MND in 2003, three years after being diagnosed with the disease. After his death, a philanthropist friend of Bill's realised the importance of increasing research funding for MND. This funding initially took the form of supporting a PhD scholarship for Steve Vucic, who is now a Professor of Medicine at the University of Sydney. To broaden the impact of the funding, it was decided to establish a long-term fellowship program, which became the Bill Gole MND Postdoctoral Fellowship. The first fellowship was awarded in 2005 and has been awarded and funded by that same friend, in memory of Bill, every year since. This year, the 21<sup>st</sup> young Australian scientist has commenced their research under this award, with total funding to date for the program amounting to approximately \$5 million.*

## Beryl Bayley MND Postdoctoral Fellowship (2022 – 2024)

Lead Investigator	Dr Mouna Haidar
Institution	Florey Institute of Neuroscience and Mental Health
Title	A novel gene therapy approach targeted to overactive brain motor neurons

There is increasing evidence that motor neurons in the brain are electrically overactive in MND, leading to damage of motor neurons in the spinal cord. We will evaluate a new gene therapy approach targeting motor neurons in the brain to reduce their overactivity in MND. Using "designer receptor" technology, we will test this approach in motor neurons grown from MND patients and mouse models. We predict that our gene therapy strategy will reduce the burden of electrical overactivity in the brain, preserving motor neurons and correcting these models, supporting future development of designer receptor therapy for MND.

*The Beryl Bayley MND Postdoctoral Fellowship was first awarded in 2015 after a bequest was made from the estate of the late Beryl Bayley in 2013. Bequests form an incredibly important part of the funding available for MNDRA to allocate to MND research. In 2022, MNDRA awarded the eighth Beryl Bayley MND Postdoctoral Fellowship – an amazing legacy from a very generous bequest.*

## Nancy Gray MND Postdoctoral Fellowship (2022 – 2024)

Lead Investigator	Dr Marnie Graco
Institution	Institute for Breathing and Sleep, VIC
Title	Optimising quality of life and survival in motor neurone disease by improving the use of overnight breathing support

Supporting breathing overnight with non-invasive ventilation improves life expectancy in motor neurone disease (MND). However only 19% of Australians living with MND currently access the treatment. This research will directly address this problem, by: 1) understanding the barriers to the uptake of non-invasive ventilation from the perspective of people living with MND, their carers / family and clinicians; 2) carefully designing a strategy that targets these barriers; and 3) implementing and testing the effectiveness of this strategy in a single Australian location. This research will optimise quality of life and survival in MND by improving the uptake of non-invasive ventilation.

*This postdoctoral fellowship is being offered for the first time in 2022, after another generous bequest was made to MNDRA in 2021. In 2022, MNDRA was able to award this postdoctoral fellowship and five Innovator Grants in memory of Nancy Gray, whose family were impacted by motor neurone disease.*

## Scott Sullivan MND Postdoctoral Fellowship (2022 – 2024)

Lead Investigator	Dr Fleur Garton
Institution	University of Queensland
Title	An investigation into MND biomarkers and genetic risk mechanisms to improve diagnosis/tracking and therapeutic avenues for sporadic ALS
<p>This fellowship aims to bring together an MND research program with two key themes to address 1) new biomarkers of disease and 2) mechanisms underlying genetic risk associations. It will focus on the relatively understudied (but most common form) sporadic ALS. Potential outcomes include new methods for diagnosing and/or tracking ALS using biomarker data (alongside other biological and clinical information) and novel avenues for therapeutic intervention. By integrating clinical, molecular, and model systems and focussing on ALS cases without a known mutation (&gt;80%), the research program will maximise the opportunity to improve the care and cure of those with MND.</p>	

*This postdoctoral fellowship is largely funded by the MND&Me Foundation with a contribution from MNDRA, and is being offered through the MNDRA funding round for the first time in 2022. MND&Me was founded by Scott Sullivan, who was himself diagnosed with motor neurone disease in 2010 at the age of 38. The Scott Sullivan Fellowship was first offered by MND&Me in 2015, following the death of Scott Sullivan in 2014.*

## MNDRA Innovator Grants 2022

17 Innovator Grants were awarded by MNDRA in 2022. Every year the top-ranked Innovator Grant is awarded the prestigious Charcot Award. In 2022, this went to Dr Emma Devenney, from the University of Sydney.

<b>Charcot Award</b>	
Lead Investigator	Dr Emma Devenney
Institution	University of Sydney
Title	Harnessing Artificial Intelligence Computer Models in MND: a novel pathway to improve patient outcomes
<p>The systems responsible for thinking and moving work together to help us complete complex tasks. These systems may become dysfunctional early in MND and can occur before the onset of physical symptoms. This project will develop objective tests, using cutting-edge technology including Artificial Intelligence models, to accurately identify and define these features. This project will also identify the earliest brain changes that cause these symptoms. Overall, this project may lead to improvements in the diagnostic process and provide markers for progression and therapeutic effect that will improve timely access to support and care and appropriate access to pharmaceutical therapies.</p>	
<b>Col Bambrick MND Research Grant</b>	
Lead Investigator	Dr Gabriel S. Trajano
Institution	Queensland University of Technology
Title	High-density electromyography as a new tool to monitor motor neurone changes in MND
<p>There is a lack of biomarkers to monitor MND progression. Current methods to evaluate motor neurone changes have limited applicability because they are invasive, painful, and can only record few motor units. We propose the use of innovative non-invasive high-density electromyography to record the activity of motor units in MND patients. Our pilot data in MND patients suggests this method is feasible and could be used to determine changes in motor neurone excitability along disease progression in specific types of motor neurones. This project results will help to develop a new biomarker to track disease progression and inform clinical practice.</p>	



### NTI MND Research Grant

Lead Investigator Dr Frederik Steyn

Institution University of Queensland

Title Preclinical validation of macimorelin, a ghrelin mimetic, as a treatment for amyotrophic lateral sclerosis (ALS)

Not all patients with ALS are the same, and so treatments must target a range of disease processes that are relevant across patients with ALS. We will complete critical preclinical studies to show that macimorelin, an FDA approved compound with wide-ranging biological actions, can improve disease outcome in ALS. Results from this project will provide critical preclinical evidence to facilitate the rapid repurposing of macimorelin into extensive preclinical and clinical testing as a treatment for ALS.

### Fat Rabbit MND Research Grant

Lead Investigator Dr Tanya McDonald

Institution University of Queensland

Title Investigating energy balance in the progression of MND

The body requires blood glucose concentrations to be tightly regulated to maintain health. This is mainly regulated by two hormones, glucagon and insulin. The actions of glucagon appear to be impaired in MND, and may promote disease progression. This study will use mouse models of MND and MND patients to investigate whether increasing glucagon signalling restore glucose homeostasis, and thereby slows disease progression. This will help determine whether targeting glucagon signalling is a viable therapeutic option to benefit people with MND.

### Run MND NSW Research Grant

Lead Investigator Dr Alison Hogan

Institution Macquarie University

Title RNA transport in Motor Neuron Disease - an investigation into dysfunction of the pathway and its potential for therapeutic intervention

Protein synthesis at motor neuron terminals is essential for nerve function and viability. This synthesis relies on efficient transport of molecules from the cell body to neuron terminals. Evidence indicates that the transport pathway is disrupted in MND and excitingly, that it presents a potential therapeutic target. One protein essential to the transport pathway, SFPQ, has recently been linked to MND. This study will examine SFPQ-dependent transport in motor neurons in healthy and disease conditions, with the aim of establishing its role in neurodegeneration. Our findings will provide valuable insight into the therapeutic potential of modifying the pathway in MND.

### **Dr Paul Brock MND NSW Research Grant**

Lead Investigator Professor Julie Atkin

Institution Macquarie University

Title New mechanisms exploring the relationship between aging and motor neuron disease

Age is the major risk factor for MND, and 'senescence' is known to drive the aging process. Surprisingly, however, little is known about how senescence contributes to MND. Using disease models, our aim is to investigate whether two major mutant proteins induce senescence in MND and whether this contributes to the spread of MND throughout various cells of the nervous system. We will also examine whether existing drugs that kill senescent cells ("senolytics") are protective in MND. These studies may identify new disease processes in MND and lead to the use of senolytic drugs as a novel treatment strategy.

### **Nancy Gray MND Research Grant**

Lead Investigator Dr Andrew Phipps

Institution University of Tasmania

Title Understanding why nerve fibres are vulnerable in MND

Axons are long processes that allow for communication between our nerve cells and muscles to enable movement. During MND, nerve cell axons breakdown, leading to loss of motor function and mortality; the mechanism of which we do not understand. In this project, we will use human nerve cells to investigate what pathways are involved in axon breakdown. By understanding why axons are vulnerable, and what pathways dysfunction during MND, we can design novel therapies to prevent axon breakdown in MND.

### **Nancy Gray MND Research Grant**

Lead Investigator Associate Professor Mary-Louise Rogers

Institution Flinders University

Title Uncovering a panel of urinary proteins present in people with MND that can be used to indicate stages of disease

Our laboratory are world leaders in identifying urinary molecules that are useful as readouts for clinical trials. We now propose to use high precision mass spectrometry to uncover a panel of molecules (proteins) in urine that can be used as a measure of disease at first visit to the neurologist (prognostic marker). These molecules will also be investigated to determine if they are related to traditional clinical measurements and also to disease state. We envisage producing a panel of 50 candidate molecules that can be useful to group patients with the same disease state in future clinical trials.

### **Nancy Gray MND Research Grant**

Lead Investigator	Dr Jessica Collins
-------------------	--------------------

Institution	University of Tasmania
-------------	------------------------

Title	Developing blood tests to diagnose and monitor MND
-------	--

This project aims to develop new blood tests for MND that can help us with one of the most challenging issues in the disease; distinguishing which nerve cells are degenerating, those in the brain or those that make up the nerves. These blood tests will help us monitor disease progression which will enable us to have a better understanding of the fundamental drivers of the disease. They will also help us understand the effects of new treatments and aid in more accurate and timely diagnoses and prognoses for people with MND.

### **Nancy Gray MND Research Grant**

Lead Investigator	Professor Tracey Dickson
-------------------	--------------------------

Institution	University of Tasmania
-------------	------------------------

Title	Rebalancing excitability dysfunction in MND by targeting non-neuronal cells
-------	---

MND has a long pre-clinical period, with dysfunction in numerous cell types and pathways converging to cause motor neuron degeneration and loss of motor function. But what keeps this dysfunction in check for so long? In this project we turn our focus to the multifaceted process of neuronal inhibition, asking what causes it to fail and trigger the onset of ALS symptoms. To answer this critical question we will determine the role of the support cells in the brain, the glia, in the onset of inhibitory network dysfunction.

### **Nancy Gray MND Research Grant**

Lead Investigator	Dr Jeffrey Liddell
-------------------	--------------------

Institution	University of Melbourne
-------------	-------------------------

Title	How corrupted glial cells perpetrate the death of neurons
-------	---

Glial cells are essential for optimal neuronal health within the central nervous system, but in MND they abandon their normal 'neuro-supportive' role and begin to secrete factors that cause neuronal death. We have discovered a trigger that instigates this neurotoxic conversion in MND. The work that we plan to undertake via this MNDRA Innovator Grant aims to thoroughly identify the cellular changes that occur in response to this trigger and the neurotoxic factors that the glial cells secrete. The new information generated will guide development of treatments for MND that prevent neuronal death by targeting glial cells.

### Jenny Simko MND Research Grant

Lead Investigator	Professor Jacqueline Wilce
-------------------	----------------------------

Institution	Monash University
-------------	-------------------

Title	Preventing toxic protein aggregation in cells by targeting stress granules
-------	--

This project investigates our newly developed TIA-1 inhibitor that has potential as a neuroprotective agent against ALS. In preliminary work we have tested the TIA-1 inhibitor in vitro and also shown that it is able to modulate stress granules (SG) in cells. SGs are subcellular structures made of protein and RNA that have been shown to trigger protein aggregation as underlies neurodegenerative disease. We anticipate that TIA-1 inhibitors will modulate SG formation, preventing the formation of neurotoxic aggregate formation. The work will provide proof-of-concept for targeting TIA-1 and potentially lead to a novel mode of intervention against ALS.

### Mavis Gallienne and Graham Lang MND Victoria Research Grant

Lead Investigator	Associate Professor Rebekah Ahmed
-------------------	-----------------------------------

Institution	University of Sydney
-------------	----------------------

Title	Sleep and autonomic function across the ALS-FTD spectrum
-------	--

It is recognised that the symptoms of ALS are not limited to motor weakness, but involve other major physiological changes within the body including sleep function, and pain/somatic symptoms. These changes are potentially related to changes in the autonomic nervous system and key neural structures (hypothalamus, insula and thalamus). Using novel approaches including wearable devices, and brain imaging, the prevalence of sleep and pain symptoms in ALS and FTD will be documented, the brain structures that control these changes and at what stage of the disease these changes occur to assist in early diagnosis and development of potential treatment targets.

### Superball XIV MND Research Grant

Lead Investigator	Professor Coral Warr
-------------------	----------------------

Institution	La Trobe University
-------------	---------------------

Title	Developing new models to help us understand the cause of variability in MND clinical presentation
-------	---

Amyotrophic lateral sclerosis (ALS) shows substantial clinical heterogeneity, however what underpins this heterogeneity is not understood. In this project we will develop and use a novel in vivo animal model motor circuit, together with an established model, to test the idea that the changes in neuron excitability observed in ALS can be caused by different mechanisms, and that different changes in individual patients contribute to clinical heterogeneity. Our findings will provide important knowledge that informs future personalised treatments for ALS.

### MonSTaR MND Research Grant

Lead Investigator Dr Shu Yang

Institution Macquarie University

Title Preclinical assessment of the therapeutic potential of CHCHD10 in the removal of insoluble protein

We recently discovered a new MND-linked mitochondrial protein CHCHD10 that is decreased in MND and FTD patient brains compared to individuals unaffected by the disease. Restoring these reduced levels of CHCHD10 in MND cell models decreased the amount of pathological protein aggregation usually seen in MND models and improved cell survival, possibly due to enhanced protein clearance pathways. Here we propose a preclinical study to assess whether increasing levels of CHCHD10 in the brains of an MND mouse model is beneficial in modifying disease onset and reducing disease severity and progression.

### Peter Stearne Familial MND Research Grant

Lead Investigator Dr Lyndal Henden

Institution Macquarie University

Title Sex and ancestry – a recipe for gene discovery in MND

More males are affected with MND, but females have a worse prognosis. The reasons for these sex-related differences are unknown but suggest a genetic component on sex chromosomes. We aim to detect X chromosome genes that cause MND or influence disease progression by using genetic data and powerful computational tools to uncover distant ancestral relationships amongst thousands of MND cases. Integrating the largest Australian MND cohort assembled to date with global MND cases from New Zealand, United Kingdom, United States and ten European countries, this is the world's largest MND genetics study to comprehensively investigate the X chromosome.

### Phyllis Diana Seman MND Research Grant

Lead Investigator Dr Albert Lee

Institution Macquarie University

Title Using proteomics to reveal the components of protein aggregates to understand MND biology and identify potential therapeutic targets

The pathological feature of MND is the presence of protein inclusions inside motor neurons – comprising mostly of the protein TDP-43. It is still not known what other protein constituents make up these protein inclusions, and their biological role(s) in causing motor neuron degeneration. We have developed a new workflow to identify what these proteins are from various stages of MND pathology. These protein 'signatures' enable us to map out their cellular and biological role in MND onset and progression which will help us identify new therapeutic targets and mechanisms of toxicity to prevent TDP-43 inclusion formation.

## MNDRA PhD Scholarship Top-Up Grants 2022-2024

MNDRA is delighted to have awarded four PhD Scholarship Top-Up Grants in 2022. PhD Scholarship Top-up Grants are awarded as an incentive to outstanding PhD students who have been awarded a full PhD scholarship for biomedical or public health research in motor neurone disease.

<b>MNDRA PhD Scholarship Top-Up Grant 2022-2024</b>	
Lead Investigator	Jeryn Chang
Institution	University of Queensland
Title	Decoding the loss of appetite and pathophysiology of the brain in motor neuron disease
<p>The loss of appetite is observed in patients with MND. This is clinically important, as energy deficits and weight loss are associated with faster disease progression and earlier death. My studies aim to identify the impact of MND on the hypothalamus, a small area of the brain that regulates appetite, and how this may contribute to functional deficits throughout the brain. Studies aim to provide a biological basis for the loss of appetite in patients with MND, which will enhance understanding of disease, and provide insights to better manage care strategies aimed at improving quality and duration of life.</p>	
<b>MNDRA PhD Scholarship Top-Up Grant 2022-2024</b>	
Lead Investigator	Sean Keating
Institution	Queensland Brain Institute, University of Queensland
Title	TDP-43 and protein clearance in the pathogenesis and treatment of MND
<p>In MND, toxic clumps of proteins accumulate within the brain and spinal cord, leading to neurodegeneration. Using human MND tissue, neurons grown in a dish, and genetically modified MND mice, I aim to investigate how dysfunctional cellular “waste removal” systems cause protein clumping in neurons. I also aim to discover new ways to effectively stimulate these “waste removal” systems with drugs and gene therapies, and determine whether this can increase the break-down of toxic protein clumps and protect against disease. By stopping protein clumping, we aim to extend neuron survival as a therapeutic strategy to treat people living with MND.</p>	

**MNDRA PhD Scholarship Top-Up Grant 2022-2024**

Lead Investigator	Katherine Lewis
Institution	University of Melbourne
Title	Characterising Myelin Changes in Motor Neuron Disease

Despite garnering much deserved attention and funding, the primary causes underlying MND onset and progression remain elusive. This, in part, may be due to most MND research being conducted with a neuroncentric focus. We know that motor neurons are encased in a lipid-rich sheath termed myelin, which is essential for neuronal health and survival. We also know that the cells that produce the myelin have been shown to exhibit MND pathology. However, the exact role of myelin-producing cells in MND remains unclear and it is unknown to what degree their dysfunction contributes to MND onset and progression. Thus, this PhD project aims to comprehensively characterise myelin changes in MND over the course of disease, using clinically relevant mouse models, complemented with sophisticated stem cell derived 'mini brain' model systems. By understanding the role of myelin in MND, we can provide insight into new treatment avenues and therapeutic targets to preserve motor neuron health and function.

**MNDRA PhD Scholarship Top-Up Grant 2022-2024**

Lead Investigator	Jianina Marallag
Institution	University of Queensland
Title	The potential role of CXCR2 activation in motor neuron disease

Excessive activation of the immune system has been found to result in motor neuron death in MND. CXCR2 is a cellular receptor that is gaining interest for its involvement in recruiting immune cells to the site of injury. Inappropriate activation of this receptor may contribute to the progression of MND. This project will utilise a drug that blocks CXCR2 in mouse models of MND and patient samples to investigate if it is able to protect motor neurons by reducing immune system activity. The results will help determine if CXCR2 can be used as a therapeutic target for MND patients.

*Thank you again to all of our donors and fundraisers who make this research possible. We are forever grateful for the work that our dedicated researchers undertake to try and better understand the causes, improve care and to find treatments and ultimately a cure for MND.*

