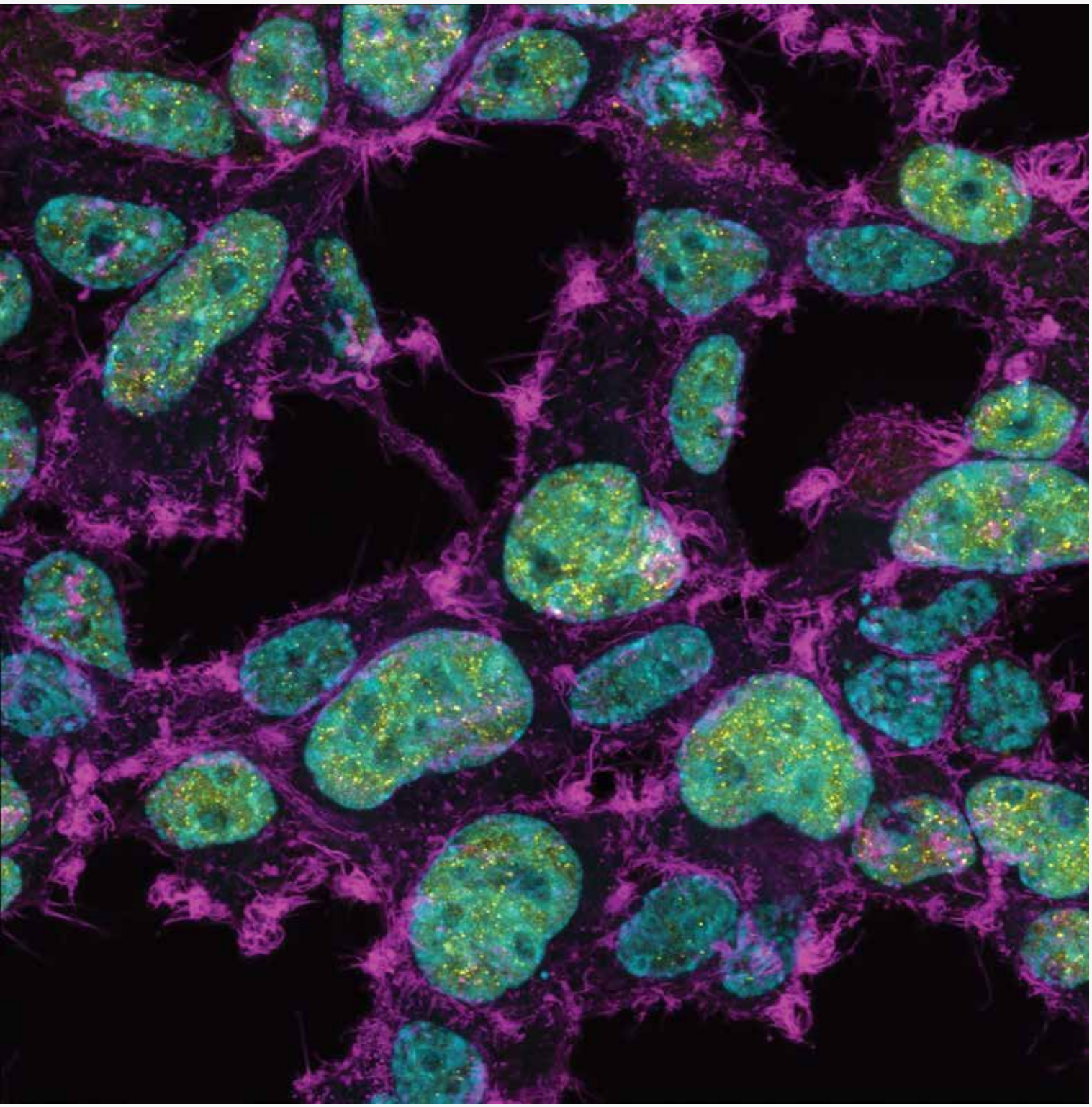
FIGHT MND.
IT TAKES PEOPLE

2022 Cure Research Grants



In 2022, FightMND will commit a further $13.41M into MND Research, including support of:

- 2 Clinical Trials
- 2 Drug Development Projects;
- 3 Discovery Projects;
- 2 Collaborative Initiatives Projects;
- 10 IMProving and Accelerating Translation (IMPACT) Projects;
- 2 Mid-Career Research Fellowships;
- 1 Early Career Research Fellowship; and
- 3 International Research Fellowships

Dr Adam Edwards and Dr Loren Flynn in the Perron Institute lab

Clinical Trials

Clinical trials will test promising new drugs, or drugs already approved for other diseases or conditions in people with MND. Phase 3 trials are studies that test the safety and effectiveness of drugs in a large group of people living with MND. Phase 2 trials are studies that test the safety and effectiveness of a drug in a small number of people living with MND. Phase 1 trials are safety studies to assess whether a drug is safe to administer to people, and in particular, people with MND.

Associate Professor Bradley Turner performing an experiment in the lab

1. PROJECT:
Phase 3 Clinical Trial – Randomised double-blind placebo-controlled Phase 3 trial of Lithium Carbonate in MND, a sub-study of a Multi-arm, Adaptive, Group-sequential trial NETwork to evaluate drug efficacy in patients with MND (MAGNET)

PRINCIPAL INVESTIGATOR:
Professor Matthew Kiernan
The University of Sydney, NSW

Above: Professor Matthew Kiernan | Below: The Forefront MND clinic at the University of Sydney (L-R): Eleanor Ramsey, Dhayalen Krishnan, Professor Matthew Kiernan, Ying-Ting Hsu, Hannah Timmins, Srestha Mazumder, Tiffany Li, Fawaz Mahfouz, Dr Sicong Tu

Although previous clinical trials showed that the drug Lithium Carbonate was not beneficial for MND patients, researchers have identified a group of patients that may have responded to the drug when looking more closely at trial data. The prognosis for MND patients with changes in the unc13A gene, who generally have a more rapid disease course, appeared to improve when given lithium carbonate. Because these results were identified by re-examining data from multiple trials after their completion, they need to be confirmed in a new trial. The objective of this international, multicentre study is to specifically test the effectiveness of lithium carbonate in this group of unc13A-determined MND patients. The Australian arm of this phase 3 trial aims to enrol 57 patients at 7 sites across Australia in Sydney, Adelaide, Perth, Brisbane and Melbourne.

KEY HIGHLIGHTS:
This trial will test the effectiveness of a drug in a specific group of MND patients that have changes in a gene called unc13A. The trial is an international study with the Australian arm including 57 MND patients at 7 sites across the country.

AMOUNT INVESTED BY FIGHTMND IN THIS RESEARCH PROJECT:
$1,287,280

***"The MAGNET clinical trial will launch precision medicine in MND, by establishing whether we can use an individual's genetic signature to determine if they are more likely to benefit from the investigative drug's neuroprotective effects."* – Professor Matthew Kiernan**

2. PROJECT:
Phase 2 Clinical Trial – A placebo-controlled safety and efficacy of ambroxol in individuals with MND

PRINCIPAL INVESTIGATOR:
Associate Professor Bradley Turner
The University of Melbourne, VIC

***"Ambroxol targets multiple key disease pathways implicated in MND, including disruption of connections between motor neurons and muscle which occurs very early in MND."* – Associate Professor Bradley Turner**

In this study researchers will assess the long-term safety and effectiveness of ambroxol in MND patients. Ambroxol is a prescription medication used as a cough suppressant. It is being re-purposed in the Fight against MND because it also restores lipid metabolism, which is dysfunctional in people living with MND. The phase 2 trial aims to enrol 50 Australian patients at 5 sites across Australia in Sydney, Adelaide, Perth and Launceston.

KEY HIGHLIGHTS:
This trial is a long-term safety and efficacy study of an already-approved drug re-purposed for MND. Preclinical studies that progressed this drug to clinical testing in people with MND were supported by a FightMND Drug Development grant.

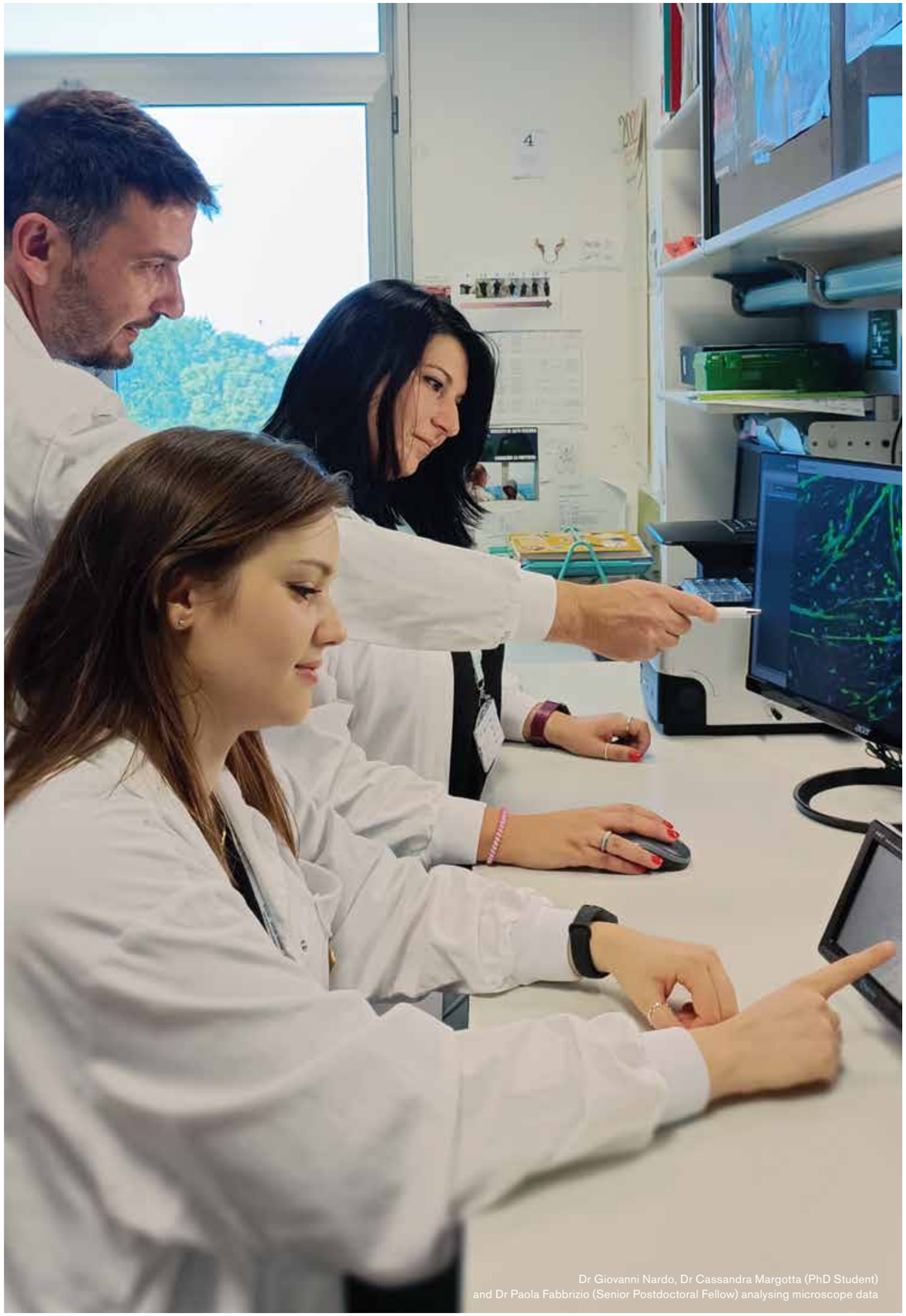
AMOUNT INVESTED BY FIGHTMND IN THIS CLINICAL TRIAL:
$2,000,000

Q&A:
Why is this important, and how could it benefit patients?
We tested ambroxol in multiple animal models of MND across different laboratories, showing a consistent benefit in motor function, muscle strength and motor neuron protection. This consistent effect across independent research teams provided convincing evidence that ambroxol may benefit MND. My team is excited to play a role in advancing a drug candidate from our lab to clinical studies in people living with MND.

Associate Professor Bradley Turner

Drug Development Grants

Drug Development projects are focused on advancing promising new drugs or therapies through the final stages of testing in preparation for advancing them through to clinical trials for MND patients.



Dr Giovanni Nardo, Dr Cassandra Margotta (PhD Student) and Dr Paola Fabbrizio (Senior Postdoctoral Fellow) analysing microscope data

1. THERAPIES TARGETING MUSCLE

PROJECT:
Intramuscular allosteric agonism of purinergic P2X7 receptor as a pharmacological approach to enhance skeletal muscle regeneration in MND

PROJECT LEAD:
Dr Giovanni Nardo
Mario Negri Institute for Pharmacological Research, Italy

In MND, motor neurons in the brain and spinal cord die and the body's muscles waste away. While researchers know that protecting motor neurons is essential to overcoming MND, the role that muscles play in the progression of the disease is poorly understood. Investigators in this innovative study will test if a drug that helps rebuild muscle can overcome muscle loss that occurs with MND and slow down disease progression. The drug being tested is safe for use in people, so a successful outcome could see its quick progression into a clinical trial for MND, either alone or combined with drugs that directly target motor neurons in the brain.

***"The main strength of our proposal lies in the use of an easily accessible and low-cost candidate drug, for which biosafety has already been tested in humans."* – Dr Giovanni Nardo**

KEY HIGHLIGHTS:
Dr Giovanni Nardo is a first-time recipient of research support from FightMND. This international project is building a collaboration between researchers at the Mario Negri Institute in Italy and The University of Queensland.

AMOUNT INVESTED BY FIGHTMND IN THIS PROJECT:
$985,328

Q&A:
What excites you about your research project?
The exciting aspect of our project is based on the opportunity of defining a therapeutic approach for ALS that will establish how the preservation of the muscular system is pivotal to protecting motor neurons. I am also excited by the possibility of developing this hypothesis with Prof Ngo and Dr Steyn at the University of Queensland with the aim of defining a stable scientific flow between Australia and Italy for the cure of ALS.

Dr Giovanni Nardo

2. TREATMENTS TARGETING MULTIPLE CAUSES OF MND

PROJECT:
Validation of the clinical stage drug candidate RRx-001 as a novel disease-modifying therapeutic for MND

PROJECT LEAD:
Dr Tony Reid
EpicentRx, Inc., California, USA

This project will perform preclinical safety tests needed to advance a drug called RRx-001 towards a clinical trial for MND patients. RRx-001 is a drug currently being tested in a Phase 3 clinical trial for treating cancer. Investigators believe it may benefit MND because it also targets many mechanisms linked to the disease, including an overactive immune system, the build-up of harmful proteins, oxidative stress in motor neurons and their overactivity. This pre-clinical study examines if RRx-001 can delay the onset and progression of MND, prevent the loss of motor neurons, and improve the performance of body movements that deteriorate because of MND.

KEY HIGHLIGHTS:
Because RRx-001's safety has already been demonstrated in people, successful project outcomes will allow quick transition of the drug to a Phase 2 clinical trial for MND. This international project is a collaboration between researchers at EpicentRx, Inc., in the USA, The University of Queensland and Royal Brisbane and Women's Hospital.

AMOUNT INVESTED BY FIGHTMND IN THIS RESEARCH PROJECT:
$719,951

Q&A:
What problem are you trying to solve with this project?
MND is a huge problem, not only because of the devastation that it wreaks on the lives of patients and their families, but also because of the profound financial, economic, and social costs that it imposes on society. The goal—and the hope—for this project is that it will contribute, even in some small way, to a fuller mechanistic understanding of the key drivers behind MND. The cause(s) of MND remain elusive; however, further understanding of how RRx-001 reduces symptoms and improves outcomes may provide key insight into MND and further our fight for effective control and a cure for this devastating disease.

Above: Dr Tony Reid | Below: Co-Investigator Dr Richard Gordon analysing the latest results from preclinical studies in MND models

***"Curiously, and unexpectedly, we found that one of the drugs we use to treat cancer, RRx-001, may have the potential to reduce the symptoms of MND and make a significant difference in the quality of life for patients with MND."* – Dr Tony Reid**

Discovery Projects

Discovery projects aim to resolve one or more current unknowns in the MND research sector, focused on discovering why MND occurs and what contributes to its progression. Outcomes should significantly advance our understanding of MND, and substantially increase the likelihood of an acceleration in the development of more effective treatments or cure for MND.

1. GENETIC AND ENVIRONMENTAL INTERACTIONS

PROJECT:
Epidemiology in a dish: using human iPSC to discover common and genotype-specific molecular signatures of the multi-step hypothesis of MND

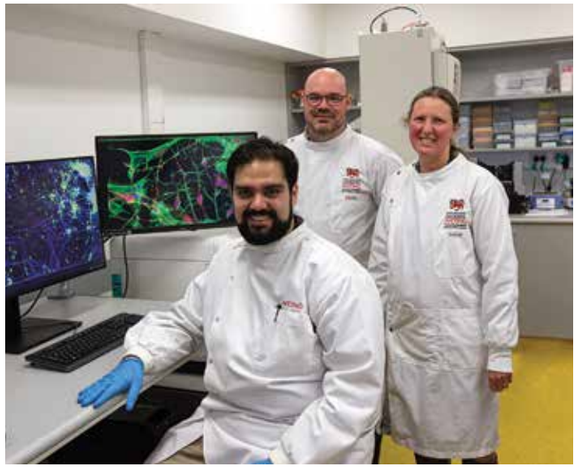
PROJECT LEAD:
Associate Professor Anthony Cook
University of Tasmania, TAS

This project aims to discover how interactions between an individual's genetics and the environment in which they live contribute to their risk of developing MND. Investigators will use human stem cells to make motor neurons that contain gene errors linked with MND and expose them to a variety of environmental risk factors for the disease, including pesticides, cholesterol and cyanotoxins such as blue-green algae. The team will search for key changes and deterioration in the structure, activity, function and health of motor neurons containing the MND gene errors as they engage with "risk-environments".

KEY HIGHLIGHTS:
A/Prof Cook is a first-time recipient of research support from FightMND. The project will provide new insights into the causes of MND and identify new targets that direct the design and development of therapeutics aiming to treat MND more effectively.

AMOUNT INVESTED BY FIGHTMND IN THIS RESEARCH PROJECT:
$999,981

Q&A:
What problem are you trying to solve with this project?
We don't fully understand how genetic risk and environmental risk combine to cause motor neurons to die but there is evidence that several steps are involved. This has made studying the role of genes and the environment in ALS difficult. By studying neurons with different combinations of genetic risk factors, and comparing their responses to exemplar environmental risk factors associated with increased risk of ALS, we anticipate our research will take a significant step to bridging this knowledge gap.



Above: Associate Professor Anthony Cook | Below: Primary Investigator Associate Professor Anthony Cook, co-investigator Professor Anna King, and co-investigator Dr Andrew Phipps examining microscope data at the University of Tasmania

"This project is the first to systematically dissect how combinations of genetics and a variety of environmental exposures promote motor neuron degeneration." – Associate Professor Anthony Cook

2. RESCUING THE BLOCKAGE OF CRITICAL FUNCTIONS IN MOTOR NEURONS CAUSED BY GENE DEFECTS

PROJECT:
Trouble at the ribosome
in C9ORF-72-driven MND

PROJECT LEAD:
Dr Danny Hatters
The University of Melbourne, VIC

Defects in the C9orf72 gene are the most common cause of hereditary MND. In MND arising because of this defect, harmful proteins, called dipeptide repeats, form in motor neurons and block critical machinery needed for them to function appropriately. The research team will use motor neurons made from stem cells obtained from patients with C9orf72-MND to investigate why these blocks occur, why they are harmful to motor neurons and how they contribute to the onset of MND. To do this, the team will use the latest microscopic technology allowing them to view the atomic structure of the dipeptide repeat proteins and determine how they interact with pathways critical to the function of motor neurons.

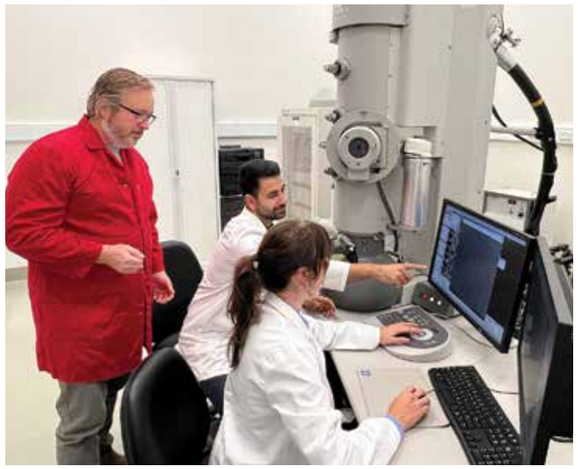
KEY HIGHLIGHTS:
Dr Hatters is a first-time recipient of research support from FightMND. Successful outcomes will identify new therapeutic targets that prevent the formation of proteins that block the function of machinery critical to the viability of motor neurons.

AMOUNT INVESTED BY FIGHTMND IN THIS PROJECT:
$852,446

Q&A:
What are you hoping to uncover from this project?
We hope to identify the molecular events involved in the blockages that harm motor neurons. By clarifying these details, we hope to unearth mechanisms that could be targeted therapeutically. This could, for example, be through boosting mechanisms involved in their clearance mechanisms.

***"More insight is needed at the fundamental level to understand what drives the earliest steps of pathogenesis to enable new therapeutic strategies to be developed. Our research is directed at this goal."* – Dr Danny Hatters**

Right: Dr Danny Hatters
Left: Dr Danny Hatters and Postdoctoral Fellows Dr Christian Makhoul and Dr Chloe Gerak examining data from an electron microscope



3. CHANGES IN THE FUNCTION OF CELLS IN THE BRAIN AND SPINAL CORD THAT NORMALLY SUPPORT MOTOR NEURON HEALTH

PROJECT:
Multiomic interrogation of patient-derived neurotoxic glia

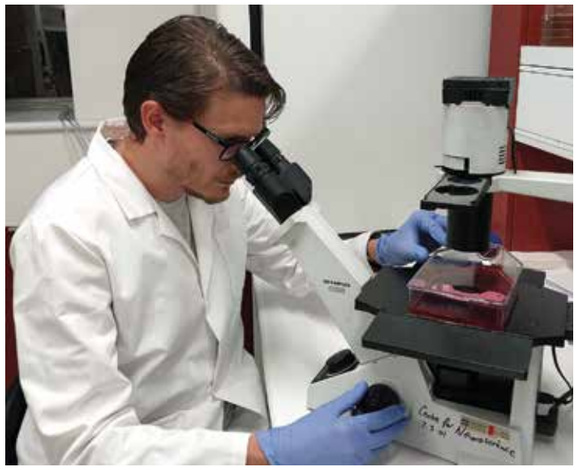
PROJECT LEAD:
Dr Jeffrey Liddell
The University of Melbourne, VIC

Motor neurons in the brain and spinal cord are surrounded by cells called glia, which support motor neurons and help to keep them healthy. However, researchers have found that in MND, glial cells may become harmful to motor neurons and contribute to their death. To discover why glial cells change to being harmful, investigators will use stem cells from people living with MND and sophisticated methods to re-create the brain's environment and accurately model interactions between glial cells and motor neurons in the laboratory.

KEY HIGHLIGHTS:
Dr Liddell is a first-time recipient of research support from FightMND. The project will identify key chemicals released by glial cells that are harmful to motor neurons, and new potential targets for developing more effective treatments for MND.

AMOUNT INVESTED BY FIGHTMND IN THIS PROJECT:
$669,313

Q&A:
What excites you about your research project?
The normally supportive glial cells in the brain and spinal cord become corrupted in MND and can actually attack and kill motor neurones. We believe we have found a trigger for how this occurs, and we are very excited to investigate it.

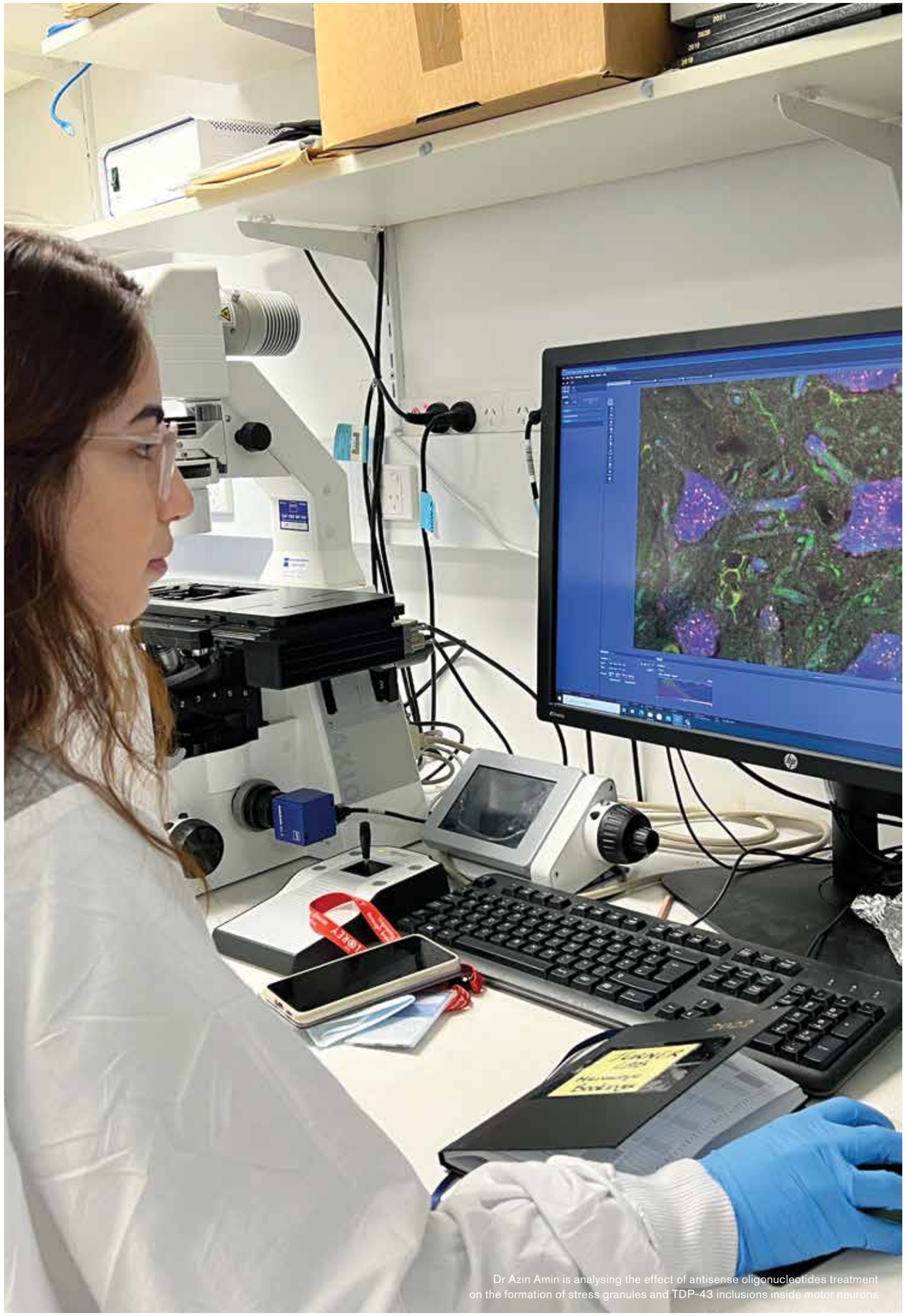


Above: Dr Jeffrey Liddell | Below: Dr Jeffrey Liddell examining patient-derived cultured cells under the microscope

***"We are seeking to develop and investigate improved models of MND."* – Dr Jeffrey Liddell**

Collaborative Initiatives Projects

Collaborative Initiatives projects aim to establish new or expand on existing MND research programs, platforms and initiatives that enable researchers to collect, share and analyse data and drive collaboration with a range of stakeholders to deliver patient-focused initiatives. Outcomes should generate data, infrastructure, or resources to help facilitate research and contribute to the growing understanding of MND.



Dr Azin Amin is analysing the effect of antisense oligonucleotides treatment on the formation of stress granules and TDP-43 inclusions inside motor neurons

1. MND BIOMARKER PROGRAM

PROJECT:
Pre-familial and early MND biomarker program

PROJECT LEAD:
Associate Professor Mary-Louise Rogers
Flinders University, SA

***"This is an exciting opportunity to work collaboratively with MND researchers in Europe and Australia to, for the first time, identify an 'early signature or fingerprint' of MND."* – Associate Professor Mary-Louise Rogers**

Above: Associate Professor Mary-Louise Rogers
Below: Vassilios Karnaros (PhD student), Dani Renfrey (Research Assistant), Megan Dubowsky (PhD student), Associate Professor Mary-Louise Rogers (Lab Head) and Dr Stephanie Shepheard (Postdoctoral Fellow)

Biomarkers are molecules that detect or confirm the presence of a specific disease. Currently, biomarkers specific to MND are not available for clinical use, which is delaying diagnosis for patients by more than 12 months. This innovative collaborative project between researchers in Australia and Europe aims to overcome this barrier. Investigators are developing a signature of early MND by measuring specific markers in body fluids such as blood, urine, and brain fluids.

KEY HIGHLIGHTS:
This international collaborative project will utilise the Ian Davis Flinders University Biomarker Facility which is funded by FightMND and named in honour of the late co-founder of FightMND, Dr Ian Davis OAM. The project will build a fingerprint of MND to fast-track diagnosis and identify causes of the disease.

AMOUNT INVESTED BY FIGHTMND IN THIS RESEARCH PROJECT:
$499,980

Q&A:
Why is this important and how will it benefit patients?
For MND patients and their carers, our project provides hope. Our large collaborative project may uncover a biomarker/signature that increases the efficiency of future clinical trials by enabling earlier diagnosis, and thus a longer window where therapy can be effective. For pre-familial MND, an early fingerprint also provides a decision tool for an earlier start of effective therapy when available.

2. MND BRAIN IMAGING INITIATIVE

PROJECT:
AMII: Asia-pacific MND Imaging Initiative

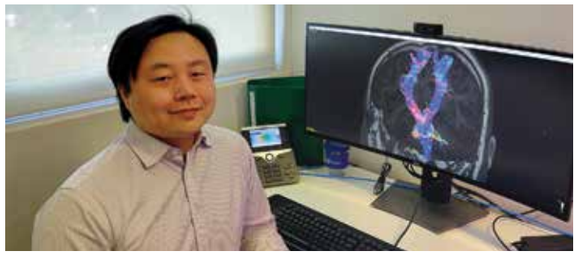
PROJECT LEAD:
Dr Sicong Tu
The University of Sydney, NSW

The location and spread of MND can be assessed by clinicians using imaging techniques such as Magnetic Resonance Imaging or MRI. These techniques are now capable of detecting loss of motor neurons from the earliest stage of disease and even before the onset of clinical symptoms. However, there are several barriers preventing imaging from being used to detect and monitor MND in the clinic. This collaborative project aims to overcome these barriers. Researchers will substantially increase the number of patient samples analysed across Australia, to validate that current imaging techniques are suitable for MND. They will also establish a platform that matches patient imaging data with their clinical assessments, enabling a comprehensive analysis of both disease stage and the effectiveness of treatments.

KEY HIGHLIGHTS:
Dr Sicong Tu is a first-time recipient of research support from FightMND. The Asia-pacific MND Imaging Initiative will create a national network that validates current imaging techniques as biomarkers for MND and tools for measuring the effectiveness of treatments for the disease.

AMOUNT INVESTED BY FIGHTMND IN THIS RESEARCH PROJECT:
$499,720

Q&A:
What excites you about your research project?
The most exciting prospect is our focus on bridging the gap and connecting leading Australian imaging researchers with leading MND clinicians to create a new national resource, through the Brain and Mind Centre, to enhance Australian MND imaging biomarkers. To achieve this, we will be working closely with industry leaders in medical imaging (GE; SIEMENS) and specialist AI-engineers.



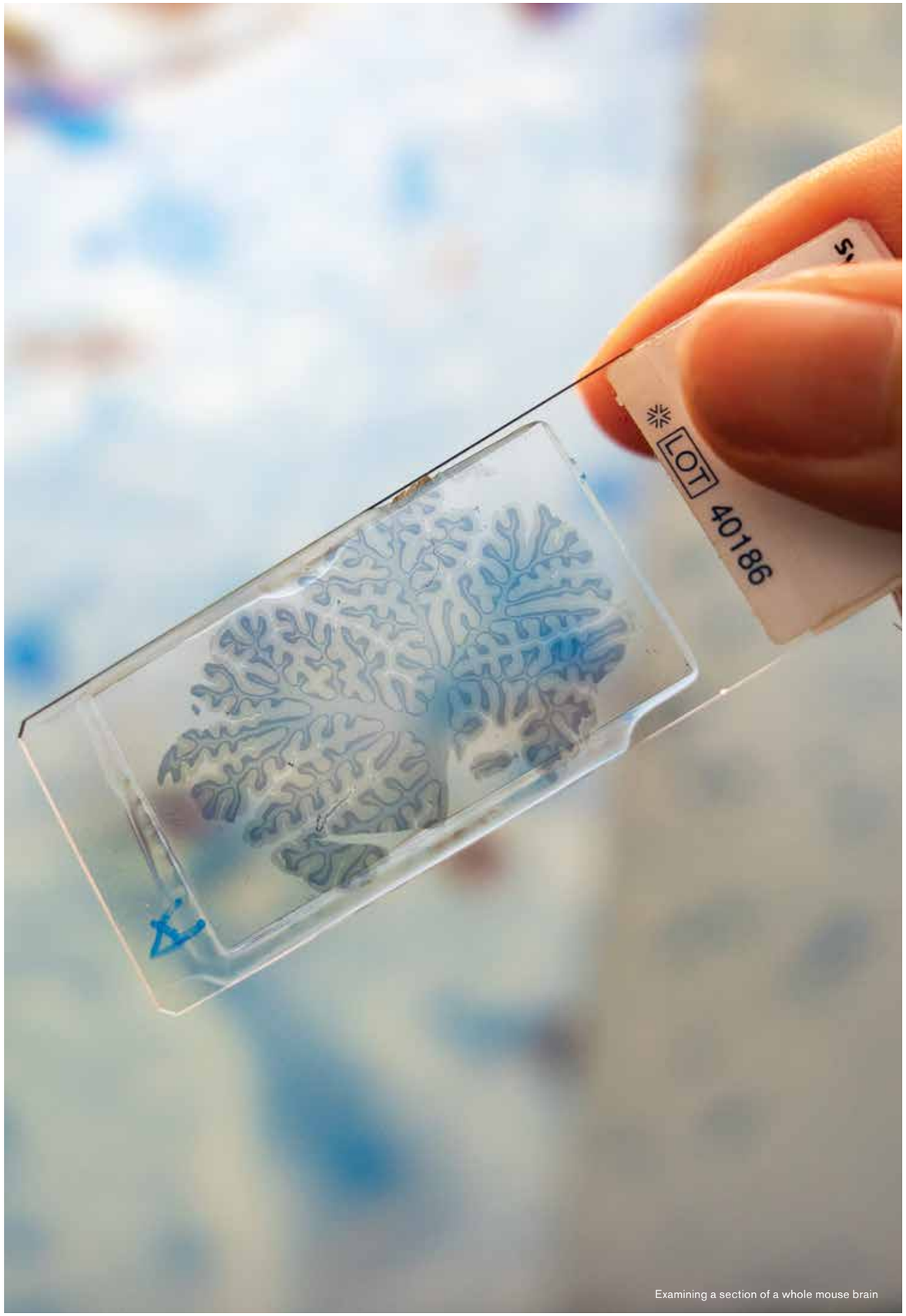
Above: Dr Sicong Tu | Below: Dr Sicong Tu examining fine-grained microstructural integrity of primary motor pathways in the MND brain

***"Accurate modelling of dynamic brain changes will add another dimension to enhance Australian clinical trial outcomes to deliver new treatment options for patients."* – Dr Sicong Tu**

IMPACT Projects

IMProving and ACcelerating Translation (IMPACT) projects support key areas of research focused on overcoming some of the hurdles and challenges in MND research that contribute to failed drug development or clinical trials. Outcomes from these projects will include:

- improvements in drug design and delivery
- treatments that target disease-causing genes
- improved understanding of the variability in disease characteristics between individuals with MND
- the development of molecular markers to help diagnose MND, or predict if a drug is effective
- better models for studying MND in the laboratory



Examining a section of a whole mouse brain

1. GENE THERAPY/DRUG DELIVERY

PROJECT:
Enhanced neuronal delivery, gene targeting and neuroprotection: development of a multimodal drug against MND

PROJECT LEAD:
Dr Loren Flynn
Murdoch University, WA

Above: Dr Loren Flynn | Below: Primary Investigator Dr Loren Flynn and Postdoctoral Fellow Dr Adam Edwards in the Perron Institute lab

A major obstacle for treating MND is the blood-brain barrier, a protective lining between the blood and brain that prevents entry of most drugs into the brain. Investigators in this project are developing a way to overcome this barrier so that a new, exciting, genetic drug targeting the SOD1 hereditary cause of MND can effectively reach motor neurons in the brain. Their pioneering approach will be to attach the genetic drug to a molecule that allows its transfer through the blood-brain barrier and promotes the health of motor neurons.

KEY HIGHLIGHTS:
Dr Flynn is a first-time recipient of FightMND funding as a lead Investigator. This project is the first step towards developing a "low-risk" way to deliver genetic drugs into the brain, which will substantially benefit the quality of life of people living with MND.

AMOUNT INVESTED BY FIGHTMND IN THIS RESEARCH PROJECT:
$249,974

Q&A:
What are you hoping to uncover from this project?
What's unique about our approach is that the carrier peptide our team has developed, on its own, protects neurons from early death. We hope to discover that, by joining the protective carrier peptide to our MND gene-targeting drugs, we can address the underlying cause of disease while protecting the neuron from further damage.

"I'm excited that this project has the potential to treat MND from multiple angles, giving us greater opportunity to solve and treat this insidious disease."
– Dr Loren Flynn

2. GENE THERAPIES

PROJECT:
Targeted degradation of misfolded TDP-43 as a therapy for MND

PROJECT LEAD:
Dr Luke McAlary
The University of Wollongong, NSW

"If these antibodies work to remove only toxic TDP-43 from cells, we have a potentially viable therapeutic method that may work in the future for those who suffer from MND." **– Dr Luke McAlary**

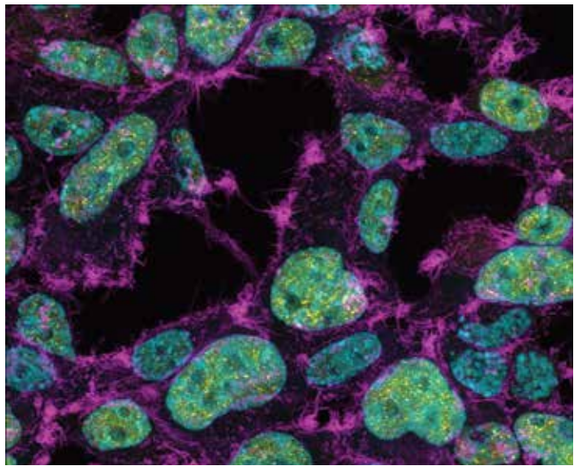
TDP-43 is a protein that normally keeps motor neurons healthy. However in MND, TDP-43 misbehaves, changes its structure, and becomes harmful to motor neurons. In this project, investigators are using exciting new drugs designed to recognise misbehaving TDP-43 protein. They will test if the drugs can identify and selectively remove the harmful TDP-43 from motor neurons, without affecting normal TDP-43 protein needed for them to function well.

KEY HIGHLIGHTS:
Dr McAlary is a first-time recipient of research support from FightMND. This project aims to target a pathology, misbehaving TDP-43 protein, present in almost all cases of MND.

AMOUNT INVESTED BY FIGHTMND IN THIS RESEARCH PROJECT:
$237,275

Q&A:
Why is this important and how will it benefit patients?
TDP-43 is a very obvious target in MND. One of the major problems associated with this protein is that it is extremely important to cell function, which means we cannot simply remove this protein altogether. If we are successful in only removing toxic TDP-43, there is potential this could become a future therapy.

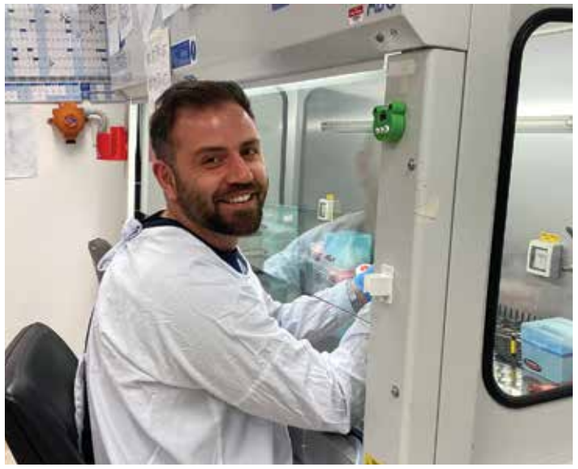
Above: Dr Luke McAlary | Below: Human cells expressing TDP-43 (yellow) in the cell nucleus (cyan) with an actin counterstain (magenta)



PROJECT:
Advanced modelling of upper motor neuron MND pathology using human pluripotent stem cells

PROJECT LEAD:
Professor Clare Parish
The University of Melbourne, VIC

Professor Clare Parish



Co-Investigator Dr Cameron Hunt

MND is complex and variable, making it difficult for researchers to develop an effective treatment for the disease. Investigators in this project aim to create a novel disease model using stem cells obtained from people living with MND. They will develop a stem cell-based model that recreates the exact types of motor neurons affected in MND and replicates the environment in the brain harmful to these motor neuron populations. Development of this superior model will lead to advanced preclinical drug screening capabilities and increase the likelihood of identifying promising disease-modifying therapies.

KEY HIGHLIGHTS:
Professor Parish is a first-time recipient of research support from FightMND. This project will use stem cells from people living with MND to establish an advanced disease model that recreates the specific types of motor neurons affected in MND.

AMOUNT INVESTED BY FIGHTMND IN THIS PROJECT:
$249,956

Q&A:
Why is this important and how will it benefit patients?
Recognising the vast number of treatments that have failed to progress from preclinical animal studies into clinical translation, it is imperative that we develop new models of diseases that better recapitulate the human condition. Human stem cells, derived from patients, provide a novel means to model aspects of disease that are not achievable using non-human models. This is likely to lead to a greater understanding of the disease progression and the cell types involved, and will enable new and better targeted therapies.

***"With a long-standing history in working with human stem cells, this is the first time our team has used patient lines to study disease mechanisms in MND."* – Professor Clare Parish**

PROJECT:
Evaluation of a novel inducible muscle-specific TDP-43 mouse model of MND

PROJECT LEAD:
Professor Aaron Russell
Deakin University, VIC

It is not yet certain where in the body MND begins. Although a potential location is the body's muscles, only a small amount of research has so far examined how muscle tissue may be involved in triggering MND. This project aims to overcome this obstacle by producing a mouse model in which TDP-43, a protein that is dysfunctional in the majority of people with MND, is designed to misbehave only in muscle. Investigators will use this new model to study specific roles for muscle in the onset and progression of MND. The model will also provide a valuable tool for testing how effective muscle targeting strategies are for treating MND.

KEY HIGHLIGHTS:
This project is developing a 'world-first' model of MND, in which the onset of the disease occurs in muscle.

AMOUNT INVESTED BY FIGHTMND IN THIS RESEARCH PROJECT:
$249,994

Q&A:
What problem are you trying to solve with this project?
Skeletal muscle appears to play a key role in MND disease progression and potentially in disease onset. This project will allow us to determine if causing a protein (TDP-43) to aggregate specifically in skeletal muscle cells causes the onset of MND-like symptoms.

***"The successful development and validation of our mouse model will provide a valuable tool to investigate the potential molecules inside muscle that impact MND."* – Professor Aaron Russell**

Above: Professor Aaron Russell | Below: Russell lab at Deakin University (L-R): Miss Anuskha Podar (PhD student), Dr Paul Della Gatta (Research Fellow), Dr Felicity Dunlop (Research Fellow) and Professor Aaron Russell

5. GENE THERAPIES

PROJECT:
Therapeutic targeting of TDP-43 through selective reduction of ataxin-2 expression with peptide-conjugated antisense oligonucleotides

PROJECT LEAD:
Dr Fazel Shabanpoor
The University of Melbourne, VIC

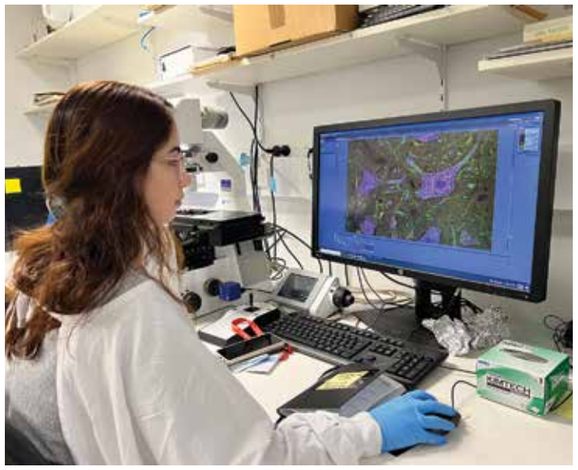
"The exciting aspect of this project is the merger of two proven technologies - antisense and brain-penetrating peptides - to develop a novel and safe brain-penetrating peptide therapy."
– Dr Fazel Shabanpoor

TDP-43 is a protein that is vital to the health of motor neurons. However, in 97% of MND cases, TDP-43 misbehaves and contributes to their death. This study is developing and testing a gene-therapy approach to overcome two problems with TDP-43 in MND: the accumulation of TDP-43 into clumps that are harmful to motor neurons; and the abnormal placement of TDP-43 in motor neurons.

KEY HIGHLIGHTS:
Dr Shabanpoor is a FightMND Mid-Career Fellow. Supporting this project enables Dr Shabanpoor to continue his research into developing novel gene therapy strategies for treating MND.

AMOUNT INVESTED BY FIGHTMND IN THIS PROJECT:
$249,731

Q&A:
Why is this important and how will it benefit patients?
The proposed antisense therapy will target a pathology associated with TDP-43 aggregates inside motor neurons. TDP-43 aggregates are toxic to motor neurons and are present in 97% of ALS patients. Therefore, preventing the formation and accumulation of TDP-43 aggregates inside motor neurons holds significant therapeutic potential and it will be applicable for treating both sporadic and familial forms of MND.

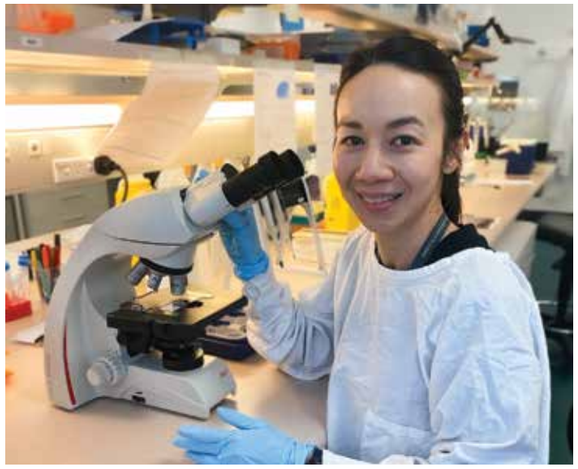


Above: Dr Fazel Shabanpoor | Below: Dr Azin Amin is analysing the effect of antisense oligonucleotides treatment on the formation of stress granules and TDP-43 inclusions inside motor neurons

6. PAUL FISHER IMPACT GRANT – DISEASE HETEROGENEITY

PROJECT:
RNA-binding proteins involved in the pathogenesis and disease heterogeneity of sporadic MND

PROJECT LEAD:
Dr Rachel Tan
The University of Sydney, NSW

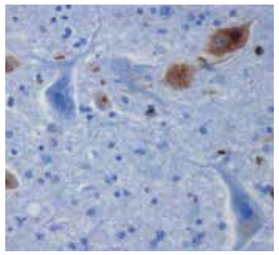


High variability in MND, including the age of onset, type and speed of disease progression between people, is a barrier to the discovery of better treatments. This project will study the brains of people that lived with MND. Investigators will search for the location of proteins recently linked to MND to determine if their distribution patterns can be used to define different types of MND. A successful outcome will be to identify new protein targets for treating specific subtypes of MND.

KEY HIGHLIGHTS:
Dr Tan is a first-time recipient of FightMND funding and was awarded a FightMND Mid-Career Research Fellowship in 2022. Identifying patterns of protein expression in the brain of people that lived with MND may help identify novel targets for treating specific subtypes of MND.

AMOUNT INVESTED BY FIGHTMND IN THIS RESEARCH PROJECT:
$208,826

Q&A:
What problem are you trying to solve with this project?
In 90% of patients, MND occurs sporadically and there is still so much that is unknown about the underlying biological pathways affected, and how these cause targeted breakdown of motor neuronal networks.



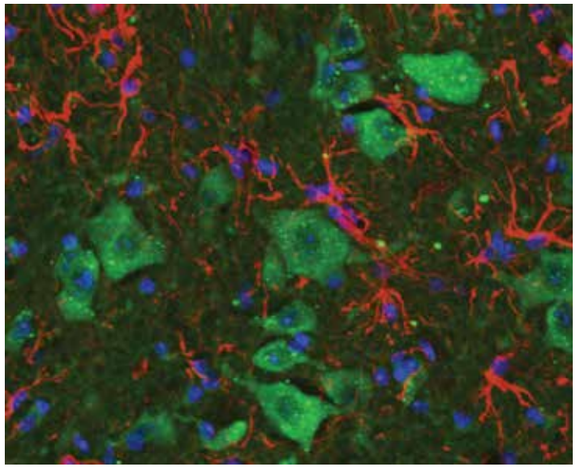
Above: Dr Rachel Tan in the lab at the University of Sydney
Below left: TDP-43 (brown) in the motor neurons of a patient with MND
Below right: Dr Rachel Tan examining a slide of a patient neuron

***"Studying brain tissue from patients with different clinical symptoms and disease trajectories will significantly advance knowledge on the molecular proteins involved in the pathogenesis of MND."* – Dr Rachel Tan**

PROJECT:
Developing a validated C9orf72 mouse model of ALS/FTD using genome editing MND

PROJECT LEAD:
Associate Professor Bradley Turner
The University of Melbourne, VIC

Associate Professor Bradley Turner



Spinal cord of mice carrying the familial MND C9ORF72 mutation

Although defects in the C9orf72 gene are the most common cause of hereditary MND, there is still no effective model available to study this type of MND. Investigators in this project will create a new model that develops symptoms and motor neuron loss mimicking C9orf72-related MND. They will do this using powerful gene modifying technology that causes defects in the C9orf72 gene. The new model of MND will allow investigators to research the cause of C9orf72-related MND and test the effectiveness of drugs with promise for treating this most common genetic form of MND.

KEY HIGHLIGHTS:
This project will address a key gap in the MND research field by developing a new model of MND that mimics the most common genetic cause of MND.

AMOUNT INVESTED BY FIGHTMND IN THIS PROJECT:
$248,787

Q&A:
What problem are you trying to solve with this project?
Despite the discovery of C9ORF72 mutations in MND over a decade ago, it remains unclear exactly how abnormal C9ORF72 triggers MND which has hampered development of treatments. A major gap in our knowledge has been the lack of a robust and reproducible animal model of C9ORF72. This project will overcome this problem by developing a new and rigorously validated C9ORF72 animal model using powerful genetic engineering.

"This model will provide an invaluable resource to the global research community for testing disease hypotheses, pathology and therapeutic agents in the most common genetic form of disease broadly applicable to the MND population."
– Associate Professor Bradley Turner

PROJECT:
New viral-mediated TDP-43 mouse models of MND

PROJECT LEAD:
Dr Adam Walker
The University of Queensland, QLD

A major barrier to developing new, effective treatments for MND is the lack of suitable animal models to test their safety and effectiveness. Animal models are slow and expensive to make, and often do not fully replicate the causes and symptoms of MND in people. This project is using the latest 'viral' technology to create new mouse models of MND that are faster and more cost-effective to generate. The viral technology will be used by investigators to introduce aberrant TDP-43 protein into motor neurons to make them unwell, which is a highly relevant pathology present in 97% of MND cases.

KEY HIGHLIGHTS:
Dr Adam Walker is the inaugural Bill Guest Mid-Career Research Fellow. This project will develop a faster and more cost-effective way to generate mouse models of MND, and provide a new resource that speeds up the testing process for new drugs with the potential to treat MND.

AMOUNT INVESTED BY FIGHTMND IN THIS RESEARCH PROJECT:
$250,000

Q&A:
Why is this important and how will it benefit patients?
New and improved animal models of MND will help us to understand how disease starts and will allow faster testing of new drugs before they are given to people. This project will produce new methods for quicker studies in MND mice, which will mean that new therapies can be moved through the development pipeline faster, so they reach people living with MND as quickly as possible.

***"We aim to create better mouse models of MND that will be faster and easier to use."* – Dr Adam Walker**

Above: Dr Adam Walker | Below: PhD student Elise Kellett and Research Assistant Juliana Venturato analysing data in Dr Walker's lab

9. DISEASE MODELS/DRUG DELIVERY

PROJECT:
Development of a human MND Neurovascular Unit model to improve therapeutic translation in drug testing.

PROJECT LEAD:
Associate Professor Anthony White
QIMR Berghofer Medical Research Institute, QLD

While the blood-brain barrier provides a protective lining between the blood and brain, it also prevents the entry of many drugs into the brain. Because of this, the blood-brain barrier is one of the greatest impediments to drug development for MND. It is also a major reason why many MND clinical trials have been unsuccessful. In this project, investigators seek to develop and test an advanced model of the human blood-brain barrier by recreating its complex structure and mix of cell types. The new model will be used as a tool to accurately screen if promising new drugs with the potential to treat MND are able to pass through the blood-brain barrier and reach intended targets in the brain.

KEY HIGHLIGHTS:
This project aims to develop an advanced model of the human blood-brain barrier. The new model will improve clinical translation by accurately screening if drugs with therapeutic potential for MND are able to access and act on intended targets in the brain.

AMOUNT INVESTED BY FIGHTMND IN THIS PROJECT:
$249,785

Q&A:
Why is this important and how will it benefit patients?
The cell model we are building will be a major advance in providing a suitable tool for identification of new therapeutic approaches for MND, including drug repositioning, with greatly improved potential for clinical translation compared to current blood-brain barrier model systems.

Above: Associate Professor Anthony White | Below: PhD student Joanna Wasielewska and Associate Professor Tony White

"We hope to show that our novel cell model can show which drugs are most likely to enter the brain and spinal cord of people with MND and reach their target cells." – Associate Professor Anthony White

10. DISEASE HETEROGENEITY/ DISEASE BIOMARKERS

PROJECT:
Profiling monocytes in MND to assess disease progression and heterogeneity

PROJECT LEAD:
Professor Trent Woodruff
The University of Queensland, QLD

MND affects people differently. The age of onset, rate of progression and location where MND begins can vary, making the disease difficult to diagnose and treat. People living with MND also have high numbers of immune cells in their blood and their body's defence mechanism (called inflammation) is highly active. The research team will build a profile of the molecular properties of immune cells in the blood of MND patients. They will link individual immune molecules identified to distinct clinical features of MND, with the aim of developing a novel blood test capable of detecting the type of MND a person has, and identifying the optimal treatment for each individual.

KEY HIGHLIGHTS:
This project aims to develop a blood test that can detect inflammatory molecules in individuals with MND, identify the type of MND they have, and predict the optimal treatment for them.

AMOUNT INVESTED BY FIGHTMND IN THIS RESEARCH PROJECT:
$249,864

Q&A:
Why is this important and how will it benefit patients?
If our research is successful, we will identify a method that could be utilised in future clinical trials in patients with MND. This will be particularly useful for drugs that target the immune system or neuroinflammation, which is an emerging area of focus for the pharmaceutical industry.

Left: Professor Trent Woodruff | Right: Professor Trent Woodruff and Dr Jenny Fung preparing to analyse blood samples obtained from MND patients

"What excites us about this project is the potential to identify an inflammatory biomarker 'signature' from blood samples obtained from patients with MND." – Professor Trent Woodruff

Mid-Career Research Fellowships

FightMND Mid-Career Research Fellowships encourage outstanding researchers to choose or to continue to focus on MND as their primary area of research. The 4-year fellowship provides the opportunity for mid-career researchers to strengthen their research team and independent programs, build collaborations and embed themselves as key players in the MND research sector. The fellowship's research program is focused on causes of MND and elucidating disease mechanisms, with the ultimate goal of developing more effective treatments, and a cure, for MND.

Research Assistant Juliana Venturato performing experiments in Dr Walker's lab

FIGHT MND.

1. BILL GUEST MID-CAREER RESEARCH FELLOWSHIP

The Bill Guest Mid-Career Research Fellowship is named in recognition of the extraordinary contribution of Bill Guest AM, the inaugural Chairman at FightMND

PROJECT:
Clearing TDP-43 pathology for MND therapy

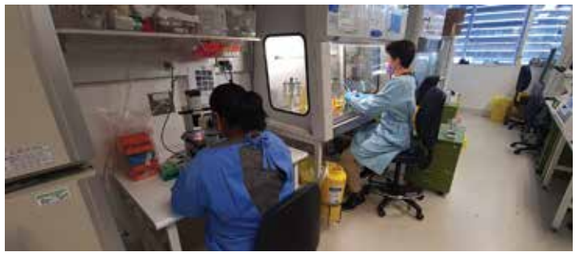
PROJECT LEAD:
Dr Adam Walker – Bill Guest Mid-Career Research Fellow The University of Queensland, QLD

TDP-43 protein is essential for keeping motor neurons healthy. However, in 97% of MND cases, TDP-43 protein becomes harmful to motor neurons by changing its structure and sticking together, causing them to progressively die. The aim of this fellowship is to use a wide variety of advanced cell and animal techniques to study why TDP-43 protein changes and clumps together and why this leads to motor neuron death. Projects will also examine how cellular pathways in motor neurons can be manipulated to prevent their death, and slow or halt MND progression.

KEY HIGHLIGHTS:
Dr Adam Walker was awarded the Bill Guest Mid-Career Research Fellow in 2022, named in honour of inaugural FightMND board chairman Bill Guest AM. Dr Walker will lead a team to study several facets of TDP-43 pathology in MND to uncover new treatment strategies.

AMOUNT INVESTED BY FIGHTMND IN THIS BILL GUEST MID-CAREER RESEARCH FELLOWSHIP:
$680,000

Q&A:
Why is this important and how will it benefit patients?
This project will allow us find ways to apply our knowledge of how problems with the TDP-43 protein cause nerves to die, to identifying the most promising strategy to stop that in people living with MND. By understanding the disease mechanisms and testing which genes and proteins can protect nerves, we will be able to design new therapies for MND in the future.



Above: Dr Adam Walker | Below: Senior Research Assistant Dr Purba Nag and PhD student Sean Keating in Dr Walker's lab

***"I'm excited to see our basic science research now moving closer towards finding ways that we can apply new knowledge to helping people with MND."* – Dr Adam Walker**

2. MID-CAREER RESEARCH FELLOWSHIP

PROJECT:
Reversing TDP-43 pathology and neuronal loss in sporadic MND

PROJECT LEAD:
Dr Rachel Tan
The University of Sydney, NSW

***"This project in a large cohort of patients with different disease presentations and trajectories will enable us to uncover significant insights into the pathobiological underpinnings that give rise to sporadic MND."* – Dr Rachel Tan**

Above: Dr Rachel Tan | Below: Dr Rachel Tan analysing staining data from patient motor neurons

Although misbehaving TDP-43 protein occurs in almost all MND cases, there are additional related proteins in motor neurons that may also contribute to the disease, and to MND's high variability. During this fellowship Dr Tan will study the expression of these proteins in brain tissue from a large group of MND patients who were followed clinically over the course of their disease. The study aims to establish if relationships exist between these proteins and the age of MND onset, speed of disease progression, and the length of disease. The study will advance current knowledge on the molecular proteins involved in MND pathology. It may also uncover new cellular targets and molecular pathways with the potential to overcome these pathologies and fast-track the development of successful drug interventions for MND.

KEY HIGHLIGHTS:
This study is examining the expression of MND-related proteins in brains from a large group of MND patients who were clinically followed over the course of disease. Dr Tan is a first-time recipient of research funding from FightMND. This 4-year Mid-Career Fellowship will help strengthen Dr Tan's independent research programs and research team.

AMOUNT INVESTED BY FIGHTMND IN THIS MID-CAREER RESEARCH FELLOWSHIP:
$679,970

Q&A:
Why is this important and how will it benefit patients?
A better understanding of the underlying disease pathogenesis is needed to accelerate the discovery of successful disease-modifying treatments for patients and their families.

Early-Career Research Fellowships

FightMND Early-Career Research Fellowships encourage researchers with outstanding ability to focus on MND as their primary area of research. The 4-year fellowship provides the opportunity for early-career researchers to establish their own independent research programs, build collaborations and further themselves as an MND researcher.
The fellowship's research program is focused on causes of MND and elucidating disease mechanisms, with the ultimate goal of developing more effective treatments, and a cure, for MND.

FIGHT MND.

1. PROJECT:
Therapeutic targeting of ferroptotic cell death in MND

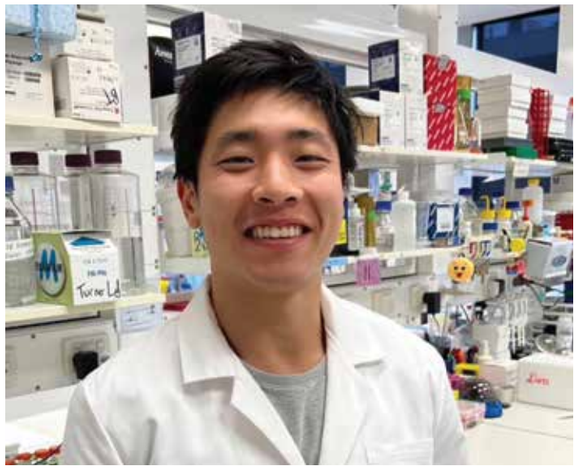
PROJECT LEAD:
Dr Taide Wang
The University of Melbourne, VIC

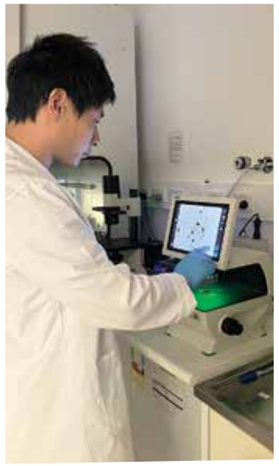
Only recently, a unique cellular pathway that regulates the life of a cell, called ferroptosis, was found to be involved in instructing motor neurons to die. The aim of this fellowship is to investigate if modulating the ferroptosis pathway has therapeutic potential for MND. Investigators in Dr Wang's team aim to block ferroptosis in MND models using genetic tools and drugs that specifically target aspects of this pathway. They will assess how effectively their agents block ferroptosis, and whether they can delay the onset and progression of MND-like symptoms and pathology. Successful outcomes will provide a strong case for progressing agents that modulate the ferroptosis pathway through the pipeline towards clinical trials for MND.

KEY HIGHLIGHTS:
Dr Wang was the inaugural recipient of the Angie Cunningham PhD Scholarship and Grant in Aid in 2019. This study is exploring a novel mechanism and cause of MND and may uncover new agents with promise for treating MND.

AMOUNT INVESTED BY FIGHTMND IN THIS EARLY-CAREER RESEARCH FELLOWSHIP:
$573,366

Q&A:
Why is this important and how will it benefit patients?
So far, there is no effective treatment for MND. This study will lead to a greater understanding of how motor neurons are lost in ALS. In addition, our selenocompound study may also provide effective and non-invasive suitable drug candidates for clinical testing.





Left: Dr Taide Wang | Right: Dr Taide Wang using the microscope to observe motor neurons in spinal cord

***"The most exciting part of the study lies in the fact that the compounds are safe and orally bio-available. Thus, they may be an effective yet non-invasive therapeutic strategy for treating MND."* – Dr Taide Wang**

FIGHT MND.

International Fellowships

FightMND has partnered with the Sean M. Healey & AMG Center for ALS and ALS finding a Cure® to support young researchers researching new treatments for people living with MND in the ALS Scholars in Therapeutics program. The international 2-year program is designed to engage physician-scientists and post-doctoral fellows to gain training and experience in therapy development for MND with a unique opportunity to gain industry experience in year two. By engaging motivated and creative individuals with a passion for bringing treatments to people living with MND, we are expanding the community of experts and expediting therapy development.

1. PROJECT:
Microtubule-targeting agents and uORF ASOs to target NEK1 loss of function in MND

PROJECT LEAD:
Dr Jacob (Jake) Mann
Northwestern University, USA

Jake earned his PhD in Neurobiology at the University of Pittsburgh under the mentorship of Dr. Christopher Donnelly, where he studied the role of RNA in the regulation of the build-up of waste proteins (protein aggregates) of MND-linked proteins like TDP-43 and FUS.

Dr. Mann is pursuing postdoctoral training in Dr. Evangelos Kiskinis' lab at Northwestern University Feinberg School of Medicine. There, he has helped to discover a function for MND-linked gene NEK1 in the maintenance of microtubules, the major component of a cells "skeleton" that are involved in internal transport systems within the cell, in human motor neurons in the dish. His research focuses on understanding how mutations in the MND gene NEK1 can cause it to stop functioning properly and contribute to MND pathology. Jake hopes to continue to work to uncover the mechanisms underlying newly discovered genetic forms of MND, such as NEK1, to discover new ways to tackle these genetic disorders in a patient-specific manner.

2. PROJECT:
microRNAs as Novel Regulators of Differential Motor Neuron Susceptibility

PROJECT LEAD:
Dr Dylan Galloway
Washington University, USA

Dylan Galloway, PhD is recognized for his research in identifying that microRNAs, a family of molecules that helps cells control the kinds and amounts of proteins they make, can regulate the susceptibility of a motor neuron in MND. He earned his PhD in Neuroscience at the Memorial University of Newfoundland where he researched how microRNAs modify inflammation in the brain and brain repair in multiple sclerosis.

Dr. Galloway is currently pursuing postdoctoral training at Washington University in St. Louis with Dr. Timothy Miller. Dylan aims to gain novel experience investigating neurodegeneration and RNA biology using laboratory models of neurodegeneration, as well as mastering cutting-edge molecular biology techniques to investigate and therapeutically target RNA. With this, he hopes to define regulators of neurodegeneration, including microRNAs, with the intent of developing novel RNA-targeting therapeutics.

3. PROJECT:
Neuromuscular Junction: a promising starting point in the identification of ALS biomarkers

PROJECT LEAD:
Dr Roberta Piovesana
University of Montreal, Canada

Roberta earned her Master's in Medical Biotechnology and later PhD in Cellular and Developmental Biology at the Sapienza, University of Rome, where she established stem cell models of a type of cell called a Schwann cell, investigating how they support branches of nerve cells and how Schwann cells adapt when nerves are damaged.

Dr. Piovesana, a postdoctoral fellow in Dr. Richard Robitaille's laboratory at the Université de Montréal, is researching the Neuromuscular Junction (NMJ) – where nerve cells meet the muscle. Roberta is investigating how proteins called endocannabinoid CB1 receptors regulate the loss of nerve cells and how these proteins help nerve cells reconnect with muscle following injury. Roberta hopes a better understanding of how NMJ proteins change in MND, will identify new biomarkers to facilitate earlier diagnosis and improve therapeutic strategies for MND.