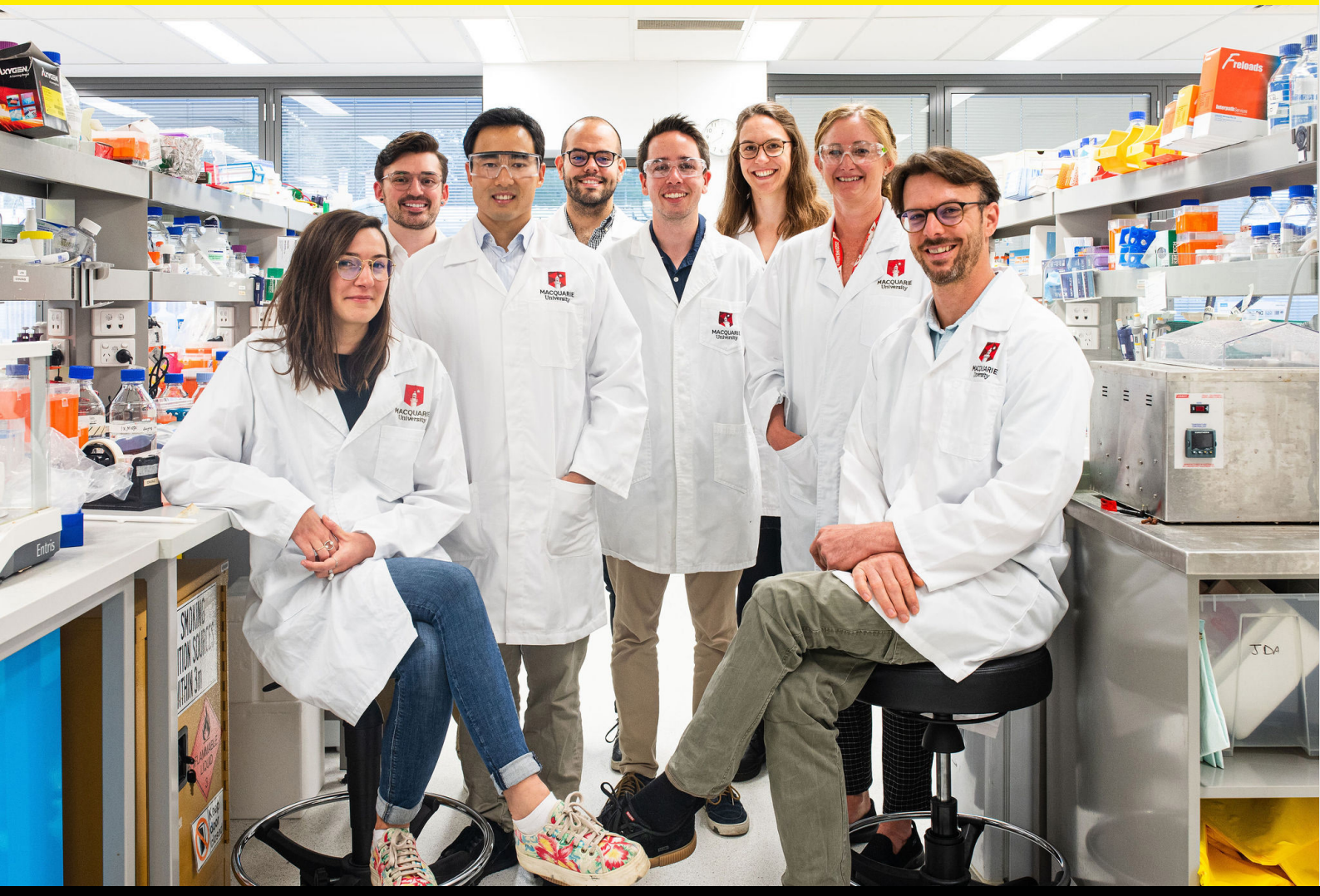
FIGHT MND.

FightMND Cure Research Grants 2021



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Clinical Trials

Test promising new drugs, or drugs already approved for other diseases or conditions in people 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.

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Project

Phase 1b – Ephrin receptor A4-Fc (new drug)

This clinical trial will investigate the safety and preliminary effectiveness of the newly developed drug mEphA4-Fc in MND patients. After showing the potential for mEphA4-Fc to delay MND disease progression and improve communication between motor neurons in preclinical studies, researchers will now confirm if this drug is safe to use in people living with MND. The phase 1b trial aims to enrol 8 patients at the Royal Brisbane and Women's hospital.

Project Lead

Prof Perry Bartlett, AO

The University of Queensland, QLD

Prof Perry Bartlett says that the discovery that has had the most impact in his career *"was the 1992 finding that the mature brain contains stem cells capable of producing new neurons."*

This opened a new horizon *"where repair and recovery of function may be possible in humans."*

Prof Bartlett says that this was further clarified when stem cells were able to be isolated in 2011 and that *"subsequent studies have [since] unravelled the role that the production of new neurons play in functions like learning and memory."*

Prof Bartlett and his colleague Emeritus Professor Andrew Boyd discovered that the ephrin receptor A4 (EphA4) was vital for motor neuron development in 1996. Subsequently they *"demonstrated that blocking its action was important in repair of motor neurons following spinal cord injuries".*

Blocking the EphA4 in MND

With this in mind, Professors Bartlett and Boyd surmised that EphA4 would have an impact on motor neurons in MND. Further studies, completed by themselves, and others, were able to demonstrate that blocking the EphA4 action would indeed be beneficial to the survival of motor neurons for those living with MND.

The molecule developed (which has been granted a patent in the USA) by Prof Bartlett and his team *"is unique in that through competitive binding it can block the action of EphA4 for a prolonged period of time, making it suitable for weekly injection into MND patients."*

The Phase 1a trial, also supported by FightMND, is now nearing its final phase and the molecule has proven to be safe and well tolerated. The funds provided by FightMND will allow for extension of the trial for an additional six months, allowing the correct dosage to be determined and further safety and tolerability to be examined.

"We will use a variety of biomarkers and clinical observations to examine whether the treatment has provided some early signs of effectiveness," said Prof Bartlett.

Data collated from the observations will allow for subsequent trials aimed at the therapeutic treatment of MND.

"Since our studies have shown that EphA4's action is to damage motor neurons directly, we would expect, like our animal studies, that blocking this action with EphA4-Fc would result in significant preservation of motor neurons, improve connectivity, and ameliorate the disease process significantly," he adds.

An award for service

Prof Bartlett was awarded an Officer of the Order of Australia in 2020, recognising his distinguished service to neuroscience research. He says the award not only recognises his laboratory's work on understanding brain function, *"but also, and more importantly, the service to the community's well-being through the establishment and output of a world leading research Institute."*

FightMND has invested $1M in this clinical trial. FightMND has provided funding to this project in previous grant rounds: $1M in 2017, and $1M in 2018.

About Prof Perry Bartlett, AO

Prof Perry Bartlett, AO completed his PhD at The University of Melbourne before commencing postdoctoral work at John Hopkins University in Baltimore, USA and The University College in London, UK. He returned to the Walter and Eliza Institute of Medical Research in 1978 where he set up the first Neuroimmunology Laboratory and later led the Development and Neurobiology Division. In 2002, he moved to The University of Queensland to establish the Queensland Brain Institute as its Founding Director.

Prof Bartlett is now the Emeritus Professor of Molecular Neuroscience at The University of Queensland. He has been a Senior Principal Research Fellow of the NHMRC and an ARC Federation Fellow.

In 2020, Prof Bartlett was awarded an Officer of the Order of Australia in recognition of his distinguished service to neuroscience research.

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Drug Development Grants

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

"ALS/MND is a war and there are many battles to fight ahead. In the end, we want complete and unmitigated surrender and we all have a part to play."

Dr John Ravits

University of California – San Diego, USA


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Project

Targeting misfolded proteins with MisfoldUbLs as a therapeutic strategy for MND

In hereditary MND caused by mutations in the SOD1 gene, a damaged or 'misfolded' protein called SOD1 sticks together in motor neurons and contributes to their death. Investigators have designed an exciting new genetic tool that selectively recognises the misfolded SOD1 protein and removes it from motor neurons, without affecting normal SOD1 protein needed for neurons to function normally. This preclinical study examines if this new genetic tool can delay the onset and progression of MND.

Successful outcomes will provide a platform to advance this genetic tool for testing in a future clinical trial for MND.

Project Lead

Prof Justin Yerbury

University of Wollongong, NSW

Prof Justin Yerbury first heard about MND 25 years ago when his uncle, cousin and mother were diagnosed with MND in quick succession. He says *"it was clear at the time that there was not enough understanding of the molecular basis of the disease to develop an effective therapeutic."*

Prof Yerbury took this as a challenge and has dedicated his career to increasing the understanding of the origins of MND.

Prof Yerbury was diagnosed with MND in 2016.

Proud moments

Prof Yerbury says it is *"all the hard work and determination of all of the staff and students that have been a part of the lab over the past decade"* that makes him proud.

"If I had to choose [one piece of research], I am particularly proud of our early work on the prion like nature [of MND] and how that might explain the ordered progression of MND," he says.

What makes this research different?

Prof Yerbury says his research differs from other genetic drugs in that *"one of the current leading ALS (MND) therapeutic strategies (in phase 3 trials) is to knock down SOD1 levels using RNAi or antisense oligonucleotides. This approach indiscriminately knocks down all forms of SOD1, both the wild-type (natural) form and the mutant dysfunctional and harmful form."*

"However, the long-term knock-down of natural SOD1 has been shown to contribute to sarcopenia [muscle loss] and hepatocarcinoma [liver cancer]."

"Similarly, the generalised knock down of all forms of other MND-related proteins such as TDP-43 also appears to be detrimental," he adds.

The priority for this research project is to be able to selectively remove mutant misfolded pathogenic forms of SOD1 protein but spare the properly folded natural protein.

Prof Yerbury's team has identified an approach to remove only the misfolded form of the protein which it is hoped will reduce the pathological accumulation of the misfolded SOD1 protein in motor neurons, providing a promising therapeutic solution.

This *"would represent a better therapeutic approach and is urgently required,"* Prof Yerbury says.

FightMND has invested $921,360 in this research.

About Professor Justin Yerbury

At the age of 25 (1999) Prof Justin Yerbury enrolled in an undergraduate science degree completing it with first class honours in 2004. He then undertook a PhD with Prof Mark Wilson on extracellular chaperones before being awarded an international ARC fellowship to do post-doctoral studies with Prof Christopher Dobson at the University of Cambridge, UK, where he studied the biochemical analysis of protein aggregates.

In 2009 Prof Yerbury was awarded the Bill Gole MND Fellowship to train with Prof Iain Campbell in neuroinflammation. In 2012 he was awarded an ARC DECRA Fellowship to build his group around proteostasis defects in ALS (MND) and in 2015 was awarded an NHMRC CDF to continue research in this area.

Ten years after graduating with a PhD, Prof Yerbury was promoted to Professor in recognition of his contributions to the fields of proteostasis and MND.

Prof Yerbury currently works at the Illawarra Health and Medical Research Institute at the University of Wollongong.

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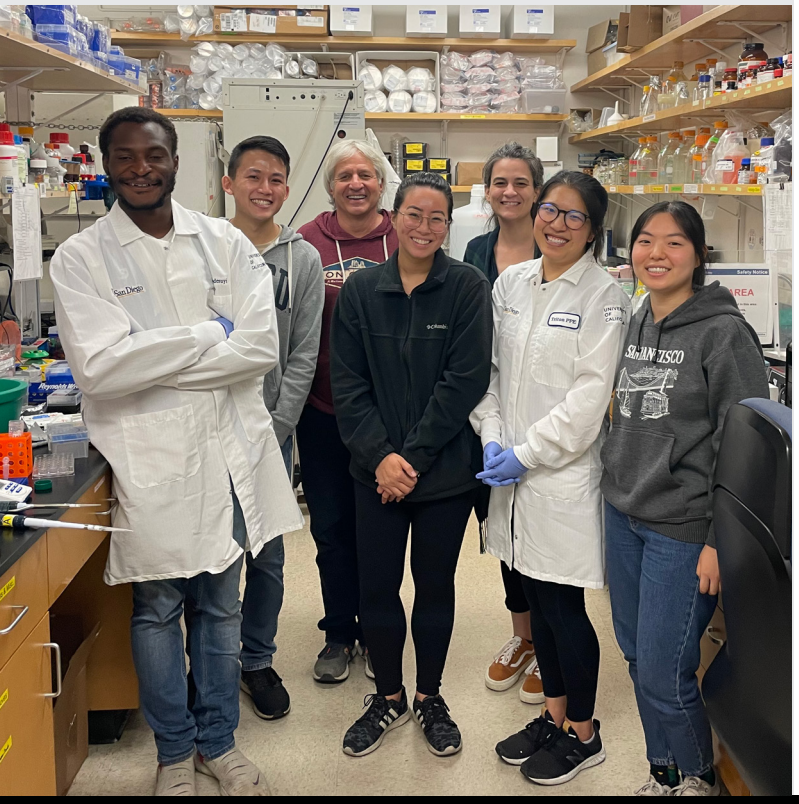
Project

Targeting CK1ε-mediated TDP-43 Phosphorylation in MND

TDP-43 is an important molecule in cells that has many functions. In almost all cases of MND, TDP-43 misbehaves by changing its structure and forming clumps in motor neurons. This preclinical study will determine if this structural change in TDP-43 is harmful or protective to motor neurons. Investigators will target a pathway called CK1ε, that causes the structural change in TDP-43. They will examine if blocking the function of CK1ε with a drug prevents the structural change to TDP-43, and delays the onset and progression of MND. Successful outcomes will help advance the drug towards phase 1 clinical trials for MND.



Project Lead

Dr John Ravits

University of California – San Diego, USA

Dr John Ravits began his MND journey with pure clinical observations of disease onset and progression. With this as a basis, he *"formulated a model of disease progression based on focal onset and neuroanatomical spread of pathobiological factor(s)."*

He has created a *"biorepository of patient nervous systems with high molecular quality and used this as the basis to study and explore molecular neuropathology by genomic profiling of laser captured motor neurons."*

This enabled Dr Ravits to pursue research in a number of areas to better understand ALS/MND pathobiology and identify targets for the therapy he is studying in his basic science laboratory *"by way of molecular neuropathology, cellular and mouse models."*

He believes ALS provides a *"unique window and special opportunity to unravel its pathobiology especially through neuropathology and genomics and validation in various disease models."*

A disease that spreads

ALS/MND is often described as a disease of upper and lower motor neurons and Dr Ravits believes it is also a spreading disease. This means that *"whatever is causing MND, it is not just a disease in which neurons degenerate over time, but also a disease that spreads over space in the brain and spinal cord."*

By acquiring optimal human tissues to be studied, the hope is that the root causes of MND can be unravelled.

Perfect timing

Dr Ravits says that the funding from FightMND *"comes at a perfect time for me to carry out experiments that have been maturing for nearly two years."*

His identification of CK1ε and its role in TDP-43 phosphorylation was published in 2018 and his lab immediately began to pursue this in cellular and mouse models. They have established the unique role of CK1ε as the principal driver of TDP-43 phosphorylation in cellular models.

He says that *"this supported that it was important but didn't answer whether or not it was a driver of toxicity or a reactive defence mechanism."*

"To study this, we turned to a mouse model with inducible mislocalisation of TDP-43 and to a CK1ε knockout mouse model. These mouse models seemed best able to test the role of CK1ε mediated TDP-43 phosphorylation, but necessarily through very complicated breeding schemes, that have taken two years with very limited funding."

"We now have the mice and [have] shown that these experiments are feasible and are poised to carry out these very elaborate experiments," he says.

The FightMND funding will allow his lab to continue to expand the scope of their studies without compromise.

Available drugs

"Interestingly, during this time, the drugs that inhibit CK1ε have been acquired by a large pharmaceutical company who have a major commitment to ALS/MND therapeutics and with whom I have worked closely in developing gene therapies, so I have an audience if I can establish proof-of-principle of the value of this target," he says.

"The fact that the drugs have been developed already is exciting. While they don't yet have an application, their availability allows me to test if these ideas are right, meaning establishing proof-of-principle," he says.

"Thanks to the FightMND funding, I can now carry this forward, with the confidence that if this target is worthy, then the complicated task of phase 1-3 testing and further drug development can proceed with the key experts and partners."

Of the fight against the 'Beast', Dr Ravits says

"ALS/MND is a war and there are many battles to fight ahead. In the end, we want complete and unmitigated surrender and we all have a part to play."

FightMND has invested $986,282 in this research.

About Dr John Ravits

Dr John Ravits is a physician-scientist in the Department of Neurosciences, University of California, San Diego (UCSD), USA. UCSD provides exciting team-oriented neurosciences and medical environments for the full range of my activities.

Dr Ravits' work is divided into three parts: research lab, translational research and clinical program. In his research laboratory, work is focused on mechanisms of motor neuron degeneration and molecular neuropathology. He has used genomic profiling of laser captured motor neurons in patient spinal cords to identify new pathways and targets for therapy. In his clinical programs, he leads a multidisciplinary team in a nationally certified ALS/MND Centre of Excellence, which provides full spectrum clinical care for a panel of 150-200 patients.

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Project

Developing a monoclonal antibody modulating CD38 against MND

This project will perform preclinical safety tests needed to advance a drug called NC-B8 toward a clinical trial for MND patients. Investigators have demonstrated that targeting a molecule located on motor neurons and their supporting cells with NC-B8 may benefit MND in three ways: 1) removing harmful built-up protein clumps in motor neurons; 2) restoring motor neuron activity; and 3) reducing the immune response linked to MND.

A positive outcome for this study will be to obtain all data needed to transition NC-B8 to a phase 1 clinical trial for people living with MND in 2023.

About ENCEFA

ENCEFA is a biotechnology company with laboratories located in Maisons-Alfort (2 miles south of Paris), in the neuromuscular diseases building at the National French Veterinary school.

It was co-founded in 2016 by Dr Laurence Bressac (CEO), Dr Serge Guerreiro (CTO) and Dr Toulorge (CSO) with the ambition of developing therapies to fight neurodegenerative diseases, including MND. The foundation of the lab was to transform in vitro discoveries (made with Dr Serge Guerreiro while Dr Toulorge was completing his PhD) into a product that could provide benefit to patients and improve their quality of life.

The first years at ENCEFA have been dedicated to obtaining a better understanding of the mechanism of action in vitro and in vivo, and then to identify a product able to trigger the identified mechanism of action. This led to the discovery of NC-B8, the lead, humanized anti-CD38 monoclonal antibody, which is now 18 months away from clinical development.

Project Lead

Dr Damien Toulorge

ENCEFA, France

When Dr Damien Toulorge and his team identified a new neuroprotective mechanism of action that demonstrated efficacy in experimental models of MND, Parkinson's disease, and Multiple sclerosis, they were at first *"disease agnostic"*.

However, when they observed that in addition to protecting neurons, their compound was also able to protect muscle cells and repress inflammation (thus act simultaneously on all the organs impacted by MND), they realised they had discovered something unique. The decision was made to focus their research primarily on MND, where their drug, NC-B8, has the potential to be game-changing.

NC-B8 compared to other MND drugs

Dr Toulorge says that in conducting their research, at first they obtained proof-of-concept of efficacy in neurons that were not motor neurons.

"Our strategy was to demonstrate that our lead product, NC-B8, is able to protect all neurons from degeneration, including motor neurons. So we first tested its effect in vitro [in cells] using mouse motor neurons," he says.

They discovered that NC-B8 was neuroprotective and the results were better than the impact of using riluzole or edaravone [existing MND drugs].

Following this initial discovery, the team tested whether NC-B8 could prevent neuronal cell death induced by Cerebrospinal fluid (CSF) taken from a person with MND, and the result was positive again. NC-B8 was also found to protect human motor neurons in cells (grown in the dish) from both healthy patients and MND patients.

When the team tested NC-B8 in vivo [inside a whole organism] of the SOD1 mouse model of MND, they observed that NC-B8 improved body weight, motor function and increased survival by simultaneously protecting neurons and muscle cells while repressing neuro-inflammation.

They also observed that NC-B8 treatment protected neurons and muscles from degeneration in canine degenerative myelopathy-diagnosed dogs, which is a canine disease very similar to MND. It is their goal now to demonstrate that NC-B8 has the same effect in humans.

Demonstrated efficacy

"What excites me the most about the antibody we are developing is that it demonstrated extraordinary efficacy. So far, whatever the neurodegeneration model we tested (MND, Parkinson's disease, Multiple sclerosis, Alzheimer's disease), whatever the stress that was faced by the neuron, whatever the species affected (mouse or dogs), it always demonstrated efficacy," said Dr Toulorge.

Dr Toulorge says that support *"from FightMND will enable us to perform regulatory toxicology studies that are required to begin NC-B8 clinical development."*

It *"will directly impact our ability to test NC-B8 in ALS (MND) patients. But more than that, we are now part of the FightMND army, which will give us additional strength to tackle MND,"* he adds.

FightMND has invested $970,000 in this research.

About Dr Damien Toulorge

Dr Damien Toulorge earned a PhD in Neurosciences in 2016 from the Université Pierre et Marie Curie, studying at La Pitié Salpetrière Hospital at the Paris Brain Institute. The hospital is known as the home of modern neurology, largely due to Dr Charcot, who practiced at the hospital and in 1865 was the first person to diagnose ALS (MND).

While studying for his PhD, Dr Toulorge worked on the neurodegenerative mechanisms at play in Parkinson's disease and tried to find new neuroprotective strategies. Following completion of his PhD, he worked as a scientific consultant and then as project manager at Pharnext, a French biotech developing compounds against neurodegenerative diseases, including MND.

In 2015 Dr Toulorge co-founded ENCEFA to pursue the development of therapeutics based on a new neuroprotective pathway that was discovered during his PhD studies.

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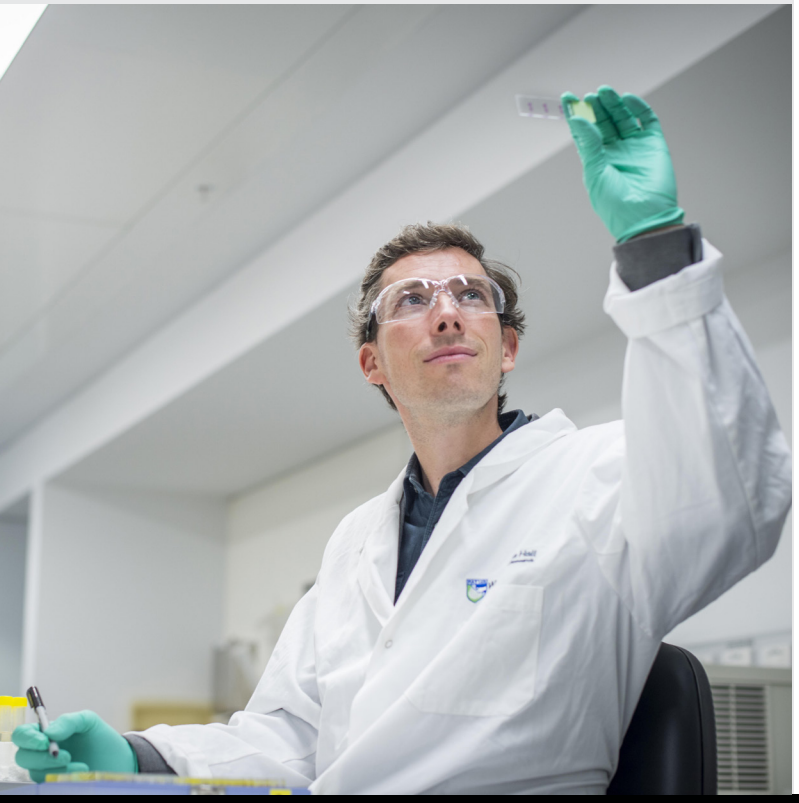
Project

Preventing neuroinflammation in MND by inhibiting the mPTP

Investigators in this study have identified that an immune response occurring before the onset of MND is triggered when the powerhouse of a motor neuron, known as mitochondria, is damaged and leaks genetic material through a channel called the mPTP.

This project will find out if drugs that block the mPTP channel and stop the genetic material from leaking, can reduce the immune response and be used to prevent or slow down the progression of MND.



Project Lead

A/Prof Seth Masters

The Walter and Eliza Hall Institute, Vic

When asked about his favourite research project to date, A/Prof Masters says that working with several families with autoinflammatory disease to understand the characterisation of a novel genetic condition known as PAAND, is at the top of his list. That project was instrumental in leading to the creation of relevant therapeutic options for people with the condition.

Inflammation and MND

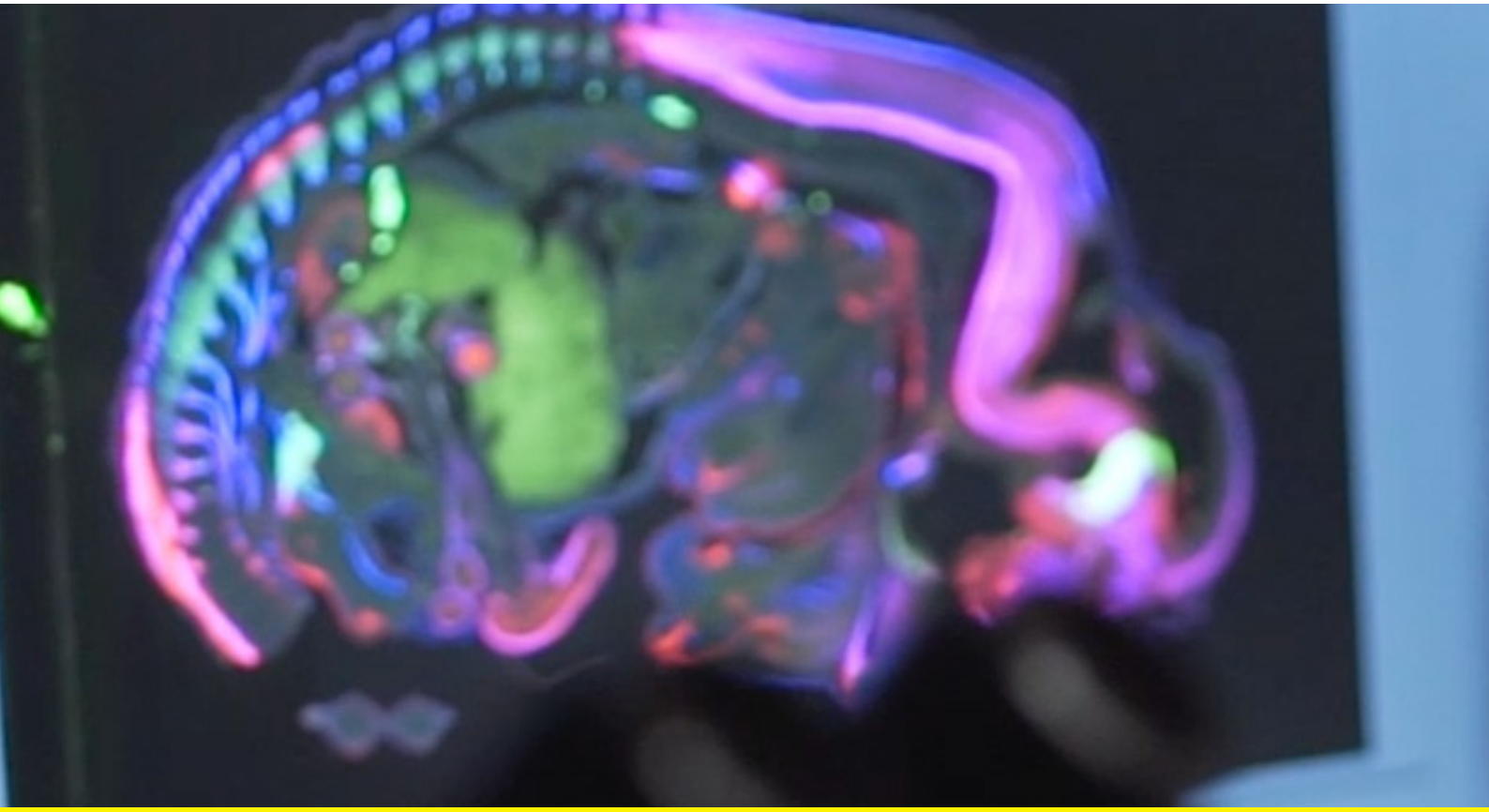
That research also has potential implications for MND. Genetic insights from inflammatory conditions are being used as the basis to show how the same pathways (mPTP) are pathogenic in complex diseases including neurodegenerative diseases.

Prof Masters says that his team has "found activation of a specific inflammatory pathway in MND, which usually recognises DNA viruses. However, in this case it was activated by the cells own DNA leaking out of the mPTP, which are small pores present in mitochondria."

"Targeting inflammation…[via] this pathway, and the mPTP specifically, is a new way to prevent disease progression," says A/Prof Masters.

When asked how the funding from FightMND will impact his work and the lives of people living with MND, Prof Masters points to "the opportunity to speed up the progress of getting molecules into the clinic to target the mPTP and block inflammation in MND."

FightMND has invested $999,718 in this research.



About A/Prof Seth Masters

A protein biochemist by training, A/Prof Seth Masters completed his PhD at The Walter and Eliza Hall Institute followed by two postdoctoral posts, one at the National Institute of Health (USA) and one at Trinity College Dublin (Ireland). He is now a researcher at the Walter and Eliza Hall Institute in Melbourne.

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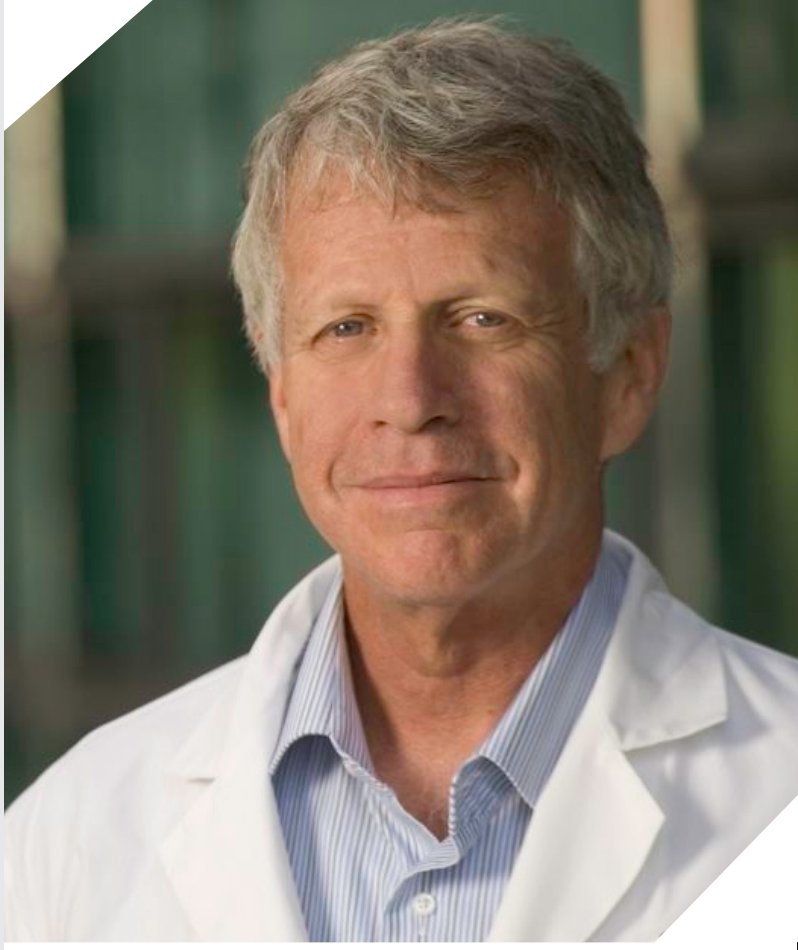
Project

Alpha 5 Beta 1 Integrin as a potential treatment for MND

Research has shown that an immune response contributes to motor neuron death and the onset of MND. Investigators in this project will examine if drugs, called alpha 5 beta 1 integrins, can silence the activity of key players in this immune response – macrophages in the body, and microglia in the brain and nervous system – and delay the progression of MND.

A positive outcome for this study will be to identify the safest and most effective alpha 5 beta 1 integrin candidate to transition to a phase 1 clinical trial for MND patients.

"Hopefully anti-alpha 5 integrin will be transformative in MND, much like anti-alpha 4 integrin antibody (Natalizumab) has been a potent and effective therapy in Multiple sclerosis."



Project Lead

Prof Lawrence Steinman

Stanford University, USA

Prof Lawrence Steinmen says that seeing patients with MND in his work as a neurologist encouraged him to want to create new and effective therapies for people living with this disease.

His research into MND is an extension of his lab's co-discovery of the first monoclonal antibody treatment for Multiple sclerosis in 1992. The discovery of this integrin, alpha 4, assisted with the development of the monoclonal antibody treatment for Multiple sclerosis.

Anti-integrin therapy and MND

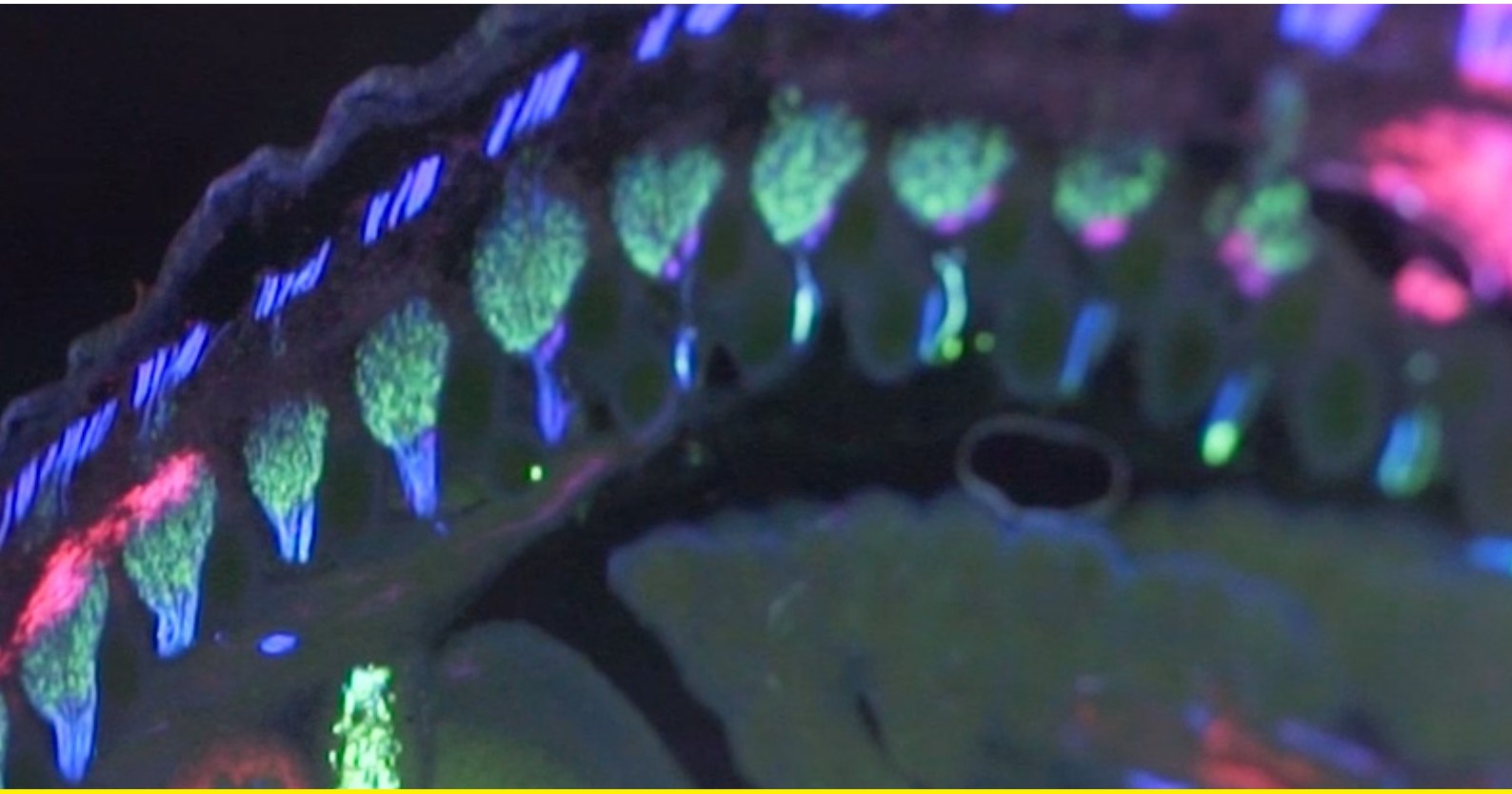
Prof Steinman has spent the past three decades extending the anti-integrin therapy to MND, and an alternative integrin, alpha 5 beta 1, may prove to play a key role when developing treatments for people living with MND.

"In animal models of MND, alpha 5 integrin increases survival and motor function and we are determined to take this potential therapy onward to a clinical trial," says Prof Steinman.

"The results thus far are encouraging... and the human studies show that the target is only in the motor areas of the central nervous system, and not in the sensory regions," he adds.

Prof Steinman says that FightMND's support *"will enable us to complete detailed studies on the role of alpha 5 integrin in ALS (MND). Hopefully anti-alpha 5 integrin will be transformative in MND, much like the anti-alpha 4 integrin antibody (Natalizumab) has been a potent and effective therapy in Multiple sclerosis."*

FightMND has invested $967,010 in this research.



About Prof Lawrence Steinman

Prof Lawrence Steinman is a Professor of Neurology and Neurological Sciences and Paediatrics at Stanford University. He practices neurology and has run an active research lab at Stanford for the past 41 years. His lab co-discovered the first monoclonal antibody treatment for Multiple sclerosis, Natalizumab in 1992.

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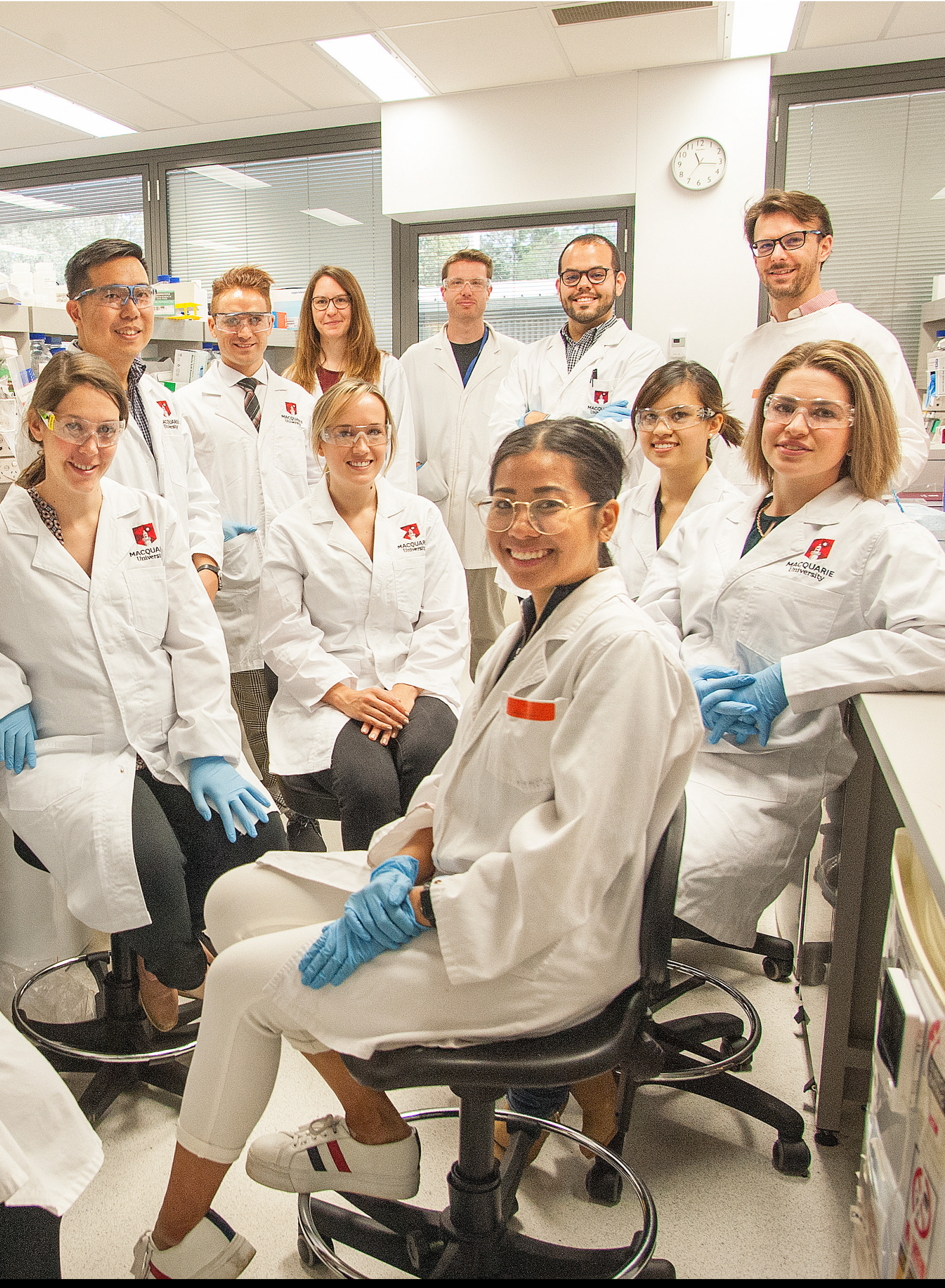
Impact Grants

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


MACQUARIE
University

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Project

Disease biomarkers

Generating a proteomics-based biomarker for MND

Currently, there is no marker that can accurately diagnose or define MND. This project aims to overcome this barrier by creating a specific profile for MND using patient blood samples and clinical data. Investigators will measure protein levels in blood samples and identify those linked to the onset and progression of MND.

This project is co-funded by FightMND and the MND and Me Foundation in Queensland. Together they have invested $250,000 in this research.

"I saw firsthand the devastation this disease causes for both the patient and their family and friends."

Project Lead

Dr Allan McRae

The University of Queensland, QLD

Dr Allan McRae was already collaborating with researchers in the Sporadic ALS Australia Systems Genomics Consortium (SALSA-SGC) when his mother-in-law was diagnosed with MND.

He says he *"saw firsthand the devastation this disease causes for both the patient and their family and friends"*, something that *"reinforced the need to identify biomarkers to improve the speed of diagnosis, monitor progression, and to identify potential avenues for treatment,"* he said.

Protein levels in blood plasma

Dr McRae's project is working to characterise neurological protein levels measured in blood plasma.

"These proteins are generated in the central nervous system and are presumably released into the blood plasma from neurons that are damaged in MND," he says.

His research hopes to determine if these proteins could serve as biomarkers that contribute to individual disease risk prediction or diagnosis, and ultimately, personalised clinical management.

"Proteins represent the main layer of information transfer from the genome to disease and represent the largest class of drug targets," he says.

"This means that findings from our study of protein differences have strong potential for identifying new biomarkers for disease diagnosis and progression monitoring, as well as identifying possible drug targets," he adds.

How FightMND helps

Dr McRae is a first-time recipient of funding from FightMND and says he was very excited to receive the investment into his research.

"I believe the proteins being investigated in this project have strong potential as MND biomarkers and will enable us to make a substantial contribution to our understanding of disease onset and progression."

Dr McRae also noted that this was the first time his group has received funding to specifically focus on MND and that the funding will firmly establish MND research within his group into the future.

"Without dedicated funding, we would not be able analyse sufficient numbers of samples to draw solid conclusions…samples provided by MND patients are a precious resource, and it would be difficult to justify performing this experiment at a smaller scale," he says.

This grant is awarded in honour of Queensland man Murray Geale (who is currently fighting MND), in recognition of his significant contribution to the MND field through fundraising, raising awareness and participation in research projects and initiatives, including his pivotal role on the inaugural MND Research Summit Committee.

This project is co-funded by FightMND and the MND and Me Foundation in Queensland. Together they have invested $250,000 in this research.

About Dr Allan McRae

Dr Allan McRae leads the Systems Genomics group at the Institute for Molecular Bioscience at The University of Queensland. With a research background in statistics and genetics, Dr McRae works with measures of molecular traits to understand the regulation of the genome and how this creates variation between people. Over the last few years, he has been applying these approaches to the understanding of the causes of MND and the heterogeneity in disease onset and progression.

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Project

Disease biomarkers

EC-FUS a novel biomarker for MND examined using a unique antibody.

Biomarkers are molecules that detect or confirm the presence of a specific disease. Currently, MND-specific biomarkers are not available for routine clinical use, which is delaying MND diagnosis for patients by up to 12 months. This project examines if a new pathological protein linked to MND, called EC-FUS, can be detected by patient blood tests to diagnose and measure the progression of MND.

Project Lead

Prof Julie Atkin

Macquarie University, NSW

Prof Julie Atkin says that her favourite personal research finding was the *"discovery of the mutations in C9orf72 in MND"* and this is because *"this gene is the most frequent cause of both MND and the related condition frontotemporal dementia"*.

She is also proud of her team who collectively were the first *"to describe the normal cellular function of the C9orf72 protein, which is significant in understanding MND"*.

Why it's hard to diagnose MND

Prof Atkin explains that MND is hard to diagnose as it can mimic other neurological diseases. There isn't a specific test or method that can confirm a diagnosis of MND. Instead, diagnosis typically involves a clinical examination and series of diagnostic tests that rule out other diseases that mimic MND.

"Diagnosis can take up to a year, which is far from ideal considering the short average survival time of MND patients following diagnosis," she says.

"This prolonged diagnostic delay also means patients cannot enrol early into clinical trials, thus preventing them from obtaining potentially disease-modifying treatments. Therefore, effective and accurate biomarkers are urgently needed to expedite the diagnosis of MND."

EC-FUS as a molecule for detecting MND

Prof Atkin's team discovered that EC-FUS was present in easily obtained biological fluids (serum, cerebrospinal fluids), as well as in MND patient spinal cords, *"where the levels of it are significantly different to individuals without neurological diseases"*.

"We recognised that it might have potential as a new biomarker to help diagnose and detect the progression of MND," she says.

FightMND has invested $249,972 in this research.

About Prof Julie Atkin

Prof Julie Atkin works at the Macquarie University Centre for Motor Neuron Disease Research, a recognised centre of expertise within the University. She is a cell biologist/biochemist and has worked predominately on MND for the last 18 years. Her research involves identifying the main cellular processes that trigger neurodegeneration in motor neuron cells and from this, designing new therapeutic approaches for MND.

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Project

Disease biomarkers

The Glymphatic System: A novel biomarker of disease severity in MND

Waste material is normally removed from the brain while we sleep. However, in MND, the system responsible for removing waste material may be impaired. This study examines if waste build-up in the brain can be detected by the latest brain imaging devices and be used as a biomarker to diagnose MND.

Project Lead

A/Prof David Wright

Monash University, VIC

A/Prof David Wright defines the glymphatic system as *"the brain's waste clearance system,"* explaining that it works *"while you sleep to get rid of the toxic waste proteins that build up during the day."*

His research is looking to see if the inefficient clearance of proteins causes them to *"accumulate in the brain and potentially result in, or exacerbate, neurodegeneration."*

Research highlights

Using magnetic resonance imaging (MRI), A/Prof Wright's team was able to show, for the first-time, that the glymphatic system is impaired in his team's mouse model of MND.

It is yet to be determined why the glymphatic system starts to fail, when it begins or how quickly it fails, but funding from FightMND will be put toward answering these questions.

Real world benefits

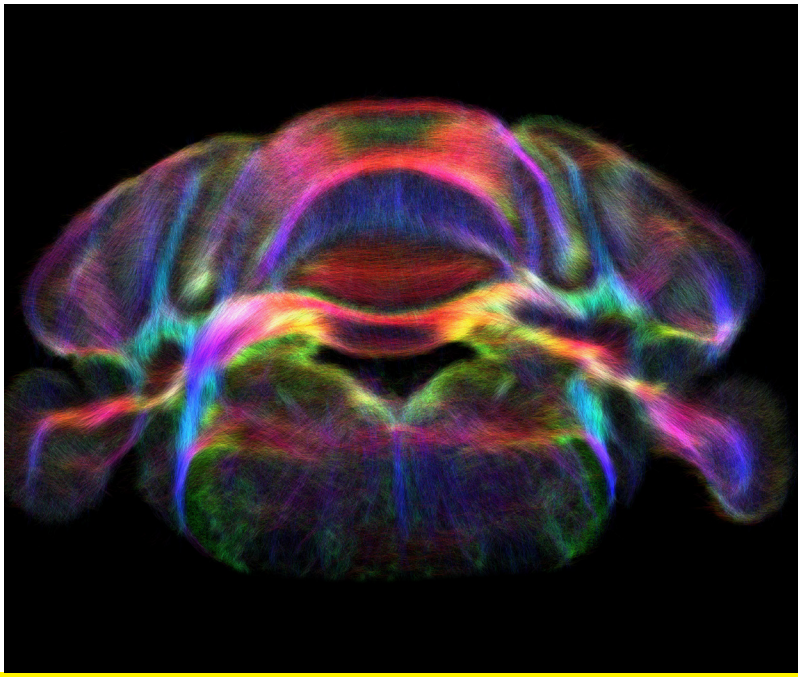
A/Prof Wright says he is excited by the potential of *"real world"* benefits for people living with MND that his research could provide.

"This support will allow us to improve our understanding of the glymphatic system and how it relates to MND disease progression," he says.

The goal of the project is to use this new knowledge to develop therapies that will specifically target the glymphatic function, improve the removal of toxic waste proteins and ultimately delay disease progression.

When asked how he felt when he heard he had received the funding from FightMND, A/Prof Wright says *"honestly, it was fantastic! To receive the recognition of our peers who judge these grants is just amazing – we're super excited that they can see the potential of our ideas!"*

FightMND has invested $249,502 in this research project.



About A/Prof David Wright

A/Prof David Wright currently works in the Department of Neuroscience, Central Clinical School, Monash University. He came to this role in a circuitous way, beginning his career with an apprenticeship in electrical-instrumentation, while going to university in the evenings after work. After finishing his trade, he went to university full-time and as part of his course, worked at a research institute in Japan. He enjoyed it so much that he returned after graduating.

After eight years in Japan, he returned to Melbourne, and took up a position at The Florey Institute of Neuroscience and Mental Health, running the preclinical MRI, while completing his PhD. On graduating he was appointed Director of Preclinical Imaging and received a highly competitive Investigator Grant from the NHMRC.

FIGHT MND.

Project

Disease heterogeneity

Exploiting cryptic relatedness in global MND to uncover disease and phenotype-linked genes

MND affects people in a variety of ways. People living with MND experience different disease courses, with variable age of onset, progression and duration of disease. This study will perform a genetic analysis of 9,000 MND cases, aiming to uncover ancestral links between cases that may identify new genes that cause MND or influence disease progression.

"I am grateful to the everyday people who donate to FightMND to support research, even if they are not impacted directly by MND."

Project Lead

Dr Kelly Williams

Macquarie University, NSW

Dr Kelly Williams knew right from her undergraduate studies that she wanted to pursue a career in medical research, specifically in human genetics.

Offered a genetics Research Assistant position in Prof Ian Blair's MND group at ANZAC Research Institute in 2007, she was part of the team that discovered MND-linked mutations in TDP-43, only the second gene to be discovered to cause MND. This gene was discovered 15 years after the first and was an enormous breakthrough discovery in MND.

Dr Williams says *"knowing what a large impact this single gene discovery had made for people living with MND and their families, I was dedicated to continue working on MND genetics research until there are no more MND genes to be discovered."*

Genetics and genealogy

Dr Williams and her group are currently studying genetic research projects that analyse genome data of individuals with familial and/or sporadic MND. However, she notes that she does *"have a strong passion for working on the hereditary form of disease because it goes back to my classical genetics background - family trees, genealogy, haplotypes – it is what I enjoy doing most."*

"A gene discovery in an MND family may not be relevant to every person living with MND, but to those whom it may be relevant, it could change their family's future," she says.

Cryptic relatedness

Dr Williams explains *"cryptic relatedness"* as a situation where study participants are genetically related, but the relatedness is unknown to the researchers.

"MND cases who are related, even distantly, may share genetic factors that cause disease, increase disease risk, or modify the presentation of MND," she says.

"In traditional genetics studies, we separate hereditary and sporadic MND into separate groups for different analysis. However cryptic relatedness studies enable us to integrate all MND patients, bridging the gap between sporadic and hereditary MND to find shared ancestry from up to 250-300 years ago."

This IMPACT project, uncovers previously unknown relatives that have a shared ancestry and identifies the *"specific regions of the genome that they share"*. It will allow Dr Williams and her team to pinpoint the gene defects that contribute to MND.

"This will be directly beneficial to MND research as a large portion of what we currently understand about the biology of MND has come from gene discoveries," she said.

Relief, gratitude and excitement

Dr Williams said that when she first heard the news that she had received a grant her thoughts were *"firstly, relief and gratitude and then excitement."*

She explains that medical research funding is very competitive and that funds provided by FightMND ensure she can keep her team of early-career researchers together to continue their genomics research. She says she is excited that they now have two years to really focus on the project and deliver some impactful results.

A worldwide project

The IMPACT grant funding from FightMND will allow Dr William's group to take their cryptic relatedness study internationally to impact MND research around the globe.

"Not only will we be searching for cryptic relatedness in more than 3,000 Australian and New Zealand MND cases (many recruited through SALSA-SGC, funded by FightMND) but also more than 7,000 MND patients from Project MinE comprising Great Britain, Ireland, United States, Belgium, Spain, France, Israel, Italy, The Netherlands, Portugal, Sweden, Turkey and Switzerland," she says.

"I am grateful to the everyday people who donate to FightMND to support research, even if they are not impacted directly by MND."

FightMND has invested $250,000 in this research project.

About Dr Kelly Williams

Dr Kelly Williams works at the Centre for MND Research within the Faculty of Medicine, Health and Human Sciences at Macquarie University. She has been researching the genetic basis of MND for almost 15 years and has played a key role in most MND gene discoveries worldwide. Her early research background was classical genetics and molecular biology to uncover genes causing hereditary MND, and now includes bioinformatics and computational biology to align with the rapidly changing research field of human genetics and large-scale genomics. In 2013, she received her PhD in MND genetics, was awarded the Bill Gole MND Fellowship and was recruited to be a founding member of the Macquarie University Centre for MND Research.

Dr Williams established Australia's first ALS/MND gene discovery bioinformatics pipeline and led the setup of the largest Neurodegenerative Diseases patient sample Biobank in Australia. This is held onsite at Macquarie University and currently comprises in excess of 50,000 biological samples. Dr Williams was awarded an NMHRC Early Career Fellowship in 2016 for MND genomics and now leads the Genomics and Bioinformatics Group within the Macquarie University Centre for MND Research.

FIGHT MND.

Project

Disease heterogeneity

Developing a high-throughput system to identify MND risk genes

For most people living with MND, their diagnosis comes as a surprise. There is no family disease history, and the cause is unknown. Research, however, is uncovering that genetic causes of MND are much larger than previously recognised, and just this year, five new regions of the genome were found to contribute to MND. Investigators in this project will study these regions in more detail to identify the specific MND risk genes. Successful outcomes will identify new lead genes responsible for MND and new targets to treat MND.

"A treatment that stops the disease in its tracks remains critical for those with sporadic MND."

Project Lead

Dr Fleur Garton

The University of Queensland, QLD

Dr Fleur Garton says although she has no specific favourite research project, she is inspired by the fact that ultimately *"research can prevent or cure a disease like MND"*.

In talking about research successes, she cites the incredible datasets that the international MND research community is now collating (including in Australia) and notes that continuing this momentum will be critical to producing a positive outcome for those living with MND.

Risk genes

Dr Garton's lab is currently working to identify risk genes for MND. 'Risk genes' can alter the likelihood of an MND diagnosis and *"knowledge about how their regulation or expression can contribute to MND could help design a treatment,"* she says.

Her project is specifically focused on sporadic MND, which is the more than 80% of MND cases that do not have a family history or single causal gene variant identified.

To help identify these risk genes, Dr Garton and her team are *"looking at biomarkers (in the blood) and genetic variation (risk genes) associated with MND"*, a task that is assisted by human patient samples garnered from the Sporadic ALS Australia - Systems Genomics Consortium (SALSA-SGC) platform (also funded by FightMND).

She is hopeful that these research avenues may help diagnose, track, and ultimately treat MND and is excited that this project has real potential.

"We are only at the cusp of risk gene discovery in ALS/MND, with many more to be investigated in the next few years. This project will help us streamline the process for these expected discoveries while also revealing new treatment avenues now," she says.

Dr Garton recognises that *"a treatment that stops the disease in its tracks remains critical for those with sporadic MND."*

"Thanks to this funding from FightMND, we hope to reveal treatment avenue/s that can do this."

FightMND has invested $250,000 in this research.

About Dr Fleur Garton

Dr Fleur Garton works at the Institute for Molecular Bioscience at The University of Queensland. Her research experience spans both molecular genetics (testing gene function with knock-out/overexpression models) and complex trait genomics (the individual differences between people caused by genetic factors).

FIGHT MND.

Project

Disease heterogeneity

Identifying novel structural variations in MND

MND affects people differently. The age of onset, rate of progression and location in the body where MND begins can vary, making the disease difficult to diagnose and treat. In this project, investigators will study the genetics unique to people affected by MND, which is likely to be responsible for the variability that occurs. They will assess genetic markers that are linked with MND to identify groups of patients that have similar genetics and determine if patients within each group respond to specific treatments in a similar way.

Project Lead

Prof P. Anthony Akkari

Perron Institute for Neurological and Translational Science, WA

Prof Akkari started his research career in the Neurogenetics Laboratory of Professor Nigel Laing at the Australian Neuromuscular Research Institute (now the Perron Institute). Professor Laing was collaborating with Professor Teepu Siddique and contributed to the discovery of the first gene for MND, the SOD1 gene.

This sparked an interest for Prof Akkari in MND and he was determined to further study this complex disease.

Prof Akkari, Dr Flynn and Frances Theunissen conducting genotyping experiments in the lab.

Inspiring research

Prof Akkari says there are many areas of his research that he finds inspiring.

"Right up there is the thrill of examining uncharacterised regions of MND genes to see what else might reside there in terms of gene function and control," he says.

A highlight is also working with students who are coming into the MND space for the first time. *"Seeing their excitement about new discoveries they make and what light that sheds on MND genetics is very rewarding,"* he says.

The opportunity to collaborate with MND researchers around Australia and around the world, in a common commitment, is something that *"just keeps me going,"* he adds.

Variation in MND

When asked about the variation in MND and its complications, Prof Akkari explains that *"structural variations are regions of DNA that vary naturally"* and that *"there are many different kinds of gene variations within DNA"*.

Prof Akkari's group is particularly interested in Short Structural Variations (SSV). These are less than *"50 base pairs of DNA, that reside within genes but can also sit between genes. Structural variations can influence neighbouring genes but also genes far away. Many are repetitive regions of DNA."*

What this means for MND

Prof Akkari explains that *"since SSV regions of DNA vary so much between people they can be highly informative for disease risk and disease mechanisms"* and that they can be useful in clinical trials where patient responses to different therapies are measured.

"As we learn more about the SSVs in MND genes they may also identify groups of patients with similar sporadic MND disease mechanisms," he says.

This would allow these patients to be selected for clinical trials where their specific form of MND can be targeted to provide a higher chance of success for the trial.

Principle investigator Prof Akkari and Co-investigator Frances Theunissen at the Perron Institute.

How FightMND is helping

Prof Akkari says that *"funding from FightMND will allow us to fund the discovery and investigations of these difficult to examine SSV regions in novel and candidate MND genes."*

He is working with PhD student and co-investigator Frances Theunissen who has been instrumental in developing this SSV project, writing the grant application and setting up the collaboration with Prof Amar Al Chalabi's group at Kings College London, which provides access to a large patient cohort. Data sourced from this cohort will inform which SSV regions Prof Akkari and his team will follow up in the lab.

"The overall benefit of this is that it's going to significantly improve our ability to examine these SSV regions within known and novel MND genes," says Prof Akkari.

"As we examine these novel SSV gene markers in MND patient samples, we will then take this a step further and test them in MND patient DNA samples from previously conducted clinical trials," he adds.

The goal is to classify MND patients into *"sub populations"*, and if the genetic markers show promise, they would then be incorporated into futur clinical trials.

FightMND has invested $249,880 into this research.

About Prof P. Anthony Akkari

Prof P. Anthony Akkari is the Head of the Motor Neuron Disease Genetics and Therapeutics group at the Perron Institute for Neurological and Translational Science, WA.

After completing his PhD in neuromuscular disease genetics, he undertook his postdoctoral research at Duke University's Division of Neurology, where he has ongoing collaborations and an adjunct professorship. From Duke he was recruited into the USA Pharmaceutical industry at GSK, and later Eli Lilly and Cabernet Pharmaceuticals. There he focused on integrating genetic data into the drug development process to drive stratified medicines for patients. He maintains an ongoing role and interest in the pharmaceutical industry and is the Chief Scientific Officer of Black Swan Pharmaceuticals, an ALS/MND drug development company.

Prof Akkari's MND research group is focused on discovering how short structural variations within the human genome contribute to the missing heritability of MND and how these can be co-developed with therapies for improving the success of MND clinical trials. In parallel, his team works to develop antisense oligonucleotide (AO) therapeutics for MND and at present have seven AOs in development, targeted toward sporadic MND.

Prof Akkari and Frances Theunissen discussing their latest results on genetic structural variants in MND at Perron Institute.

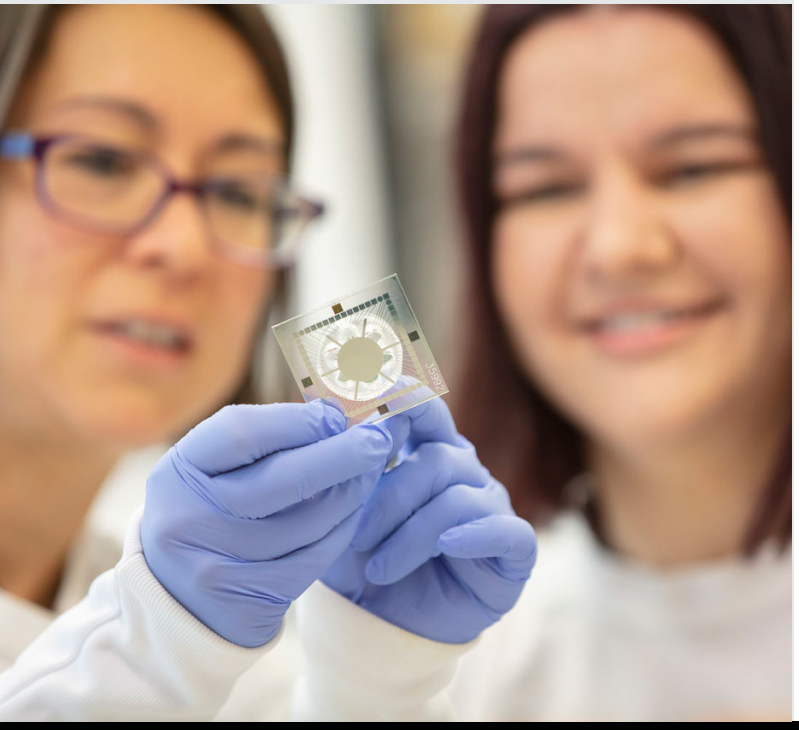
FIGHT MND.

Project

Gene therapies

Restoring autoregulation of TDP43 in MND using splice-switching antisense oligonucleotides

Investigators in this project are using a two-pronged genetic approach targeting a molecule called TDP-43, an important molecule in cells that has many functions. In almost all cases of MND, TDP-43 sticks together to form clumps that make motor neurons unwell. The first genetic drug being tested is designed to prevent the production of TDP-43 clumps in motor neurons. The second drug will restore levels of a molecule in motor neurons, which is essential for their health and repair, but whose levels are reduced when TDP-43 clumps form. The study will test the benefit of this combination genetic therapy in motor neurons made from MND-patient stem cells.



Project Lead

A/Prof Lezanne Ooi

University of Wollongong, NSW

A/Prof Lezanne Ooi's project uses stem cells that are 'reprogrammed' from skin cells donated by MND patients or healthy people. From these she and her team *"can make motor neurons that bear the same genetic sequence as patients."*

Motor neurons created from skin cells

A/Prof Ooi says she *"still finds it incredible that motor neurons created from the skin cells of MND patients show some of the same characteristics as can be measured in living patients. This provides an opportunity to use these cells to understand the traits of each person's disease and to test potential therapies."*

Bringing together experts from multiple fields

Currently working on TDP-43-targeted gene therapy, A/Prof Ooi explains how this therapy has potential for disease intervention.

"Several 'antisense oligomers' have been approved for use in the clinic in recent years, including for the treatment of spinal muscular atrophy, and Duchenne muscular dystrophy. This research brings together the strengths of experts in gene therapy, stem cells, inflammation and bioinformatics."

"It will be exciting to work with these talented collaborators," she says.

Funding from FightMND will help A/Prof Ooi and her team to *"test a combination gene therapy in cells from a range of patients to see if we can restore normal levels and function of TDP-43 and whether this strategy can protect motor neurons,"* says A/Prof Ooi.

"Toxic accumulation of TDP-43 protein into "aggregations" occurs in around 97% of MND patients, so if we are able to successfully restore TDP-43 to its healthy levels and functions, this has the potential to benefit many patients."

FightMND has invested $249,349 in this research

About A/Prof Lezanne Ooi

A/Prof Lezanne Ooi is a Principal Research Fellow and Group Leader of the Neurodevelopment and Neurodegeneration Lab at the University of Wollongong, Australia. She established her lab in the Illawarra Health and Medical Research Institute and the University of Wollongong in 2012.

A/Prof Ooi's research speciality is cellular neuroscience and the regulation of neuronal function in neurodegenerative disease. She trained in the UK and was awarded a Wellcome Trust Prize PhD with studies on gene regulation and neurodegenerative disease from the University of Leeds. During her post doctoral research, she studied the regulation of ion channels and signalling molecules and developed cellular imaging techniques and used electrophysiology to understand the control of neuronal excitability and function in development and disease.

FIGHT MND.

Project

Drug delivery/Gene therapies

Enhancing delivery of gene therapy to motor neurons and glial cells using focused ultrasound

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. This project aims to enhance the delivery of a genetic drug for MND to the brain using focused ultrasound, a safe new technique that temporarily opens the blood-brain barrier. Investigators will assess if focused ultrasound allows the genetic drug to pass from the body into the brain of a preclinical MND model more readily, to increase its ability to reach and act on motor neurons.

Project Lead

Dr Kara Vine

University of Wollongong, NSW

Dr Kara Vine says it was the diagnosis of MND in a close friend and work colleague in 2016 that led her to think about ways we could improve the delivery drugs to the central nervous system, and treat those living with MND. Her background in drug delivery meant she was well placed to tackle this challenge.

Site-specific drug delivery

Currently, Dr Vine's team is focused on improving site-specific drug delivery for cancer and MND.

"We use targeted nanoparticles and polymeric scaffolds to enhance drug solubility, enable targeted delivery, and provide improved therapeutic efficacy with reduced toxicity profiles," she says.

Dr Vine explains that *"a major obstacle facing the effective treatment of diseases such as MND is the blood-brain barrier (BBB) and blood-spinal cord barrier (BSCB)."*

"The BBB is a physical barrier between the brain's blood vessels and the cells and other components that make up brain tissue."

"Together, the BBB and BSCB prevent the passage of certain drugs from the circulatory system into the central nervous system where they are required. Therefore, it is nearly impossible for therapeutic drugs to target the diseased cells without the assistance of drug 'carriers' and/or physical disruption to overcome such barriers," she explains.

Dr Vine and her team have designed a drug carrier (nanoparticle) that can increase the delivery of drugs into the brain and are now working to enhance the penetration and targeting capabilities of this drug carrier by using externally applied, non-invasive focused ultrasound.

"Focused ultrasound is a safe and relatively new technique that selectively disrupts the BBB/BSCB, thereby increasing its permeability to drugs into regions of interest within the central nervous system," she explains.

Excitement and gratitude

Dr Vine says she was *"absolutely thrilled"* to learn that she had been awarded an IMPACT grant from FightMND.

"My immediate reaction was that of excitement and gratitude. The outcomes of this project will have major impact on the types of drugs that can be delivered to motor neurons, opening up many new potential avenues of therapy for both sporadic and familial forms of the disease. I am extremely grateful to FightMND and their fundraising community for supporting this work," she says.

FightMND has invested $249,939 in this research.

About Dr Kara Vine

Dr Kara Vine is a Senior Research Fellow in the School of Chemistry and Molecular Bioscience at the University of Wollongong. Her lab is based in the Illawarra Health and Medical Research Institute, Wollongong.

Dr Vine has over a decade of experience in the design and preclinical assessment of targeted anti-cancer and MND therapeutics. Her program of research is centred on developing novel nanomedicines and polymeric scaffolds for site specific drugs. She is the lead inventor on four drug delivery patents and has made significant contributions to an all-in-one chemotherapy formulation that has completed a Phase1b/2a clinical trial in Wollongong. Dr Vine has trained internationally at the Finsen Laboratory, Copenhagen, Denmark and University of Malmo, Sweden.

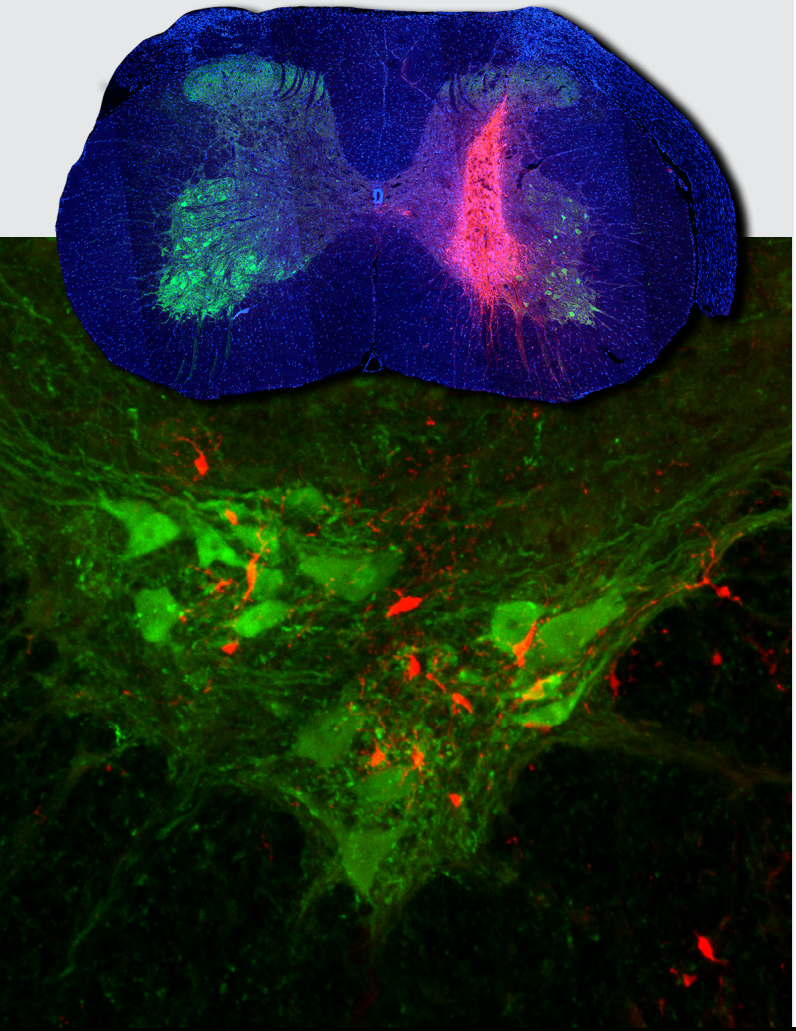
FIGHT MND.

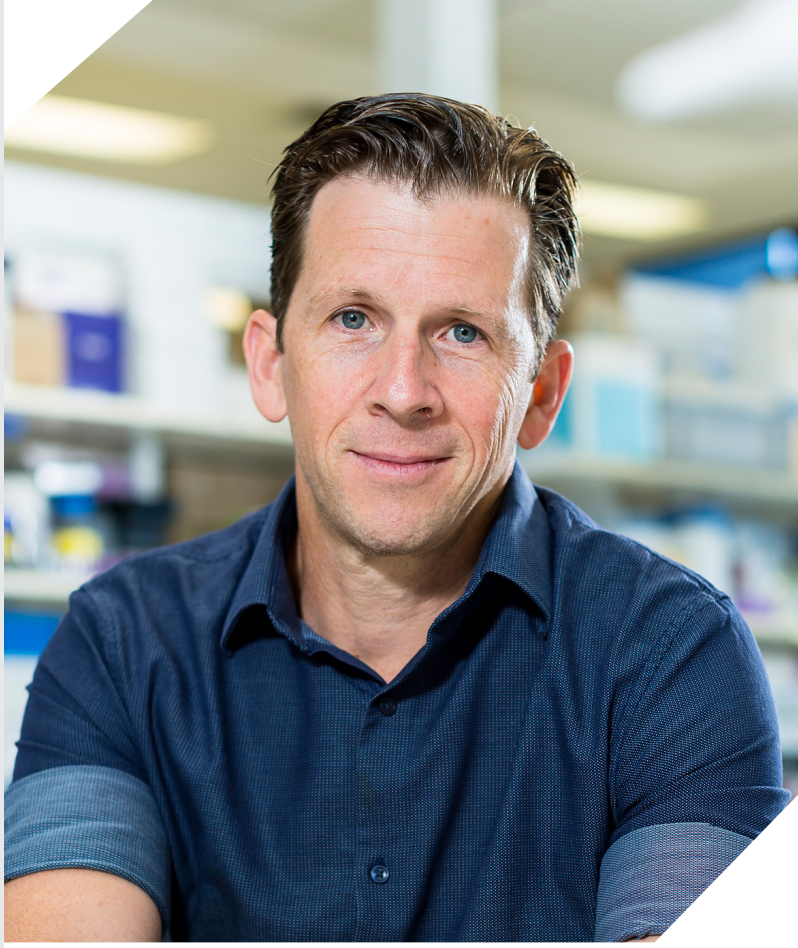
Project

Regenerative medicine

Subpial spinal cord delivery as a stem cell-based treatment for MND

Recent clinical trials showed that transplantation of stem cell-derived products into the spinal cord can partially delay disease progression in MND patients. This project will explore a promising new approach to improve stem cell-based therapy for MND. If successful, it will deliver a platform for rapid translation of outcomes to clinical application in patients with MND.





Project Lead

A/Prof Lachlan Thompson

The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, VIC

With a career mostly dedicated to developing cell-based therapies for Parkinson's disease (PD), A/Prof Lachlan Thompson has established a *"strong foundation of understanding around how neural circuitry can be re-established in the damaged central nervous system (CNS) through transplantation of the correct cell type."*

"Stem cells are an exciting resource in the context of CNS repair but we are yet to see their full potential. I'm really optimistic that pre-clinical research aimed at harnessing that potential, by understanding the best cell type and how to deliver them, will lead to promising new clinical trials in patients," A/Prof Thompson says.

Stem cell research

The focus of A/Prof Thompson's research team is pre-clinical development of stem cell-based therapies, to develop treatments for various neurological conditions, including Parkinson's disease, stroke and MND. The goal of the work at this pre-clinical level *"is to try and identify therapeutic efficacy as a platform to launch clinical trials in patients,"* says A/Prof Thompson.

The project A/Prof Thompson and his team are currently investigating is stem cell therapy for MND.

"Stem cells are a special cell type in that they are essentially the 'building blocks' for biology. They are responsible not only for the early stages of life in embryonic development, but also for tissue repair later throughout life," says A/Prof Thompson.

"In the laboratory, we can grow these cells in large numbers in order to generate other specific cell types that may be therapeutic in certain settings," he adds.

Stem cells and some of the immature 'progenitor' cells they can generate can release molecules that can be therapeutic.

A/Prof Thompson provides an example: *"in a damaged nervous system, transplantation of stem or progenitor cells can slow the loss of cells affected by damage or disease. There is some pre-clinical evidence that transplantation of these cells in models of MND can protect motor neurons from degenerating,"* he says.

Deploying knowledge to slow or stop MND

This creates the exciting prospect of translating this knowledge to treatment in patients that would slow or even stop disease progression.

"The challenge is to identify the best way to deploy this for the greatest chance of success. We are still at the early phase of this research and need to understand fundamental questions such as which exact cell type to use and how best to deliver it," says A/Prof Thompson.

A tremendous impact

A/Prof Thompson says that the funding provided by FightMND *"will have a tremendous impact on the capacity to push forward our aspiration to establish a stem cell therapy for MND."*

"There is a lot of pre-clinical work to do in this area and the rate-limiting factor is overwhelmingly the ability to support talented research scientists to undertake the work," he says.

"While there is undoubtedly potential there, harnessing and understanding this so that a therapy can be established with predictable and effective outcomes remains the key challenge for this field. Certainly a surmountable one we think," says A/Prof Thompson.

"This funding will allow a postdoctoral scientist that might have otherwise been drawn to another field to remain dedicated to pursuing the establishment of a stem cell therapy for MND. It will undoubtedly move us closer to realising this goal."

FightMND has invested $250,000 in this research.

About A/Prof Lachlan Thompson

A/Prof Lachlan Thompson completed his undergraduate studies (BSc) at The University of Melbourne before completing his doctoral degree at Monash University in 2002. He then undertook 5 years of postdoctoral training at Lund University in Sweden between 2003 and 2007 where he developed expertise in the area of neural transplantation and cell-based therapies for repair of the central nervous system.

In 2008 A/Prof Thompson moved back to Melbourne to establish a laboratory in this field at The Florey. It is an important and steadily growing area on the Australian research landscape and A/Prof Thompson's team are aggressively exploring the capacity for stem cells to be utilised as a therapy for MND.

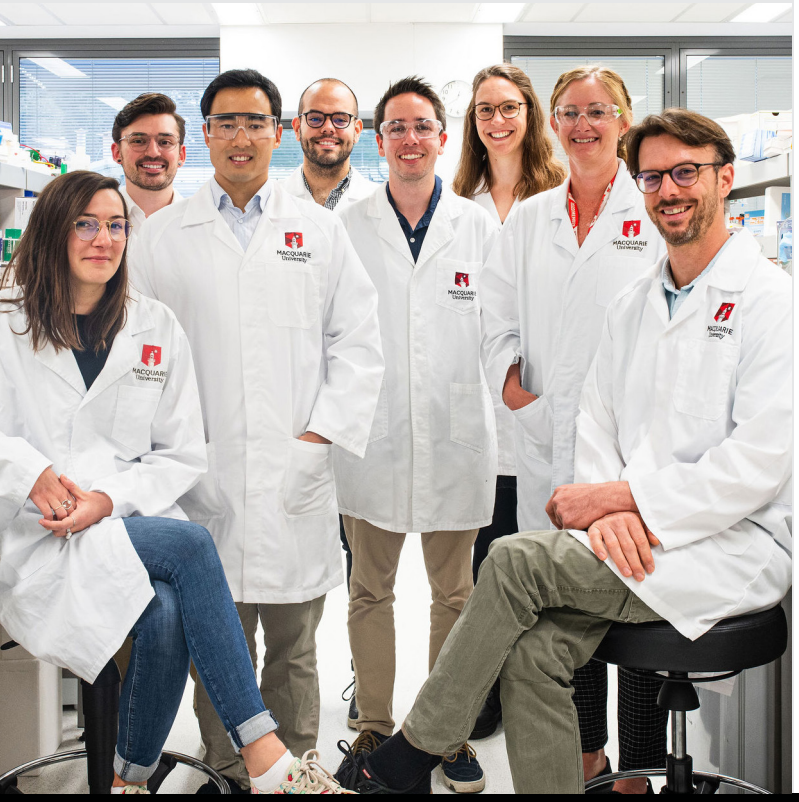
FIGHT MND.

Project

Disease Models

Harnessing phase separation as a preclinical strategy for the treatment of MND

TDP-43 is an important molecule in cells that has many functions. In almost all cases of MND, TDP-43 misbehaves and sticks together to form clumps that are thought to be harmful to motor neurons. This project aims to study a novel mechanism, called phase separation, that may cause the formation of TDP-43 clumps. Investigators will determine if preventing phase separation of TDP-43, by altering its structure, can delay the formation of TDP-43 clumps in motor neurons.



Project Lead

Dr Marco Morsch

Macquarie University, NSW

Dr Marco Morsch says that learning about MND was an eye-opener and that trying to develop new therapeutic opportunities for people living with MND is the best motivation to continue his work. *"The prospect of helping to delay or stop MND in its tracks one day is just the best inspiration ever,"* he says.

"I truly believe that the answers are out there, we must dare to look carefully."

He is quick to note that so much progress has already been made. For example, people living with familial MND are now able to have kids knowing that they don't carry the faulty genes (through IVF and genetic testing).

Dr Morsch says working with his team who strive relentlessly to push scientific frontiers every day in the lab while being incredibly motivated, kind, and passionate is one of the highlights of his job.

Phase Separation

Dr Mosch's research is examining phase separation, a biological process where some molecules or proteins accumulate much more in one location than another. *"The concept of oil in water is a good comparison, where you have drops of oil bonding together when surrounded by water,"* he says.

Thorough mixing or a change in the environment can alter this separation of liquids and the same is true in cells, *"where it is believed that proteins come together in high density to perform important cellular processes without the need to get transported into another compartment."*

"The process allows fast regulation of certain events and is quite common in cells. For example, we know of many other cell bodies that form through this process and are critical for cellular health."

A first step

This concept is in its infancy for MND and disease proteins explains Dr Morsch. *"It is an important model that might help to explain how toxic aggregates can form in the nerve cells that die during the disease."*

"If these phase-separated proteins become too 'sticky', this might be one of the first steps that causes aggregation in MND," he adds.

Dr Morsch says the fact that phase separation *"is such a fundamental biological process that has not been explored enough in MND is a very stimulating prospect."*

"If phase separation goes wrong early in the process of protein aggregation, we might have a new handle on how to delay or ultimately stop disease progression."

More work is needed to be done, however the exploration of *"novel concepts such as phase separation is critically important to come up with new ways to stop this beast of a disease."*

Driving scientific discoveries

Dr Morsch says that support from FightMND is important in so many ways.

"It not only helps to drive scientific discoveries, but it also enables the next generation of researchers who dedicate their careers to finding a cure for MND."

"Such investment with clear short-term and long-term benefits is most critical in a time where scientific news and advice is at the forefront of our everyday lives. And for a young laboratory like mine, support like this means that we can focus on what we do best, the research in the labs with some form of continuity," he says.

"My hope is that we will develop a range of therapeutic opportunities for people living with MND. In all reality, there won't be a one-size-fits-all approach and investing into the broad spectrum of therapeutic avenues might be the key to multi-facetted treatment options in the future."

FightMND has invested $249,996 in this research.

About Dr Marco Morsch

Dr Marco Morsch is a neuroscientist with passion for investigating cellular interactions. He has experience in a range of techniques, including microscopy, electrophysiology, and animal models of disease. Early in his career, Dr Marco Morsch focussed on other neuromuscular diseases, but in 2014 had the opportunity to join the newly formed Centre for MND Research at Macquarie University and apply his skills to MND. He is currently a group leader at the Centre for MND Research at Macquarie University, Sydney, Australia.

FIGHT MND.

Thank you

This year's $8.4 million dollar investment takes FightMND's total investment in MND research to $55.9 million since we began in 2014.

None of this would be possible without the support of our FightMND Army.

To our generous donors, major partners, volunteers and supporters – thank you for taking up the fight with us.