# MND research investment

In 2021, FightMND will commit a further $8.4 million into MND research, including support of:

- 1 Clinical Trial;
- 5 Drug Development Projects; and
- 10 IMPACT Projects.

## RESEARCH PROJECTS FUNDED IN 2021

| 1. Clinical Trials | | |
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| **PI and Affiliations** | **Project** | **Budget** |
| **Prof Perry Bartlett** (University of Queensland, QLD) | Phase 1b – Ephrin receptor A4-Fc (new drug) | $1,000,000 |
| | **Clinical Trials Total** | **$1,000,000** |
| **2. Drug Development grants** | | |
| **PI and Affiliations** | **Project** | **Budget** |
| **A/Prof Seth Masters** (WEHI, VIC) | Preventing neuroinflammation in MND by inhibiting the mPTP | $999,718 |
| **Prof Lawrence Steinman** (Alpha 5 Integrin LLC, CA, USA) | Alpha 5 Beta 1 Integrin as a potential Treatment for MND | $967,010 |
| **Dr Damien Toulorge** (ENCEFA, France) | Developing a monoclonal antibody modulating CD38 against MND | $970,000 |
| **Prof Justin Yerbury** (University of Wollongong, NSW) | Targeting misfolded proteins with MisfoldUbLs as a therapeutic strategy for MND | $921,360 |
| **Dr John Ravits** (University of California – San Diego, CA, USA) | Targeting CK1e-mediated TDP-43 Phosphorylation in MND | $986,282 |
| | **Drug Development Total** | **$4,844,370** |
| **3. IMPACT Grants** | | |
| **PI and Affiliations** | **Project** | **Budget** |
| **Dr Allan McRae** (University of Queensland, QLD) | *Disease biomarkers* – Generating a proteomics-based biomarker for MND | $250,000 |
| **Prof Julie Atkin** (Macquarie University, NSW) | *Disease biomarkers* – EC-FUS – A novel bio marker for MND examined using a unique antibody | $249,972 |
| **A/Prof David Wright** (Monash University, VIC) | *Disease biomarkers* – The Glymphatic System: A novel biomarker of disease severity in MND | $249,502 |

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| **Dr Kelly Williams** (Macquarie University, NSW) | *Disease heterogeneity* – Exploiting cryptic relatedness in global MND to uncover disease- and phenotype-linked genes | $250,000 |
| **Dr Fleur Garton** (University of Queensland, QLD) | *Disease heterogeneity* – Developing a high-throughput system to identify MND risk genes | $250,000 |
| **Prof P. Anthony Akkari** (Perron Institute for Neurological and Translational Science, WA) | *Disease heterogeneity* – Identifying novel structural variations in MND genes to improve clinical trial outcomes | $249,880 |
| **A/Prof Lezanne Ooi** (University of Wollongong, NSW) | *Gene therapies* – Restoring autoregulation of TDP43 in MND using splice-switching antisense oligonucleotides | $249,349 |
| **Dr Kara Vine** (University of Wollongong, NSW) | *Drug delivery/Gene therapies* – Enhancing delivery of gene therapy to motor neurons and glial cells using focused ultrasound | $249,939 |
| **Prof Lachlan Thompson** (University of Melbourne, Florey, VIC) | *Regenerative medicine* – Subpial spinal cord delivery as a stem cell-based treatment for MND | $250,000 |
| **Dr Marco Morsch** (Macquarie University, NSW) | *Disease models* – Harnessing phase separation as a preclinical strategy for the treatment of MND | $249,996 |
| | **IMPACT Grants Total** | **$2,498,638** |
| **4. Other Research Initiatives** | | |
| **PI and Affiliations** | **Project** | **Budget** |
| Other research initiatives | Victorian Brain Bank | $70,000 |
| | **Other Research Initiatives Total** | $70,000 |
| | **2021 Total Funding Committed** | **$8,413,008** |

# RESEARCH PROJECTS FUNDED SUMMARIES:

## 1x Clinical Trials

***Clinical trials will 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.***

**Project:** Phase 1b Clinical Trial – Safety and preliminary efficacy of mEphA4-Fc in individuals with MND.

**Principal Investigator: Prof Perry Bartlett** (University of Queensland, QLD)

This study investigates 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.

**Key highlights:** The first time that the safety and early effectiveness of a molecule discovered and developed in Australia will be examined in MND patients. The development and preclinical testing of mEphA4-Fc, which fast-tracked its transition to testing in people with MND, was supported by a FightMND translational research grant.

## 5x Drug Development Projects

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

### Therapies targeting the immune system

**Project:** Preventing neuroinflammation in MND by inhibiting the mPTP.

**Principal Investigator: A/Prof Seth Masters** (The Walter and Eliza Hall Institute, VIC)

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 reduced the immune response and be used to prevent MND.

**Key highlights:** This researcher is a first-time recipient. This drug targets a disease pathology that is found in almost all cases of MND.

**Project:** Alpha 5 Beta 1 Integrin as a potential Treatment for MND.

**Principal Investigator: Prof Lawrence Steinman** (Alpha 5 Integrin LLC, San Fransisco, CA, USA)

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 α5β1 integrins can silence the activity of key parts of 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 α5β1 integrin candidate to transition to a phase 1 clinical trial for MND patients.

**Key highlights:** This is an international team including a pharmaceutical company and leading MND researchers the USA and Australia. α5β1 integrins block the overactive immune defence system, a disease pathology that is found in almost all cases of MND.

### Treatments targeting multiple causes of MND

**Project:** Preclinical development of a monoclonal antibody modulating CD38 against MND.

**Principal Investigator: Dr Damien Toulorge** (ENCEFA, France)

This project will perform preclinical safety tests needed to advance a drug called NC-B8 towards 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.

**Key highlights:** This is an international team embedded within a pharmaceutical company with strong links to the Pitié Salpêtrière Hospital in Paris. The drug NC-B8 has a number of mechanisms of action to tackle MND in multiple areas.

### Genetics-based therapies

**Project:** Targeting misfolded proteins with MisfoldUbLs as a therapeutic strategy for MND

**Principal Investigator: Prof Justin Yerbury** (University of Wollongong, NSW)

In hereditary MND, 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 the neurons to function well. 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.

**Key highlights:** Development of a genetic tool that identifies and selectively removes harmful misfolded SOD1 protein from a motor neuron. Prof Yerbury is a leading MND researcher who entered the scientific research field after losing a number of his family members to MND. He is also living with MND.

## Validating new targets for treating MND

**Project:** Targeting CK1ε-mediated TDP-43 Phosphorylation in ALS

**Principal Investigator: Dr John Ravits** (University of California San Diego, CA, USA)

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.

**Key highlights:** This international researcher is a first-time recipient. The project targets a disease pathology common to most cases of MND. The study tests a drug that has already advanced through phase 1 testing in people for non-MND-related applications.

## 10x 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***

## Disease biomarkers

**Project:** Generating a proteomics-based biomarker for MND – *Disease biomarkers*

**Project lead: Dr Allan McRae** (University of Queensland, QLD)

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 from patients, and identify those linked to the onset and progression of MND.

**Key highlights:** This researcher is a first-time recipient of funding from FightMND. The study measures protein levels in biological samples obtained from MND patients from 5 MND clinics across Australia.

**Project:** EC-FUS - A novel biomarker for MND examined using a unique antibody – *Disease biomarkers*

**Project lead: Prof Julie Atkin** (Macquarie University, NSW)

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.

**Key highlights:** This study will determine if a newly identified molecule can be used by clinicians to diagnose MND.

**Project:** The Glymphatic System: Novel Biomarker of Disease Severity and Therapeutic Target – *Disease biomarkers*

**Project lead: A/Prof David Wright** (Monash University, VIC)

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.

**Key highlights:** This researcher is a first-time recipient of funding from FightMND. The preclinical study is using the latest 'cutting-edge' imaging technology to detect the build-up of waste material in the brain.

## Disease heterogeneity

**Project:** Exploiting cryptic relatedness in global familial and sporadic MND to uncover disease- and phenotype-linked genes – *Disease heterogeneity*

**Project lead: Dr Kelly Williams** (Macquarie University, NSW)

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 9000 MND cases, aiming to uncover ancestral links between cases that may identify new genes that cause MND or influence disease progression.

**Key highlights:** This researcher is a first-time recipient. Genetic analysis of 9000 MND cases world-wide, to identify new genes that cause MND.

**Project:** A high-throughput system to identify MND risk genes from genome-wide association studies – *Disease heterogeneity*

**Project lead: Dr Fleur Garton** (University of Queensland, QLD)

For most people living with MND 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, 5 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.

**Key highlights:** Identification of new genes that contribute to forms of MND with an unknown cause. Collaboration with 4 MND clinics across Australia.

**Project:** Identification of novel structural variations in MND genes to improve outcomes of clinical trials – *Disease heterogeneity*

**Project lead: Prof P. Anthony Akkari** (Perron Institute for Neurological and Translational Science, WA)

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.

**Key highlights:** Identifying new genetic markers used to classify MND patients into groups predicted will have a similar response to treatments. If successful, the new genetic markers could be applied to clinical trials for MND, to reduce patient disease variability and increase the likelihood of positive outcomes.

## Gene therapies

**Project:** Restoring autoregulation of TDP43 in sporadic MND using splice-switching antisense oligonucleotides – *Gene Therapies*

**Project lead: A/Prof Lezanne Ooi** (University of Wollongong, NSW)

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 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.

**Key highlights:** This combination approach is using two novel genetic drugs targeting a disease pathology found in almost all cases of MND.

## Gene therapies/Drug delivery

**Project:** Enhancing delivery of gene therapy to motor neurons and glial cells using focused ultrasound – *Gene Therapies/Drug delivery*

**Project lead: Dr Kara Vine** (University of Wollongong, NSW)

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.

**Key highlights:** This researcher is a first-time recipient of funding from FightMND. This is one of the first studies to test if focused ultrasound can improve the delivery of drugs for MND.

## Regenerative Medicine

**Project:** Subpial spinal cord delivery as a stem cell-based treatment for MND – *Regenerative Medicine*

**Project lead: Prof Lachlan Thompson** (University of Melbourne, VIC)

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.

**Key highlights:** This project will build preclinical evidence for the most advantageous way to deliver stem cells therapies for MND.

## Disease models

**Project:** Harnessing phase separation as a preclinical strategy for the treatment of MND – *Disease models*

**Project lead: Dr Marco Morsch** (Macquarie University, NSW)

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. The 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.

**Key highlights:** This researcher is a first-time recipient of funding from FightMND. This project examines a novel mechanism involved in forming TDP-43 clumps that are harmful for motor neurons.

## Additional Research Investments

FightMND will also provide further support to strengthen operations of the Victorian Brain Bank. The Victoria Brain Bank is an important resource for Australian researchers, providing them with access to well-characterised post-mortem brains and clinical data that may give clues to why MND occurs and improve diagnosis.

FightMND will continue to foster the advancement of promising treatments for MND by providing additional support for two clinical trials with multiple clinical sites across Australia, which ensures equity of access to clinical trials for MND patients across Australia.