FIGHT MND.
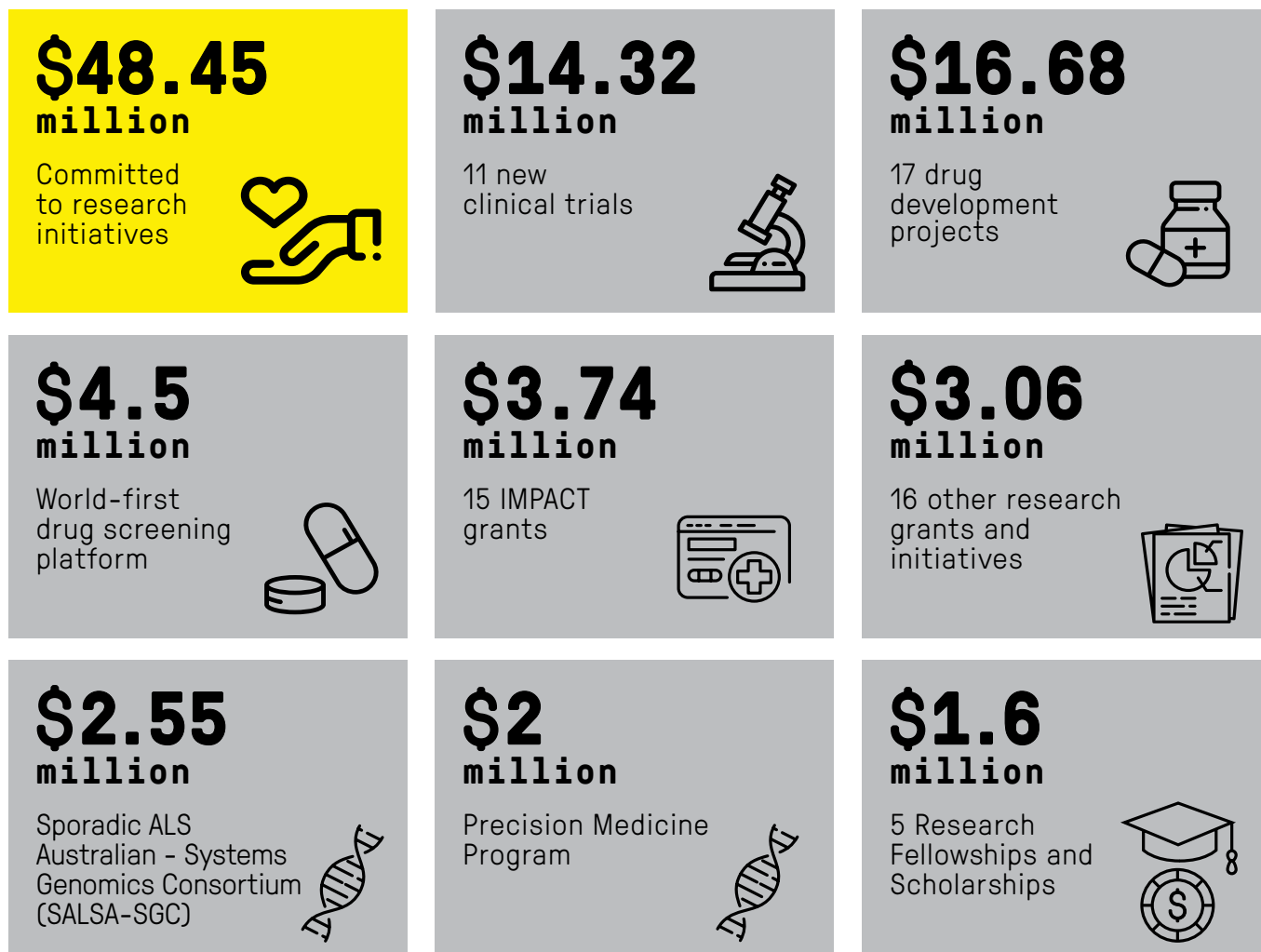
In 2020, FightMND will commit another $10.68M into MND research projects across Australia. Potential projects were reviewed and assessed by both national and international MND experts and an expert panel of MND clinicians and researchers to identify and support projects with the most promising potential to fast track a more effective therapy or cure.

This year the successful research projects include:

- 1 Clinical Trial,
- 7 Drug Development Projects, and
- 8 IMPACT Projects

OUR IMPACT

A snapshot of investments to fight MND since 2014:

$48.45 million
Committed to research initiatives

$14.32 million
11 new clinical trials

$16.68 million
17 drug development projects

$4.5 million
World-first drug screening platform

$3.74 million
15 IMPACT grants

$3.06 million
16 other research grants and initiatives

$2.55 million
Sporadic ALS Australian - Systems Genomics Consortium (SALSA-SGC)

$2 million
Precision Medicine Program

$1.6 million
5 Research Fellowships and Scholarships

MND Clinical Trials test promising new drugs, or drugs already approved for other diseases, in people living with MND. Phase 1 trials are primarily safety studies to asses if a drug is safe to administer to people, and in particular, people with MND. If a drug is shown to be safe in a Phase 1 study, it can advance to a Phase 2 study where it will look at the impact of the drug on disease progression.

PHASE 1 CLINICAL TRIAL - ORAL MONEPANTEL

Dr Susan Mathers
(Calvary Health Care Bethlehem, Melbourne, VIC) &
Dr Richard Mollard (PharmAust Ltd)

Background

Monepantel is a well-known veterinary drug approved to treat parasites in animals. It has demonstrated a high safety profile in anti-cancer clinical trials in people and is being re-purposed in the fight against MND. Monepantel works by stopping the activity of a cellular pathway called mTOR that regulates the metabolism, growth and survival of the cell. Drugs that inhibit the mTOR pathway have been shown to help clear away proteins/molecules that clump together and accumulate within cells and can cause damage and death of these cells. Pre-clinical studies have shown that Monepantel can slow disease progression in MND models by clearing harmful materials in a motor neuron that stick together and make them unwell. This study aims to advance Monepantel as a potential therapeutic for MND.

The Project

This Phase 1 trial will test the safety and tolerability of oral Monepantel tablets in 8 Australian MND patients across 2 clinical sites at Calvary Health Care Bethlehem in Melbourne, and Macquarie University Hospital in Sydney. The study aims to find the most appropriate dose of Monepantel to treat MND in humans. The study will also explore if Monepantel shows signs of efficacy to support the design of a larger Phase 2 clinical trial. The Phase 1 study will be completed at the end of 2021 and a successful trial would support the advancement of Monepantel towards a Phase 2 trial.

Neale Daniher visiting Calvary Care Bethlehem

Drug Development Projects

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

Genetics-based Therapies

DEVELOPMENT OF A TDP-43-TARGETING GENE THERAPY FOR MND

Prof Roger Chung (Macquarie University)

Background

TDP-43 is an important molecule in cells that has many functions. In almost all cases of MND, TDP-43 behaves abnormally and sticks together to form clumps that are thought to be harmful to motor neurons. Investigators in this study have identified key molecules that normally allow motor neurons to remove TDP-43 and prevent its accumulation. They have also found a way to initiate the removal of harmful TDP-43 from motor neurons using an innovative gene therapy approach.

The Project

This study will test if a new gene therapy tool can break up and remove harmful TDP-43, restore health to motor neurons, and stop MND in preclinical sporadic MND models. The research team will evaluate if their gene therapy can delay or prevent TDP-43 clumps from forming and improve survival in sporadic MND models. They also aim to identify the forms of TDP-43 that the gene therapy clears from motor neurons and determine the safety profile of the gene therapy in preclinical MND models. A positive outcome of this study will be to establish data that generates a clear pathway for the advancement of the gene therapy towards future MND clinical trials.

PRECLINICAL DEVELOPMENT OF A SOD1 GENETIC THERAPY IN SPORADIC MND

Prof Steve Wilton (Murdoch University)

Background

Several proteins have been linked to inherited and sporadic forms of MND. In MND, mutations in the SOD1 gene produce harmful changes to one of these proteins, called SOD1 protein. These changes cause SOD1 protein to clump together and prevent removal of harmful substances from motor neurons, which contributes to their death. Investigators in this project have developed a synthetic drug, called an antisense oligomer, to reduce levels of harmful SOD1 protein and prevent its detrimental effects on motor neurons.

The Project

The research team is aiming to advance an exciting new genetic drug to treat MND. The study will evaluate if their SOD1-targeted drug delays the onset and slows progression of MND in preclinical models. The project will also demonstrate target engagement and assess the safety of their drug in a variety of preclinical models. A promising project outcome for this study would be the delivery of preclinical evidence that builds a strong case for testing the SOD1 antisense oligomer in a clinical trial for MND patients in the next 2-3 years.

FIGHT MND.

SMN2 SPLICE-SWITCHING OLIGONUCLEOTIDE THERAPY DEVELOPMENT FOR MND

A/Prof Bradley Turner (Florey Institute of Neuroscience and Mental Health)

Background

Survival motor neuron (SMN) is a protein that has a number of vital roles that are essential to the health of motor neurons. Deficiency of SMN causes a form of MND called spinal muscular atrophy (SMA) that usually is seen in children. Recently, the development of a gene therapy called Spinraza that elevates SMN levels, has provided significant benefit to SMA patients and is now an approved therapy. However, while effective, the therapy is invasive, requiring direct access to the patient's spinal cord. Investigators in this project have now discovered that SMN deficiency also occurs in adults with MND. They have also obtained promising results using an advanced 'non-invasive' gene therapy approach to deliver a drug that elevates SMN levels in preclinical adult MND models. The research team is hopeful that drugs that restore SMN levels may effectively treat MND.

The Project

In this project investigators will advance their genetic drug, a new form of Spinraza, to maximise its therapeutic benefit and access into the brain. The research team will design, screen and develop an optimal form of brain-penetrating Spinraza. They will also assess if brain-penetrating Spinraza elevates SMN levels in motor neurons and improves motor neuron health, movement and life expectancy in preclinical MND models. A promising outcome from this study would be the testing of brain-penetrating Spinraza in a clinical trial for MND patients within the next 4-5 years.

MODULATING ACTIN DYNAMICS IN MND AS A NOVEL THERAPEUTIC APPROACH

Prof Julie Atkin (Macquarie University)

Background

Cells, including motor neurons in the body, have their own type of skeleton, known as a 'cytoskeleton'. A key protein/molecule that makes up the cytoskeleton is called 'actin'. In healthy cells, actin forms long branch-like cellular structures that continuously form and break. By looking at human MND spinal cord and MND models, this research team identified that actin does not function properly in MND, leading to the formation of too many long branches that accumulate in cells and disrupt normal cellular functions.

Project

The team have identified a new class of drugs that can break apart these long branches and restore the balance of actin in cells. In this study, they will test these novel drugs in multiple MND disease models and develop new drugs as promising candidates to prevent actin abnormalities. They will determine if these drugs are able to effectively enter the brain and which one is the best to develop as a potential drug candidate for MND. A positive outcome of this study will be to have this 'actin-repair' drug ready to test in a future clinical trial for MND patients in Australia.

FIGHT MND.

COMBINATION THERAPY TO IMPROVE CuATSM OUTCOMES IN MND

Prof Justin Yerbury
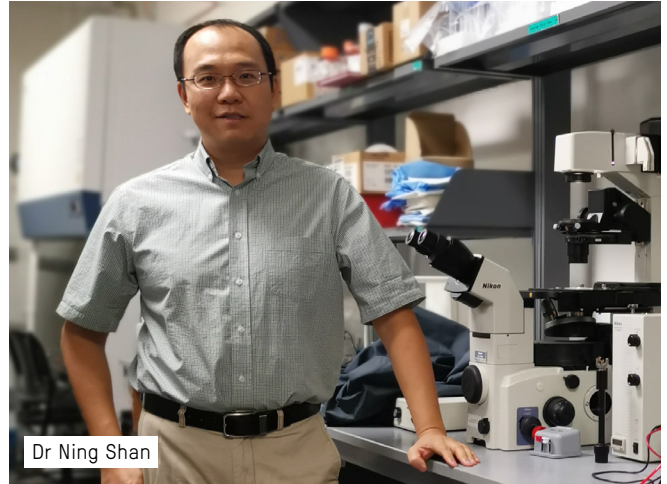(University of Wollongong)

Background

About 35% of people with inherited MND in Australia have mutations in the SOD1 gene. There are 150 different mutations in the SOD1 gene associated with MND and all change the structure and stability of the SOD1 protein. In motor neurons, such structural changes cause SOD1 protein to clump together, prevent harmful substances from being removed, and compromise the supply of energy to the cell, all of which are triggers for their death.

In preclinical studies, a drug called CuATSM (currently being tested in a Phase 2 MND clinical trial in Australia funded by FightMND) was effective in treating a variety of SOD1 MND models, and stopped the activity of a specific signal instructing motor neurons to die. Researchers hypothesise that the effectiveness of CuATSM may be enhanced if the treatment was combined with drugs that repair the structure of SOD1 protein and prevent SOD1 from clumping together.

The Project

Researchers in this project are using a three-pronged approach to tackle a hereditary form of MND in which a damaged molecule called SOD1 forms clumps and makes motor neurons unwell. The approach will test CuATSM in combination with two new drugs aiming to repair damaged SOD1 protein, prevent harmful SOD1 clumps from forming and block signals instructing motor neurons to die. The research team will determine the optimal drug combination ratio, and perform safety and efficacy tests of the combination therapy in preclinical MND models. The two new drugs are both approved medications, meaning that if effective, they can be fast-tracked through to a clinical trial. A successful project could deliver a new potential combination therapy for testing in a clinical trial for MND patients within 24 months.

Dr Ning Shan

DEVELOPING M102 TO TREAT MND

Dr Ning Shan (Aclipse One Inc, PA, USA)

Background

While the cause of MND is still unclear, it is widely accepted that a number of different cellular pathways contribute to the death of motor neurons. Drugs that target one of these pathways have the potential to slow down both the loss of motor neurons, and disease progression. M102, a novel small-molecule, acts on multiple pathways and therefore can target multiple disease mechanisms, offering enhanced opportunities for intervention. Investigators have identified that the antioxidant and anti-inflammatory properties of M102, together with its ability to improve a motor neuron's energy levels and its communication with other cells and muscles, may be beneficial for MND.

The Project

This project is focused on supporting the development of a drug called M102 through the final stages of testing so that it is ready to use in MND clinical trials within the next 3 years. These studies will include upscaling the manufacturing of M102, toxicology studies and biomarker studies that will develop a test to determine if M102 is reaching its target and having the desired effect. These studies are all critical final steps in the advancement of M102 towards a clinical trial in people with MND. The team hope to initiate a Phase 1 clinical study at the completion of this study in 2022.

COMPLEMENT C3A RECEPTOR MODULATORS AS DISEASE-MODIFYING DRUGS FOR MND

Prof Trent Woodruff
(University of Queensland)

Background

Although MND is a disease of the motor neurons, a number of other cells types also contribute to the disease. Immune cells are recognised as having an impact on the rate of disease progression in MND, with immune cell modulating drugs showing some early promising results in pre-clinical studies. Previous work from this team have identified a key protective role for a component of the immune system called C3a. They have shown that C3a is able to protect neurons, improves movement and prolongs life in preclinical MND models. The team have developed novel stable and selective drugs that can reach the brain at effective concentrations and can activate C3a.

The Project

This project aims to develop a new immune-protective drug to treat MND. The study will test their lead drug in both familial and sporadic models of MND and will also perform additional medicinal chemistry on the drugs to allow for the development of an orally active and brain-penetrating drug that will be appropriate for testing in clinical trials. Safety studies will also be performed to ensure the drug is safe for use in patients. A successful project outcome could be the development of a lead drug engaging and activating C3a, that is ready to test in a clinical trial for MND.

FIGHT MND.

IMPACT Projects

IMProving and **AC**celerating **T**ranslation (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
- Developing better models for studying MND in the laboratory

DEVELOPING BLOOD-BRAIN BARRIER PENETRATING PEPTIDES

Dr Fazel Shabanpoor (Florey Institute of Neuroscience and Mental Health)

Priority Area: Drug Delivery

Background

In the body, the brain and spinal cord are protected from circulating pathogens by a protective barrier called the blood-brain barrier. While the blood-brain barrier is vital to protect the brain from infection, it also creates one of the biggest challenges in treating any neurodegenerative disease - getting drugs across the barrier and into the brain and spinal cord where they are needed. Over the past two decades, the majority of human clinical trials for MND have failed to produce new treatments. This may not be due to the lack of drug potency, but rather the inability of the drugs to reach their targets in the brain and spinal cord in amounts which can achieve a therapeutic effect.

The Project

This project aims to address this critical issue by developing a drug delivery platform technology for safe and efficient drug delivery into the brain and spinal cord. The effectiveness of this drug delivery system will be tested by delivering 3 different classes of drugs into the brain and spinal cord. The expected outcomes of this project will be a safe and innovative drug delivery technology that allows drugs to reach their targets at sufficient amounts to achieve the desired therapeutic effects. Additionally, this delivery system is minimally invasive compared to current technologies, such as intrathecal injection, currently being used in the clinic. Overall, the outcomes of this project will have a significant potential to provide therapeutic benefit for this devastating neurodegenerative disease.

DEVELOPMENT OF A DOSE-ESCALATABLE AAV DELIVERY SYSTEM FOR MND GENE THERAPIES

Prof Roger Chung (Macquarie University)

Priority Area: Gene Therapies

Background

There is strong scientific interest in developing treatments called 'gene therapies' for rare neurodegenerative diseases such as MND. This is emphasised by the recent successful development and approval of a gene-therapy for a type of motor neuron disease called Spinal Muscular Atrophy (SMA). Gene therapies can work in a number of ways, either by delivering a lost gene, or acting as a gene switch, turning on a gene that has been inactivated or switching off a gene that is behaving abnormally. The switching on and off of genes is a tightly regulated process as too much or too little gene expression can have drastic consequences. While gene therapies have excellent potential for treating diseases, the control over the level of gene expression is critically important. Current methods do not have this level of control – they provide always on, high levels of gene expression – which may have adverse or detrimental effects if prolonged for many years.

The Project

This project will establish a new method for precise control of therapeutic gene expression by a gene therapy. The team will perform a proof-of-concept study of their new gene expression control system by combining it with a new gene therapy they are developing for MND. The gene therapy in this project will deliver a gene into motor neurons that removes a molecule called TDP-43. In MND, TDP-43 sticks together to form clumps that make motor neurons unwell. Investigators will establish a way to precisely control the dose of the gene therapy and target it specifically to motor neurons, to maximise its benefit and limit side-effects. Successful outcomes of this project will make an important contribution towards clinical development of this gene therapy for MND.

PRION-LIKE STRAINS OF TDP-43 AGGREGATES IN MND

Prof Justin Yerbury
(University of Wollongong)

Priority Area: Disease heterogeneity

Background

The clumping of materials called proteins within motor neurons is a key feature of MND. In the majority of MND patients, a protein called TDP-43 behaves abnormally, forming clumps that are thought to be harmful to motor neurons. Some of the TDP-43 clumps adopt a fibrillar 'rod-like' structure, similar to fibrils found in amyloid or 'prion-like' diseases, where harmful protein clumps begin forming at a single location, before spreading from cell-to-cell throughout the brain. The idea that TDP-43 acts in a prion-like manner in MND fits with the progressive nature of the disease, and is beginning to be supported by increasing evidence.

The Project

This project will test if TDP-43 protein from MND patients can initiate the clumping of TDP-43 in motor neuron models unaffected by MND, and determine if the structure of TDP-43 'rod-like' fibrils can affect the speed at which TDP-43 clumps form. The research team will examine the kinetic and biophysical properties of the TDP-43 clumps, and use cryo-electron microscopy, a new technology, to assess the structure of individual TDP-43 fibrils to define how their shape causes MND and variability in the speed and severity of MND among patients. An outcome of this project may be the identification of new components of TDP-43 protein clumps that can be specifically targeted with drugs in future studies.

Prof Justin Yerbury

USING BIOMARKERS TO ADDRESS MND HETEROGENEITY AND IMPROVE DETECTION TO BENEFIT CLINICAL TRIALS

Dr Mary-Louise Rogers (Flinders University)

Priority Area: Disease biomarkers and heterogeneity

Background

One of the barriers to developing treatments for MND are the highly variable rate of progression, and severity. A disease 'biomarker' (biological marker) is a measurable marker that changes with changes in disease progression. Biomarkers can be used to help diagnose patients, predict the rate of disease progression, create sub-groups of patients, or provide a measurable readout that a drug is providing benefit in clinical trials. This research team have previously identified a protein in urine of people with MND called p75ECD that can track progress of MND and be used in clinical trials to track disease progression. This was a significant break-through and p75ECD has been used as a validated biomarker to track treatment effect in many clinical trials. The team have also recently identified another urinary biomarker called Neopterin, related to the immune system activation, that is increased in MND compared to healthy people.

Project

This project will investigate how fluid based biomarkers can be used to evaluate variability in disease severity, progression and response to treatment for MND. The team will utilise the Ian Davis Flinders University Biomarker Facility, a new high-through-put facility that enables large numbers of patient samples from clinical trials to be assessed for MND biomarkers rapidly and effectively. The team will use these novel urinary biomarkers to measure the rate of progression and response to treatment in a clinical trial setting. This will determine if biomarkers can be used to identify groups of patients with the same rate of decline and survival. Grouping patients with similar speed and severity of MND will help with clinical trial patient recruitment and increases the chance of identifying effective treatments in clinical trials.

IDENTIFYING BIOMARKERS FROM EXTRACELLULAR VESICLES FOR EARLY DETECTION, DISEASE PROGRESSION AND THERAPEUTIC EFFICIENCY IN MND

Prof Aaron Russell (Deakin University)

Priority Area: Disease biomarkers

Background

A major stumbling block in developing a cure for MND is a lack of reliable biofluid biomarkers for diagnosis and prognosis of the disease. It is also hard to know if treatments are actually reaching their intended targets. A recently developed preclinical model of sporadic MND may provide a solution owing to its unique properties in which MND can be precisely initiated, halted, and reversed. This allows researchers to know exactly when to look for early diagnostic biomarkers before symptoms appear, prognostic biomarkers as MND progresses, and biomarkers of recovery that may assist in quickly recognising if drugs designed to treat MND are effective.

The Project

This project will measure and compare changes in proteins found in the blood of the new preclinical model of MND and MND patients to try to identify ways to accurately detect MND and pinpoint how long a person has lived with MND. Using the latest proteomics and bioinformatics technologies, the research team will assess the amount of proteins in a small component of blood called extracellular vesicles to establish a biomarker profile of MND onset, progression and recovery in the preclinical model, and a biomarker profile in MND patients when asymptomatic and symptomatic. A successful project could deliver a suite of new biomarker signatures for use in current and future clinical trials to accurately measure treatment responsiveness. By enabling the identification of MND patients with a similar prognostic outlook, the biomarkers could also improve clinical trial outcomes.

LIPIDOMIC SIGNATURES IN BLOOD AS A NOVEL BIOMARKER FOR MND

Dr Sophia Luikinga (Florey Institute of Neuroscience and Mental Health)

Priority Area: Disease biomarkers

Background

Diagnosis of MND is a lengthy and complicated process, and it can take 2 years to get a conclusive diagnosis after symptoms are first detected. So far, no biological marker that can shorten this process or predict the prognosis of MND is available. However, researchers are beginning to uncover links that may exist between the body's fat composition, metabolism and MND prognosis. Metabolic lipids, for example, which are essential for motor neuron function and their communication with muscles, are dysregulated in both preclinical MND models and MND patients. Because lipids can be detected in blood samples, they have the potential to be developed into specific MND biomarkers for accurate diagnosis and prognosis of the disease.

The Project

This project aims to develop a blood test that detects materials, called lipids, that are known to change in MND. Investigators will use a highly sensitive detection method to assess the levels of specific lipid metabolites in serum and plasma of both preclinical MND models and MND patients. The research team aims to validate that their panel of blood-based lipid biomarkers can accurately diagnose MND in people and, in preclinical models, test the prognostic ability of the blood-based lipid biomarkers. The investigators will also examine if the lipid biomarkers can measure the effectiveness of drugs used to treat MND now and in the future. A successful project could deliver new biological markers that detect MND, accurately predict the speed of disease progression, and quickly assess the effectiveness of potential treatments for MND patients.

DEFINING AN ELECTRICAL SIGNATURE OF SPORADIC MND, AND DEVELOPING A DRUG SCREENING TECHNOLOGY AND NOVEL THERAPY

A/Prof Lezanne Ooi (University of Wollongong)

Priority Area: Disease biomarkers and models

Background

Motor neurons talk to each other using electrical signals. However, motor neurons are excessively active in MND, which prevents them from communicating appropriately. Ultimately, the excessive activity in motor neurons causes them to lose function and die, as has been demonstrated in preclinical MND models. Previously, this research team has shown that motor neurons developed from MND patient stem cells are also overactive. They are now predicting that the overactivity of these motor neurons can be measured to identify an electrical signature and biomarker of MND.

The Project

This project aims to identify how electrical signals change in motor neurons to make them unwell. The research team will use stem cells from MND patients to develop spinal cord-like motor neurons and 3-dimensional models of the cortex, called cortical organoids. Electrical signals used by motor neurons within these models will be assessed using cutting-edge technologies such as microelectrode array stimulation, machine learning and artificial intelligence. Investigators hope to identify an electrical biomarker signature of motor neurons affected by MND, and will attempt to modify their activity to enable them to function like healthy motor neurons. A positive outcome for this project would be the development of a high-throughput screening platform for preclinical testing of new strategies aimed at reversing hyperactivity, loss of function and death of motor neurons.

USING 3D SPINAL CORD ORGANOIDS TO MODEL OLIGODENDROCYTE NEUROTOXICITY IN MND

Dr Samantha Barton (Florey Institute of Neuroscience and Mental Health)

Priority Area: Disease models

Background

In order to study MND in the laboratory, researchers use models of the disease developed to replicate hallmarks or disease signatures seen in the human disease. In the past, researchers have relied on animal models to study MND, but recent advances in technology have allowed them to grow stem cells (called iPSCs) from MND patient skin cells, creating a "human" model of MND. These stem cells can be turned into almost any cell type in the body, depending on which cell type or disease that is being studied. For MND, these cells include motor neurons, but also supporting cells called 'glia'.

More recently, this technology has advanced even further, with researchers now able to grow multiple cells types in parallel. When cells and their support cells are grown together, they develop into complex 3-dimensional mini organs or 'organoids' which provide a unique and sophisticated 'human' model of the affected organ.

The Project

This project will use MND patient's skin cells to grow stem cells and generate motor neurons and glia in order to create a 3-dimensional mini-spinal cord organoid. The team will use the mini-spinal cord to study a type of glia called an oligodendrocyte, which are important in providing structural support and energy supply to motor neurons. In MND, both structural support and energy supply to motor neurons are significantly altered and could contribute to the death of motor neurons. Using this novel mini-spinal cord model, the team will comprehensively characterise the contribution of oligodendrocytes to motor neuron dysfunction and death. Importantly, because they use patient's own stem cells, they will be able to generate mini-spinal cords from an array of patients with familial and sporadic MND, thereby attempting to span the variability of MND. By determining how oligodendrocytes contribute to motor neuron dysfunction, the team hope to unravel new drug targets surrounding oligodendrocyte function.

FIGHT MND.

Additional Research Investments

FightMND will also provide further support to strengthen operations of the Sporadic ALS Australian Systems Genomics Consortium (SALSA-SGC) and the Victorian Brain Bank.

Through SALSA-SGC, Australians with MND are contributing to a big-data research resource that combines clinical, lifestyle and biological information. The resource will be a powerful tool for uncovering the causes of MND, advancing clinical trials and developing more effective treatments.

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.

A PhD student will be supported by the Angie Cunningham Scholarship throughout their 3.5-year candidature, enabling a bright and vibrant young researcher to embark on their pursuit of developing a cure for MND.

FightMND will continue to foster and advance MND Research in Australia through its support of the Australian Summit for MND Research in November this year. In collaboration with MND Australia, FightMND is playing a leading role in facilitating the national summit that will set a pathway that drives MND research in Australia into the future.