2019 FightMND IMPACT Projects

INTRODUCTION

Motor Neurone Disease was first described over 150 years ago but still remains a terminal diagnosis with no effective treatments or cure. While advances in research over the last 25 years have been remarkable, innovations and progress have so far failed to translate into significant disease modifying therapies or a cure.

To accelerate the development of effective therapies for MND, FightMND IMProving and Accelerating Translation (IMPACT) grants support projects focused on overcoming one or more key barriers preventing the translation of potential treatments through to clinical trial.

In 2019, FightMND awarded 7 IMPACT projects dedicated to accelerating promising research discoveries through to clinical trials and effective treatments for MND. Profiles of leading researchers awarded IMPACT projects and details of each project are outlined in this document.

FightMND IMPACT PROJECTS AWARDED IN 2019

FIGHT MND.


Prof Julie Atkin

Researcher.
PROF JULIE ATKIN

IMPACT Project.
DISEASE SUSCEPTIBILITY, PRECISION MEDICINE AND ALS

Where do you work?

At the Macquarie University Centre for Motor Neuron Disease Research, a recognised centre of expertise within the university.

What is your research experience and background?

I am a cell biologist/biochemist and I have worked exclusively on MND for the last 16 years. My research involves investigating the basic cellular processes that trigger neurodegeneration in motor neuron cells in this disease.

Which of your scientific findings so far do you value most?

We were the first group to identify the normal function of C9orf72, the protein which becomes mutated in the most common genetic forms of MND. We have also uncovered several molecular pathways that are triggered in MND. From this, using funding obtained previously from FightMND, we are developing drug-like compounds as possible new treatments. These compounds are based on accurate understanding of the underlying cellular mechanisms involved in MND.

Can you describe the current focus of your research team?

My group aims to discover at the molecular and cellular level what makes motor neurons begin to degenerate and ultimately die in MND, with the aim of designing new drugs to prevent this from happening.

What is exciting to you about the Macquarie Neurodegenerative diseases biobank?

The scale and scope of the patient samples available in the Macquarie Neurodegenerative Diseases Biobank is unique in Australia. The Macquarie Neurology clinic, led by Professor Dominic Rowe, treats approx. 10% of Australians living with MND (~220 patients), and we collect blood, urine, hair and skin biopsies from participants at each visit. Importantly, we have extensive clinical information available, and we can assess patients as the disease progresses over time, providing valuable insights into the disease mechanisms involved in MND. We also have the unique opportunity to integrate our findings with other studies using the biobank in the Centre. Our biobank is therefore unparalleled in its breadth of MND samples for which detailed clinical information is available. In addition, we have been awarded NSW Health certification for the Biobank, which attests to the high-quality of our sample collection protocols and procedures for sample processing, which will ultimately improve the accuracy of our research findings. In summary we have access to a unique platform in Australia in the Biobank with an unrivalled set of clinical information.

What will this funding allow your team to achieve?

MND is very variable in terms of clinical symptoms, site/age of onset, disease duration, and its association with other conditions such as dementia. In fact, it is sometimes thought that MND is a

group of disorders rather than a single disease. Remarkably, not all motor neurons in the body are targeted equally, which leads to this clinical diversity. This project aims to identify protein markers that dictate why specific motor neurons are more vulnerable than others in MND, leading to this clinical heterogeneity. From this, we aim to identify subgroups of patients that display unique characteristics, in which specific therapeutic approaches may be more effective than in other types of MND. The protein markers we will examine have never been examined before with such an extensive collection of clinical samples. We therefore aim to lay the groundwork for the development of a 'precision medicine' approach to MND, to develop optimal targeting and timing of treatments.

IMPACT Project.
DISEASE SUSCEPTIBILITY, PRECISION MEDICINE AND ALS

This project will make use of the extensive collection of samples from MND/ALS patients in the Macquarie University Neurodegenerative Diseases Biobank. This Biobank is unparalleled in Australia in its breadth of MND samples, for which extensive clinical information is available. It collects blood, urine, hair and skin biopsies from participants at each clinic visit over the course of disease. The high-quality of the biological samples in this Biobank is recognised with certification by NSW Health in March 2019.

This project aims to identify protein markers that are closely linked to the vulnerability of motor neurons in MND/ALS. We aim to identify subgroups of patients that display specific or unique molecular characteristics using these markers, in which therapeutic approaches may be particularly effective, using innovative new statistical approaches such as machine learning. These markers have never been examined before with such an extensive collection of clinical samples. We therefore aim to lay the groundwork for the development of a 'precision medicine' approach to MND, to ultimately develop optimal targeting and timing of treatments for MND. This project should therefore lead to tailored interventions and the development of precision medicine approaches in the future.

OBJECTIVES:

- To accurately identify and categorise MND/ALS patients into groups defined by the presentation of distinct biochemical markers and disease features.

OUTCOMES:

- Identify biomarkers of MND/ALS based on disease mechanisms and symptoms, that categorise specific patient subgroups, and can be used to determine therapeutic approaches for patients that optimally target their disease causes.
- Provide the first steps towards the development of new therapeutic strategies that are tailored to specific sub-groups of MND/ALS patients that share distinct symptoms.

Processing samples at the Macquarie University Neurodegenerative Diseases Biobank.

FIGHT MND.


Dr Mouna Haidar

Researcher.
DR MOUNA HAIDAR

IMPACT Project.
ESTABLISHING A NOVEL MOUSE MODEL OF SPORADIC MND

Where do you work?

In the MND Laboratory at The Florey Institute of Neuroscience and Mental Health, University of Melbourne.

What is your research experience and background?

I obtained my PhD in Neuroscience and am now a Postdoctoral Fellow in the MND Laboratory at The Florey headed by A/Prof Bradley Turner.

How did you begin your research into MND?

I have always had an interest in understanding how the brain works, both under healthy and diseased states. I am passionate in applying this knowledge to the MND field to help further elucidate what goes wrong in brain circuits and motor neurons in MND.

Can you describe the work you are currently pursuing?

I am using an innovative and powerful chemogenetic technique called “DREADD” technology, which allows for the selective and chronic activation of targeted neuronal populations in the mouse central nervous system. I am using this technique to experimentally model an early and common pathological feature which occurs in all MND patients, called brain cortical hyperexcitability, and the associated subsequent MND neuropathology and symptoms. Brain cortical hyperexcitability is a disease process occurring in MND in which motor neurons become electrically overstimulated and overloaded, leading to their demise.

Why did you choose to develop this model of MND?

Inherited MND is quite rare, occurring in only 10% of patients, with the remaining 90% of patients having sporadic MND. So far, translation of promising therapeutic outcomes from MND mouse models to patients have been unsuccessful. This is partly because most studies have utilised mouse models based on rare genetic forms of MND, which may not adequately replicate disease features common to the mostly sporadic MND population. Therefore, there is an urgent need to develop a preclinical mouse model relevant to sporadic MND patients.

What excites you about this model?

This is a world-first attempt to model features of sporadic MND in a mouse model. Our model opens an exciting and novel avenue to study the disease mechanisms of sporadic MND, and test therapeutic candidates in a mouse model which recapitulates the core features of sporadic MND.

What difference will this funding make to your work?

Funding for this IMPACT project from FightMND will allow for the development and validation of the first mouse model that displays core features of sporadic MND, which would have otherwise not been possible. This project will open up an exciting avenue to study the disease processes of sporadic MND and test therapeutic candidates in a novel and relevant preclinical model.

FIGHT MND.

IMPACT Project.
ESTABLISHING A NOVEL MOUSE MODEL OF SPORADIC MND

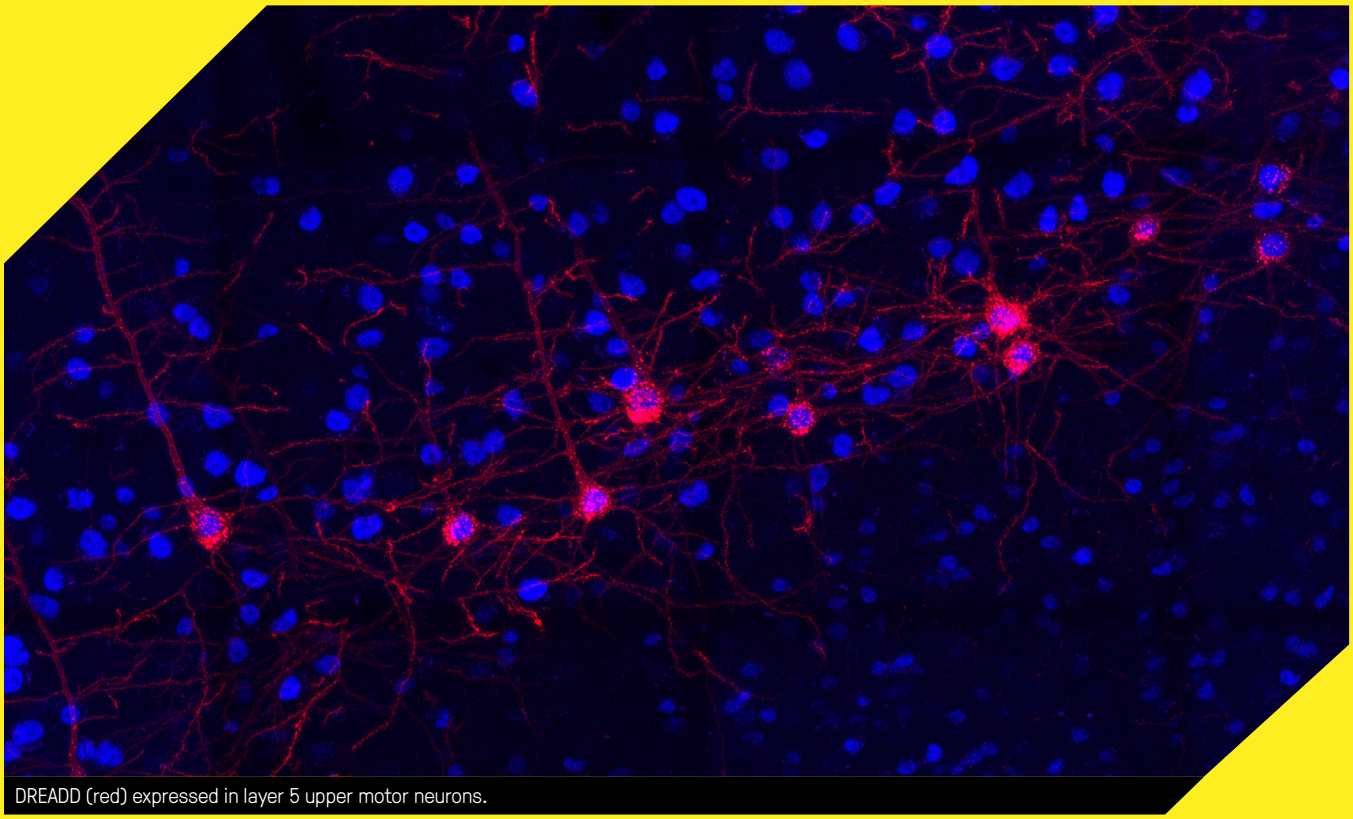
Inherited motor neuron disease (MND) occurs in only 10% of patients, with the remaining 90% of MND patients having sporadic disease. To date, translation of findings from MND mouse models to the clinic have been unsuccessful partly because most studies have been based on genetic mouse models of MND, which have subsequently failed in a mostly sporadic MND population. The failure to translate the positive outcomes of drug testing in mice into successful drug trials in humans has questioned the relevance of existing preclinical models for sporadic MND patients.

OBJECTIVE:

To overcome this major limitation, this project will develop a novel mouse model of sporadic MND that does not have genetic links. To achieve this, an innovative and powerful tool called DREADD technology will be used in mice to experimentally model the hyperexcitability and overactivity of motor neurons that occurs in all forms of MND.

OUTCOMES:

- Development of the first mouse model that mimics sporadic MND.
- Testing of potential therapeutic agents in this new preclinical mouse model aimed at preventing the onset/progression of MND.



DREADD (red) expressed in layer 5 upper motor neurons.

FIGHT MND.

Researcher.
A/PROF ANTHONY WHITE

IMPACT Project.
PATIENT MONOCYTE-DERIVED MICROGLIA FOR PRECISION TREATMENT OF NEUROINFLAMMATION IN MND


A/Prof Anthony White

Where do you work?

QIMR Berghofer Medical Research Institute, Queensland.

Can you summarise your research experience and background?

I have spent more than twenty years researching degenerative diseases of the brain, including motor neuron disease, and dementia. My research has focused on understanding the underlying disease pathways and developing potential therapeutic treatments for these diseases. This has included research experience at University of Melbourne, and Imperial College of Medicine in the UK. Now, much of my research is done in close collaboration with researchers in Finland and Italy.

What has been your favourite scientific finding so far?

My favourite and most important scientific finding was when my research team demonstrated the therapeutic potential of copper-delivery agents that were developed in collaboration with Profs. Paul Donnelly and Kevin Barnham, University of Melbourne. This led to the development of copper-ATSM, which is now in clinical trials for MND.

What is the current focus of your research laboratory?

We are now developing new human, and patient-focused cell models of MND and dementia. These are urgently needed to improve drug targeting, especially to individual patients, and improving the success of drug translation into the clinic.

How did you identify that monocyte-derived microglia could be beneficial for developing new treatments for MND?

Once we had developed the model system through a lot of great work by Dr Hazel Quek in my group, we already had a strong collaboration with Prof. Vincenzo La Bella in Italy, who heads an ALS research centre in Palermo. We were both very excited at the prospect of examining microglia generated from people with MND/ALS and were able to achieve this through the collaboration. We didn't know what to expect, but the initial experiments identified key changes in the function of the microglia from people with ALS.

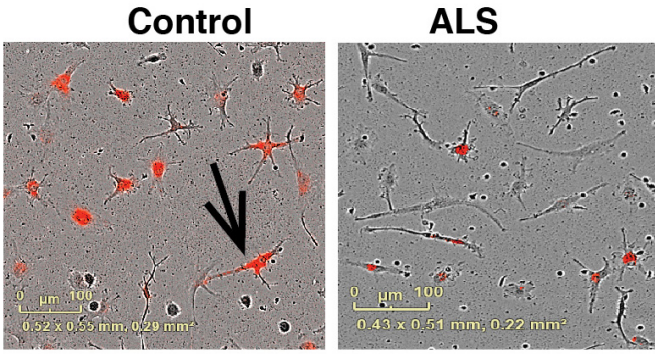
What excites you about this approach to developing new treatments?

This is really the best approach available to characterise the differences between MND/ALS patient microglia and matched controls in a time and cost-effective model. It also will allow a clinically applicable approach to testing new and re-purposed drugs, and allow us to determine if there are patient-to-patient differences in drug action. This patient-oriented approach cannot be achieved on a suitable scale with any other system at present.

FIGHT MND.

What will this funding allow you to achieve?

The funding will be an extraordinary boost for us and we are very excited to receive this wonderful support from FightMND. The funds will allow us to gain a strong insight into how microglia differ between people with MND and healthy controls, and identify patient-specific changes that can be targeted. We will also be able to set up a drug screening platform to search for new and re-purposed drugs to target individual patients. This will put us in a great position to boost clinical translation of drugs for treatment of MND.



The difference between phagocytosis (uptake of red particles) in MND/ALS microglia compared to control.

IMPACT Project.
PATIENT MONOCYTE-DERIVED MICROGLIA FOR PRECISION TREATMENT OF NEUROINFLAMMATION IN MND

We are developing a unique assay platform that will allow, for the first time, the testing of immune-modulating drugs on individual patient brain immune cells (called microglia). Microglia provide the main form of immune defence in the brain, and their function is compromised in MND. A major issue in developing new drugs for treating MND is the diverse nature of the disease course and the individual patient genetic background and lifestyle. These factors have a major influence on how the immune system, including microglia, acts in each person. This diversity has contributed to the failure of many drugs in clinical trials designed to normalise microglia function in MND.

To overcome this problem and provide better outcomes for people with MND, we need a lab-based test that allows us to examine drug effects on each person's own microglia in a rapid and reproducible manner.

Our advanced cell-based platform will allow drugs to be tested for efficacy on individual patients, and allow real-time monitoring of drug efficacy across the disease course and during clinical trials. The approach will help select appropriate patients for clinical trials of new drugs, avoiding unnecessary treatment of people who are less likely to benefit, and enabling these patients to be involved in alternative treatment options. Our platform is generated using microglia grown from human peripheral blood monocytes. This approach is highly cost-effective and rapid compared to other methods for preparing human microglia. These microglial cells can be screened with different drugs to enhance their protective functions, allowing us to determine which drugs will likely benefit each patient.

OBJECTIVE:

- Demonstrate that microglia from MND patients can be used to screen for potential inflammatory modulating compounds in 'real-time', and personalise MND treatment.

OUTCOMES:

- Devise a rapid and cost-effective patient-specific drug targeting scheme to normalise immune cells in MND patients.
- Using microglia from MND patients, identify patients best suited for clinical trials of newly developed drugs aimed at normalising the function of immune cells in the brain.

FIGHT MND.

Researcher.
DR FREDERIK STEYN

IMPACT Project.
POINT OF CARE ASSESSMENT OF VENOUS ACID-BASE BALANCE AND CREATININE AS MARKERS FOR DISEASE PROGRESSION IN MND


Dr Frederik Steyn

Where do you work?

The University of Queensland. My position is with the School of Biomedical Sciences (Lecturer, Anatomy and Pathology, Medicine) and my research is conducted between the Centre for Clinical Research and The School of Biomedical Sciences.

What is your research experience and background?

I received a Master's Degree in Anatomy in 2002, and a PhD in Anatomy, Structural Biology and Neuroendocrinology in 2007. I then relocated to Australia commencing postdoctoral research at the University of Queensland, studying the hypothalamic integration of energy homeostasis, growth and reproduction, with a focus on the impact of obesity and metabolic syndrome on overall health. During this time I developed an interest in understanding the metabolic changes that occur in preclinical models of MND, and how this might be relevant to disease progression. I completed a series of experiments that improved our understanding of the release and impact of growth factors that promote the reinnervation of muscle. Subsequently, I expanded my research program to include clinically-focussed studies, to better capture the heterogeneity of MND. In 2015, I co-founded the first Australian project to comprehensively assess the metabolic impact of MND on disease progression in patients. These studies were the foundation for a much larger research program that includes preclinical and clinical studies aimed to improve our understanding of the impact of MND on the body, and how this relates to disease heterogeneity and progression.

What led you to pursue your investigations into MND?

I moved to Australia in 2008 to support my parents in Brisbane. My mother had been diagnosed with early-onset frontotemporal dementia (FTD). She had a rapid progressing form of disease, and I took on the role as care-giver. She passed away within a year of my arrival. This was a very challenging experience, and following my mother's passing I was motivated to reposition my career focus to improve knowledge that could contribute to the treatment of neurodegenerative disease. I found it easier to focus on neurodegenerative diseases other than FTD as I was still coming to terms with my mother's death. It was difficult to process emotions around the impact of FTD, both on the individual but also on their families. We never completely recovered. I gravitated towards MND. During this time, I also met research collaborator and wife, Dr Shyuan Ngo. Shu was conducting studies in MND and we combined her interests in neuroscience research and my expertise in the field of metabolism to create a combined MND/Metabolism research program. As I became more involved in studies in MND I had opportunities to meet and spend time with people living with MND;

this included the late Dr Ian Davis. I spent two weeks travelling from Brisbane to Sydney with Ian, during which I learnt more about the impact of MND on the individual, and their community. Since, my motivation to develop treatments for MND is largely motivated through the friendships I have developed within the MND community, and the people directly impacted by MND. I am inspired by their refusal to allow MND to change who they are, and their commitment to create a better world for future patients with MND. I am inspired by the families of those living with MND, and the strength of the MND community.

Can you describe the research your team is currently focusing on?

My team conducts preclinical and clinical studies in MND, with a specific focus on factors that impact disease progression. My research is based around three C's: Care, Cure and Community. Under the umbrella of Care, I conduct preclinical (i.e. animal model) and clinical (i.e. patient studies) studies that focus on factors that impact the progression of disease and quality of life; this includes studies on metabolism and appetite. I am also developing novel approaches to improve our capacity to monitor the progression of disease (biomarkers). My focus is on causes and markers of weight loss, and factors that can improve detection of respiratory insufficiency and the progressive worsening of disability. Under the umbrella of "Cure", I am testing drugs that target multiple components of disease, with the hope that these compounds will offer therapeutic benefits across a wider spectrum of patients and across multiple disease subtypes. A key component of my work involves the MND "Community"; I am committed to connecting with as many patients as possible. This is through regular engagement with MND organisations to share research insights, the development of patient-focussed seminars and symposia, and involvement in events that raise awareness for MND. I am also developing strategies to allow inclusion of more people with MND in research; In 2020 this will include the provision of support for people across Queensland to attend research studies in Brisbane. Queensland is a very large state, and many patients with MND are isolated. I'm aware that research, while providing critical information to improve our understanding of MND, can offer hope. Through engagement with the community I get to say thank you for the support we receive to conduct our studies, and found that discussions with people living with MND also highlight critical areas for improved research focus.

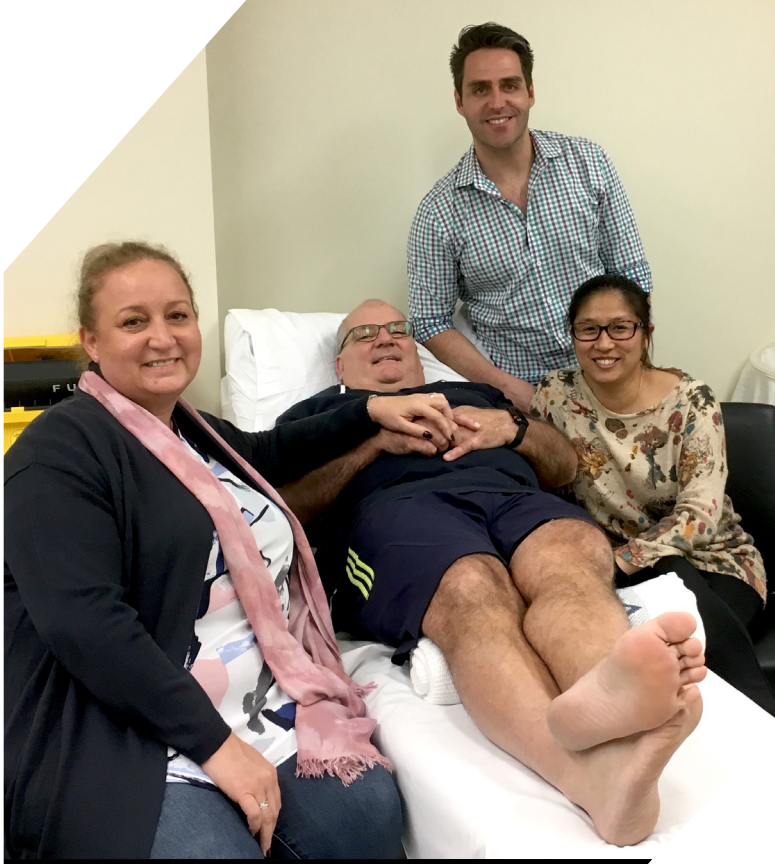
What excites you about the new tests you are developing?

Developing this blood analysis technology will free up valuable time for people living with MND. I am most excited by the fact that this test could provide measures that will better direct the individual to seek support when needed. There is the added benefit that this method will also help people that are far from specialists centres that conduct respiratory tests. I am hopeful that these measures will direct patients to a respiratory physiologist at the most appropriate time for introducing effective breathing support. This will greatly improve their quality of life, and there is potential to slow the progression of MND. If this technology allows one patient to spend more quality of time with their families then I will consider this project a success.

What difference will this grant make to your work?

We have completed pilot studies at the Royal Brisbane & Women's Hospital to show the utility of point of care testing of blood gas markers in MND, however these results are not likely to change clinical practise. Measures are collected from a relatively small cohort of patients within a single MND research clinic. To expand the utility of this method, and to convince an international body of researchers and clinicians to use the technology, this grant will allow the conduct of a much larger and multi-site study. The study will be conducted across Australian and European sites, and will incorporate new and evolving questionaries that are being developed to inform our understanding of respiratory failure in MND. Ultimately, this should fast-track the development of measures that promise to improve clinical care for people with MND.

FIGHT MND.



A typical day for Dr Frederik Steyn, Dr Shyuan Ngo and study participants in the research clinic.

IMPACT Project.

POINT OF CARE ASSESSMENT OF VENOUS ACID-BASE BALANCE AND CREATININE AS MARKERS FOR DISEASE PROGRESSION IN MND

This project will test the use of a portal blood analysis device that can measure components of blood-gas exchange in less than a minute – it is expected that these measures will provide critical information on the health of a person's lungs, in the context of MND. This is important as impaired breathing in MND is a leading cause for loss of quality of life, and most patients die as a consequence of respiratory failure. Early and effective intervention to improve oxygen supply improves quality of life and delays death. During research visits with patients', discussions often centre around their frustration with having to complete routine breathing tests. Patients noted that these tests were exhausting, and felt that they were not always needed. Patients felt that the time spent at the hospital could be better invested. Many patients missed critical breathing exams, and mentioned that their results from these exams could vary greatly relative to how they felt on the day, based on who conducted the test, and their ability to use equipment needed for lung function testing (for example, patients with bulbar symptoms could not reliably conducts tests). This is of concern, as improper testing and the resulting delayed intervention could significantly impact quality of life.

These discussions motivated me to look for alternative methods to monitor breathing in patients with MND. I tested a number of approaches, and ultimately settled on the device tested in this project as the technology offers a reliable measure that doesn't increase patient burden. I was also motivated to develop a technology that provides immediate feedback to clinicians (i.e. results are generated immediately), as this will ensure that information can be used to inform immediate care – in this case, results will hopefully identify patients with immediate needs for specialists breathing assessments.

OBJECTIVES:

- To validate that specific biomarkers measured during on-the-spot blood tests reliably detect symptoms of MND, including insufficient breathing and weakening of muscles required for breathing, as well as the onset and progression of MND.
- To assess blood gas exchange biomarkers in MND patients and compare them with clinical measures of respiratory function and progression of MND.
- Adoption of these biomarkers for detecting the onset and progression of MND within 2 years.

FIGHT MND.


Dr Fleur Garton

Researcher.
DR FLEUR GARTON

IMPACT Project.
A NOVEL BIOMARKER FOR ALS

Where do you work?

I work at the University of Queensland's Institute for Molecular Biosciences.

What is your research experience and background?

I began my research career in a neuromuscular research group based at Westmead Children's Hospital in Sydney under the guidance of Professor Kathryn North. My PhD investigated the genetic contribution of a variant involved in muscle function and following this, I moved with Kathy to Murdoch Children's Research Institute in Melbourne. I have been at the University of Queensland with Professor Naomi Wray since 2016 where the research has focused on understanding the genetic contribution to Motor Neurone Disease.

What led you to pursue your research into MND?

I have a passion for improving the lives of those affected by neuromuscular disease. MND is a devastating disease with a severe prognosis. Without a clear cause for many of those affected – I was keen to make a difference.

Can you describe the research your laboratory is currently focusing on?

We are focused on understanding the genetic contribution of MND. This includes tracking disease and we have begun an investigative study to look at cell-free DNA (short fragments of DNA floating in the bloodstream) to see if it can provide insight into mechanisms involved in MND and an easy way to diagnose or track the condition.

How did you identify that cell-free DNA has the potential to detect MND?

Cell-free DNA is a by-product of cells turning over. It is widely used in prenatal screening to analyse the baby's DNA using the mother's blood and is also being used in cancer – where tumour DNA can be assessed for causative mutations. Given MND is a rapid disease with many cells affected, we thought investigating the cell-free DNA profile was a worthwhile project to initiate and complement our other genetic and phenotypic investigations.

What excites you about cell-free DNA?

A simple blood test that can provide a snapshot of what is going on in the body would be a game changer for MND – cell-free DNA might help us in this domain.

What difference will this grant make to your work?

This grant will provide us with the means to collect and analyse cell-free DNA profiles from those with and without MND. Any findings can then be followed up in a larger cohort to see if they can contribute to the development of a robust biomarker test to diagnose and track MND. We are incredibly thankful for the FightMND organisation and its supporters for making this possible.

FIGHT MND.

IMPACT Project.
A NOVEL BIOMARKER FOR ALS

Motor neurone disease (MND) currently affects ~2000 Australians, many of whom have spent over one year searching for a diagnosis. MND typically involves a rapid decline of function and there is no validated biomarker to speed up diagnosis, track or evaluate treatment effectiveness. The lack of a robust, objective biomarker is a critically missing element needed to evaluate MND clinical trials.

Cell-free DNA (cfDNA) may provide a rapid, efficient and sensitive solution to this problem. cfDNA is simply the product of cellular turnover, in which DNA originating from a cell's nucleus is detected in the circulating blood. cfDNA is increased in the blood of ALS patients (the most common type of MND) and can be profiled to recognise the originating tissue/cell. We propose that an MND/ALS specific cfDNA signature may be detectable during the disease course, ultimately leading to a blood test that could be requested at first presentation to a local clinic, or used to track disease progression.

OBJECTIVES:

To genetically profile blood-test-derived cfDNA samples from individuals presenting with MND symptoms and age-matched controls. Results from testing will be paired with a rich set of clinical data to ensure development of a robust and 'fit for purpose' test for the diagnosis, prognosis, prediction or tracking of MND.

OUTCOMES:

1. Development of a rapid, efficient, sensitive and economical way to speed up diagnosis and track the progression of MND/ALS with blood sample-derived genetic biomarkers. An early detection diagnostic screening test for MND would open the window to earlier therapeutic interventions, well before the disease has progressed.
2. cfDNA profiling will build a deeper understanding into the biology of ALS and provide unique insights into therapeutic avenues that have not yet been considered.
3. Advancement of a test that provides an accurate evaluation of MND clinical trials and the effectiveness of treatment.

FIGHT MND.

Researcher.
A/PROF JOSEPH NICOLAZZO

IMPACT Project.
CHARACTERISING BLOOD-BRAIN BARRIER DYNAMICS TO ENHANCE DRUG DELIVERY AND OPTIMISE MEDICINE USE IN MND


A/Prof Joseph Nicolazzo

Where do you work?

I am an Associate Professor and Associate Dean, Graduate Research, at the Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, and a researcher at Monash Institute of Pharmaceutical Sciences.

What is your research experience and background?

I trained as a pharmacist and have always been interested in how drugs accessed different parts of the body. My PhD focused on how drugs could be absorbed across the buccal mucosa as an alternative route to oral drug delivery, a research area in which I am still active. My current major research interest, however, is understanding how drugs and endogenous agents are trafficked across the blood-brain barrier (BBB) and how this alters in neurodegenerative diseases - a better appreciation of these phenomena will assist in identifying approaches to more effectively deliver drugs to their site of action in the brain, given the restrictive nature of the BBB in preventing drug access to the central nervous system.

How did you come to work in MND research?

In my BBB research program, I have mainly focused on Alzheimer's disease. In 2018, I was invited to present my findings on the BBB in Alzheimer's disease at the Australasian MND Symposium. I was not only taken by the enthusiasm of the MND research community, but I was particularly touched by the number of individuals with MND at the symposium rightly advocating for more research to cure this disease. I felt that applying my BBB experience to MND could therefore benefit the many individuals with MND by accelerating the drug development process for MND therapeutics.

Can you describe the research your team is currently pursuing?

My research focuses on identifying how the trafficking of drugs across the BBB alters in neurodegenerative disease, particularly Alzheimer's disease and now MND. In this research project, we will use both mouse models of MND and stem-cell based BBB models to assess whether the levels of drug transporters are altered in MND and whether this leads to altered brain uptake of drugs and naturally-occurring molecules.

How can the blood-brain barrier be used to improve MND treatments?

By understanding if BBB drug transporters and drug access to the brain are altered in MND, we will be able to identify approaches that may be exploited to enhance brain access of drugs in MND. One of the major barriers to the clinical success of potential therapeutics for brain diseases is their inability to cross the BBB. By identifying which BBB drug transporters are increased, we can design drugs or delivery vectors to overcome the restrictive nature of the BBB and improve the potential for new drugs to reach their site of action within the brain.

FIGHT MND.

What excites you about induced-pluripotent stem cell models?

The ability to develop a BBB model based on stem cells derived from individuals with MND means we can, for the first time, recapitulate a biological barrier present in individuals with MND. This should enhance the translation of results obtained in the laboratory and accelerate the application of our drug delivery approaches into the clinical domain.

How will this funding impact on your work?

This funding will really allow our research group to extend the knowledge we have gained on the BBB in Alzheimer's disease to MND, another major neurodegenerative disease. I strongly believe that, due to the funding provided by FightMND, we can identify novel ways to target therapeutics to the brain, overcoming one of the major barriers in central nervous system drug development. This will ultimately bring us one step closer to a therapeutic solution for MND.

IMPACT Project.
CHARACTERISING BLOOD-BRAIN BARRIER DYNAMICS TO ENHANCE DRUG DELIVERY AND OPTIMISE MEDICINE USE IN MND

In order for any potential therapeutic for MND to exert its disease-modifying effect, it needs to reach the brain. However, the ability of a drug to cross from the bloodstream into the brain is extremely low given the presence of a protective lining between the blood and brain; the blood-brain barrier (BBB). Based on what is known about the healthy BBB, researchers attempt to trick shuttles present on the BBB to carry drugs across the BBB; this has not resulted in success to date as the levels of such BBB shuttles are likely to be modified in MND, as they are in other brain diseases, altering drug uptake capacity and questioning the utility of these targeting approaches.

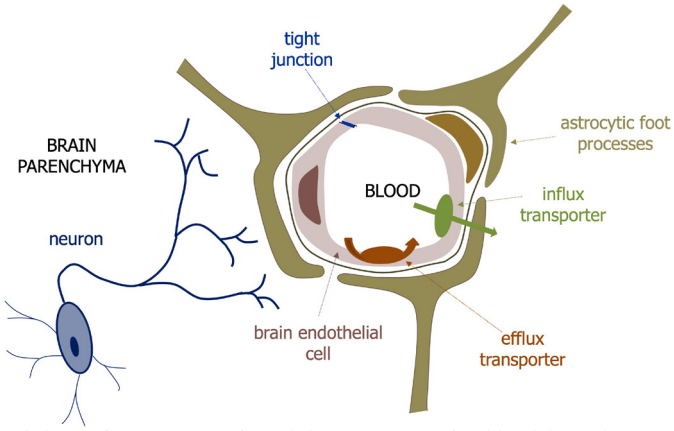
Altered brain uptake of drugs is also a concern for the multiple medicines that individuals with MND are prescribed for other conditions, which may place them at a greater risk of drug-induced brain toxicity. Knowing changes to altered brain dynamics in advance can lead to tailoring of the dosages of these non-MND medicines to minimise their potential for brain toxicity. Therefore, this IMPACT project will lead to approaches that increase the brain uptake of drugs intended to treat MND, but also minimise the brain uptake of drugs not intended to reach the brain, increasing the quality of life of individuals with MND.

OBJECTIVES:

- Evaluate the BBB status in MND, focusing on understanding which shuttles are increased or decreased. This will provide an understanding of which shuttles should be exploited for carrying therapeutics across the BBB specifically for MND.
- Assess which classes of drugs have modified access to the brain in preclinical models of MND. This will provide insight for advancing drug design to optimise their uptake in the brain of MND patients.

OUTCOMES:

- Identify pathways that give therapeutics optimal access to the brain in MND, for greater efficacy, and limit the entry of harmful drugs to minimise side-effects.
- Develop a blood-brain barrier model using stem cells from MND patients, that assesses the ability of novel preclinical therapeutics to transfer from the blood to the brain



Schematic representation of the BBB separating blood from the brain parenchyma with influx (green) and efflux (red) transporters (or shuttles).

FIGHT MND.


A/Prof Lachlan Thompson

Researcher.
A/PROF LACHLAN THOMPSON

IMPACT Project.
ESSENTIAL PRECLINICAL STEPS TOWARDS A STEM CELL TRIAL FOR MND

Where do you work?

I work at The Florey Institute of Neuroscience and Mental Health, University of Melbourne.

Can you summarise your research experience and background?

I did my undergraduate studies (BSc) at UoM before completing my doctoral degree at Monash (2002). I then undertook 5 years of postdoctoral training at Lund University in Sweden (2003-2007) where I developed expertise in the area of neural transplantation and cell-based therapies for repair of the central nervous system. In 2008 I 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. We are aggressively exploring the capacity for stem cells to be utilised as a therapy for MND. 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, it is a surmountable challenge, we think.

Why did you decide to pursue research into MND?

Most of my career has been dedicated to developing cell-based therapies for Parkinson's disease. This has allowed us to establish a strong foundation of understanding around how neural circuitry can be re-established in the damaged central nervous system through transplantation of the correct cell type. In the context of central nervous system repair, an important similarity shared by PD and MND is that the neurodegenerative process involves primarily a single cell type. It struck us that many of the principles that have underpinned success in the establishment of cellular therapy for Parkinson's disease could be applied to MND, and thus we were motivated to explore this.

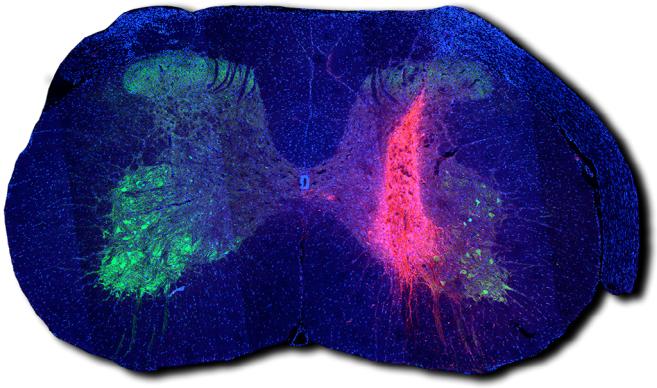
What is your most surprising finding?

In Parkinson's disease research, it has long been established that stem cells must form the cell type lost in the disease in order to replace those cells and effectively restore function to the patient. A surprising finding in this area has been that stem cells can also provide therapeutic benefit by protecting the host cells from degenerating. For MND, this means that it may be valuable to transplant suitable stem cells in a relatively non-invasive way, in order to protect the patient's own cells and significantly slow the degenerative process.

How did you identify that stem cell therapy may be beneficial for MND?

We use a rat model of MND, in which a progressive loss of spinal motor neurons is associated with a continuing decline in movement in much the same way that occurs in MND. We found that transplanting human cells into these rats could significantly slow the development of these movement-related symptoms.

FIGHT MND.



Stem cell graft (red) in rat spinal cord.

What do you find exciting about your stem cells approach?

We are only just beginning to realise the potential for stem cells for therapeutic application in the central nervous system. The fact that stem cells have shown so much potential while we still have so much to learn about how to harness and apply this potential means that there is tremendous scope for developing therapies. It also means that we need to take a rigorous and methodical approach to preclinical research to establish evidence-based procedures that can be translated to clinical practice. I have no doubt this is achievable.

How will this funding impact on your research?

This 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 preclinical work to do in this area and the rate-limiting factor is overwhelmingly the ability to support talented researchers to undertake the work. 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.

IMPACT Project.
ESSENTIAL PRECLINICAL STEPS TOWARDS A STEM CELL TRIAL FOR MND

Stem cells have the potential to treat neurological conditions such as MND, but their capacity to do so in preclinical models of MND remains poorly explored. Also, the best stem cell type and the most optimal way to deliver stem cells for therapeutic benefit in MND requires investigation.

OBJECTIVE:

This IMPACT project aims to establish preclinical efficacy for stem cell therapy in a model of MND and provide the framework for a well-rationalised clinical trial for MND patients.

OUTCOMES:

- Build solid preclinical evidence for therapeutic efficacy of stem cell therapy in a preclinical model of MND.
- Identify the best kind of stem cell for treating MND and establish the optimal route of delivery in a preclinical model of MND.
- Develop a thorough understanding of the mechanisms underlying the beneficial effects of stem cell therapy in a preclinical model of MND.
- Advance the pathway to a well rationalised, evidence-based stem cell clinical trial for MND patients.