2019 FightMND RESEARCH FELLOWSHIPS

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.

FightMND research fellowships are awarded to outstanding researchers, encouraging them to pursue MND as their selected field of research, and supporting their quest to identify the causes of MND, advance effective therapies for MND, and develop a cure for MND.

In 2019, FightMND awarded 2 Mid-Career and 1 Early Career Research Fellowships to outstanding researchers in Australia. Profiles of researchers awarded FightMND Research Fellowship and details of their research focus are outlined in this document.

FightMND Research Fellowships AWARDED IN 2019

FightMND Mid-Career Research Fellows

FightMND Early-Career Research Fellow

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Mid-Career FightMND Research Fellow.

DR SHYUAN NGO

Research.

TARGETING METABOLIOC FLEXIBILITY AS A THERAPEUTIC APPROACH FOR ALS (METALS)

Dr Shyuan Ngo

Who are you and where do you work?

I am Dr Shyuan Ngo, and I lead a research team at The University of Queensland. I hold a joint research appointment between The Australian Institute for Bioengineering and Nanotechnology and the Queensland Brain Institute. I am also appointed as a visiting researcher at the Department of Neurology at the Royal Brisbane & Women's Hospital.

Can you summarise your research background and experience?

I completed my PhD training in neuroscience at The University of Queensland, where I studied the cellular pathways that control the formation and maintenance of synapses between the central and peripheral nervous systems.

How did you decide to focus on MND research?

Towards the end of my PhD, I met a neurologist, Stephen Reddel, who would come into the lab to do experiments! He was amazing, and I was inspired by his approach to research. After submitting my thesis, I searched for an opportunity to conduct research across the clinical and basic science settings, so that I could contribute to scientific discoveries that help people in a more direct way. I interviewed with Pamela McCombe and Robert Henderson in 2009. I was immediately taken by their dedication to people living with MND, and I knew it was where I wanted to be.

Can you describe the work your laboratory is currently pursuing?

Our research focuses on understanding causes and consequences of metabolic dysfunction in MND. We are interested in identifying which biological pathways are disrupted in MND and how targeting these pathways might correct for defective energy use or improve energy use, as this is important for sustaining cell function and survival. We use mouse and human-derived models in our laboratory because it is integral to our goal of translating research findings into clinical trials for MND.

What is your favourite aspect of your research?

My favourite thing about my group's research is that we are able to work with people living with MND - we are always learning from people living with MND, their families, and their carers. Conversations that we have about MND drives us to refine our research approaches and ask new research questions. Sometimes, it challenges us to revamp old and forgotten research questions. I feel very lucky to be able to conduct research that is built off what we learn from these conversations.

Describe the day you identified that Trimetazidine may be an effective treatment for MND?

Since 2015, my colleague Jean-Philippe Loeffler and I have been discussing the potential for fatty acid oxidation inhibitors to be drug candidates for MND. By 2018, a PhD student started some preclinical testing of Trimetazidine in a mouse model of MND. I had a look at the data and found it to be very encouraging. At this moment, we thought that Trimetazidine might be a very promising drug candidate for MND.

What excites you most about Ranolazine and Trimetazidine?

Ranolazine and Trimetazidine are both drugs that modify metabolic flexibility, but they do so via different mechanisms. By integrating this information with what we know about metabolic dysfunction in heart failure and MND, we could accelerate the use of these drugs for MND. This is what excites me most!

What difference will this fellowship make to your achievements?

This FightMND fellowship allows me to continue testing the effectiveness of Ranolazine and Trimetazidine in our laboratory MND models, while also supporting the capacity to transition these compounds into clinical trials. For me, the biggest difference this fellowship makes is that it offers me an opportunity to continue with research that aligns with my ultimate research goal - to improve the quality and duration of life for people living with MND.

Research.
TARGETING METABOLIOC FLEXIBILITY AS A THERAPEUTIC APPROACH FOR ALS (METALS)

About half of all patients with MND/ALS experience a dramatic increase in energy use (known as hypermetabolism), and my team has generated clinical data showing that ALS patients who experience this change in energy use are those who have a more aggressive disease and shorter survival. Complementing these studies with ALS patients, my research in preclinical MND/ALS models shows that changes in energy use occurs alongside a decrease in the ability of animals to switch between the use of sugar and fat as energy substrates. This loss of metabolic flexibility contributes to MND/ALS, as repurposed compounds that improve metabolic flexibility can slow disease progression, and improve nerve-muscle connections and muscle strength in preclinical models.

During this fellowship, I will build on my promising results. My team will comprehensively test lead drugs in MND/ALS patient-derived motor neurons that are grown in petri dishes, and in preclinical models that are more applicable to sporadic disease, to ensure that targeting metabolic flexibility is relevant for MND/ALS. I anticipate these drugs will improve motor neuron survival, nerve-muscle connections, motor function and lifespan across numerous cell models and preclinical disease models. I will also conduct studies in ALS patients to show that changes in energy use occur throughout the course of disease, and that this is a persistent change that can be used to identify patients who will most likely benefit from the proposed treatment strategy.

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Dr Shyuan Ngo operating the Body Composition Tracking equipment that examines metabolic flexibility parameters, such as body fat and muscle mass in MND/ALS patients.

OBJECTIVES:

1. Normalise energy use and restore appropriate balance between sugar and fat as energy substrates to improve movement, communication between nerves and muscles and muscle strength, and lengthen the life of preclinical MND/ALS models.
2. Confirm that increased energy use is a common occurrence in all MND/ALS patients, and the precise onset of increased energy use relative to the emergence of disease symptoms.
3. Generate data on the suitability of translating lead metabolic flexibility normalising compounds into Phase I/II MND/ALS clinical trials.

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Mid-Career FightMND Research Fellow.

DR FAZEL SHABANPOOR

Research.

DEVELOPMENT OF NOVEL BLOOD-BRAIN-BARRIER PERMEABLE PEPTIDES AND ANTISENSE OLIGONUCLEOTIDES AS BIOTHERAPEUTICS FOR ALS


Dr Fazel Shabanpoor

Who are you and where do you work?

My name is Fazel Shabanpoor and I am a Research Fellow and Head of the Oligonucleotide and Peptide Therapeutics laboratory at the Florey Institute of Neuroscience and Mental Health, University of Melbourne.

Can you give us a summary of your research experience and background?

I started my research training in pharmacology and chemistry through an Honours degree in 2005. Following completion of my Bachelor of Biomedical Science (Hons) degree, I continued my doctoral research training in the laboratory of Prof. John Wade (The Florey Institute, University of Melbourne). My time as a PhD student was highly productive and I received training in all levels of peptide drug development, delivery and preclinical evaluation. Following completion of my PhD in 2010, I started a post-doctoral tenure at The Florey. In 2011, I was awarded a highly competitive NHMRC CJ Martin Fellowship which allowed me to undertake my post-doctoral training in the UK at two medical research laboratories, MRC Laboratory of Molecular Biology in Cambridge and the University of Oxford. During my tenure in the UK, I acquired a unique set of skills and expertise on using antisense technology to develop personalised antisense therapy for neurodegenerative diseases. In 2014, I returned to Australia where I established my independent research group at The Florey.

What drew you to MND research?

During my time in the UK, I worked on the development of peptide-antisense oligonucleotide conjugates for the treatment of Duchenne muscular dystrophy and spinal muscular atrophy (childhood form of MND). Over this time, I gained an interest in additional neurodegenerative diseases, including ALS, through interactions and collaboration with other neuroscientists and neurologists. Over the last 6 years, I have set up an antisense gene therapy platform and developed the brain penetrating peptides for the delivery of antisense oligonucleotides at The Florey.

Can you describe your current research focus?

The work in my laboratory focuses on the development of:

- Personalised genetic medicine using antisense oligonucleotide-based drugs targeting mutant genes in SMA (SMN2) and ALS (SOD1, C9ORF72, Ataxin-2);
- Autophagy-inducing peptides to clear toxic protein aggregates from motor neurons as a potential therapy for MND; and
- Peptide-based drug delivery platforms to deliver therapeutic antisense oligonucleotides and peptides into the brain and spinal cord.

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Share a defining moment in your work as a scientist?

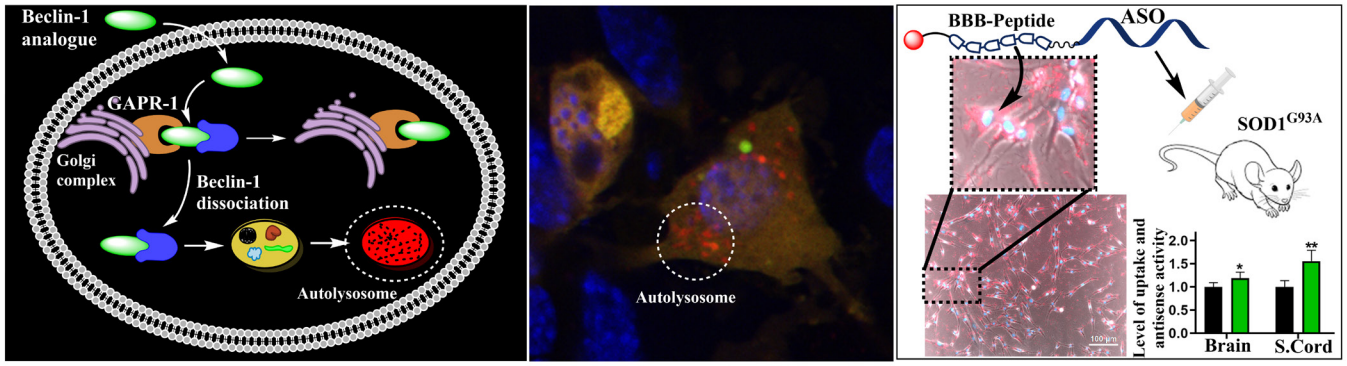
Receiving one of the most prestigious early career fellowships (NHMRC CJ Martin) in 2012 as acknowledgment of what I had achieved in my career as a scientist, but also to pursue my research training on antisense gene therapy. Looking back at my research, the discovery of a peptide that could cross the blood-brain barrier and deliver an antisense oligonucleotide to correct a genetic mutation in motor neurons in the brain and spinal cord was one of the significant achievements and a defining moment in my career to date.

What excites you about your antisense oligonucleotides?

The antisense oligonucleotides are simple yet powerful biomolecules that have only four letters in their alphabet. They have an exquisite mode of action and can be tailored to target any gene with high precision.

What will this fellowship allow you to achieve?

The award of this fellowship makes an enormous difference to my career, especially during this time that funding for medical research has significantly fallen. This fellowship will set me up for achieving my vision of establishing a multidisciplinary research team and to expand my national and international collaborative network to develop translationally relevant therapeutic peptide-antisense oligonucleotides for the treatment of MND.



Cell-penetrating Beclin-1 derived peptides inhibit GAPR1-Beclin1 interaction (Left panel) and significantly increase autophagy flux measured by increased levels of autolysosmes (middle panel). Efficient cell uptake of blood-brain barrier crossing peptide-antisense oligonucleotides and systemic central nervous system delivery of Blood Brain Barrier-peptide-ASO conjugate in preclinical SOD1^{G93A} mouse model of MND, with significant uptake and antisense activity in the brain and spinal cord (right panel).

FIGHT MND.

Research.
DEVELOPMENT OF NOVEL BLOOD-BRAIN-BARRIER PERMEABLE PEPTIDES AND ANTISENSE OLIGONUCLEOTIDES AS BIOTHERAPEUTICS FOR ALS

One of the most common pathological hallmarks of neurodegenerative diseases, and in particular amyotrophic lateral sclerosis (ALS), is the production of toxic proteins inside a group of nerve cells known as motor neurons. The toxic proteins can stick together and form large aggregates/clumps or they can attach to other regulatory proteins inside motor neurons and block their function. This leads to the progressive degeneration of motor neurons.

The toxic protein aggregates are formed inside motor neurons as a result of mutations in certain genes. In most cases, a cleansing system inside motor neurons known as “autophagy”, which is responsible for clearing these toxic proteins, is compromised. This leads to the accumulation of toxic protein aggregates inside motor neurons leading to paralysis of voluntary muscles and death by respiratory failure within a median of 3 years from onset.

The main objective of this study is to develop and validate the ability of two novel classes of drugs to:

(i) degrade the mutant genes inside motor neurons and prevent production of toxic protein aggregates; and

(ii) stimulate autophagy to enhance removal of protein aggregates.

These novel therapeutic approaches will advance the development of blood-brain barrier crossing antisense oligonucleotide drugs that restore the ability of motor neurons to clear toxic protein aggregates and prevent their death.

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Early-Career FightMND Research Fellow.
DR REBECCA SAN GIL

Research.
GENOME-WIDE CRISPR SCREENS TO REVEAL REGULATORS OF TDP-43 AGGREGATION AND TOXICITY IN MND


Dr Rebecca San Gil

Who are you and where do you work?

My name is Rebecca San Gil and I am excited to be Fight MND's first Early-Career Research Fellow awarded in 2019. I conduct my research at the Queensland Brain Institute, University of Queensland, in the Neurodegeneration Pathobiology Laboratory.

Summarise your research experience and background?

My PhD at the Illawarra Health and Medical Research Institute studied the role of the cellular heat shock response as a first responder to protein aggregation and neuroinflammation in neurodegenerative diseases. I showed that protein aggregation impairs or evades the detection of the heat shock response. This means that neurons likely can't protect themselves from a major pathology that drives neurodegenerative diseases. During my PhD I undertook an Endeavour Research Fellowship at the Sobell Department of Motor Neuroscience and Movement Disorders, University College London. There, I developed an intensive research focus on MND and acquired skills in a range of techniques to study the pathogenesis of disease in motor neurons and other cell types that support motor neuron health and survival (astroglia and microglia). After completing my PhD in 2018, I was recruited by the Queensland Brain Institute to continue research into advancing our understanding of the molecular triggers of MND and identifying therapeutic targets in motor neurons, the brain, and spinal cord.

What got you interested in researching on MND?

I had the privilege to work alongside Prof Yerbury, who is a world leading expert in protein homeostasis in MND, but is sadly also battling MND. I have witnessed firsthand the daily trials of living with MND and the persistence and dedication Prof Yerbury has shown. He is an exceptional role model and mentor and his journey has inspired me on my research path investigating and developing therapeutics to improve and extend the lives of patients with MND. Despite the many breakthroughs in recent years, I felt it was important to put the skills and techniques I had learnt to good use to better understand essential questions about the pathogenesis and strategies to treat MND more effectively.

What is your favourite scientific finding so far?

The discovery of CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats) technology is my favourite finding so far. I think it is the versatility of CRISPR/Cas9 that makes it the greatest discovery of all time. CRISPR/Cas9 can be used to very precisely edit, knock-out, inhibit and activate genes. It is highly likely that CRISPR/Cas9 will be a key player in drug-target discovery for many human diseases in the future.

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Can you update us on the research you are currently pursuing?

I am very excited to be starting a new project using human genome-wide CRISPR screening to identify genes and proteins that regulate protein aggregation in MND. Aggregation of the TDP-43 protein is associated with toxicity that causes the death of motor neurons in 97% of MND cases. One potential therapeutic strategy is to target and prevent this toxic process of TDP-43 clumping, however, the mechanisms involved in driving TDP-43 aggregation remain unclear. This project will use revolutionary new gene editing technology to scan all 20,000 genes in the human genome, to identify the mechanisms in cells that can trigger or stop TDP-43 aggregation. This will reveal new targets that will be tested for therapeutic potential in preclinical models of MND, with the ultimate objective of identifying future avenues to treat people living with MND.

What excites you most about the potential to eradicate TDP-43 aggregation?

Many lines of evidence point to protein aggregation being one of the initial molecular dysfunctions that lead to neuroinflammation and neurodegeneration in MND. I strongly believe that by understanding and inhibiting aggregation, the first step, we can stop disease onset and progression. This concept will be directly tested as part of this Fellowship. In addition, TDP-43 aggregation is a key unifying pathology common to 97% of MND cases. Therefore, targeting TDP-43 aggregation might provide us with the insight to treat nearly all cases of MND.

What difference will this fellowship make to your research?

This FightMND Fellowship is an excellent opportunity for continued development of my professional and experimental skillset. This project will be conducted in collaboration with Prof Naomi Wray FAA (UQ), Dr Shyuan Ngo (UQ), Prof Aaron Gitler (Stanford), A/Prof Todd Cohen (University of North Carolina) and will represent an invaluable opportunity to learn from world leaders in MND research. In addition, this project will generate a career's-worth of drug targets to pursue and enable me to build on my existing skillset by developing skills in CRISPR/Cas9 gene editing, next generation sequencing, and bioinformatic analysis pipelines. Ultimately, this fellowship is a career-making opportunity and excellent stepping stone for me to continue to build a career in research with a focus on finding new therapeutics to treat or cure people living with MND.

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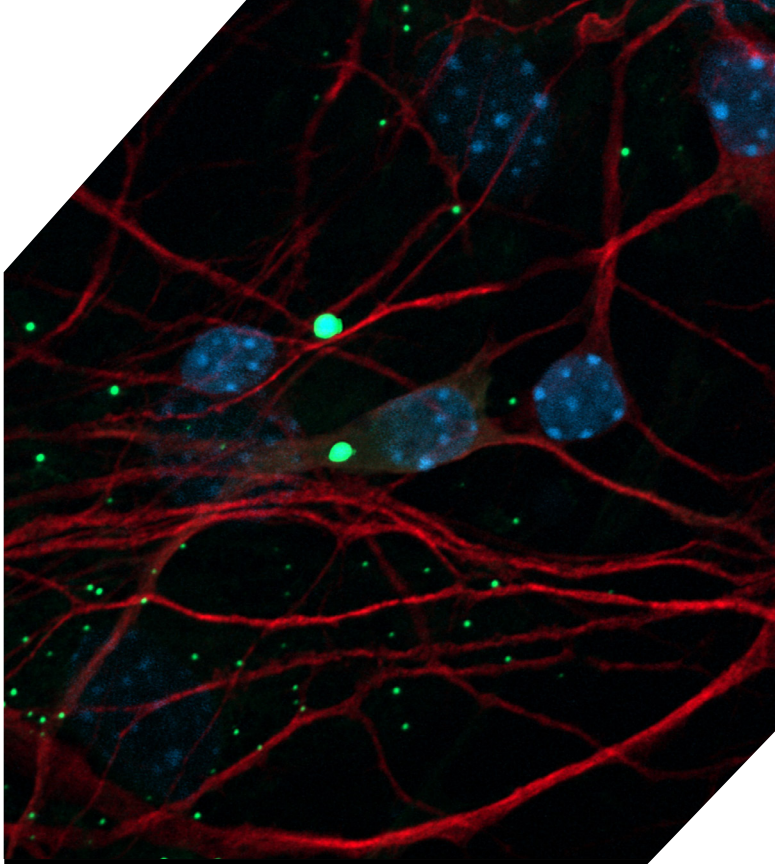

Mouse primary spinal cord neurons (red) transduced with lentiviral particles to over-express aggregation-prone TDP-43 (GFP-tagged; green) in the cytoplasm.

Early-Career FightMND Research Fellow.
DR REBECCA SAN GIL

Research.
GENOME-WIDE CRISPR SCREENS TO REVEAL REGULATORS OF TDP-43 AGGREGATION AND TOXICITY IN MND

One of the first events, at the molecular level, which leads to disease onset in all sporadic (and most familial) cases of motor neuron disease (MND) involves the build-up of a protein called TDP-43 in motor neurons. TDP-43 proteins stick together to form small toxic clumps. Over time these small clumps become the building blocks of larger protein inclusions that are strongly associated with the death of motor neurons in MND and are clearly visible under a microscope. Therefore, one potential therapeutic strategy is to prevent this toxic process of TDP-43 clumping. Unfortunately, there is currently a limited understanding of how TDP-43 clumps and why it is toxic.

The primary aims of this Fight MND Fellowship are to identify biochemical pathways that enhance or inhibit TDP-43 clumping and its associated neurotoxicity, and to conduct preclinical testing of promising regulators of TDP-43 clumping in a validated TDP-43 mouse model of MND. This project will use revolutionary gene editing technology to scan all 19,000 protein-encoding human genes in the human genome to identify the genes that modulate TDP-43 clumping. The innovative gene editing technology that enables us to scan every human gene is cutting-edge, and the experimental strategy that will be implemented would not have been possible even a few years ago.

The research performed will be crucial for identifying mechanisms that regulate the processes that cause MND. There will be a strong focus on validating the preclinical value of these findings in studies using a mouse model of TDP-43-associated MND, on the path towards more effective treatments for people living with MND.

OUTCOMES:

1. To conduct human genome-wide CRISPR/Cas9 gene knockout and activation screens to identify enhancers and inhibitors of TDP-43 aggregation and its associated neurotoxicity.
2. To establish the mechanisms of action of the strongest regulators of TDP-43 aggregation in neuroblastoma cell lines, and motor neurons derived from preclinical MND models and MND patients.
3. To perform preclinical testing of promising regulators of TDP-43 aggregation in a validated TDP-43 mouse model of MND, using gene delivery to the central nervous system.