FIGHT MND.

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.

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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.