FIGHT MND.


Dr Shyuan Ngo

Researcher.
DR SHYUAN NGO
Clinical Trial.
TRIMETAZIDINE TRIAL

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 (AIBN), and the Queensland Brain Institute (QBI). Because my research also involves working closely with people living with MND, 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 identify that a loss of metabolic flexibility may contribute to MND?

In 2012, I started collaborating with Jean-Philippe Loeffler, who is a pioneer in the field of metabolism in MND. We were working on different aspects of metabolism at the whole-body level and at the cellular level in mice. I remember saying to my PhD student at the time, "Rui, it's the Randle cycle!" I skyped JP and we were very excited to find that we had come to the same conclusion. By 2015, we published our first collaborative paper to indicate that a change in the regulation of glucose and fatty acid flux (i.e. metabolic flexibility) might be important in MND.

How did you identify Trimetazidine as a potential treatment for MND?

From 2015, we have been conducting research under the premise that a loss in metabolic flexibility was an underlying cause for a phenomenon called hypermetabolism (an increase in whole-body energy use) in MND. Because a number of previous studies had proposed that hypermetabolism might be detrimental in MND, we wanted to identify a drug that could improve metabolic flexibility and reverse hypermetabolism.

In 2018, my team showed, for the first time, that hypermetabolism in patients with MND was linked to worse outcomes. I skyped my collaborators, and it was during this time that Trimetazidine came up on our radar as a drug candidate. A vital piece of evidence suggesting that Trimetazidine might be an effective treatment for MND came from studies where Trimetazidine reversed hypermetabolism in patients with chronic heart failure.

What excites you about Trimetazidine?

Trimetazidine is a partial fatty acid oxidation inhibitor. So, while it does modify metabolic flexibility, being a partial inhibitor means that the cell still has the option of using fatty acids, which are a very important energy substrates. I anticipate that Trimetazidine will allow us to tweak the way in which the body and cells use energy. Most importantly, because Trimetazidine is EMA approved, there is potential to expedite the use of Trimetazidine for people living with MND.

FIGHT MND.

Dr Shyuan Ngo operating equipment that measures levels of metabolic and oxidative stress biomarkers in samples from MND/ALS patients.

What will this funding allow you to achieve?

Funding through this Drug Development Grant will allow us to complete an international Phase I trial that will establish if Trimetazidine is safe and well tolerated in people living with MND. This information is crucial for determining whether we can progress to a Phase II trial.

Clinical Trial.
TRIMETAZIDINE TRIAL

About half of all patients with MND/ALS experience a change in their energy use that causes their body to consume more energy, which accelerates the spreading of MND/ALS throughout the body. This change in energy use, called hypermetabolism, is clinically important as it is linked to an increased risk of death and faster rate of disease progression in people with MND/ALS.

This Phase I Clinical Trial investigates the safety and tolerability of Trimetazidine in 36 MND/ASL patients across 3 centres in Brisbane, The Netherlands and UK. Trimetazidine, a partial fatty acid oxidation inhibitor, is a repurposed drug that reduces hypermetabolism in patients with chronic heart failure, and is licensed as treatment for angina. Trimetazidine has a favourable safety profile and, more importantly, reduces the expression of oxidative stress markers that are also increased in patients with MND/ALS. The ability of Trimetazidine to lower hypermetabolism and oxidative stress, may slow disease progression and functional decline in patients.

OUTCOMES:

1. Assessment of whether Trimetazidine is safe and tolerable for MND/ALS patients.
2. Determine if Trimetazidine can modulate energy expenditure and oxidative stress, and restore metabolic flexibility, in people with MND/ALS.
3. Generation of data supporting the progression of Trimetazidine to Phase II Clinical Trials.