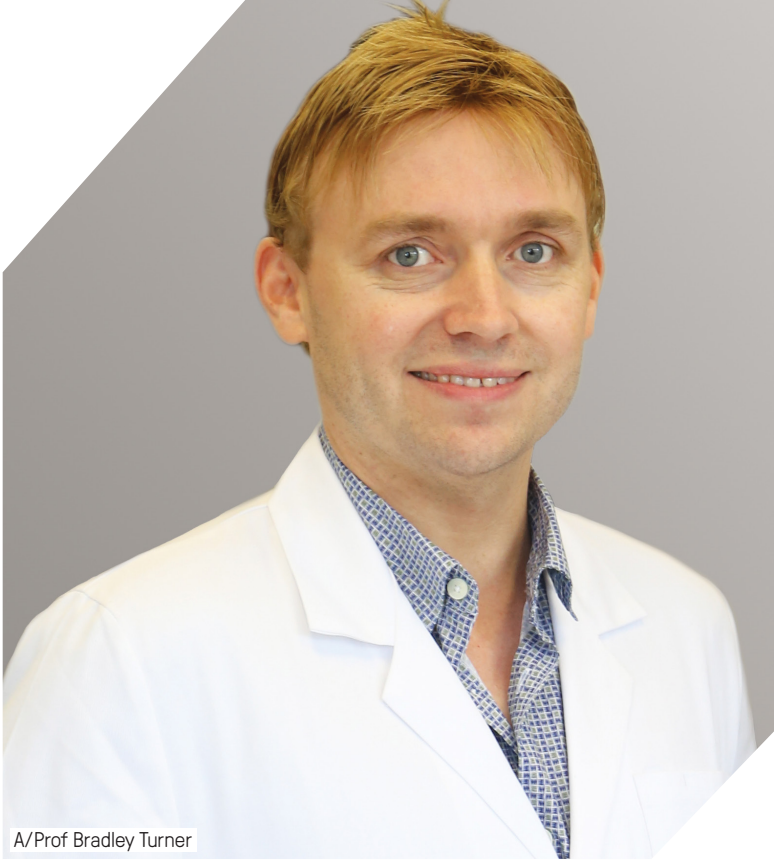
FIGHT MND.



A/Prof Bradley Turner

Researcher.

A/PROF BRADLEY TURNER

Drug Development Project.

SMN2 SPLICE-SWITCHING OLIGONUCLEOTIDE THERAPY DEVELOPMENT FOR MND

Where do you work?

I head the MND Laboratory at the Florey Institute of Neuroscience and Mental Health, located at the University of Melbourne.

Can you summarise your research background and experience?

I completed my PhD studies on MND and have been researching MND for 15 years now. My research background is cell and molecular biology which means studying the individual cells and biological molecules that make up MND. I have extensive experience in using research animals and recently MND patient donated stem cells to model MND in the laboratory and importantly, for drug discovery and development.

What led you to be a researcher focused on developing treatments for MND?

I have always had a fascination for mysteries of the human brain, especially degenerative diseases of the brain. I became interested in “mad cow disease” in my undergraduate years. My honours project was on Alzheimer’s disease which led me to MND. MND shows some clinical and pathological overlap with dementia, suggesting that if we can solve one, we can most likely help the other. My passion for MND research is largely driven by MND patients and their families who battle the disease daily and hope for a cure.

Can you describe the research your team is currently pursuing?

Our team has a strong focus on drug discovery, screening, development and translational medicine with the ultimate goal to develop effective treatments and a cure for MND. We screen drugs using MND patient donated cells and genetically engineered models of the disease. We have recently turned to drug re-purposing which means re-using existing licensed drugs for other conditions and exploiting their properties for MND. Given the safety profile of these drugs is already known, this fast-tracks their development for MND and speeds up the clinical trial process.

Spinraza effectively treats a childhood form of MND, how did you identify that it may be effective for adults living with MND?

We recently showed that MND has a common disease pathway with a childhood form of MND called spinal muscular atrophy (SMA). This discovery raised the exciting idea that SMA therapies, both approved and in development, may have potential for MND. Spinraza is a blockbuster drug that was approved for SMA in 2016 and has transformed the lives of patients and families living with SMA. It works by correcting a gene defect responsible for SMA.

Importantly, all MND patients carry the SMA gene. Our hope is that the tremendous success of Spinraza for SMA will translate to significant benefits for people living with MND.

Can you tell us how the newest genetic tools you are using in this project are advancing treatments for MND?

We will design and develop new formulations of Spinraza with increased potency and delivery into the brain. This will firstly be achieved using next-generation designer DNA technology already in use for treatment of SMA, which allows us to precisely target and correct the genetic defect and minimise potential side-effects. Second, we will combine our designer DNA technology with a peptide delivery system to maximise drug delivery to the brain, and therapeutic outcomes for motor neurons. Our final product will be a superior form of Spinraza for MND that effectively crosses from blood into the brain.

What will this funding allow your team to achieve?

This funding will allow us to fast-track rigorous testing of Spinraza in the best available laboratory models of MND. We will also advance Spinraza to maximise its benefit and delivery into the brain by designing, screening and developing a superior formulation of the drug that can be administered into the bloodstream. Our goal is to confirm whether Spinraza is effective in laboratory models of MND, so we can advance this drug to clinical trial in the shortest timeframe possible. This funding also catalyses a new international collaboration between scientists, chemists, neurologists and pharmaceutical industry committed to this objective.

The Drug Development Project

Survival motor neuron (SMN) is a protein that has a number of vital roles 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 that elevates SMN levels, called Spinraza, 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.

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 their advanced Spinraza elevates SMN levels in motor neurons and improves motor neuron health, movement and life expectancy in preclinical MND models.

Team member and FightMND Research Fellow Dr Fazel Shabanpoor developing brain-penetrating Spinraza analogues in the laboratory at the Florey.

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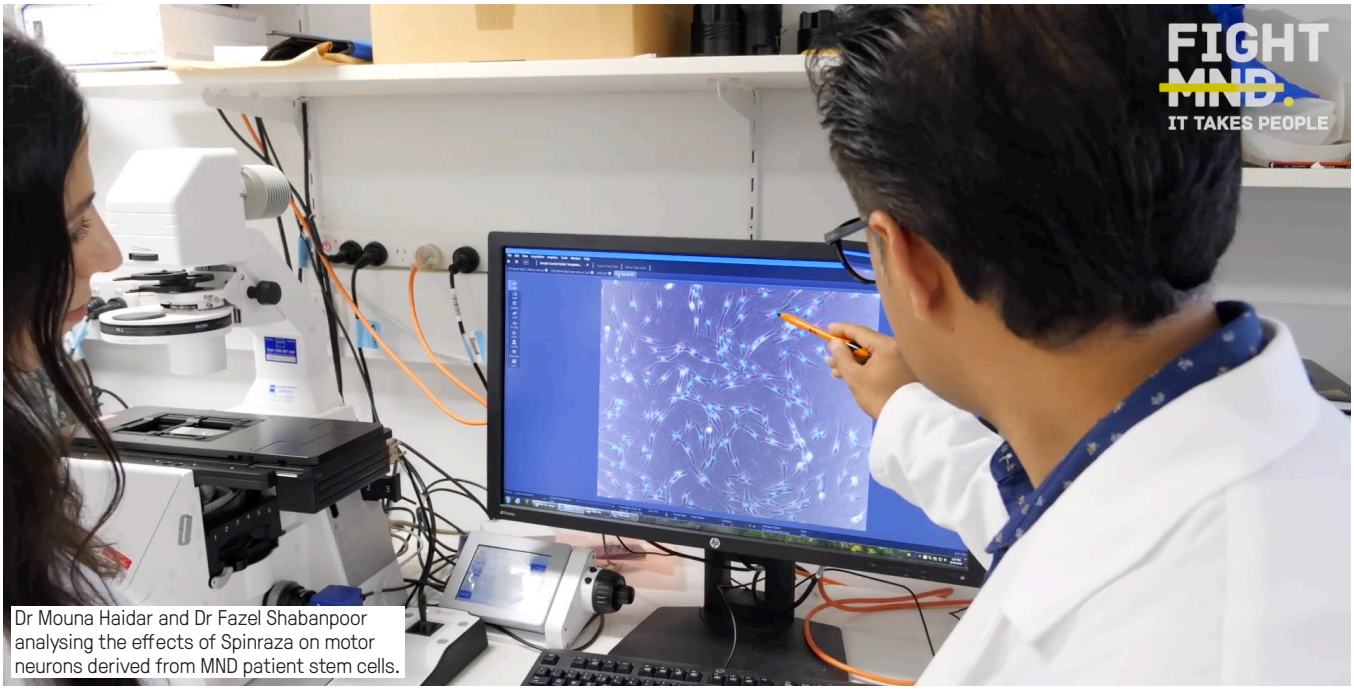

Dr Mouna Haidar and Dr Fazel Shabanpoor analysing the effects of Spinraza on motor neurons derived from MND patient stem cells.

OBJECTIVES

- Assess the effectiveness of Spinraza in three preclinical MND models.
- Develop a new form of Spinraza that can readily access the brain following systemic administration.
- Test the therapeutic effects of the lead brain-penetrating Spinraza in three preclinical MND models.

OUTCOMES

- Preclinical evidence supporting Phase 1 clinical trials of Spinraza, or brain-penetrating Spinraza, for MND patients within the next 4-5 years.