FIGHT MND.

Researcher.

**DR FAZEL SHABANPOOR**

IMPACT Project.

**DEVELOPING BLOOD-BRAIN BARRIER PENETRATING PEPTIDES**

Priority Area.

**DRUG DELIVERY**

Dr Fazel Shabanpoor

## Where do you work?

I am a FightMND mid-career Research Fellow and Head of the Oligonucleotide and Peptide Therapeutics laboratory at the Florey Institute of Neuroscience and Mental Health, University of Melbourne.

## What is 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 at The Florey. My time as a PhD student was highly productive and I received training in all levels of peptide drug development, delivery and preclinical evaluation. In 2011, I was awarded a NHMRC CJ Martin Fellowship to undertake my postdoctoral 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 led you to pursue your investigations into MND?

During my time in the UK, I worked on developing peptide-antisense oligonucleotide conjugates for the treatment of Duchenne muscular dystrophy and Spinal Muscular Atrophy (a childhood form of MND). Over this time, I gained an interest in MND 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 brain penetrating peptides for the delivery of antisense oligonucleotides.

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

Research in my laboratory spans across the fields of oligonucleotides and peptides, and developing these biomolecules as therapeutics for neurodegenerative diseases. The main focus is to develop: (1) Antisense oligonucleotides targeting several genes (SOD1, C9ORF72, Ataxin-2) as a personalised genetic medicine for MND patients; (2) Autophagy-inducing peptides to clear toxic protein aggregates from motor neurons as a potential therapy for MND; and (3) A peptide-based drug delivery platform to deliver therapeutic ASOs and peptides into the brain and spinal cord.

## Tell us about the blood-brain barrier, its difficulties, and how it can be targeted to improve MND treatments?

The blood-brain barrier is a protective structure surrounding blood vessels in the brain that allows the passage of certain substances from the blood stream into the brain. The barrier can also restrict the passage of drugs into the brain, creating an obstacle for treating many neurological diseases. To overcome this challenge, we are developing peptides capable of penetrating this barrier, and deliver

drugs such as Riluzole, and potential therapeutic ASOs and peptides, into the brain in a safe and an efficient manner to achieve desired therapeutic outcomes for MND.

## What are antisense oligonucleotides and how are you using them to develop a treatment for MND?

Antisense oligonucleotides are synthetic DNA-like molecules that join to their target RNA to enhance or prevent gene expression. They are very selective and can be tailored to target any gene with high precision. We are exploiting this technology to develop antisense therapy targeting several MND-causing genes.

## What will this funding allow you to achieve?

The award of this funding will allow us to develop a safe and innovative drug delivery platform based on blood-brain barrier-penetrating peptides. This safe and innovative delivery technology will allow for systemic administration of three distinct classes of neurotherapeutics targeting MND. Importantly, the delivery platform will avoid invasive and potentially hazardous methods, such as intrathecal injections, that are currently used in the clinic to deliver drugs into the central nervous system.

Dr Shabanpoor making a blood-brain barrier peptide-ASO conjugate in the laboratory at The Florey.

FIGHT MND.

## The IMPACT Project

In the body, the brain and spinal cord are protected from harmful substances, or pathogens, in the blood stream by a protective barrier called the blood-brain barrier. While the blood-brain barrier is vital to protect the brain, it also creates one of the biggest challenges for treating any neurodegenerative disease - getting drugs across the barrier and into the brain and spinal cord where they are needed. Over the past two decades, the majority of human clinical trials for MND have failed to produce new treatments. This may not be due to the lack of drug potency, but rather the inability of drugs to reach their targets in the brain and spinal cord in amounts that can achieve a therapeutic effect.

This project aims to address this critical issue by developing a drug delivery platform technology that allows safe and efficient delivery of drugs into the brain and spinal cord. The effectiveness of this drug delivery system will be tested by delivering 3 different classes of drugs into the brain and spinal cord. Because this delivery system is minimally invasive, it should significantly advance on technologies, such as intrathecal injections, currently being used in the clinic. Overall, the outcomes of this project have a significant potential to provide therapeutic benefit for MND.

### OBJECTIVES

- Develop and optimise a 'brain-penetrating peptide' platform that enhances the delivery of drugs to the brain and spinal cord, and increases their effectiveness.
- Assess the safety of the 'brain-penetrating peptide' platform in preclinical MND models.
- Demonstrate how effectively three different classes of drugs reach the brain and spinal cord of preclinical MND models using the 'brain-penetrating peptide' platform.

### OUTCOMES

- A safe and innovative drug delivery technology that allows drugs to reach their targets in the brain and spinal cord in amounts sufficient to achieve desired therapeutic effects for MND.