FIGHT MND.

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?

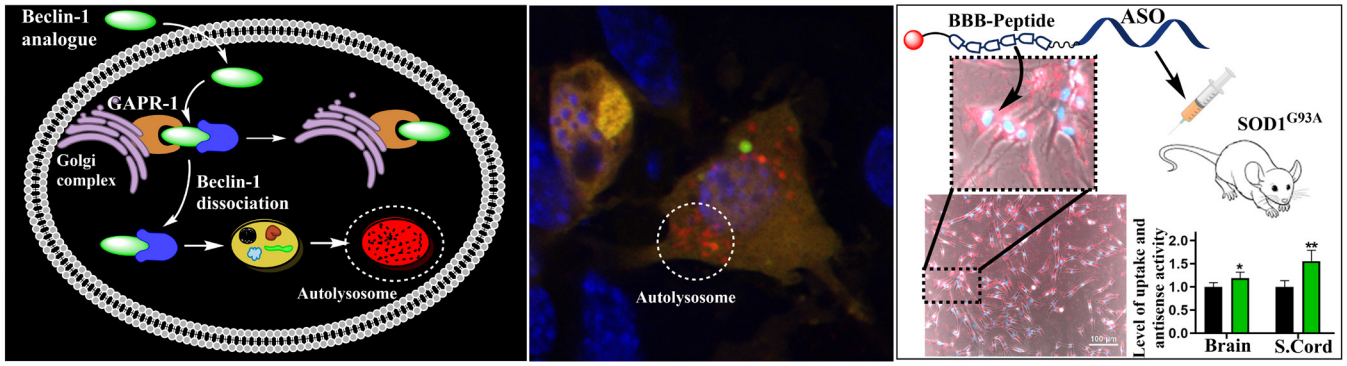
Receiving one of the most prestigious early career fellowships (NHMRC CJ Martin) in 2012 as acknowledgment of what I had achieved in my career as a scientist, but also to pursue my research training on antisense gene therapy. Looking back at my research, the discovery of a peptide that could cross the 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).

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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.