FIGHT MND.

Prof Steve Wilton, Dr Loren Flynn and Prof Anthony Akkari (left to right).

Researchers.

PROF STEVE WILTON
PROF ANTHONY AKKARI
DR LOREN FLYNN

Drug Development Project.

PRECLINICAL DEVELOPMENT OF A SOD1 GENETIC THERAPY IN SPORADIC MND

Where do you work?

We all work at Murdoch University at the Centre for Molecular Medicine and Innovative Therapeutics, and we are based at the Perron Institute for Neurological and Translational Science on the QEII medical campus, both in Perth, Western Australia. We are also involved with Black Swan Pharmaceuticals, based in the US, which is a Perron Institute collaboration to help accelerate our MND therapeutics into clinical development.

What is your research experience and background?

Our broad experience ranges from neurodegenerative and neuromuscular disease genetic studies spanning both basic and clinical research, as well as industry. Our group has integrated genetics into drug development and successfully designed antisense therapeutics for Duchenne muscular dystrophy that are available to patients. We have significant expertise in engaging with regulatory agencies to ensure rapid progression of therapeutics into the clinic. The core capability of the lab-based team is in the design of antisense therapies and we have focused our effort on a pipeline of these for MND.

Can you describe the research your team is currently pursuing?

One area that our MND research focuses on is in identifying genetic markers that may explain the missing heritability of MND and could help to predict age of onset and duration of disease. In discovering such markers, we will co-develop these with our antisense therapy pipeline to identify the best drug for the right patients.

What has been your favourite scientific finding so far?

Our group has experienced several “favourite” scientific findings, most excitingly, the successful development of the first antisense drugs for Duchenne muscular dystrophy. We have also identified genetic markers that appear to play an important role in sporadic MND. We predict that these markers could contribute to understanding patient response to clinical trials. We are hopeful that our discovery of the SOD1 suppression molecule will have broad implications for treating sporadic MND.

How did you identify that antisense oligomers could be beneficial for developing new treatments for MND?

We have always been interested in SOD1, given that a Perth family contributed to the identification of SOD1 as the first MND gene. With the advancement of antisense therapies, and as we developed our capabilities in this field, we realised that we could apply this exciting technology to SOD1 and to other MND genes. Our SOD1 suppression molecule is our lead drug, but we have several other targets that are being advanced in parallel for sporadic and familial MND.

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What excites you most about this approach to developing new treatments?

Research into treatments for rare and genetic diseases has greatly expanded with the discovery of antisense therapies. These drugs have enormous potential to overcome disease mechanisms and there is a growing international effort to develop antisense drugs for MND. What excites us most is that the options and applications for these drugs are endless, and by co-developing these with our genetic markers, treatments can be personally tailored for MND patients. It is also very exciting that antisense therapies have the potential to be developed quickly and fast-tracked into clinical use.

How will this funding impact on your work and MND?

This is the first time that FightMND has funded MND research at Murdoch University and the Perron Institute and we're proud that it is the first drug development grant FightMND has funded in Western Australia. This funding now allows us to perform the necessary safety studies that are required by the US Food and Drug Administration so that we can progress our molecule into the clinic. The funding will also allow us to do the necessary laboratory work to determine how this therapy could help not only people carrying SOD1 mutations, but also those living with sporadic disease.

The Drug Development Project

Several proteins have been linked to inherited and sporadic forms of MND. In MND, mutations in the SOD1 gene produce harmful changes to one of these proteins, called SOD1 protein. These changes cause SOD1 protein to clump together and prevent removal of harmful substances from motor neurons, which contributes to their death. Investigators in this project have developed a synthetic drug, called an antisense oligomer, to reduce levels of harmful SOD1 protein and prevent its detrimental effects on motor neurons.

The research team is aiming to advance their exciting new genetic drug so that it is ready to test in MND clinical trials. Recently, the team found that their lead drug, a SOD1-targeted antisense oligomer, delays the onset and slows progression of MND-like symptoms in a hereditary preclinical model of the disease. In this study, they will evaluate if the antisense oligomer has beneficial effects in a sporadic preclinical model of MND. The project will also demonstrate target engagement of their lead SOD1-targeted antisense oligomer and assess its safety in a variety of preclinical models.

Dr Flynn weighing materials in preparation for her experiments at Perron Institute.

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Prof Akkari, Dr Flynn and team member Frances Theunissen assessing their latest results on genetic structural variants in MND in their laboratory at Perron Institute.

OBJECTIVES

- Evaluate if the lead candidate SOD1-targeted antisense oligomer delays the onset of MND symptoms, preserves motor neuron structure, and increases survival in preclinical sporadic MND models.
- Build a toxicology and pre-clinical safety profile for the SOD1-targeted antisense oligomer.

OUTCOMES

- Preclinical evidence that builds a strong case for testing the SOD1 antisense oligomer in a Phase 1 clinical trial for MND patients in the next 2-3 years.
- A submission-ready Investigational New Drug application to the US Food and Drug Administration.