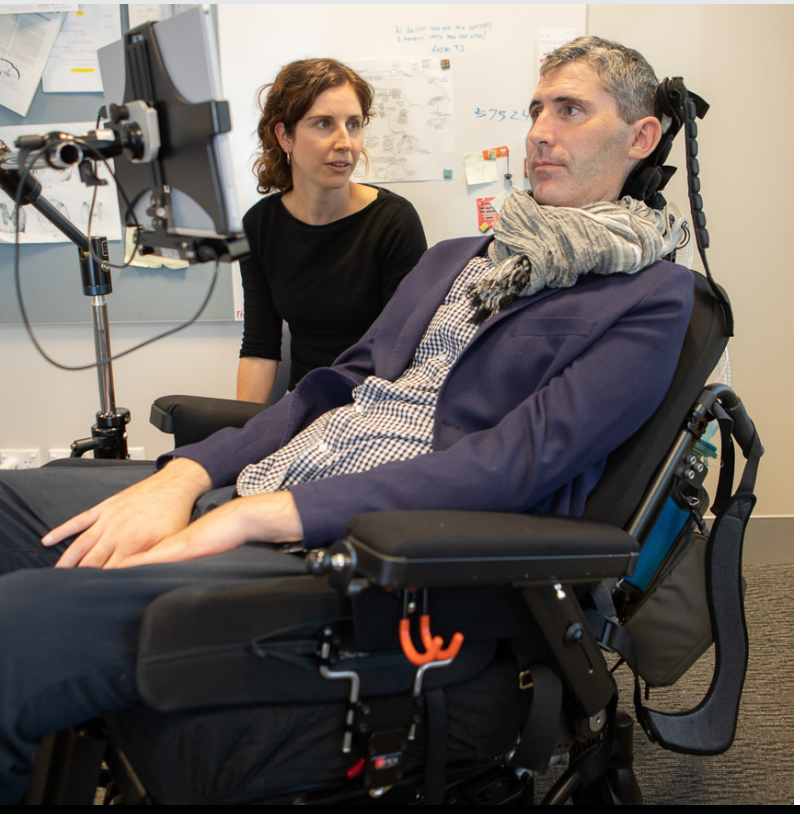
FIGHT MND.

Project

Targeting misfolded proteins with MisfoldUbLs as a therapeutic strategy for MND

In hereditary MND caused by mutations in the SOD1 gene, a damaged or 'misfolded' protein called SOD1 sticks together in motor neurons and contributes to their death. Investigators have designed an exciting new genetic tool that selectively recognises the misfolded SOD1 protein and removes it from motor neurons, without affecting normal SOD1 protein needed for neurons to function normally. This preclinical study examines if this new genetic tool can delay the onset and progression of MND.

Successful outcomes will provide a platform to advance this genetic tool for testing in a future clinical trial for MND.



Project Lead

Prof Justin Yerbury

University of Wollongong, NSW

Prof Justin Yerbury first heard about MND 25 years ago when his uncle, cousin and mother were diagnosed with MND in quick succession. He says *"it was clear at the time that there was not enough understanding of the molecular basis of the disease to develop an effective therapeutic."*

Prof Yerbury took this as a challenge and has dedicated his career to increasing the understanding of the origins of MND.

Prof Yerbury was diagnosed with MND in 2016.

Proud moments

Prof Yerbury says it is *"all the hard work and determination of all of the staff and students that have been a part of the lab over the past decade"* that makes him proud.

"If I had to choose [one piece of research], I am particularly proud of our early work on the prion like nature [of MND] and how that might explain the ordered progression of MND," he says.

What makes this research different?

Prof Yerbury says his research differs from other genetic drugs in that *"one of the current leading ALS (MND) therapeutic strategies (in phase 3 trials) is to knock down SOD1 levels using RNAi or antisense oligonucleotides. This approach indiscriminately knocks down all forms of SOD1, both the wild-type (natural) form and the mutant dysfunctional and harmful form."*

"However, the long-term knock-down of natural SOD1 has been shown to contribute to sarcopenia [muscle loss] and hepatocarcinoma [liver cancer]."

"Similarly, the generalised knock down of all forms of other MND-related proteins such as TDP-43 also appears to be detrimental," he adds.

The priority for this research project is to be able to selectively remove mutant misfolded pathogenic forms of SOD1 protein but spare the properly folded natural protein.

Prof Yerbury's team has identified an approach to remove only the misfolded form of the protein which it is hoped will reduce the pathological accumulation of the misfolded SOD1 protein in motor neurons, providing a promising therapeutic solution.

This *"would represent a better therapeutic approach and is urgently required,"* Prof Yerbury says.

FightMND has invested $921,360 in this research.

About Professor Justin Yerbury

At the age of 25 (1999) Prof Justin Yerbury enrolled in an undergraduate science degree completing it with first class honours in 2004. He then undertook a PhD with Prof Mark Wilson on extracellular chaperones before being awarded an international ARC fellowship to do post-doctoral studies with Prof Christopher Dobson at the University of Cambridge, UK, where he studied the biochemical analysis of protein aggregates.

In 2009 Prof Yerbury was awarded the Bill Gole MND Fellowship to train with Prof Iain Campbell in neuroinflammation. In 2012 he was awarded an ARC DECRA Fellowship to build his group around proteostasis defects in ALS (MND) and in 2015 was awarded an NHMRC CDF to continue research in this area.

Ten years after graduating with a PhD, Prof Yerbury was promoted to Professor in recognition of his contributions to the fields of proteostasis and MND.

Prof Yerbury currently works at the Illawarra Health and Medical Research Institute at the University of Wollongong.