FIGHT MND.


Prof Justin Yerbury

Researcher.
PROF JUSTIN YERBURY

Drug Development Project.
COMBINATION THERAPY TO IMPROVE CuATSM OUTCOMES IN MND

Where do you work?

We are in the Illawarra Health and Medical Research Institute on the main campus of the University of Wollongong.

Can you summarise your research experience and background?

I undertook a PhD at the University of Wollongong before being awarded an international fellowship from the Australian Research Council to study the biochemical analysis of protein aggregates at the University of Cambridge, UK. In 2009 I was awarded the Bill Gole MND Fellowship, and in 2011 the vice chancellors emerging researcher prize. In 2012 I was awarded an ARC DECRA Fellowship to build my group around proteostasis defects in ALS and in 2015 was awarded an NHMRC Career Development Fellowship to continue in this area. Ten years after graduating with a PhD I was appointed Professor in Neurodegenerative Diseases. I was awarded the Betty Laidlaw prize in 2018, and in 2019 I was Wollongong's Citizen of the year, and placed in the top 0.1% of the protein misfolding field worldwide by Expertscape. In 2020 I was in the top 3 of the Daily Telegraph's Most Powerful and Influential People in Wollongong, and that same year was made a Member of the Order of Australia (AM). As of August 2020, I have 75 career publications. Since I was diagnosed with MND in May 2016 I have published more than 35 papers. In January 2018 I underwent laryngectomy surgery and am now mechanically ventilated, drastically increasing my survival. The application for this project was put together using eye gaze technology.

What has been your favourite scientific finding so far?

For me the most important findings are the ones that have the best chance to lead us to an effective treatment for MND. Our work showing that misshapen proteins can propagate from cell to cell does that I think.

Can you describe the research your team is currently pursuing?

We are pursuing a few main areas of research. Firstly, we are using our laboratory models to identify small molecule drugs that may be effective in MND. Next we are working on ways to improve drug delivery across the blood-brain barrier, utilise a cells own recycling system to remove proteins that form deposits, and we are also working on a motor neuron regeneration project. Lastly, we are working to understand the structure of the MND proteins that form deposits.

Your project tests a drug called CuATSM (currently being tested in a Phase 2 MND clinical trial in Australia) in combination with additional drugs. What do you find exciting about this combination approach?

MND is a complex disease and we think that a combination of drugs targeting different aspects of MND biology will provide additional benefit above what one drug alone can provide. We are excited to be building on the work our colleagues have established with many years of hard work.

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How will the combination approach improve outcomes for people living with MND?

We believe that the combination approach will provide additional benefit above and beyond what is possible with a single drug. CuATSM has shown hints of promise in clinical trials to date where it appears to slow disease progression. We hope that our combination will further slow progression of MND.

This is the first time your research has received funding from FightMND. What will this funding allow your team to do?

This very generous funding will allow us to develop our combination therapy to a point where, if successful, we will be ready to move into clinical trials. We need to be able to test for safety, maximum tolerated dose and effectiveness against CuATSM alone. These are labour intensive and expensive experiments. This would not be possible without FightMND and the generosity of the Australian public.

Prof Yerbury presenting at the University of Wollongong Big Ideas Festival in 2019.

The Drug Development Project

About 35% of people with inherited MND in Australia have mutations in the SOD1 gene. There are 150 different mutations in the SOD1 gene associated with MND and all change the structure and stability of the SOD1 protein. In motor neurons, such structural changes cause SOD1 protein to clump together, prevent harmful substances from being removed, and compromise the supply of energy to the cell, all of which are triggers for their death.

In preclinical studies, a drug called CuATSM (currently being tested in a Phase 2 MND clinical trial in Australia funded by FightMND) was effective in treating a variety of SOD1 MND models, and stopped the activity of a specific signal instructing motor neurons to die. Researchers hypothesise that the effectiveness of CuATSM may be enhanced if the treatment was combined with drugs that repair the structure of SOD1 protein and prevent SOD1 from clumping together.

Researchers in this project are using a three-pronged approach to tackle a hereditary form of MND in which a damaged molecule called SOD1 forms clumps and makes motor neurons unwell. The approach will test CuATSM in combination with two new drugs aiming to repair damaged SOD1 protein, prevent harmful SOD1 clumps from forming and block signals instructing motor neurons to die. The research team will determine the optimal drug combination ratio, and perform safety and efficacy tests of the combination therapy in preclinical MND models. The two new drugs are both approved medications, meaning that if effective they can be fast-tracked through to a clinical trial.

OBJECTIVES

- Determine the optimal combination ratio of three novel drugs for testing in preclinical MND models.
- Perform preclinical toxicity and efficacy testing of the combination drug in preclinical MND models.

OUTCOMES

- A successful project could deliver a new potential combination therapy for testing in a clinical trial for MND patients within 24 months.