FIGHT MND.

Researcher.

PROF JUSTIN YERBURY

IMPACT Project.

PRION-LIKE STRAINS OF TDP-43 AGGREGATES IN MND

Priority Area.

DISEASE HETEROGENEITY

Prof Yerbury discussing latest MND research developments with team member Natalie Farrawell.

Where do you work?

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

What is 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 in Prof Christopher Dobson's laboratory 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.

How did you come to work in MND research?

I first heard about MND 20 years ago when my uncle, cousin and mother were diagnosed in quick succession. It was clear at the time that there was not enough understanding of the molecular basis of the disease to develop an effective therapeutic. I have, as a result, dedicated myself to increasing the understanding of the origins of MND.

What is your favourite aspect of your research?

The best part about the work that I do is the people I get to work with. I have an amazing team who I get to see every week and I have a network of fantastic collaborators here and abroad.

Tell us about the cryo-electron microscopy your project is using?

At the University of Wollongong we have one of the most powerful microscopes in the world. The Titan Krios G3 is housed in the cryo-EM suite of the new Molecular Horizons building, which is purpose-built to satisfy the strictest criteria for operating these types of microscopes, making it one of the few such buildings in the world.

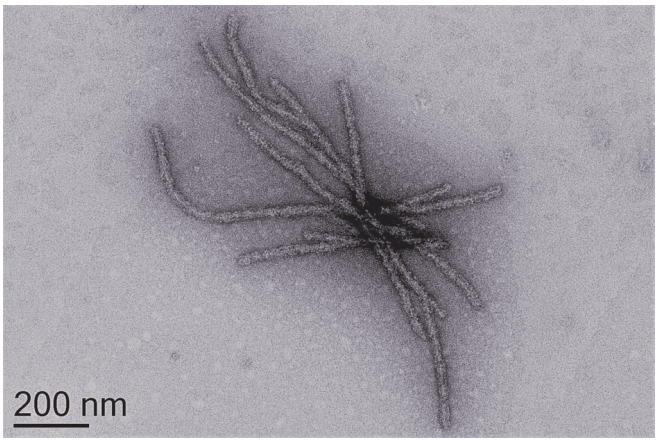
What will the cryo-EM technology allow you to do?

There is very little known about the structure of the proteins that make up the deposits in MND. This is important because if we know the structure, we can design drugs to block their formation. With the new cryo-EM at the Molecular Horizons Research Institute recently opened at UOW, this no longer poses a barrier to research progress in this area.

The cryo-electron microscope can generate image data that allows us to reconstruct the protein structures of biological macromolecules in three dimensions at atomic resolution, so we can examine these structures at the atomic level. Once we determine the structures of these proteins, further studies can be carried out towards developing novel drugs that can slow the deposits forming in MND.

How will this funding impact on your work and MND?

This funding will provide much needed support to keep this work moving. Without funding it just would not be possible to investigate this area so thoroughly. We sincerely thank FightMND for giving us this opportunity and we would like to thank all the people who donated or who bought beanies because without them this work would not be possible.



Long, well-defined fibrils from TDP-43 aggregates, viewed with an electron microscope.

The IMPACT Project

The clumping of materials called proteins within motor neurons is a key feature of MND. In the majority of MND patients, a protein called TDP-43 behaves abnormally, forming clumps that are thought to be harmful to motor neurons. Some of the TDP-43 clumps adopt a fibrillar 'rod-like' structure, similar to fibrils found in amyloid or 'prion-like' diseases, where harmful protein clumps begin forming at a single location, before spreading from cell-to-cell throughout the brain. The idea that TDP-43 acts in a prion-like manner in MND fits with the progressive nature of the disease, and is beginning to be supported by increasing evidence.

This project will test if TDP-43 protein from MND patients can initiate the clumping of TDP-43 in motor neuron models unaffected by MND, and determine if the structure of TDP-43 'rod-like' fibrils can affect the speed at which TDP-43 clumps form. The research team will examine the kinetic and biophysical properties of the TDP-43 clumps, and use cryo-electron microscopy, a new technology, to assess the structure of individual TDP-43 fibrils to define how their shape causes MND and variability in the speed and severity of MND among patients.

OBJECTIVES

- Examine toxic protein clumps from MND patients at the atomic level, using cryo-electron microscopy.
- Define how the shape of toxic protein clumps give rise to MND, and how differences in the structure of protein clumps lead to variations in the speed that MND progresses in people.

OUTCOMES

- The identification of new components of TDP-43 protein clumps that can be specifically targeted with drugs in future studies.