FIGHT MND.


Prof Roger Chung

Researcher.
PROF ROGER CHUNG

Drug Development Project.

DEVELOPMENT OF A TDP-43-TARGETING GENE THERAPY FOR MND

Where do you work?

Our work is undertaken within the Centre for MND Research, in the Faculty of Medicine, Health & Human Sciences at Macquarie University. This project will involve collaborators based at the Children's Medical Research Institute (Sydney), Flinders University and University of Queensland.

Can you give us a summary of your research experience and background?

I completed my PhD studies in biochemistry in 2003 at the University of Tasmania, and since this time have undertaken research in brain injury, nerve regeneration and the study of neurodegenerative diseases such as MND and Alzheimer's disease. One of my major research achievements was the discovery of proteins that promote nerve regeneration following injury, which has been patented and led to the development of therapeutic peptides that are undergoing pre-clinical evaluation for nerve protection and regeneration.

Why did you decide to pursue MND research?

I became interested in MND research very early in my career, through one of my research supervisors at the University of Tasmania (James Vickers). He was interested to understand what makes motor neurons specifically vulnerable to degeneration in MND, with a focus on the structural proteins that distinguish motor neurons from other types of neurons. I was fortunate to receive the inaugural Bill Gole Postdoctoral Research Fellowship from the MND Research Institute of Australia to investigate the role of oxidative stress in motor neuron degeneration at UTAS. I have maintained an interest in MND research since this time, with specific focus on MND research when we established the Centre for MND Research at Macquarie University in 2013.

Can you describe the current focus of your research team?

My research team is focussed on understanding the molecular mechanisms that cause MND. We focus on how proteins become dysfunctional in MND, and why they accumulate inside motor neurons leading to neurodegeneration. We then use this information on the cause of MND to develop and test potential therapeutic strategies. This project is an excellent example of this – we identified a new MND gene, determined how the mutation alters the function of the protein, and have subsequently developed a potential therapeutic based upon this discovery.

What has been your most surprising finding?

Our first step in studying how the new MND gene causes disease was to understand how the function of the MND protein encoded by the MND gene is altered. To do this, we performed a "fishing experiment" to identify proteins that are directly interacting with the MND protein, and how this changes in MND. To our surprise, we identified that the MND protein regulates the levels of a protein called TDP-43 inside cells. This is important, because TDP-43 abnormally accumulates inside motor neurons and this leads to neurodegeneration.

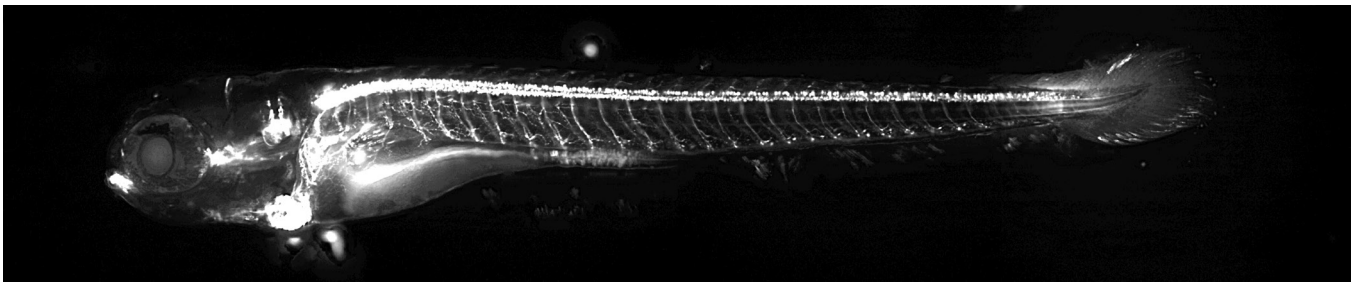
Therefore, we have identified a “smoking gun” that links a genetic cause of MND to the molecular mechanism of disease.

What excites you about TDP-43-targeted gene therapy?

We are excited about the potential of gene therapies. This is a technology that allows us to deliver and express a therapeutic gene in a specific part of the body. Gene therapies offer a potential way to target a therapeutic specifically to motor neurons and have a therapeutic effect for a number of years. Our approach is directly disease-modifying, it targets the specific clearance of TDP-43 from motor neurons, which if successful should have a substantial therapeutic impact.

What will this funding allow your team to do?

Our research project has completed a basic discovery phase and is now progressing towards translation. We have extensive evidence that our potential therapy targets TDP-43, and this funding is essential to support us in developing a therapeutically-optimised gene therapy and validating it in appropriate pre-clinical disease models. Importantly this can’t be done by one research group alone – we need experts from different disciplines to collaborate together to achieve this – and this funding provides us with the scale and duration required to undertake this project. We are excited to launch this large collaborative project, and accelerate towards developing a potential therapeutic for MND.



Preclinical zebrafish model used for MND research in Prof Chung’s laboratory, in which TDP-43 protein in motor neurons is fluorescent (shown as white here).

The Drug Development Project

TDP-43 is an important molecule in cells that has many functions. In almost all cases of MND, TDP-43 behaves abnormally and sticks together to form clumps that are thought to be harmful to motor neurons. Investigators in this study have identified key molecules that normally allow motor neurons to remove TDP-43 and prevent its accumulation. They have also found a way to initiate the removal of harmful TDP-43 from motor neurons using an innovative gene therapy approach.

This study will test if a new gene therapy tool can break up and remove harmful TDP-43, restore health to motor neurons, and stop MND in preclinical sporadic MND models. The research team will evaluate if their gene therapy can delay or prevent TDP-43 clumps from forming and improve survival in sporadic MND models. They also aim to identify the forms of TDP-43 that the gene therapy clears from motor neurons and determine the safety profile of the gene therapy in preclinical MND models.

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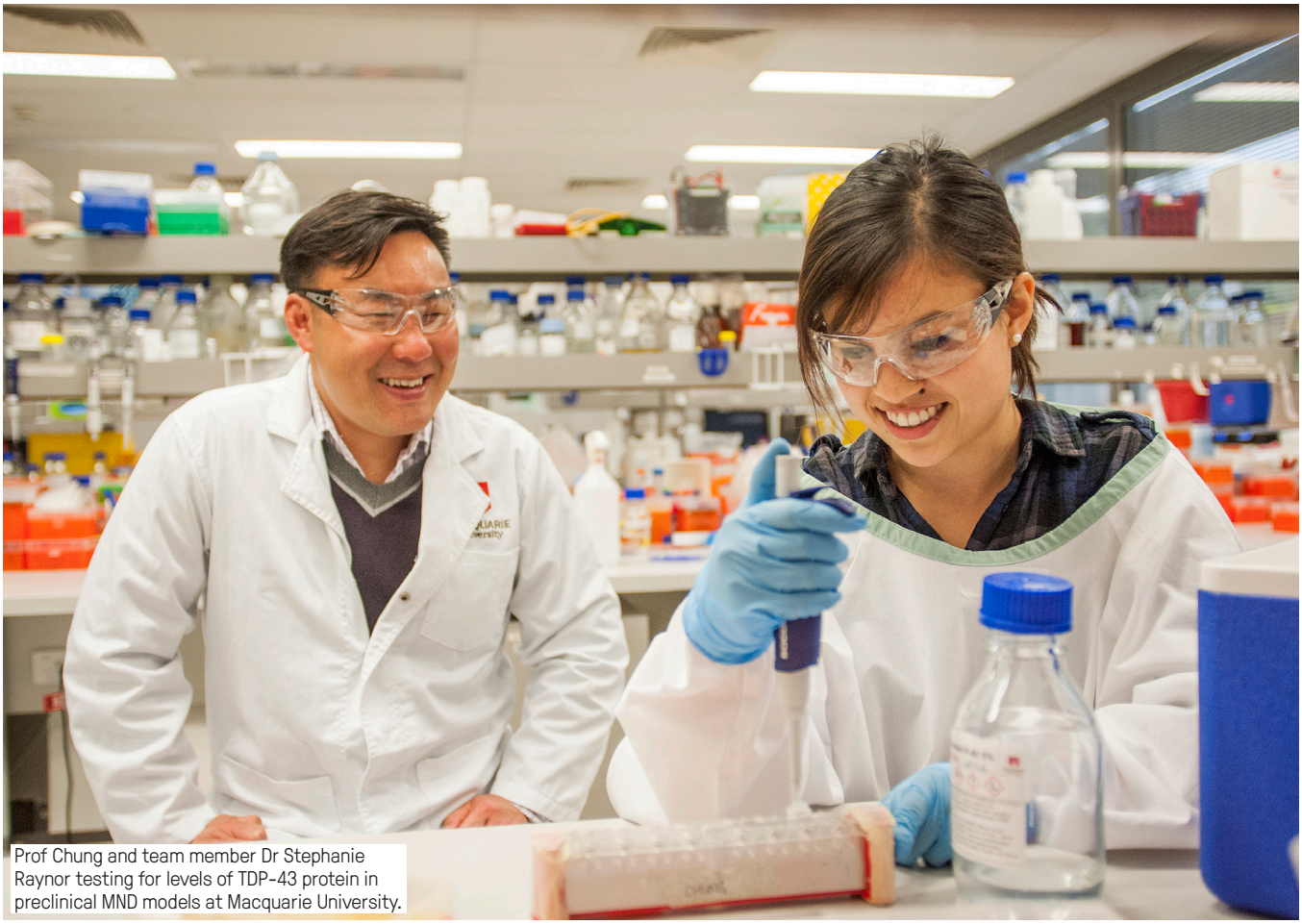

Prof Chung and team member Dr Stephanie Raynor testing for levels of TDP-43 protein in preclinical MND models at Macquarie University.

OBJECTIVES

- Evaluate if a new TDP-43-targeted gene therapy delays or prevents TDP-43 pathology and improves survival in two preclinical models of MND.
- Identify forms of TDP-43 that the gene therapy removes from motor neurons.
- Determine the safety/toxicology profile of the TDP-43 gene therapy in preclinical models, and the dose required to remove harmful TDP-43 from motor neurons.

OUTCOMES

- Evidence that the TDP-43-targeted gene therapy could be beneficial for the majority of people with MND.
- Delivery of preclinical data addressing key requirements for an Investigational New Drug application to the US Food and Drug Administration, for approval to advance the gene therapy to clinical trials for MND.