FIGHT MND.

Researcher.

**PROF ROGER CHUNG**

IMPACT Project.

**DEVELOPMENT OF A DOSE-ESCALATABLE AAV DELIVERY SYSTEM FOR MND GENE THERAPIES**

Priority Area.

**GENE THERAPIES**


Prof Roger Chung

### 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 IMPACT project will involve collaborators based at the Children's Medical Research Institute (Sydney).

### What is 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.

### Can you describe the work you are currently pursuing?

My research program has spent a number of years understanding the molecular mechanisms that cause MND. This has been informative, and we are now in the position to use this knowledge to develop and test potential therapeutic strategies. A particular challenge that we have encountered is how to specifically deliver a potential therapeutic to the motor neurons – because the brain and spinal cord are "protected" by the blood-brain barrier, a cellular barrier that stops toxins, cells and potential therapeutics from crossing from the blood into the brain. This IMPACT grant represents an exciting new approach we have developed to overcome this challenge.

### Which of your scientific findings so far do you value most?

I am excited by the findings that underpin this project. We have identified a molecular pathway that regulates the levels of TDP-43 inside motor neurons, and have developed a gene therapy approach that can activate this pathway as a potential therapeutic. At the same time, we have been developing drug delivery methods that allow us to specifically and efficiently deliver drugs to motor neurons. We are now combining these scientific discoveries together, to produce an innovative therapeutic approach for treating MND.

### What is an AAV delivery system and what is unique about the one you are developing in this project?

Recent technology advances have made it possible to develop gene therapies for neurodegenerative diseases such as MND. A gene therapy involves the delivery and expression of a therapeutic gene in the specific organ or cell type affected by the disease (for MND the target is motor neurons). The therapeutic gene has to be delivered via a carrier – and modified viruses have proven to be very good carriers for therapeutic genes. For this project we will use a modified adeno-associated virus (AAV), because a recent AAV gene therapy has

been developed and is successful for treating spinal muscular atrophy, a childhood disease with some similarities to MND.

This project is unique because we will directly address two of the current challenges faced by gene therapies. Firstly, we will develop nano-sized particles (nanoparticles) that can deliver AAVs efficiently across the blood-brain barrier and into motor neurons. And secondly, we will establish a novel method for precise control of therapeutic gene expression. This is very important, because the expression of the therapeutic gene must be tightly controlled – our method will allow on/off control, as well as regulation of gene expression at desired levels. Current methods do not have this level of control – they provide always on, high levels of gene expression – which may have side-effects if prolonged for many years.

## How will this funding impact on your work and MND?

This project brings together two different technologies and scientific expertise – AAV gene therapies and nanoparticle-drug delivery systems. This funding will allow us to combine these two technologies together in a completely new way, and test whether the combination of these approaches can make a breakthrough in developing an AAV gene therapy that can target motor neurons in MND. If successful, this would have a significant IMPACT towards developing a gene therapy pathway for treating MND. We are incredibly excited about the new approach that we can test because of this funding.

Prof Chung and team in the laboratory at Macquarie University in Sydney.

FIGHT MND.

## The IMPACT Project

There is strong interest in developing treatments called 'gene therapies' for neurodegenerative diseases, such as MND. This is emphasised by the recent successful development and approval of a gene-therapy for a type of MND in infants, called Spinal Muscular Atrophy (SMA). Gene therapies can work in a number of ways, by: delivering a lost gene; or acting as a gene switch – turning on a gene that has been inactivated, or switching off a gene that is behaving abnormally. Switching genes on or off is a tightly regulated process, as too much or too little gene expression can have drastic consequences. While gene therapies have excellent potential for treating diseases, control over the level of gene expression is critically important. Current methods do not have this level of control – they provide always on, high levels of gene expression – which may have adverse or detrimental effects if prolonged for many years.

This project aims to establish a new method for precise control of gene expression by a gene therapy. Investigators will perform a proof-of-concept study of their new gene expression control system by combining it with a new gene therapy they are developing for MND. The team will deliver a gene into motor neurons that removes a molecule called TDP-43, which in MND, sticks together to form clumps that make motor neurons unwell.

### OBJECTIVES

- Establish a way to precisely control the dose of a TDP-43-targeted gene therapy in motor neurons, to maximise its benefit and limit side-effects.
- Develop a way for the TDP-43-targeted gene therapy to reach motor neurons in the brain and spinal cord from the bloodstream.

### OUTCOMES

- A major advance towards developing a clinically viable, dose-controllable, gene therapy for MND.