FIGHT MND.


Prof Trent Woodruff

Researcher.

PROF TRENT WOODRUFF

Drug Development Project.

COMPLEMENT C3A RECEPTOR MODULATORS AS DISEASE-MODIFYING DRUGS FOR MND

Where do you work?

I work within the School of Biomedical Sciences, at the University of Queensland (St Lucia campus in Brisbane).

Can you summarise your research experience and background?

I am a pharmacologist by training, completing my PhD in 2003 helping to develop a new class of orally active drugs for arthritis. After my PhD, I worked for a biotech company that was formed to commercialise this drug that was progressed into human clinical trials, before being licensed overseas. I returned to the University of Queensland in 2007 to begin working on a similar drug approach for MND. I now head a research team aiming to develop and progress new drugs for MND and other neurodegenerative diseases.

What is the current focus of your research laboratory?

We are focussing on the role of a key immune system, called the Complement System, in MND, and how increased Complement activity can lead to inflammation, that can worsen and accelerate disease. Our latest research has discovered a component of the Complement System, called C3a, can act as a 'brake' to halt inflammation, and thus slow MND progression.

What has been your favourite scientific finding so far?

My favourite finding has been that our laboratory discoveries have allowed for the testing of new drugs in MND patients. There are several anti-complement drugs currently in human clinical trials for MND. This is the best possible outcome for a laboratory aimed at 'translating' our research to help people with disease.

How did you identify that C3a receptors may play a key role in MND?

Perhaps like all key discoveries, this was an 'accidental' finding. We were investigating the role of other complement factors in MND (such as C5a receptors, from our prior FightMND project), and decided to additionally study C3a receptors. Surprisingly, we found that by contrast to C5a, C3a was actually protecting against motor neuron death in our MND models.

What excites you most about C3a receptors and their potential for MND?

We are particularly excited about the possibility of C3a receptors being used as an approach to halt global immune and inflammatory pathways in MND. We have evidence that C3a may act not only to limit complement-mediated inflammation, but also act as a general 'neuro-protectant' in the diseased central nervous system.

How will this funding impact on your work and people living with MND?

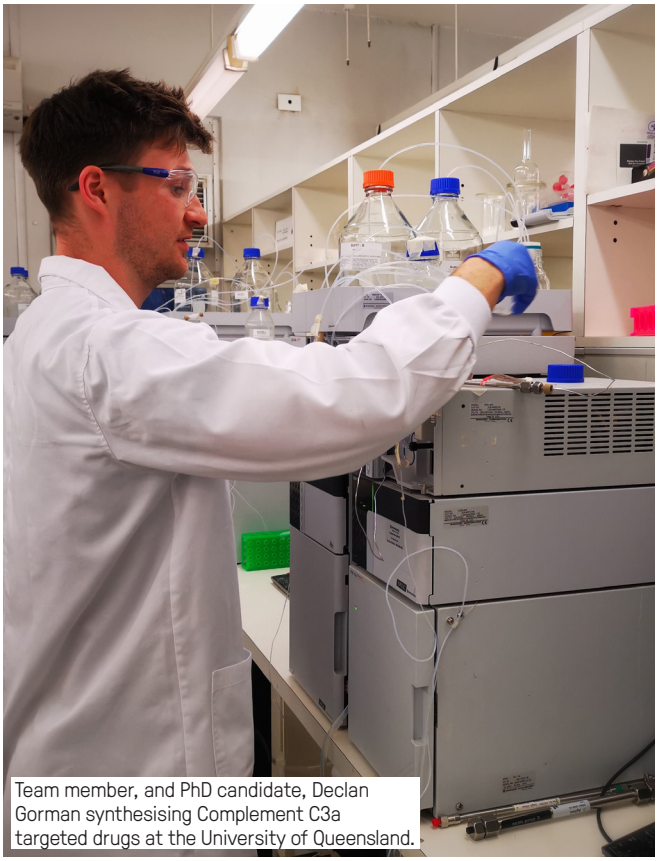
This funding from FightMND is really critical in enabling our work to develop new therapeutic drugs that can target C3a receptors in the central nervous system. Without this funding, we would be unable to discover these drugs, and test them in MND models. This is essential work before we can progress drugs into human clinical trials. We hope our new drugs can lead to future clinical trials in MND patients, that could potentially slow or halt disease.

FIGHT MND.

The Drug Development Project

Although MND is a disease of the motor neurons, a number of other cell types also contribute to the disease. Immune cells are recognised as having an impact on the rate of disease progression in MND, with immune cell modulating drugs showing some early promising results in preclinical studies. Previous work from this team has identified a key protective role for a component of the immune system called C3a. They have shown that C3a is able to protect neurons, improve movement and prolong life in preclinical MND models.

This project aims to advance the preclinical development of immune-protective drugs to treat MND. The team have developed novel stable and selective drugs that can reach the brain at effective concentrations and activate C3a pathways. The study will test their lead drug in both familial and sporadic models of MND. They will also perform medicinal chemistry on the drug to allow for the development of an orally active and brain-penetrating drug that is appropriate for testing in clinical trials. Preclinical safety studies will also be performed to ensure the drug is safe for use in patients.



Team member, and PhD candidate, Declan Gorman synthesising Complement C3a targeted drugs at the University of Queensland.

OBJECTIVES

- Test the efficacy of a new drug targeting the C3a component of the immune system in preclinical models of familial and sporadic MND.
- Perform comprehensive pharmacokinetic, metabolism and safety screens of lead candidate C3a drugs in preclinical models.

OUTCOMES

- Development of a lead drug engaging and activating C3a pathways, that is ready to test in a clinical trial for MND.