FIGHT MND.


A/Prof Trent Woodruff

Researcher.
A/PROF TRENT WOODRUFF

Project.
PROGRESSION OF THE C5A ANTAGONIST PMX205 TO CLINICAL TRIALS FOR MND

Who are you and where do you work?

I am a research Academic located at the School of Biomedical Sciences, The University of Queensland (UQ), on the St Lucia campus. I am supported by an NHMRC Career Development Fellowship, and also work as an Associate Professor of Pharmacology for the School.

Can you give us a summary of your training/experience background?

My training is in pharmacology and drug development. I undertook my undergraduate studies at UQ, and then completed my Honours and PhD training in the laboratory of Professor Stephen Taylor at UQ. My PhD examined a new anti-inflammatory drug in models of rheumatoid arthritis and inflammatory bowel disease. I showed this drug could protect animals from these diseases. During my PhD, a biotechnology start-up company, Promics Pty Ltd, was formed, which aimed to take this drug to human trials. Following my PhD, I moved out of the University and worked for Promics as a research scientist, helping to progress the drug into human clinical trials and veterinary applications. In 2006, Promics was sold to Peptech, and I made the decision to move back into Academic research at UQ as a post-doctoral scientist.

How did you come to work in MND research?

Following my return to UQ, I wanted to tackle 'something different' from my PhD studies, however, I was still interested in the therapeutic potential of the drug compounds discovered during my PhD. I thus turned my attention to examining the role of inflammation in brain disease, a field, which at that stage, was still in its infancy. I scoured the literature for an appropriate disease and model system to begin with, and immediately saw the potential of motor neurone disease (MND), as inflammation had been observed in the blood and brains of these patients, and current drugs for this disease were (and still are) inadequate. I thus began examining MND in collaboration with several MND researchers including A/Prof Peter Noakes and Prof Pamela McCombe. We also recruited a very talented PhD student, Dr John Lee. Our group has since focused much of our research efforts on this terrible disease.

Can you describe the work your lab is currently pursuing?

In relation to MND, our group is identifying new therapeutic targets, focusing on inflammation and the immune system. In addition to our lead compound PMX205, we have several other promising targets and drug candidates, that we are testing in mouse models of MND.

How did you identify PMX205 as a potential treatment for MND?

When I returned to UQ as a post-doctoral researcher, I began by administering the anti-inflammatory drugs discovered during my PhD (called 'PMX' compounds), to MND rats. I discovered that the 'second generation' compound, PMX205, was very effective at improving muscle function and extending survival. We have subsequently confirmed the efficacy of PMX205 in a mouse model of MND, as well as uncovering the mechanisms by which the drug works to reduce motor neuron death.

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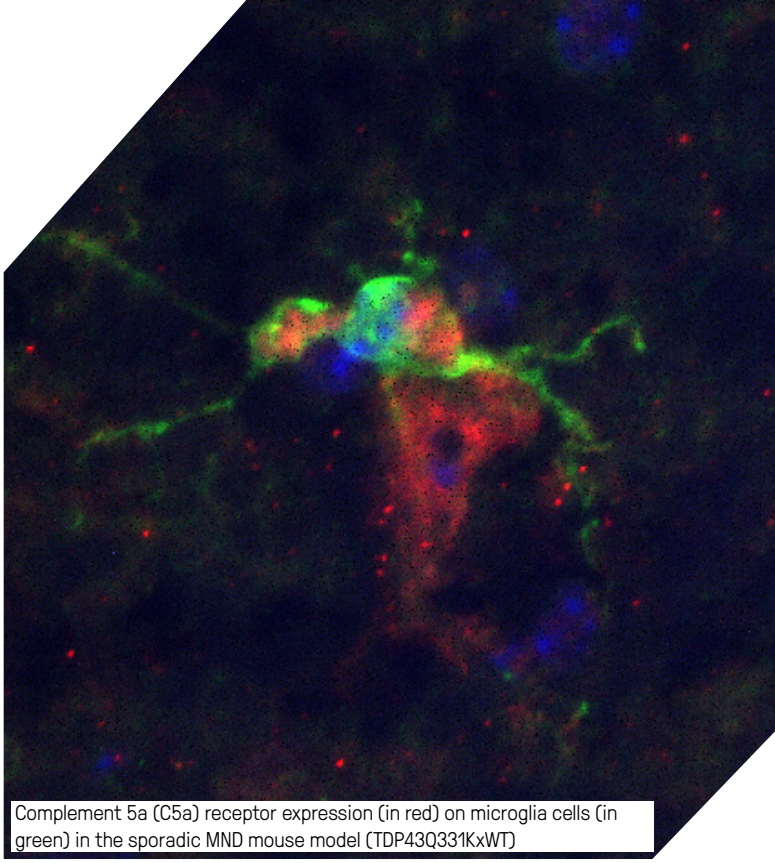

Complement 5a (C5a) receptor expression (in red) on microglia cells (in green) in the sporadic MND mouse model (TDP43Q331KxWT)

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The aim of this project is to bring to the clinic a novel drug for MND treatment called PMX205 - an immune system modulator. The drug is a highly selective inhibitor of the complement cascade, which is a key component of our immune system. PMX205 acts both in the brain, and outside the brain, and is anticipated to slow disease progression, improve quality of life, and extend the lives of MND patients.

Inflammation is the immune response to the injury of an organ in the body. Inflammation that becomes chronic can damage the body's own organs, as the inflammatory cells release damaging substances in an attempt to destroy the source of inflammation. Often, and particularly in the brain, the body is unable to repair tissue damage, and a cascade of events occurs creating further damage. Inflammation has been measured in the brains of patients with MND and is found to be increased compared to healthy patients. A key component driving this inflammation is a suite of proteins known as the complement system. PMX205 is an inhibitor of complement, and is designed to dampen down inflammation, return the brain to a more normal homeostatic condition and prevent further damage.

This project will see PMX205 advance through scale-up synthesis and pre-clinical safety testing, to Food and Drug Administration (FDA) approval to conduct clinical trials in human volunteers. The early clinical trials will be conducted in Australia. PMX205 has been extensively studied in one particular animal model of MND, called SOD1 mice, that reflects a subset of patients with MND but also shares features common to other forms of MND. This project will expand on these studies into a distinct model of MND to demonstrate that PMX205 is suitable for all patients with diagnosed MND, both sporadic and familial.

On successful completion of this project, the first clinical trials in healthy volunteers with PMX205 are currently expected to commence in late 2018, with clinical trials in patients with MND possible during 2019.

ON SUCCESSFUL COMPLETION OF THIS PROJECT, THE FIRST CLINICAL TRIALS IN HEALTHY VOLUNTEERS WITH PMX205 ARE CURRENTLY EXPECTED TO COMMENCE IN LATE 2018, WITH CLINICAL TRIALS IN PATIENTS WITH MND POSSIBLE DURING 2019.