Researcher: A/PROF PETER CROUCH
Project: TARGETING A DEREGULATED COPPER-IRON AXIS TO TREAT SPORADIC MND: A COMBINATION TREATMENT STRATEGY

Who are you and where do you work?
My name is Peter Crouch and I work in the Department of Pathology at the University of Melbourne.

Can you describe the work your lab is currently pursuing?
The major focus in my lab is on relating the therapeutic activity of copper-ATSM to human cases of MND. New therapeutics for MND need to be tested and developed in the research lab, and for us this means testing and examining drugs in mice. The mice we use develop many features of human MND; motor neurones in the brain and spinal cord gradually deteriorate and die, causing progressive paralysis and premature death. Treating the mice with copper-ATSM is effective, and over the years we have built a body of evidence that has enabled us to start testing copper-ATSM in people with MND. But the mice have their limitations, so to circumvent these limitations we examine brain and spinal cord tissue collected from people who died because of MND. Having access to human brain and spinal cord tissue is critical to our work; we are very fortunate to have access to samples and support from Catriona McLean and her colleagues at the Victorian Brain Bank. Finding commonalities across the mice, the human tissue, and what we know about the drug's mechanism of action helps us build a better understanding of what causes MND and what needs to be fixed in order to stop symptom progression.

How did you identify Cu and Fe manipulation as a potential treatment for MND?
Copper is an essential element. We need it because it is required for healthy functionality of many proteins throughout the body. Several years ago, we established that copper-ATSM can deliver copper to proteins which become copper-deficient in MND mice, so since then we have been examining a greater range of copper-dependent proteins in mouse and human MND-affected tissue. We have found that many copper-dependent proteins are disrupted in MND. One of these copper-dependent proteins is responsible for regulating iron levels. As per copper, iron is also an essential element; too little iron starves a biological system of fundamental capabilities, and too much iron is toxic. Basically, we have found that in the MND-affected brain, diminished activity of a specific copper-dependent protein is associated with toxic iron accumulation. This has led us to hypothesise that using a combination of drugs to modulate copper and iron simultaneously may be an effective treatment option for MND.

What excites you about this drug(s)?
One of the things that really excites me is the reproducibility of our lead drug, copper-ATSM. Many research groups around the world have developed their own drugs which appear to work well when tested in the lab. But unfortunately, most of these drugs fail to show the same therapeutic effects when interrogated and tested in an independent

lab. Reproducibility of research outcomes is very important - it indicates that the outcome is robust.
Following on from the promising outcomes generated by us here in Melbourne, other groups around the world have started testing copper-ATSM. To date, everyone who has tested copper-ATSM has reported that the drug is effective.

THE PROJECT
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Our team has developed the compound copper-ATSM as a treatment option for MND. Based on our extensive positive outcomes from testing in animal models of MND, and via our partnership with Collaborative Medicinal Development, Phase 1 clinical testing for safety and tolerability commenced in Australian MND patients in November 2016.
Copper is an essential element required for the survival and healthy functionality of every cell in our body.

In developing copper-ATSM as a treatment for MND our research has revealed that:
1. Essential copper-dependent processes are disrupted in the human brain and spinal cord affected by MND.
2. The neuroprotective activity of copper-ATSM in MND model mice involves restoration of healthy functionality to these copper-dependent processes.

Some of our more recent outcomes now show that one of the deleterious consequences of copper malfunction in MND is a toxic accumulation of iron. Like copper, iron is also an essential element required for healthy cell function, but excess accumulation of iron is toxic. By analysing human tissue we have now mapped a biochemical pathway that links copper malfunction to iron accumulation in MND. In other words, copper malfunction and iron accumulation are connected components of a neurotoxic axis in MND.

This discovery opens a new opportunity which we now intend to explore within our MND drug development program. In brief, we will assess the potential to treat MND via a novel combination therapy approach - copper-ATSM will be used to restore functionality to essential copper-dependent processes, and additional drugs (some already existing, and some currently being developed in-house) will be used to suppress the toxic consequences of iron accumulation.