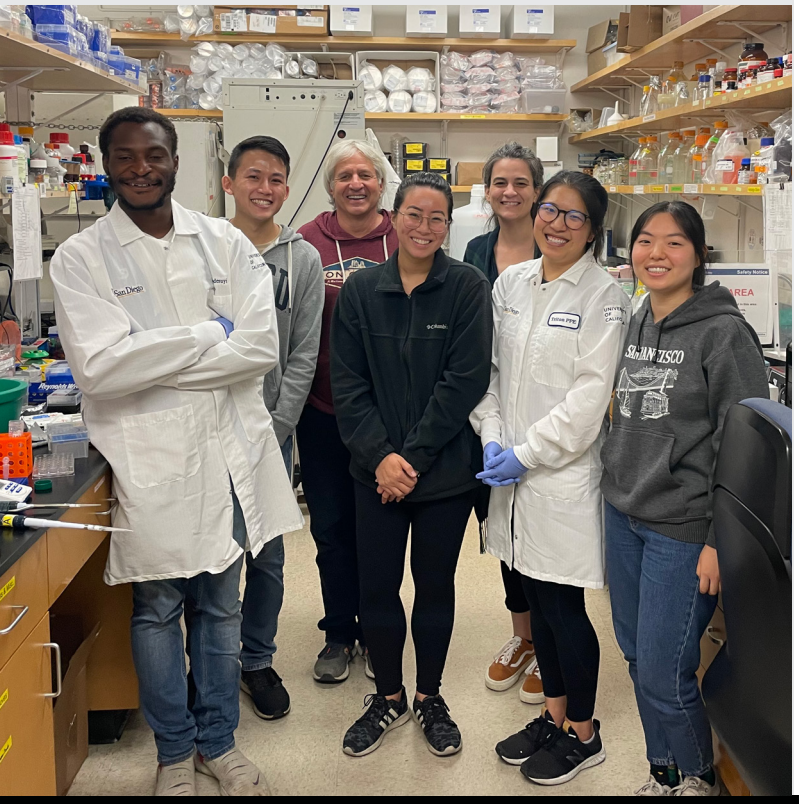
FIGHT MND.

Project

Targeting CK1ε-mediated TDP-43 Phosphorylation in MND

TDP-43 is an important molecule in cells that has many functions. In almost all cases of MND, TDP-43 misbehaves by changing its structure and forming clumps in motor neurons. This preclinical study will determine if this structural change in TDP-43 is harmful or protective to motor neurons. Investigators will target a pathway called CK1ε, that causes the structural change in TDP-43. They will examine if blocking the function of CK1ε with a drug prevents the structural change to TDP-43, and delays the onset and progression of MND. Successful outcomes will help advance the drug towards phase 1 clinical trials for MND.



Project Lead

Dr John Ravits

University of California – San Diego, USA

Dr John Ravits began his MND journey with pure clinical observations of disease onset and progression. With this as a basis, he *"formulated a model of disease progression based on focal onset and neuroanatomical spread of pathobiological factor(s)."*

He has created a *"biorepository of patient nervous systems with high molecular quality and used this as the basis to study and explore molecular neuropathology by genomic profiling of laser captured motor neurons."*

This enabled Dr Ravits to pursue research in a number of areas to better understand ALS/MND pathobiology and identify targets for the therapy he is studying in his basic science laboratory *"by way of molecular neuropathology, cellular and mouse models."*

He believes ALS provides a *"unique window and special opportunity to unravel its pathobiology especially through neuropathology and genomics and validation in various disease models."*

A disease that spreads

ALS/MND is often described as a disease of upper and lower motor neurons and Dr Ravits believes it is also a spreading disease. This means that *"whatever is causing MND, it is not just a disease in which neurons degenerate over time, but also a disease that spreads over space in the brain and spinal cord."*

By acquiring optimal human tissues to be studied, the hope is that the root causes of MND can be unravelled.

Perfect timing

Dr Ravits says that the funding from FightMND *"comes at a perfect time for me to carry out experiments that have been maturing for nearly two years."*

His identification of CK1ε and its role in TDP-43 phosphorylation was published in 2018 and his lab immediately began to pursue this in cellular and mouse models. They have established the unique role of CK1ε as the principal driver of TDP-43 phosphorylation in cellular models.

He says that *"this supported that it was important but didn't answer whether or not it was a driver of toxicity or a reactive defence mechanism."*

"To study this, we turned to a mouse model with inducible mislocalisation of TDP-43 and to a CK1ε knockout mouse model. These mouse models seemed best able to test the role of CK1ε mediated TDP-43 phosphorylation, but necessarily through very complicated breeding schemes, that have taken two years with very limited funding."

"We now have the mice and [have] shown that these experiments are feasible and are poised to carry out these very elaborate experiments," he says.

The FightMND funding will allow his lab to continue to expand the scope of their studies without compromise.

Available drugs

"Interestingly, during this time, the drugs that inhibit CK1ε have been acquired by a large pharmaceutical company who have a major commitment to ALS/MND therapeutics and with whom I have worked closely in developing gene therapies, so I have an audience if I can establish proof-of-principle of the value of this target," he says.

"The fact that the drugs have been developed already is exciting. While they don't yet have an application, their availability allows me to test if these ideas are right, meaning establishing proof-of-principle," he says.

"Thanks to the FightMND funding, I can now carry this forward, with the confidence that if this target is worthy, then the complicated task of phase 1-3 testing and further drug development can proceed with the key experts and partners."

Of the fight against the 'Beast', Dr Ravits says

"ALS/MND is a war and there are many battles to fight ahead. In the end, we want complete and unmitigated surrender and we all have a part to play."

FightMND has invested $986,282 in this research.

About Dr John Ravits

Dr John Ravits is a physician-scientist in the Department of Neurosciences, University of California, San Diego (UCSD), USA. UCSD provides exciting team-oriented neurosciences and medical environments for the full range of my activities.

Dr Ravits' work is divided into three parts: research lab, translational research and clinical program. In his research laboratory, work is focused on mechanisms of motor neuron degeneration and molecular neuropathology. He has used genomic profiling of laser captured motor neurons in patient spinal cords to identify new pathways and targets for therapy. In his clinical programs, he leads a multidisciplinary team in a nationally certified ALS/MND Centre of Excellence, which provides full spectrum clinical care for a panel of 150-200 patients.