

FIGHT MND.

Project

Disease Models

Harnessing phase separation as a preclinical strategy for the treatment of MND

TDP-43 is an important molecule in cells that has many functions. In almost all cases of MND, TDP-43 misbehaves and sticks together to form clumps that are thought to be harmful to motor neurons. This project aims to study a novel mechanism, called phase separation, that may cause the formation of TDP-43 clumps. Investigators will determine if preventing phase separation of TDP-43, by altering its structure, can delay the formation of TDP-43 clumps in motor neurons.



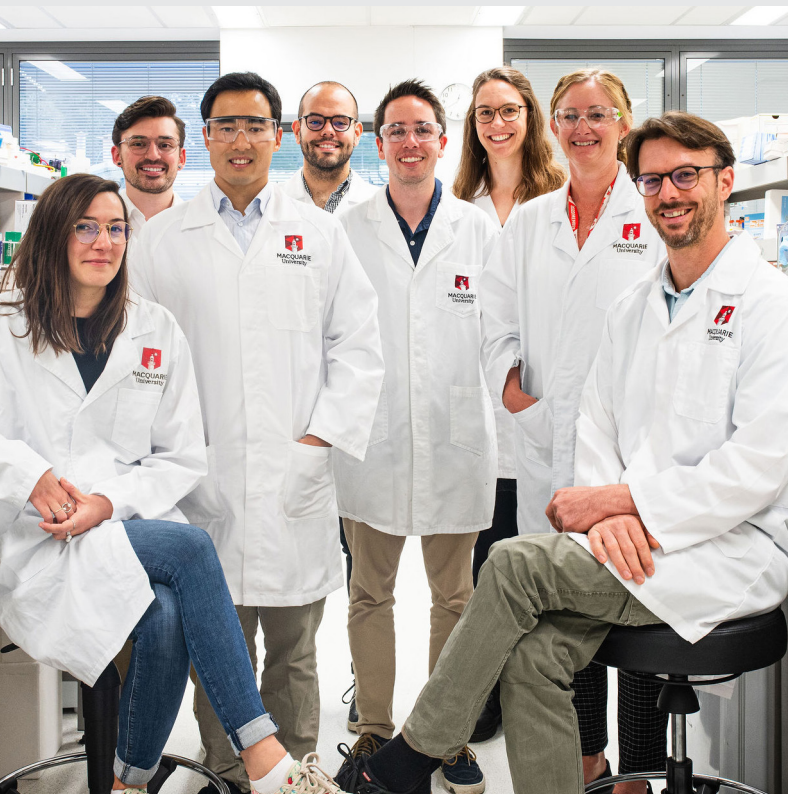
Project Lead Dr Marco Morsch Macquarie University, NSW

Dr Marco Morsch says that learning about MND was an eye-opener and that trying to develop new therapeutic opportunities for people living with MND is the best motivation to continue his work. *"The prospect of helping to delay or stop MND in its tracks one day is just the best inspiration ever,"* he says.

"I truly believe that the answers are out there, we must dare to look carefully."

He is quick to note that so much progress has already been made. For example, people living with familial MND are now able to have kids knowing that they don't carry the faulty genes (through IVF and genetic testing).

Dr Morsch says working with his team who strive relentlessly to push scientific frontiers every day in the lab while being incredibly motivated, kind, and passionate is one of the highlights of his job.



Phase Separation

Dr Mosch's research is examining phase separation, a biological process where some molecules or proteins accumulate much more in one location than another. *"The concept of oil in water is a good comparison, where you have drops of oil bonding together when surrounded by water,"* he says.

Thorough mixing or a change in the environment can alter this separation of liquids and the same is true in cells, *"where it is believed that proteins come together in high density to perform important cellular processes without the need to get transported into another compartment."*

"The process allows fast regulation of certain events and is quite common in cells. For example, we know of many other cell bodies that form through this process and are critical for cellular health."

A first step

This concept is in its infancy for MND and disease proteins explains Dr Morsch. *"It is an important model that might help to explain how toxic aggregates can form in the nerve cells that die during the disease."*

"If these phase-separated proteins become too 'sticky', this might be one of the first steps that causes aggregation in MND," he adds.

Dr Morsch says the fact that phase separation *"is such a fundamental biological process that has not been explored enough in MND is a very stimulating prospect."*

"If phase separation goes wrong early in the process of protein aggregation, we might have a new handle on how to delay or ultimately stop disease progression."

More work is needed to be done, however the exploration of *"novel concepts such as phase separation is critically important to come up with new ways to stop this beast of a disease."*

Driving scientific discoveries

Dr Morsch says that support from FightMND is important in so many ways.

"It not only helps to drive scientific discoveries, but it also enables the next generation of researchers who dedicate their careers to finding a cure for MND."

"Such investment with clear short-term and long-term benefits is most critical in a time where scientific news and advice is at the forefront of our everyday lives. And for a young laboratory like mine, support like this means that we can focus on what we do best, the research in the labs with some form of continuity," he says.

"My hope is that we will develop a range of therapeutic opportunities for people living with MND. In all reality, there won't be a one-size-fits-all approach and investing into the broad spectrum of therapeutic avenues might be the key to multi-faceted treatment options in the future."

FightMND has invested \$249,996 in this research.

About Dr Marco Morsch

Dr Marco Morsch is a neuroscientist with passion for investigating cellular interactions. He has experience in a range of techniques, including microscopy, electrophysiology, and animal models of disease. Early in his career, Dr Marco Morsch focussed on other neuromuscular diseases, but in 2014 had the opportunity to join

the newly formed Centre for MND Research at Macquarie University and apply his skills to MND. He is currently a group leader at the Centre for MND Research at Macquarie University, Sydney, Australia.