FIGHT ~~MND~~.

Researcher.

DR SAMANTHA BARTON

IMPACT Project.

USING 3D SPINAL CORD ORGANOIDS TO MODEL OLIGODENDROCYTE NEUROTOXICITY IN MND

Priority Area.

DISEASE MODELS

Dr Samantha Barton

Where do you work?

I am a post-doctoral researcher in the Motor Neurone Disease Laboratory at the Florey Institute of Neuroscience and Mental Health in Melbourne.

What is your research experience and background?

I received my PhD in 2015 and then completed my first post-doctoral position at the University of Edinburgh, Scotland. It was in Edinburgh that I learnt how to culture patient induced pluripotent stem cells and differentiate them into key cell types, and make three-dimensional structures like organoids. I returned to Melbourne in 2018 where I have established these techniques and am continuing my research within the Motor Neurone Disease laboratory at the Florey Institute.

Why did you begin your research into MND?

I have always been fascinated by the inner workings of the brain and understanding how it functions in both development and disease. My PhD focussed on understanding the development of the brain and how these developmental processes can be disrupted with pregnancy/birth complications. Interestingly, many of these dysregulated pathways are also similarly affected in neurodegeneration. I shifted my focus to understanding neurodegeneration and I became drawn to understanding the biology of MND. It is such a complicated disease with such a challenging prognosis. I hope with my research background and expertise that I can contribute to the understanding of the underlying causes of MND.

What is the coolest thing about your work or research?

One of the constant battles we face as scientists is identifying the best model system that will allow us to accurately and reproducibly study MND. The cool thing about my research is that I use induced pluripotent stem cells which are directly sourced from people that have MND. We can then make these stem cells into the various cells of the brain and spinal cord. This means that we can grow human brain cells that are genetically identical to the person we took the initial stem cells from! This is a very powerful model to allow us to interrogate how these cells differ from those taken from a person without MND with my goal being to identify early changes that could be contributing to the onset of MND.

What is a 3D spinal cord organoid?

Using patient induced pluripotent stem cells, I have been able to differentiate them into the various cell types of the brain and spinal cord. During my training in Scotland, I acquired a very cool technique that allows me to differentiate these stem cells into more complex three-dimensional structures, called organoids, that mirror some of the structure and cellular components of the spinal cord. The beauty of organoids is they allow us to assess cell-to-cell interactions from cell types that harbour the genetics of the original person who donated the stem cells.

FIGHT MND.

Why did you choose to develop this 3D-organoid model of MND?

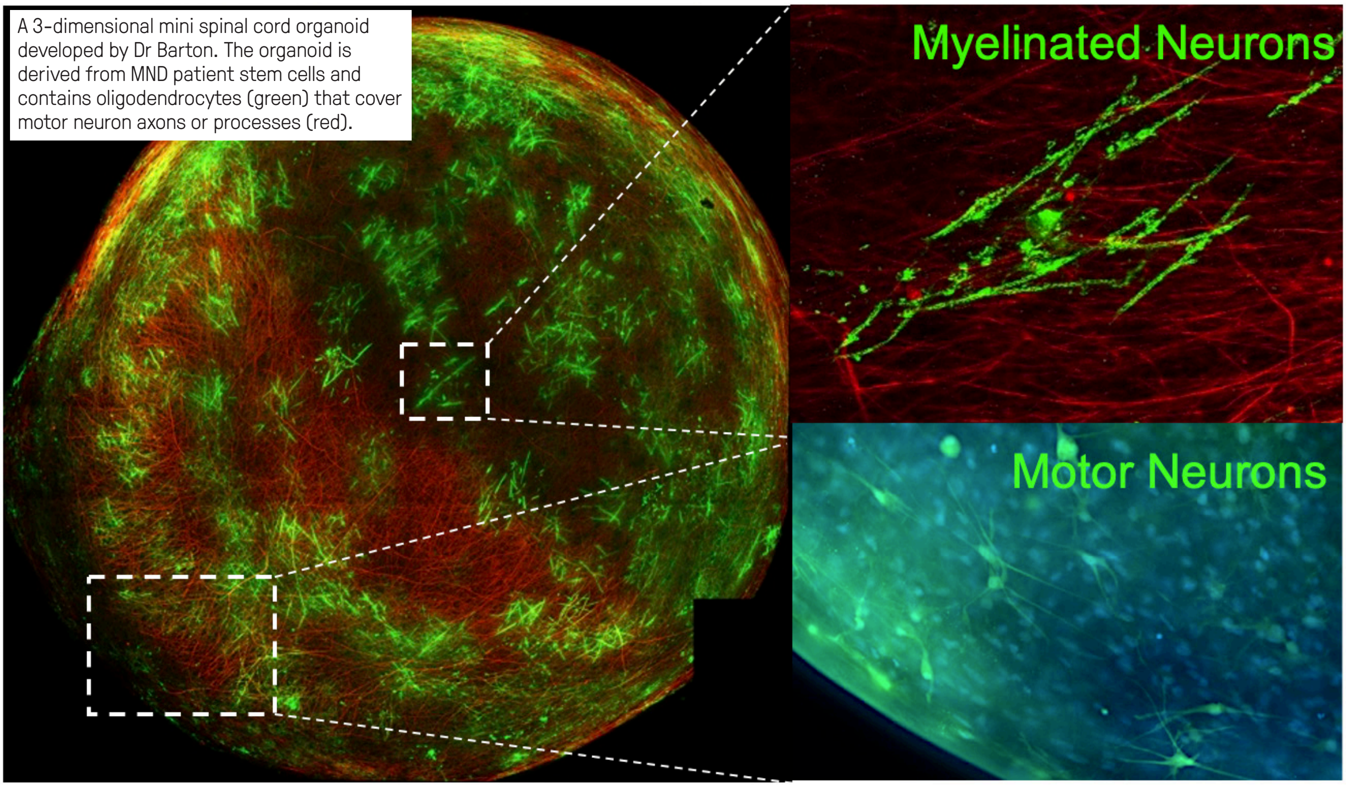
My specific interest is actually in glial cells – these are cells that support the health and function of motor neurons. It is likely that these glial cells are also affected in MND and could be contributing to motor neuron dysfunction and death. The 3D-organoid model of MND I am developing contains two of the critical glial cell types so it is a powerful humanised model that will allow me to further understand the contribution of glia to MND onset and progression.

What excites you about this model?

One of the glial cell types is called an oligodendrocyte and this cell produces an insulating sheath around motor neurons that is essential for their normal electrical firing, which is called myelin (think of the rubber coating on the electrical cord for your toaster – same!). In fact, 95% of a motor neuron is composed of its axon which is the section of the neuron that is covered in myelin, and myelin is essential to not only insulate but it can also pass nutrients and other factors into the neuron. Oligodendrocytes, and their myelin, remain relatively unexplored in MND but, given their importance in supporting motor neurons, are likely to play a role. This 3D-organoid model of MND is one of the first in the world to contain myelinated motor neurons, so is an unparalleled model system for the interrogation of this very important cellular relationship.

This is your first Grant from FightMND. What difference will this funding make to your work and for people living with MND?

Using patient induced pluripotent stem cells, and deriving complex structures like 3D-organoids, is a very powerful system but is a time and cost heavy endeavour! I am so fortunate to be supported by FightMND to allow me to continue on my quest of understanding the role of glia, like oligodendrocytes, in MND onset and progression. Characterising the underlying biology of MND will uncover new therapeutic targets that will allow us to more accurately target the causes, rather than the symptoms, and will therefore be of a much more significant benefit to people living with MND.



A 3-dimensional mini spinal cord organoid developed by Dr Barton. The organoid is derived from MND patient stem cells and contains oligodendrocytes (green) that cover motor neuron axons or processes (red).

The IMPACT Project

To study MND in the laboratory, researchers use models of the disease developed to replicate hallmarks or disease signatures that occur in the human disease. In the past, researchers have relied on animal models to study MND, but recent advances in technology have allowed them to grow stem cells (called iPSCs) from MND patient skin cells, creating a "human" model of MND. These stem cells can be turned into almost any cell type in the body. For MND, these cells include motor neurons, and supporting cells called 'glia'. More recently, this technology has advanced even further. Researchers can now grow multiple cells types in parallel, and combine them to form complex 3-dimensional mini organs, or 'organoids', which provide a unique and sophisticated 'human' model of the desired organ.

This project will use MND patient's skin cells to grow stem cells, generate motor neurons and glia, and create 3-dimensional mini-spinal cord organoids. The team will use the mini-spinal cords to study a type of glia called an oligodendrocyte, that provides structural support and energy supply to motor neurons. In MND, both structural support and energy supply to motor neurons are significantly altered, and could contribute to their death. Using this novel mini-spinal cord model, the team will comprehensively characterise the contribution of oligodendrocytes to motor neuron dysfunction and death in MND.

OBJECTIVES

- Generate mini-spinal cord organoids from an array of patients with familial and sporadic MND.
- Determine how deficits in structural support and energy provided by oligodendrocytes contribute to death of motor neurons, and verify if these deficits occur across different subtypes of MND.

OUTCOMES

- A major advance on understanding the contribution of oligodendrocytes to motor neuron dysfunction in MND.
- Unravelling of new drug targets for MND around previously unexplored oligodendrocytes and their function.