FIGHT MND.

Researcher.

A/PROF JULIE ATKIN

Project 1.

NOVEL THERAPEUTICS TARGETING NEURONAL TRANSPORT PATHWAYS IN MND

Project 2.

THERAPEUTICS BASED ON THE PROTECTIVE ACTIVITY OF PROTEIN DISULPHIDE ISOMERASE IN MND

A/Prof Julie Atkin

Associate Professor Atkin was awarded two Grants in 2017

Who are you and where do you work?

My name is A/Prof Julie Atkin and I work in the Department of Biomedical Sciences, Faculty of Medicine and Health Sciences at Macquarie University, Sydney. I also have an honorary position in the Department of Biochemistry and Genetics at La Trobe Institute of Molecular Science, Melbourne.

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

I obtained my PhD at the University of Sheffield, UK, where I studied antibody engineering in the Department of Biochemistry and Molecular Biology, in collaboration with Celltech Pty Ltd, a UK biotechnology company. I then moved to Melbourne where I undertook immunology research, including four years based at Cytopia Pty Ltd, a Melbourne based Biotechnology Company focussed on drug discovery for immune diseases and cancer. I began working on MND in 2003 at the Florey Institute for Neuroscience and Mental Health, where I headed the MND research group. Here I began investigating basic cellular mechanisms that trigger the death of motor neurons in MND. My group and I relocated to La Trobe Institute of Molecular Science, Melbourne in 2009, and in 2014 I was recruited to Macquarie University, Sydney to establish the MND Centre..

How did you come to work in MND research?

Whilst I enjoyed working on basic science, I really wanted to work on something that had more relevance to human health. Neuroscience really fascinated me and MND is a disease for which there is no effective treatment. Hence there is a real need to find new treatments for this terrible illness.

Can you describe the work your lab is currently pursuing?

We are investigating the basic molecular mechanisms that cause motor neurons to die in MND, with the idea of designing new drugs that can target these processes. We have identified a mechanism common to the diverse forms of MND: failure of transport within motor neurons. Transport is necessary to supply the motor neuron with components necessary for its maintenance and survival, and to remove waste products. When transport fails, the supply line is cut off and the motor neuron dies. Motor neurons are unique in that they are very large so rely on transport much more so than other cell types. Hence this mechanism may explain why motor neurons are selectively targeted in MND. Furthermore, we have evidence that this mechanism fails early in both the sporadic forms of MND and in multiple types of the rarer, genetic forms.

How did you identify your compounds as a potential treatment for MND?

Our compounds have come about from a solid understanding of the basic underlying disease mechanisms that trigger the death of motor neurons. We have identified a way to restore transport, and thus protect motor neurons from dying.

FIGHT MND.

What excites you about these compounds?

These drugs are unique in that nothing of this type has ever been trialled before in MND. Our drug-like molecules are based on a strong foundation; a disease mechanism we have identified that fails early in MND, suggesting it is more likely to be an important process causing motor neurons to die, rather than simply a secondary effect. This mechanism may also explain why motor neurons are selectively targeted in MND and they target a mechanism that we have identified fails in both sporadic MND as well as rare genetic forms. Hence there is the potential that targeting this mechanism can treat many diverse types of MND.

What difference will the awarding of this grant make to your work?

These awards will make an enormous difference to our work. Whilst we have identified two promising targets, moving them forward into drug development is very expensive and hence impossible to do without appropriate funding. In addition, funding for medical research has dropped significantly in real terms in recent years, and this type of research is particularly difficult to find funding for. We are very excited about this next stage of our work and grateful to the Cure for MND Foundation for the opportunity and funding.

Project 1.

NOVEL THERAPEUTICS TARGETING NEURONAL TRANSPORT PATHWAYS IN MND

We have identified a mechanism common to the diverse forms of MND: failure of transport within motor neurons. Transport is necessary to supply the motor neuron with components necessary for its maintenance and survival, and to remove waste products. When transport fails, the supply line is cut off and the motor neuron dies. Motor neurons are unique in that they are very large and rely on transport much more so than other cell types. Hence this mechanism may explain why motor neurons are selectively targeted in MND. Furthermore, we have evidence that this mechanism fails early in both the sporadic forms of MND and in multiple types of the rarer, genetic forms. We have identified a way to restore transport, and thus protect motor neurons from dying. This restores the normal function of faulty proteins in MND, and subsequently restores the health of motor neurons and keeps them alive. We have generated a new class of drug-like molecules based on these features. This study will allow us to optimize these drugs for the treatment of MND in human patients.

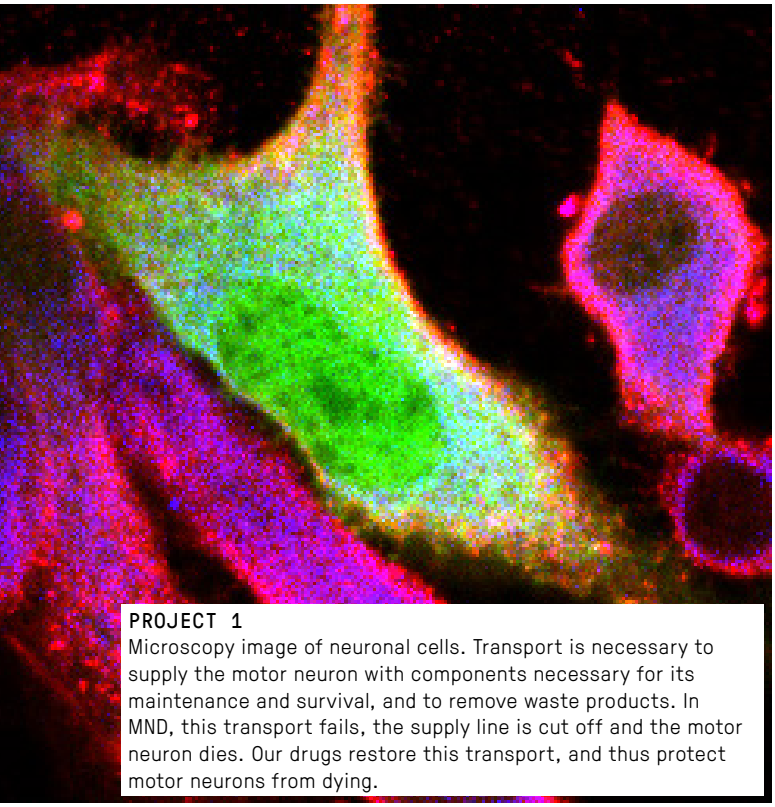
Hypothesis.

That a new class of hydroquinolones with potent activity in disease models of MND can be structurally modified through medicinal chemistry approaches to discover more drug-like compounds, in order to provide cures in animal models of sporadic/familial MND, leading to development for human use

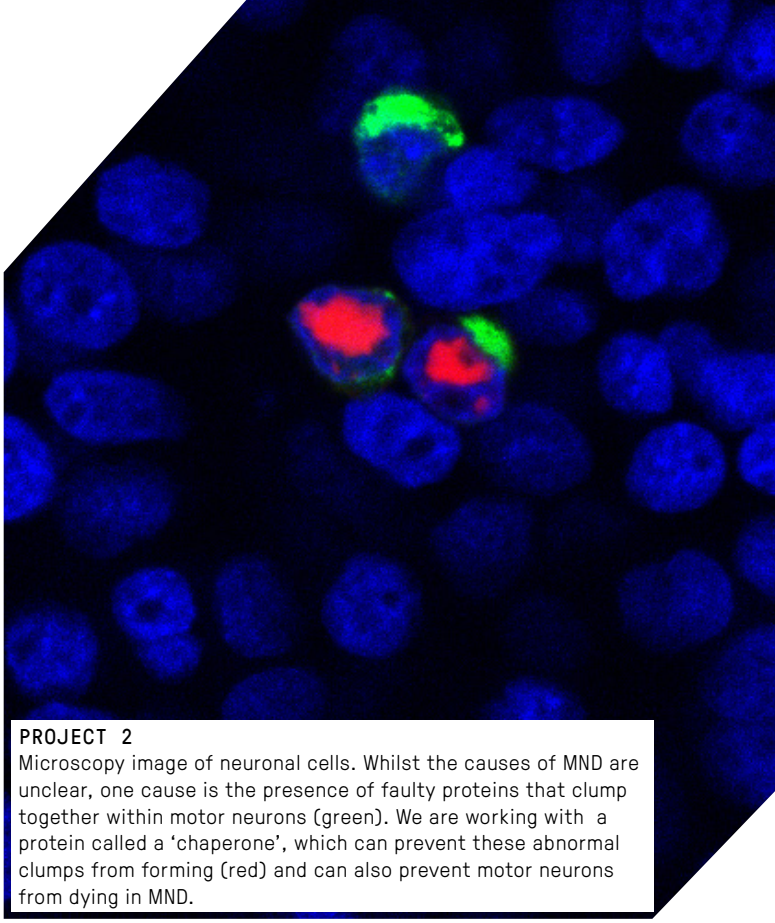
In summary from 10 years of study into the basic disease mechanisms of MND we have identified new types of drug-like molecules with the potential to treat human MND. This proposal aims to develop and optimize these molecules, so they can be used as a treatment for MND in the future, for the most common sporadic forms as well as the rare genetic forms.

THE SPECIFIC AIMS OF THIS PROJECT ARE:

1. Optimisation of lead compounds for potency/ pharmacology in cellular/zebrafish models.
2. Assessment of drug-likeness in cellular, zebrafish and mouse models (SOD 1 G93A and TDP-43).
3. Preclinical efficacy studies in mouse models of familial (SOD1 G93A) and sporadic (TDP-43) MND.



PROJECT 1
Microscopy image of neuronal cells. Transport is necessary to supply the motor neuron with components necessary for its maintenance and survival, and to remove waste products. In MND, this transport fails, the supply line is cut off and the motor neuron dies. Our drugs restore this transport, and thus protect motor neurons from dying.



PROJECT 2
Microscopy image of neuronal cells. Whilst the causes of MND are unclear, one cause is the presence of faulty proteins that clump together within motor neurons (green). We are working with a protein called a 'chaperone', which can prevent these abnormal clumps from forming (red) and can also prevent motor neurons from dying in MND.

Project 2.

THERAPEUTICS BASED ON THE PROTECTIVE ACTIVITY OF PROTEIN DISULPHIDE ISOMERASE IN MND

Whilst the causes of MND are unclear, it is known that one cause is the presence of faulty proteins within motor neurons, which form abnormal protein clumps or 'inclusions' as a characteristic hallmark. This occurs in the diverse forms of MND as well as the more common sporadic forms, implying that it is an important process that is central to pathology. We have identified that a protein called a 'chaperone', which can prevent these abnormal clumps from forming, is protective against pathology and the death of motor neurons in MND. Whilst this chaperone is protective, it cannot be used as a new drug because it is too large to be delivered efficiently to the brain. However, we have found that only a small part of the chaperone is actually necessary for its protective ability. Importantly we have shown that this small region is responsible for all the protective functions in MND. Hence we have designed new drugs based on this region only, that mimic the activity of the chaperone. Importantly, these drugs have improved properties compared to the much larger chaperone in terms of being administered to humans, and these drugs also retain the full protective activity of the intact chaperone. This study will allow us to optimize these drugs for treatment of MND in human patients.

Hypothesis.

Protein misfolding is an important pathological hallmark in MND and our studies have shown that disruption to intracellular trafficking is another primary, early and central event in neurodegeneration, linked to other disease mechanisms. PDI can restore both cellular trafficking and protein misfolding and can prevent many others cellular events linked to MND. PDI will therefore have therapeutic efficacy in MND.

THE SPECIFIC AIMS OF THIS PROJECT ARE:

1. Optimisation of peptides for potency/pharmacological properties in cellular and zebrafish models.
2. Determine the pharmacokinetic properties of optimised peptides in vivo.
3. Determine if peptides can improve disease outcomes and prolong survival in SOD1 G93A and TDP-43 mice.