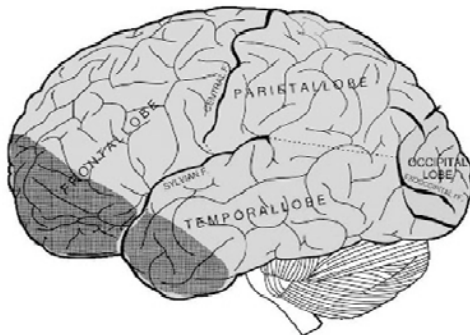


*You may be surprised that the first two updates you will read in this issue are actually about research that seemingly didn't help in the fight against motor neurone disease and wonder why it is important. Indeed, in science historically, people have not published negative results as frequently as positive ones mainly because, at the end of the day, they don't get us any closer to curing the disease. But this is changing as all information, whether negative or positive, is valuable. Motor neurone disease is incredibly complicated and sometimes it is hard to know where to start. For that reason, as researchers we rely on information published from all around the world to make educated guesses on what questions we should ask and what the best experiments will be. Negative results tell us a lot about the disease and where to look next.*

### Progranulin does not improve the prognosis for motor neurone disease

Research over the last decade has convincingly shown that there are a lot of similarities between MND and a dementia known as frontotemporal dementia (FTD). There are similarities in the genetic cause, the way neurones die and the patient's symptoms. For this reason many scientists are trying to discover all the similarities and differences between FTD and MND in a hope to find a therapeutic that will work in both.



Frontotemporal dementia involves the selective loss of neurones from the front areas of the brain. This area of the brain controls people's personality and their behaviour and these are affected in this form of dementia.

FTD can also cause loss of motor function, similar to that which occurs in MND. One genetic fault which has been shown to cause FTD is a loss of progranulin. Progranulin is a growth factor that has also been shown to help the growth and survival of motor neurones suggesting it could be used as a therapeutic for both diseases. Sarah Herdewyn and colleagues at the University of Leuven, Belgium investigated the effect of progranulin on MND progression in rodent models with the SOD1 mutation. They found that neither the over expression nor the injection of progranulin had any effect in these models of MND. This means that progranulin is unlikely to be a universal therapeutic for both motor neurone disease and frontotemporal dementia.

### Oiling the energy machine is not enough

It is well known that mitochondria, the power plants of the neurone, stop working properly in MND. Philippe Parone and colleagues at the University of California have recently worked out a way to help mitochondria function better in mouse models of MND. By reducing the amount of cyclophilin D, which controls the ability of mitochondria to store calcium, mitochondrial energy production was increased. Additionally there was less swelling of the mitochondria, less glial activation and also a reduction in the level of SOD1 aggregates in these mouse models of MND. Whilst this sounds very promising, surprisingly, all these improvements did not produce any change in the rate of progression of the disease. Motor neurone death and muscle denervation were also unchanged. This suggests that there must be an underlying problem that causes MND in these models that was not fixed by improving the health of the mitochondria.

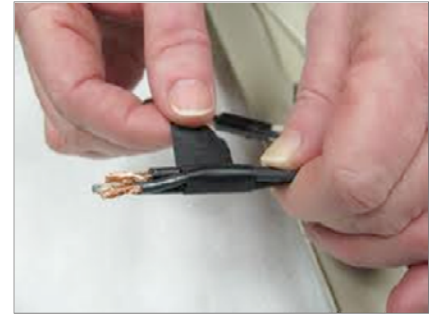
### A gatekeeper for Riluzole

There is currently only one drug on the market to treat MND, Riluzole. While it is believed that this drug works by controlling the excitability of motor neurones, the exact mechanism by which the drug does this is unclear. Maria Dimitriadi and colleagues at Brown University, USA have got a little bit closer to working out the specific action of Riluzole. They investigated how this drug worked in models of spinal muscular atrophy (SMA), an early onset form of motor neurone disease. In these SMA models, Riluzole improved motor neurone outgrowth and connection formation. They found, in the worm model of SMA, that this effect required a specific activation of an ion channel that allows potassium into the neurone. This work takes us one step closer to understanding how Riluzole works and possibly finding a better therapeutic that is more directed to the specific mechanism.



## Can we fix motor neurone disease with electrical tape?

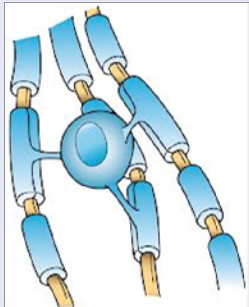
Shin Kang and colleagues at the Johns Hopkins University School of Medicine, USA have discovered that oligodendrocytes may play an important role in motor neurone disease. They investigated these glial cells (which are mainly responsible for myelinating neuronal axons) in the most common SOD1 mutation mouse model of MND as well as in human patients. Their work, which was recently published in the prestigious journal Nature, showed that changes to oligodendrocytes were actually occurring before disease onset in the mouse model. This means that these alterations could be a very earlier marker of the disease. What they found was that oligodendrocytes were degenerating and losing their ability to myelinate axons before the motor neurones were dying. Additionally, the new oligodendrocytes that were made were failing to mature which was causing a loss of their ability to myelinate axons. This reduction in myelination from oligodendrocytes not working properly was also shown to be occurring in the human patients they investigated. Interestingly they found in the mouse model, if they genetically manipulated the oligodendrocytes to not express the SOD1 mutation that causes the disease, the neurones were healthier and delayed the disease onset. This research could represent a new way to look at MND by focusing on different cell types and potentially finding a new therapeutic.



### Oligowhat?

#### Glial cells in the brain and spinal cord

Neurons are the cells that control how we think and move. These cells are supported by other cell types, which are known as glia. In the brain and spinal cord there are three main types of glia, microglia, astrocytes and oligodendrocytes. Microglia are very small cells that act like the immune system for the brain and spinal cord. Astrocytes support neurones by making sure the environment around the neurone has the right content of vital growth factors and ions. Astrocytes also are involved in forming the blood brain barrier which acts as a strong barrier to prevent bugs in the blood stream from entering the central nervous system.



Oligodendrocytes help neurones communicate. Oligodendrocytes are really interesting cells as they have many processes extending from their cell body and these cell processes are full of a fatty substance

known as myelin. These cell processes actually wrap around the large axons of neurones myelinating the axon which acts as electrical tape, insulating the axon. This insulation ensures that the axon they are wrapping is very healthy. This allows signals to travel down the axon at very fast speeds. This is particularly important in motor neurones as they have very long axons and so they need their signals to be travelling efficiently to make it to their target in time. Throughout adulthood, new oligodendrocytes are made to replace the old ones to ensure that all the appropriate axons are myelinated.

### Lost in translation

Protein production is a very complicated process. It involves the unraveling of DNA, the DNA is then read and translated into RNA, and this RNA is then edited and read into a sequence of amino acids that make a protein. Toshiyuki Handa and others at the Institute of Molecular Biotechnology of the Austrian Academy of Sciences have linked a disruption in the processing of RNA to motor neurone loss. They created mice in which a protein that is required for RNA editing was deleted. These mice developed a progressive loss of spinal motor neurones, leading to muscle denervation and paralysis. This work provides hard evidence that change to RNA leads to motor neurone death. Disruption in RNA processing has been shown to be important in diseases such as MND and now we are one step closer to understanding why.

### Waking up to motor neurone disease

Melatonin is a hormone that is most well known for its role in regulating the body's biological clock, the sleep-wake cycle. Recent research has suggested that melatonin may also have an antioxidant effect and potentially plays a role in preventing programmed cell death. Yi Zhang and colleagues at Harvard Medical School, USA investigated the protective effect of melatonin in a mouse model of MND. They gave these mice daily injections of melatonin from 6 weeks of age (adolescent mouse) till the end of the disease. They found that melatonin exerted its neuroprotective effect by preventing cell death in this model. This suggests that melatonin could be a potential new drug candidate for the treatment of MND.



### MND research shorts

- *Researchers in the USA have found a way to fix motor neurone transport problems in the giant squid.*
- *Using a rapidly progressing mouse model of MND, researchers in Denmark have shown the axonal degeneration occurs faster the more times the axon is activated.*
- *Researchers in Italy have found a drug that is more effective on male mice with MND than female mice with MND. This research could uncover important gender difference in the disease.*
- *Also in Italy, astrocytes with the SOD1 mutation have been shown to release mutant SOD1 through vesicles into the extracellular space between astrocytes and neurones. This SOD1 can be toxic to motor neurones which means the astrocytes are contributing to motor neurone death in this model.*