# MND AUSTRALIA INTERNATIONAL RESEARCH UPDATE

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## Almost six months into the year post-COVID

Although going back to "normal" post-COVID is a tad optimistic, with the vaccine rolling out, and Australia keeping a second wave at bay with safety measures brought in, hopefully we can be moving back to some semblance of normality. However, due to our advantageous position compared to other countries, research has been allowed to progress with only minor interruptions, and with vaccines being administered in other countries, research has continued, and will hopefully be returning to pre-COVID levels soon.

This issue of the IRU has no specific focus, but rather entails a broad range of topics that have been investigated in relation to Motor Neuron Disease (MND). The broadening scope of MND research is expected to yield new ideas and opportunities for the MND community.

## Diagnosing different forms of MND

MND is also known as amyotrophic lateral sclerosis (ALS) and is closely linked to the form of dementia, frontotemporal dementia (FTD), known together as ALS-FTD (TDP-43 is also involved in both of these diseases). The motor cortex is the part of the brain that sends the messages to the rest of the body and, in this part of the brain, cortical motor neurons can become "hyperexcitable", where they have erratic electrical signals. A technique known as transcranial magnetic stimulation (TMS) allows non-invasive imaging of the brain, specifically the motor cortex. Using this technique a study from the University of Sydney, published in Scientific Reports, could identify a spectrum of those with ALS to those with ALS-FTD[1]. This study showed that TMS imaging was capable of identifying distinct patterns of excitability between different forms of ALS/MND. This suggests that imaging may present an option to identify different forms of ALS/MND.

### Better communication at diagnosis

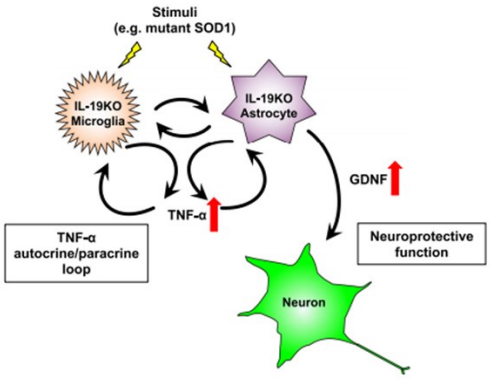
A UK based study has highlighted both doctor and patient experiences when discussing the diagnosis of MND. Published in BMC Neurology, the researchers from Lancaster (England)[2], have found most doctors felt they spent 30-40 minutes when communicating the diagnosis, but a lot of patients (almost 40%!) found that they felt that doctors spent less time than this, highlighting an area for improvement. However, in good news a large majority of doctors surveyed (79%) expressed interest in further training on how to break the news of a diagnosis.

### Information on MND

Most, if not all, of you reading this are aware of the level of care that is required to help someone coping with MND. A recent paper out of Trinity College Dublin, Ireland, investigated what information is most desired from both MND sufferers and the caregivers themselves. Understanding the perspectives and complex needs of both patients and their caregivers is often challenging for health care professionals. The paper published in BMC Health Services Research[3] asked about the preferences for health services of MND patients and caregivers and the relative importance of various aspects of care, such as timing of care, availability of services, and decision making. The study demonstrated differences in preferences between those recently diagnosed, and those with a more established diagnosis. Those in early disease stages were more interested in receiving information about their illness at the time of diagnosis, whereas those at a later stage of the disease were less interested in learning everything about the condition. In general, patients tended to demonstrate preferences toward clinical aspects of their illness (obtaining information about disease progression and prognosis) while caregivers focussed on services and supports that could assist them to provide the best possible care. Such insights can help to adjust the manner by which care is delivered, taking into account the autonomy of patients and the needs of caregivers, and can also help to inform and improve communication between providers and users of services.

## Neuroinflammation

Cytokines are signalling molecules produced by cells that can either suppress or promote inflammation, which is part of the immune response, the body's defence against bacteria and viruses. Interestingly, despite the large numbers of inflammatory biomarkers with increased levels found in the study above, a different study out of Japan, published in Molecular Brain, found that genetically eliminating interleukin-19 (IL-19) improved the motor function and reduced inflammation in mice[4]. Mice that had no IL-19, when exposed to SOD1, were able to better protect themselves from MND, by producing another cytokine, TNF-α, leading to production of GDNF and protection of neurons. This shows that different parts of the immune system act in different ways in MND and treatments need to be developed that specifically target MND-associated changes.

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## TDP-43

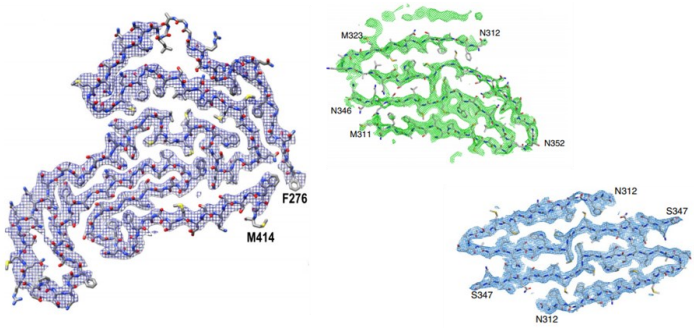
### TDP-43 aggregation as a cause and marker of MND

TDP-43 is a protein expressed in cells that is essential for the cell to function properly. However, when it isn't degraded correctly after performing its function, it can interact unfavourably with other TDP-43 molecules, or "aggregate", and TDP-43 aggregation has been found in ~97% of cases of MND.

In the March edition of IRU, Dr Luke McAlary talked about a study that described the role of oxidative stress caused by TDP-43 aggregation[5], how the aggregates travel along the spinal cord (through the pyramidal tract) in a prion-like manner[6], and found that antibodies (the naturally produced proteins that tag other proteins for destruction) specific for TDP-43, are increased in the blood and may potentially be used to diagnose MND[7].

### The structure of TDP-43 and disease

TDP-43 aggregation leads to problems in the cell, ultimately leading to MND. However, it isn't always the whole TDP-43 protein that aggregates. Sometimes TDP -43 can break apart, and the "N-terminal" and "C-terminal" fragments of TDP-43 start to aggregate, forming long chains called fibrils. A study out of Case Western Reserve University, in Cleveland, Ohio, published in Nature Communications[8] used cryo-electron microscopy, which is a very high-powered microscope that looks at samples literally frozen in time (using liquid ethane), to show that the structure of these aggregates (see image, left) differ from other TDP-43 aggregates (right two, previously published in Nature Communications in 2019[9]). Such insights allow us to better predict how different mutations might drive disease and how we can better develop treatments targeting these aggregates.




### TDP-43; cause or consequence? The role of C9orf72

As mentioned above, although TDP-43 is implicated in almost all MND cases, has been shown to travel along the neurons, and preventing its aggregation can prevent MND, it may not be the initial trigger. A recent study from the University of California San Diego, also published in Acta Neuropathologica Communications found that a different gene previously linked to MND called "chromosome 9 open reading frame 72" (C9ORF72), causes problems in a cell prior to any other complications. C9ORF72 causes a cellular compartment known as a nucleolus to shrink before TDP-43 aggregates[10].

### Targeting different C9orf72

The C9ORF72 gene mentioned above causes MND due to a large "dipeptide repeat" which is basically extra genetic material that is produced when it shouldn't be. A recent study from Massacheusetts University and a company Wave Life sciences, has found that a repeat in C9ORF72 is specific to the disease causing protein[11]. This highlights the potential for development of an anti-sense oligonucleotide (ASO), which works similar to an antibody, where it binds the protein produced to prevent it causing disease. The study developed a number of ASOs which were able to reduce the MND and prolong survival in mice. This is a similar approach to that being followed by Biogen for their SOD1 targeting drug, Tofersen, which is currently in Phase 3 clinical trial.

Biogen are also developing a C9ORF72-targeting drug.

### Using computers to identify MND biomarkers

Biomarkers are proteins or signalling molecules that can act as indicators of disease when their levels change. A study out of Italy has used a large dataset of 700 blood samples and clinical information to help develop an algorithm to diagnose MND and predict disease progression. They then tested this algorithm by feeding in a new set of blood samples and clinical data and discovered a number of blood biomarkers that appeared to be associated with disease progression[12]. These biomarkers were associated with disease processes such as oxidative stress (mentioned above) where cells fail to remove free radicals (normally achieved by antioxidants), metabolism (strengthening the link between the gut and the rest of the body, including the nervous system), and the immune system (our body's natural defence against disease).

### A new model to study MND

Motor neurones usually extend arms known as neurites out from the cell body, which are used to transmit messages through the nervous system. A new "OrganoPlateTM" technology from the Netherlands, published in Scientific Reports, uses a model that enables researchers to grow cells in a 3-D matrix so they can grow and interact with each other as they might do inside the body[13]. Using induced pluripotent stem cells (iPSCs; which are neurons that can be created by "reprogramming" skin cells from a person), this system could be used to study iPSCs from different people to determine what exactly goes wrong to cause motor neurones to become damaged and die causing MND. Additionally, potential therapies can be developed and tested for the treatment of MND in a cell system closer to testing in patients than many other cell models.


**References**

1. https://www.nature.com/articles/s41598-021-81612-x
2. https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-021-02062-6
3. https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-021-06191-z
4. https://molecularbrain.biomedcentral.com/articles/10.1186/s13041-021-00785-8
5. https://www.nature.com/articles/s41594-020-00537-7
6. https://actaneurocomms.biomedcentral.com/articles/10.1186/s40478-020-01112-3
7. https://www.nature.com/articles/s41598-021-81599-5
8. https://www.nature.com/articles/s41467-021-21912-y
9. https://www.nature.com/articles/s41594-019-0248-4
10. https://actaneurocomms.biomedcentral.com/articles/10.1186/s40478-021-01125-6
11. https://www.nature.com/articles/s41467-021-21112-8
12. https://www.nature.com/articles/s41598-021-82940-8
13. https://www.nature.com/articles/s41598-021-81335-z