MND AUSTRALIA INTERNATIONAL RESEARCH UPDATE

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Locking down on Motor Neuron Disease Research

As the global population continues deal with the COVID-19 pandemic and the various issues it has caused, Motor Neuron Disease (MND) researchers worldwide continue to work on discovering new information about MND and testing potential therapies.

This issue of the international research update takes a broad look at the MND research landscape as it currently stands, providing updates on some interesting developments across the field. We look at some basic science, patient diagnoses, and potential therapeutic interventions.

A new mechanism of TDP-43 toxicity through STING

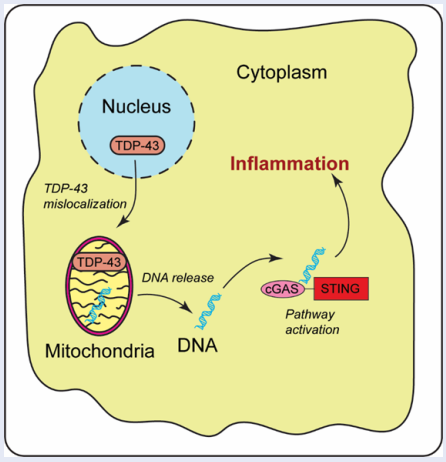
Researchers from the Walter and Eliza Hall Institute of Medical Research in Melbourne recently published their work on TDP-43 causing the release of mitochondrial DNA. Dr Seth Masters and his colleagues found that when they expressed TDP-43 in cells, the TDP-43 would wrongly enter mitochondria. Mitochondria are small compartments within cells that generate all of the energy that cells need to survive. When TDP-43 entered mitochondria, it caused the mitochondria to spit out their DNA (mitochondria have DNA separate from that the rest of a cell uses) into the cell cytoplasm, which is not supposed to contain DNA.

cGAS and STING

In fact, when cells detect DNA in their cytoplasm they think that they are being infected by a virus and activate inflammation pathways that cause lots of stress. Our cells have evolved this response, called the cGAS/STING pathway, in order to take care of viral infection. Chronic activation of this pathway is a potential cause of the cell death observed in MND.

Blocking the cGAS/STING pathway prevents neurodegeneration in model systems

The team further went on to examine not just that TDP-43 would cause toxicity through this DNA release mechanism, but determined if blocking DNA release would alleviate neurodegeneration. Using an array of models including patient -derived cell lines and mice and a compound called H-151, the team rescued cells and animals partially from TDP-43 toxicity. The authors finally suggest that drugs that stop cGAS/STING may have benefit and should be trialled in the clinic.

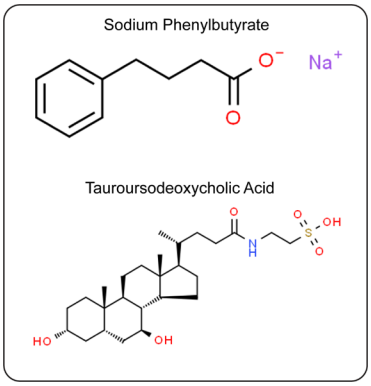


A clinical trial of sodium phenylbutyrate–taurursodiol for MND

Researchers from multiple institutes across the United States of America have reported the results from an early-phase clinical trial (Phase 2) examining the safety and potential efficacy of a combination of sodium phenylbutyrate and tauroursodeoxycholic acid (taurursodiol)(AMX0035 produced by Amylx Pharmaceuticals).

What are sodium phenylbutyrate and taurursodiol?

Sodium phenylbutyrate is a small compound that has been found to be neuroprotective in multiple models of neurodegeneration, prompting its use in MND. Taurursodiol prevents mitochondria from initiating cell death. In conjunction, they may act in unison to prevent neurodegeneration as it occurs in MND.



Favourable outcomes

Early-phase clinical trials are carried out to determine the safety of a therapy and only make reserved interpretations of clinical efficacy. Further, there are many measures of patient decline in MND, making it even more difficult to ascribe effects in early-phase clinical trials. Even so, this report showed a slowing of patient decline as measured by the ALS-FRS-R scale, which is a scale of how functional patients are in normal daily activities. This is an encouraging result and, in conjunction with the tolerability and safety profile of the compounds, further trials should likely commence.

Early detection and tracking of bulbar onset MND

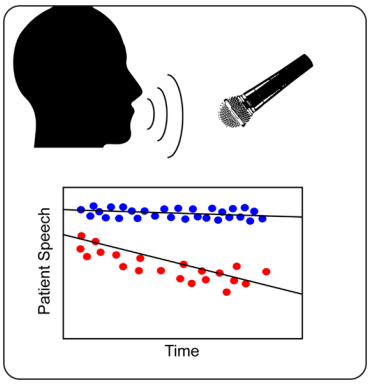
A team of researchers, led by Dr Visar Barisha from Arizona State University in the United States of America, have recently shown that they can effectively detect and track the decline of people who suffer from bulbar onset MND using automated speech analysis tools.

Bulbar onset MND

Bulbar onset MND is often first recognised by impairments to speech such as slurring and drawling. Those MND patients who present with bulbar onset of disease often have a much worse prognosis than those who do not.

Speech analysis for detection and tracking

The researchers used their knowledge of transforming human speech into algorithmic output for quantitative analysis. By measuring the time it took patients to pronounce a set of sentences (speaking rate) and the difference in expected acoustic features *vs.* those measured (precision of speech), a score was given to those who participated in the study. The score of those with bulbar MND consistently was worse than healthy controls and also deteriorated across time. This sort of method has wide ranging application for disease detection, predicting patient prognosis, and tracking disease progression.

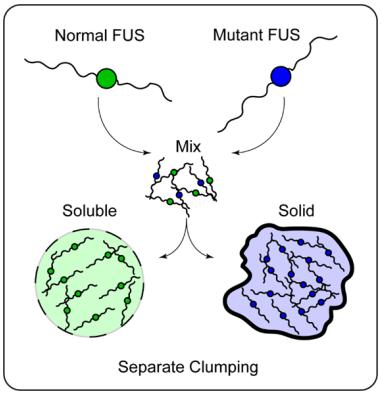


Solidification of fused-in-sarcoma (FUS) mutants is a feature of MND and FTLD

Dr Sua Myong and her team from John Hopkins University in the USA recently published some work that sheds new light on how FUS mutants may cause neurodegeneration. By using advanced biophysical methods and a strong understanding of protein physics, the team determined that specific mutants of FUS fail to interact with normal FUS.

Mutant and normal FUS need to interact?

Everyone carries two copies of each gene from each of their parents, and in MND you often only need a mutation in one gene to cause disease. This means that the mutated genes often gain a toxic function, rather than a person losing function. In this case, the research team determined that some mutants of FUS did not interact with normal FUS, where the mutant FUS preferred to form its own dense insoluble solid protein clumps that characterise MND and contribute to neuronal cell death. The normal FUS clumped together but was easily dissolved.



Promising direction

This work provides strong evidence for the notion of a gain of toxic function in mutant FUS-associated MND, and points translational researchers towards therapies that target the mutant forms of FUS and spare the normal. By keeping normal FUS functional, any problems that may arise from its loss of function are alleviated.

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MND Research Shorts

- There is very strong evidence to suggest that proteins involved in neurodegenerative disease can act in a 'prion-like' manner, spreading from cell-to-cell and throughout the nervous system. Researchers from the International School for Advanced Studies (SISSA) in Italy have published work showing that even minute amounts of cerebrospinal fluid from ALS and FTD patients can make normal TDP-43 protein aggregate in the test tube. This provides not only new knowledge, but also a possible diagnostic and prognostic tool for future clinical studies.
- Men are more likely to develop MND and have a more aggressive disease progression in comparison to women. A team of researchers in the UK performed a study examining TDP-43 model mice and found that indeed the female mice appear to be more resistant to the expression of mutant TDP-43. Taking into account sex specific differences in MND will help us guide research and also discover new therapies.
- The majority of MND cases do not have a known genetic link. This indicates that perhaps something in the environment may contribute to MND. BMAA (a toxin) is a candidate environmental cause for MND. Researchers from Portugal determined that BMAA treatment of cells resulted in severe neuroinflammation and mitochondrial dysfunction, which are features of MND. It will be important in future to examine the relationship between those who develop MND and any potential environmental links.
- Astrocytes from ALS patients are very toxic to motor neurons from healthy people. Researchers from Columbia University have shed new light on why this might be. By using a systems-wide approach, they determined that astrocytes release a protein that interacts with a motor neuron death receptor. By blocking this interaction, the research team was able to prevent motor neuron death. This holds potential for future therapy development.

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