MND Australia
International Research Update

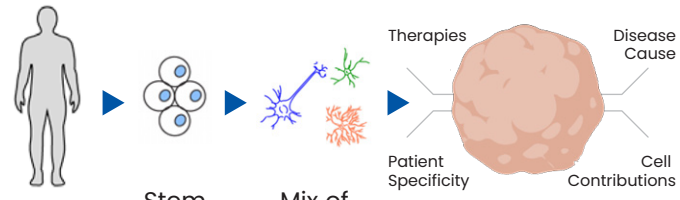
Dr Luke McAlary, Bill Gole MND Postdoctoral Fellow, University of Wollongong

End of the year brings new prospects

As we come to the end of another year fraught with COVID-associated events, I take heart in knowing that the MND research community has been steadfastly continuing to work. For some who don't know, academic research always contains a component of education that is focused on inspiring the next generation of young researchers. Teaching effectively during COVID has been especially difficult due to issues with lab access and now ongoing supply shortages. Nevertheless, there has been gains made in both teaching and research, so much so that we are still moving forward in our understanding of both cause and cure for MND.

Organoids[1]

Since the discovery that we can reprogram human skin cells into stem cells and subsequently any other cell type, research into how we can use these cell models in disease studies has progressed rapidly. The main caveat to this method, however, is that cells in a dish in a 2-dimensional arrangement are not like cells in an organism. Attempts to get closer to an organism have yielded 'organoids', which are 3-dimensional clusters of reprogrammed cells that talk to each other similar to how they would within an organism.



Building on organoids: One of the problems that scientists face with organoids is that they are difficult to study and measure using standard techniques. Most scientific equipment is not set up to take spherical samples. Typically, we want flat samples for microscopy. In this work, researchers not only generated an effective MND-associated organoid growth methodology, but also showed that you can slice the organoids into smaller pieces and maintain the functionality of the cells within.

Proteostasis, DNA repair, and transcriptional alterations: Having established the system using cells from MND patients carrying the C9orf72 mutation, the researchers set about to examining if they could determine what molecular disturbances the cells in the organoids were undergoing. They determined several already discovered pathways including DNA repair, proteostasis, and transcriptional regulation. This is great news because it shows that this new model represents the disease quite well.

Examining a therapy using organoids: The researchers then set about to seeing if they could treat the disease features detected within the organoids using a drug called GSK2606414, which is an unfolded protein response modulator. They found that the drug was capable of rescuing the neurons from degeneration likely via reducing the levels of the toxic C9orf72-associated dipeptide repeat proteins. All up, this research provides a valuable tool for personalised medicine for MND patients.

MND Research Shorts

RNA, like proteins, can adopt specific 3-dimensional structures within the cell. The MND-associated protein FUS interacts very strongly with what is called quadruplex RNA. Researchers from Hosei University in Japan investigated the quadruplex-FUS interaction and found that RNA quadruplexes promoted the aggregation of some FUS mutants but not all. This research sheds more light on the important protein-nucleic acid interactions that underpin ALS pathogenesis[2]

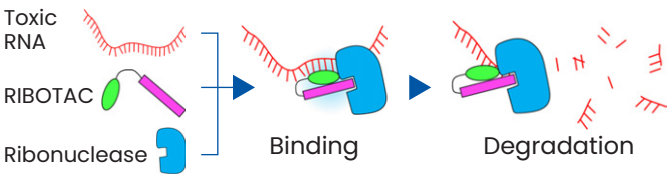
Frontotemporal dementia (FTD) exists on a disease axis with MND. C9orf72 mutations can cause both MND and FTD. Investigations into C9orf72 give us insights into both diseases. A consortium of researchers from Europe determined that changes in the SLITRK2 gene are associated with an earlier age of onset of C90rf72-FTD, but had no effect on C9orf72-MND. This is important because determining differences between the pathogenesis of MND and FTD could yield fruitful therapeutic targets and also provide important insights into the these disease processes[3]

Incorrect protein self-assembly is a key component of neurodegenerative research. The aberrant clumping of proteins into toxic aggregates is strongly associated with MND. Researchers from Texas determined that FUS is capable of self-assembling into protein clumps through two particular regions in the protein and that the balance of these two regions is disturbed by mutation. This is important because determining how normal proteins may self-assemble into pathological forms gives insight to both cause and cure[4]

As governments around the world seek to centralise electronic healthcare data there is an opportunity to cast a wider net to examine and help patients suffering from MND. Researchers from Florida developed an 'ALS Toolkit' as part of the USA electronic health record system. The toolkit allows medical professionals and researchers to seamlessly integrate and collect patient information to better aid in patient care and clinical trial. This type of system would be beneficial worldwide[5]

RNA repeats in C9orf72[6]

In C9orf72-associated MND, a gene has a tail code of GGGCC that repeats thousands of times. In healthy people, the gene repeats only about 20 times. The consequence of this repeat is that the gene is transcribed into large RNA molecules containing these repeats that wreak havoc on cells. Therefore, a possible way to treat C9orf72-associated MND is to target these large RNA repeats.



Selective targeting of RNA: A sought after method of targeting RNA for degradation in cells is to use a complementary strand of RNA to bind the cellular RNA and break down the repeat-containing molecules. This is effective, but has a major drawback in neurodegenerative diseases, namely that the complementary RNA treatment has to be administered via invasive injections into the spine (intrathecal injections). A less invasive method of selectively degrading RNA would be preferable for patients.

A two-part molecule that introduces C9orf72 RNA to its enemy: Cells contain proteins called ribonucleases, whose role is to degrade unwanted RNA. The mutated C9orf72 RNA is capable of eluding these proteins normally in an MND patient. In this study, the researchers developed a molecule called a RIBOTAC that binds selectively to C9orf72 RNA, and then recruits a ribonuclease to degrade the RNA, effectively preventing the toxicity of either the RNA or the dipeptide repeats that translate from the RNA. Using a small molecule approach such as this provides a number of different options for administering the drug beyond spinal injections.

Works in cells and in animals: Excitingly, this new molecule worked to prevent C9orf72-related toxicity in both cells and animals. The animals treated were mice genetically altered to develop C9orf72-associated disease in a manner similar to humans. That they respond positively to the drug is a great sign for human trials in future.

Assessing Patient Progression[7]

One of the key issues in both diagnosis of MND and for tracking patient progression is accurately measuring patient outcomes at a certain point. This is also key for determining if any therapeutics are having an effect in a clinical trial. The MND field has struggled with accurate patient assessment due to the clinical heterogeneity of MND and different scoring systems utilised around the world.

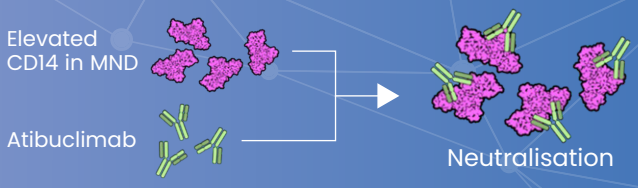
King's College Progression rate
One such method of scoring MND patients outcomes is the King's College ALS Clinical Staging System (KC scale), which examines patients for affected anatomical regions, respiratory function, and nutritional deficiency. This method is used globally by both researchers and medical professionals to score MND patient decline.

What is new?
The work presented here, by researchers from San Paolo Hospital in Italy, meticulously examined if the change in a patient's KC scale across multiple medical examinations could predict patient outcomes more accurately. This idea is very basic, but it is extremely important that it is tested to help with better measures for clinical trials and when to give patients medical interventions.

What did they find?
The authors describe that this method was accurate at predicting patient outcomes and could be an additional method to normal scoring. This is particularly useful as the authors did not perform any new examination techniques, they simply transformed the collected data differently. Of most interest is the report from the authors of the robust prognostic value of the method, where this will possibly be highly useful in clinical trials for grouping patients based on their progression rates.

Immune system targeting in MND[8]

Part of MND pathology, like other neurodegenerative diseases, involves the immune system. It is thought that the immune cells within the central nervous system become hyperactive and contribute to the death of the motor neurones they are supposed to protect. Immunotherapies that modulate these cells are an avenue of interest in neurodegeneration in general.



Cluster of differentiation 14 (CD14): CD14 is one of roughly 370 immune system proteins that either mark cells or control your immune system. It was discovered that MND patients had elevated levels of CD14, making this a potential target for therapeutic intervention.

The idea is to target CD14 with a monoclonal antibody called atibuclimab and reduce the levels of CD14 in MND patients.

Safety is Key: Prior to examining if the targeting of CD14 can help MND patients, safety trials must be carried out. In this work, the researchers recruited MND patients and administered varying doses of atibuclimab, in the hope that this antibody would bind the CD14 and reduce the levels in patients. The main outcomes monitored were the safety and tolerability of the antibody. For any clinical trial, safety is the first thing examined because if a drug is not safe, then it is unethical to use it for humans.

Outcomes are good: The researchers found that the intravenous administration of atibuclimab was safe and tolerable in the patients. Further, they showed that the atibuclimab was capable of reducing the levels of CD14 in the patients and also remaining active for up to 8 days after infusion. This is great news for carrying out a phase II trial to examine efficacy in future.

References:
[1]https://pubmed.ncbi.nlm.nih.gov/34675437
[2]https://pubmed.ncbi.nlm.nih.gov/34624313
[3]https://pubmed.ncbi.nlm.nih.gov/34687211
[4]https://pubmed.ncbi.nlm.nih.gov/34654750
[5]https://onlinelibrary.wiley.com/doi/10.1002/mus.27454
[6]https://pubmed.ncbi.nlm.nih.gov/34705518
[7]https://pubmed.ncbi.nlm.nih.gov/34736124
[8]https://pubmed.ncbi.nlm.nih.gov/34678870