Latest clinical trial activity

Clinical trials have featured heavily in the last couple of editions of Advance. Again, there is considerable activity in these areas to highlight in this report reflecting the high numbers of potential new treatments currently being trialled. As we all appreciate, a lack of truly effective treatments is the biggest challenge for the MND community. Care models are advancing significantly but the best possible care regime needs effective treatments.

In the last few months we have seen results released from several pivotal trials as well as significant shifts in the attitudes of regulatory bodies.

Amylyx's AMX0035 which showed strong positive results from the CENTAUR Phase 2 trial has been submitted for regulatory approval to both the US FDA and Health Canada. This is very unusual as these agencies usually require Phase 3 trial results. Initially the US FDA refused to accept the submission citing its requirement for Phase 3 data but relented following community-wide pressure. Amylyx also hope to submit for regulatory approval to the European Medicines Agency (EMA) by the end of 2021. While the regulatory applications are being considered, Amylyx is also pushing ahead with the 600 participant PHOENIX clinical trial in the US and Europe. We are hoping that such flexibility reflects a change in attitude from regulatory authorities. Perhaps agencies will recognise that the pressing need of patients justifies a more open approach to drugs that have proven to cause no harm and show some benefit. It is still critical however, that we ensure treatments do provide demonstrated benefit.

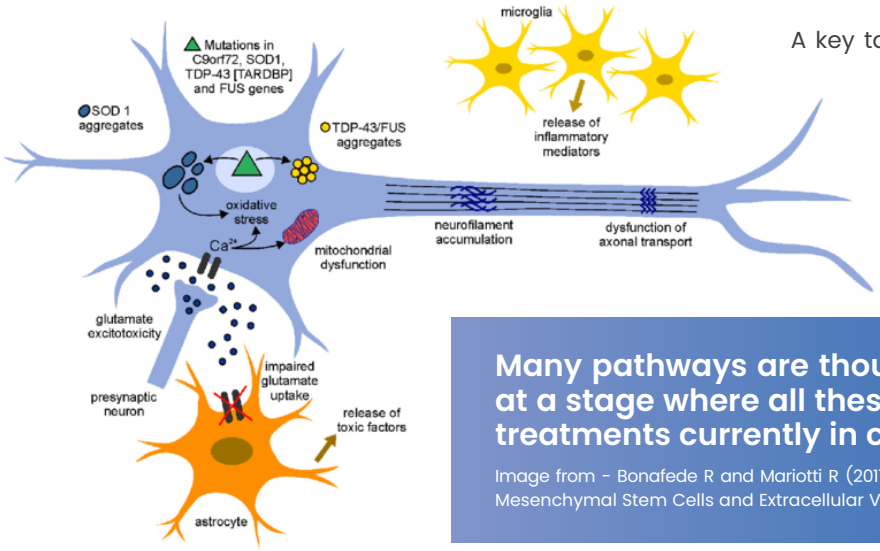
Biogen released the initial findings from their Phase 3 VALOR trial for the anti-SOD1 gene therapy, tofersen. Hopes were high as this targeted a known cause of MND in those patient carrying the mutation. Unfortunately, the results did not reach significance for the primary endpoint, ALSFRS-R, but encouraging trends were seen in secondary endpoints, such as other functional measures and the neurofilament light biomarker.

With only a 6-month trial duration and small participant numbers due to the requirement that they carry the SOD1 mutation, the need for better functional measures and a battery of reliable biomarkers has become even more apparent.

The results also triggered discussions around the potential for tofersen to be more effective in the early stages of disease. Biogen are now running a "preventative" trial (the ATLAS trial) where participants carrying the SOD1 mutation will be monitored for changes in their Nfl levels and when these increase (an indication of neurone degradation), they will be placed into treatment or placebo groups to see if tofersen can prevent or slow disease development from the very early stages. Any placebo patients that do show disease progression will be immediately switched into an open-label treatment arm to ensure they are not disadvantaged. This is a truly unique trial in MND and will be watched carefully. As biomarkers improve such an approach may be used beyond specific genetic forms of MND.

In other trial updates, Alexion discontinued the CHAMPION-ALS Phase III clinical trial of Ultomiris (ravulizumab), an anti-neuroinflammation drug targeting the complement pathway, due to a lack of efficacy. There are a number of other drugs targeting the same pathway still in trial however. Results from the trial of the multiple sclerosis drug Tecfidera were also published earlier this year. This trial was run by Professors Matthew Kiernan and Steve Vucic from the University of Sydney and unfortunately did not show significant efficacy. On a brighter note, another trial run by Professors Kiernan and Vucic, the RESCUE-ALS trial for CNM-Au8 manufactured by Clene Pharmaceuticals, showed some encouraging trends. Positive results were seen for the MUNIX biomarker endpoint and significant treatment benefits were observed for limb onset ALS. Positive effects were also indicated in patient quality of life, slowing disease progression, and even long-term survival benefit. A larger study is currently underway through the Healey Platform Trial in the US with results expected later in 2022.

A key takeout from all this recent activity is that we still need better ways of measuring MND, so we can test treatments quickly and be more certain about how well they work. For this, we need more research and many groups in Australia are leading the world in developing better ways to measure disease and improve clinical trials.



Many pathways are thought to impact MND - we are now at a stage where all these pathways are being targeted by treatments currently in clinical trial

Image from - Bonafede R and Mariotti R (2017) ALS Pathogenesis and Therapeutic Approaches: The Role of Mesenchymal Stem Cells and Extracellular Vesicles. Front. Cell. Neurosci. 11:80. doi: 10.3389/fncel.2017.00080

Executive Director Research Report

Well here we are – almost 2 years into the worldwide COVID-19 pandemic and we are still fighting it. The good news is that we can well and truly see the light at the end of the tunnel with vaccines driving down case numbers and reducing the impact to those infected. The bad news is that vulnerable community members such as MND patients are still more susceptible to the consequences of catching COVID-19 and have significant concerns about mixing in the general community. We therefore wholeheartedly support vaccination to ensure we minimise the risk to those vulnerable to the virus and those who cannot be vaccinated for medical reasons. This will allow these members of our community to enjoy relatively the same freedoms as the rest of us.

It has been another busy year for MND Research Australia.

Firstly, I would just like to give a massive thanks to all our donors and fundraisers. We have had one of our best ever years and had the privilege of awarding over $3.1M in grants for projects commencing in 2022 with a ~30% success rate. We awarded 17 Innovator Grants, 3 Post-Doctoral Fellowships and the Betty and John Laidlaw Prize. With the NHMRC grant rounds only having ~10% success rates, there is a lot of great research not being funded by the biggest national funding body. It is becoming ever more critical for organisations such as MNDRA to support up and coming as well as established researchers to improve the lives of people living with MND. Much of the research we fund is early stage research where new ideas are being tested – such innovation is critical if we are to keep the field moving forward. This year we are supporting projects including a number of different approaches to develop better clinical measurement, early stage testing of new treatments, identifying new genes involved in MND and improving uptake of non-invasive ventilation. We also worked with MND and ME to jointly award the Scott Sullivan MND Research Fellowship. Please take a look later in this newsletter for details on the research your incredible contributions are supporting.

We have continued to push ahead with building the framework to launch the MND Research Collective. By the time you read this newsletter you will have seen our proposed narrative, structure and priorities. We are very keen to have as much input from right across the MND community as possible.

Hopefully you will have had the opportunity to catch some of our State-of-Play presentations that have been running monthly throughout 2021. These have been a great way for us to introduce our brilliant researchers to the community and I hope you have found them beneficial – we have certainly been getting some great feedback. The 2021 sessions culminated with our first online MND Connect – Research live session on Saturday 6th November. We had Peter Chambers, who is living with MND set the scene followed by talks from a range of researchers across the basic science and clinical spectrum as well as Bec Sheean, my counterpart at FightMND. We then wrapped up with a fast-moving panel discussion fuelled by brilliant questions from our audience. I strongly recommend you look up this session as well as the other sessions on our website if you missed them -

https://www.mndaustralia.org.au/state-of-play

In March 2022 we will be hosting the first Australian and NZ MND Research Symposium jointly with FightMND. Originally planned for October of this year, we decided to postpone the event to allow us to meet in person for the first time in two years. We will also be broadcasting the event in parallel online to ensure those who cannot make it to Brisbane will not miss out. There will be two days of research presentations followed by a MND Connect panel session on day three. Keep an eye on our website and social media for more details. All will be welcome to attend.

MNDRA continues to build our profile within the International Alliance of ALS/MND Associations. I am a member of the Alliance Scientific Advisory Council where we provide advice on research matters and clinical trial outcomes. I have also participated in a number of Alliance roundtables around Innovation and technology and Genetic Counselling.

Again it has been a year where it has been truly a privilege to work with the MND community. Even during these tough times, the support for research has been incredibly strong. My biggest regret is not being able to get out and about to meet more of our donors, researchers and those living with MND. Next year we will hopefully be out and about a lot more.

Dr Gethin Thomas,
Executive Director of Research, MND Australia

MND Connect: Research Live

MND Research Australia Grants in 2022

We are incredibly grateful to our supporters who have made it possible to fund more than $3.1M of MND research in 2022, despite the ongoing uncertainty and impacts of COVID-19.

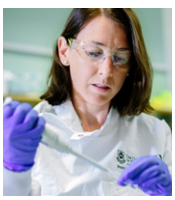
On November 10, the MNDRA Research Committee met to allocate $3,121,037 across 22 projects, made up of the Betty and John Laidlaw MND Research Prize, four postdoctoral fellowships and 17 Innovator Grants.

In memory of both Betty and John Laidlaw, MNDRA has again awarded the **Betty and John Laidlaw MND Research Prize in 2022.** This $200,000 two-year grant was awarded to Associate Professor Parvathi Menon from the University of Sydney for her project "Improved Understanding of Brain Excitability in ALS/MND". This project will look at cortical hyperexcitability, which is an important mechanism underlying MND and contributes to nerve degeneration and consequent muscle wasting, varying MND types, adverse prognosis and disease progression.

The Bill Gole MND Postdoctoral Fellowship for 2022-24 has been awarded to Dr Fiona Bright from Macquarie University. Her project is titled "Exploring undefined regions & novel functions of the TDP-43 protein - The molecular pursuit to uncover the cause and ultimately find a cure for MND" and will look at the abnormal TDP-43 protein deposits that are present within the cells of the brain and spinal cords of 95% of MND patients.

The Beryl Bayley MND Postdoctoral Fellowship for 2022-24 has been awarded to Dr Mouna Haidar from The Florey Institute of Neuroscience and Mental Health. Her project is titled "A novel gene therapy approach targeted to overactive brain motor neurons". This gene therapy approach will be tested in motor neurons grown from MND patients and mouse models and will hopefully reduce the burden of electrical overactivity in the brain.

The Nancy Gray MND Postdoctoral Fellowship 2022-24 has been awarded to Dr Marnie Graco from The Institute for Breathing and Sleep in Victoria. Her project is titled "Optimising quality of life and survival in motor neurone disease by improving the use of overnight breathing support" and will look at increasing access to non-invasive ventilation amongst Australians living with MND. With only 19% of Australians living with MND currently accessing non-invasive ventilation, this research will examine the barriers to uptake and design and implement a strategy to combat these barriers.



The Scott Sullivan MND Postdoctoral Fellowship 2022-24 has been awarded to Dr Fleur Garton from the University of Queensland. This grant is largely funded by MND&Me Foundation with a contribution from MNDRA, and is being offered through our funding program for the first time in 2022. Fleur's project is titled "An investigation into MND biomarkers and genetic risk mechanisms to improve diagnosis/tracking and therapeutic avenues for sporadic ALS" and will aim to improve diagnosis/ tracking and treatment options for those with MND, with a focus on the sporadic form of ALS.

Innovator Grants for 2022

In addition to the prestigious Charcot Award, a further 16 innovator grants were awarded across a range of research areas – clinical measurement, cell biology, genetics, proteomics, metabolism and preclinical animal testing. The titles of the projects are included below and more details, including a summary of each project, can be found on our website: **https://www.mndaustralia.org.au/currentresearch**

For 2022, the top-ranked Innovator Grant was awarded the **Charcot Award**. This award went to Dr Emma Devenney at the University of Sydney. Her project is titled "Harnessing Artificial Intelligence Computer Models in MND: a novel pathway to improve patient outcomes". This project will look at the systems that are responsible for thinking and moving, which work together to help us complete tasks. It will develop objective tests to accurately identify and define these systems, which may become dysfunctional early in MND, prior to the onset of physical symptoms. This project may lead to improvements in the diagnostic process and provide markers for progression.

Col Bambrick MND Research Grant

Dr Gabriel S. Trajano, Queensland University of Technology
High-density electromyography as a new tool to monitor motor neurone changes in MND

NTI MND Research Grant

Dr Frederik Steyn, University of Queensland
Preclinical validation of macimorelin, a ghrelin mimetic, as a treatment for amyotrophic lateral sclerosis (ALS)

Fat Rabbit MND Research Grant

Dr Tanya McDonald, University of Queensland
Investigating energy balance in the progression of MND

Run MND NSW Research Grant

Dr Alison Hogan, Macquarie University
RNA transport in Motor Neuron Disease - an investigation into dysfunction of the pathway and its potential for therapeutic intervention

Dr Paul Brock MND NSW Research Grant

Professor Julie Atkin, Macquarie University
New mechanisms exploring the relationship between aging and motor neuron disease

Nancy Gray MND Research Grant

Dr Andrew Phipps, University of Tasmania
Understanding why nerve fibres are vulnerable in MND

Nancy Gray MND Research Grant

Associate Professor Mary-Louise Rogers, Flinders University
Uncovering a panel of urinary proteins present in people with MND that can be used to indicate stages of disease

Nancy Gray MND Research Grant

Dr Jessica Collins, University of Tasmania
Developing blood tests to diagnose and monitor MND

Nancy Gray MND Research Grant

Professor Tracey Dickson, University of Tasmania
Rebalancing excitability dysfunction in MND by targeting non-neuronal cells

Nancy Gray MND Research Grant

Dr Jeffrey Liddell, University of Melbourne
How corrupted glial cells perpetrate the death of neurons

Jenny Simko MND Research Grant

Professor Jacqueline Wilce, Monash University
Preventing toxic protein aggregation in cells by targeting stress granules

Mavis Gallienne and Graham Lang MND Victoria Research Grant

Associate Professor Rebekah Ahmed, University of Sydney
Sleep and autonomic function across the ALS-FTD spectrum

Superball XIV MND Research Grant

Professor Coral Warr, La Trobe University
Developing new models to help us understand the cause of variability in MND clinical presentation

MonSTaR MND Research Grant

Dr Shu Yang, Macquarie University
Preclinical assessment of the therapeutic potential of CHCHD10 in the removal of insoluble protein

Peter Stearne Familial MND Research Grant

Dr Lyndal Henden, Macquarie University
Sex and ancestry – a recipe for gene discovery in sporadic MND

Phyllis Diana Seman MND Research Grant

Dr Albert Lee, Macquarie University
Using proteomics to reveal the components of protein aggregates to understand MND biology and identify potential therapeutic targets

MND Australia
International Research Update

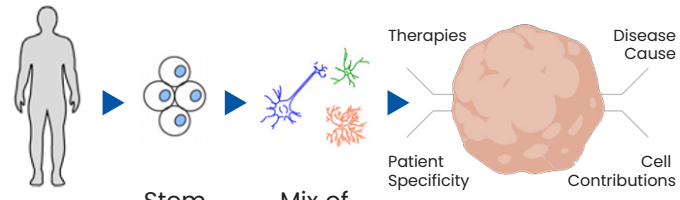
Dr Luke McAlary, Bill Gole MND Postdoctoral Fellow, University of Wollongong

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]

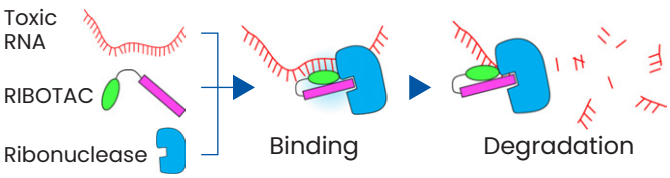
Frontotemporal dementia (FTD) exists on a disease axis with MND. C9orf72 mutations can cause both MND and FTD. Investigations into C9orf72 give us insights into both diseases. A consortium of researchers from Europe determined that changes in the SLITRK2 gene are associated with an earlier age of onset 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.

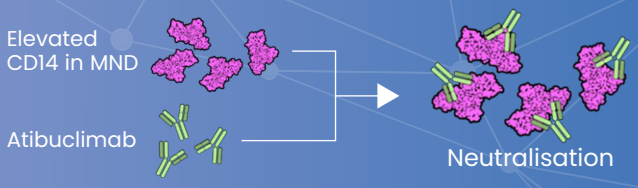
King's College Progression rate
One such method of scoring MND patients outcomes is the King's College ALS Clinical Staging System (KC scale), which examines patients for affected anatomical regions, respiratory function, and nutritional deficiency. This method is used globally by both researchers and 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
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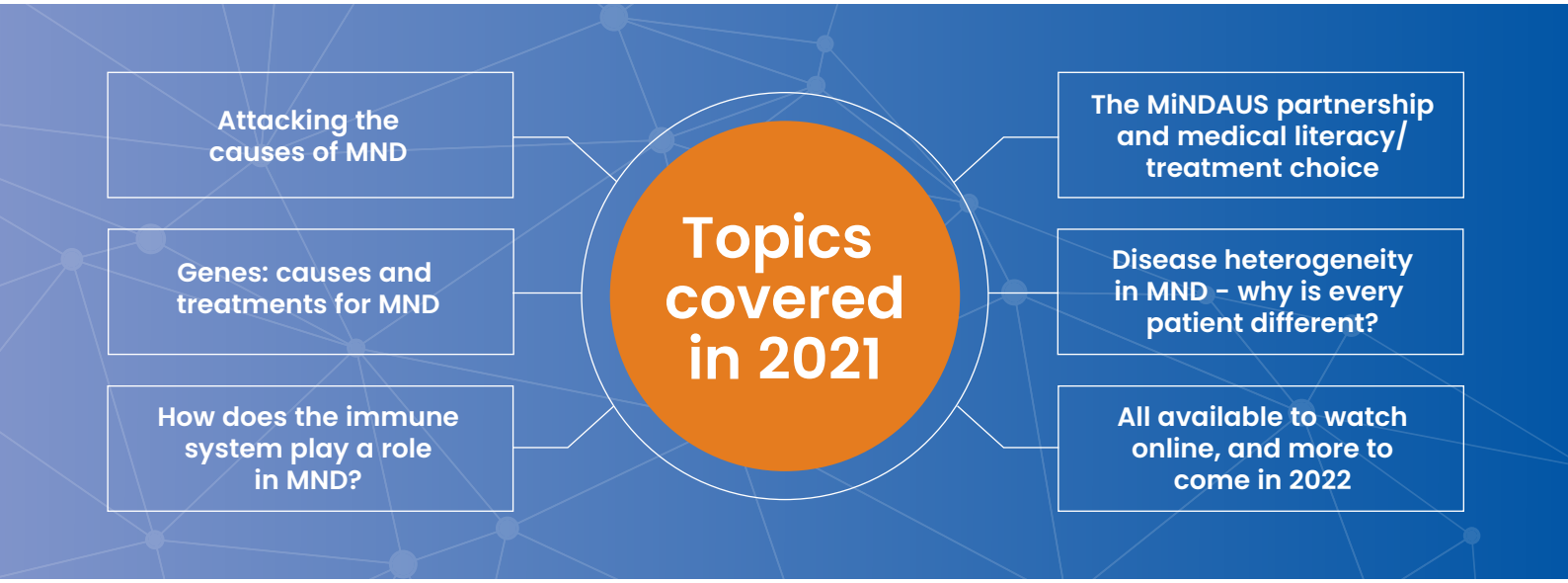
[6]https://pubmed.ncbi.nlm.nih.gov/34705518
[7]https://pubmed.ncbi.nlm.nih.gov/34736124
[8]https://pubmed.ncbi.nlm.nih.gov/34678870

MNDRA updates and information sessions

Throughout 2021 MNDRA has continued to host regular webinars to provide updates to the community on MND research. We are so grateful to the researchers and others from the broader MND community who have been involved in these webinars, providing an incredible amount of well-presented and easy to understand information. We have loved seeing the 'Q&A' parts of these webinars grow to become more interactive – thank you to everyone who has contributed to these discussions and to our amazing researchers and clinicians who have provided their time to communicate advances in MND research. All of the State of Play webinars from 2020 and 2021 are available to watch online at: **https://www.mndaustralia.org.au/state-of-play**

Also available at the link above is the 2021 "MND Connect: Research Live" webinar, which featured a number of experts in the field of MND research. This is one you do not want to miss!

The State of Play webinars will continue in 2022, so please keep an eye on our website and social media for details. If you have any ideas on topics you would like us to cover in our 2022 State of Play program then please get in touch with us: **research@mndaustralia.org.au**



PACTALS 2021 summary

By Dr Stephanie Shepheard, Research Associate, MND & Neurotrophic Research Lab, College of Medicine & Public Health, Flinders Health & Medical Research Institute, Flinders University, South Australia

The Pan-Asian Consortium for Treatment and Research in ALS (PACTALS) 2021 International Conference was held online over two days in September. While speakers included leading MND researchers and clinicians from all over the world, discussions from the 1100-odd participants discussion focussed on more local themes such as the factors that influence MND clinical care and research in the PACTALS member countries of Japan (Nagoya was this years host), Australia, China, India, Indonesia, Malaysia, Myanmar, New Zealand, Singapore, South Korea, Taiwan, Thailand and Vietnam.

The conference opened with an optimistic presentation from Dr Merit Cudkowicz of Harvard University and Massachusetts General Hospital, detailing the current progress in therapy developments. The conference then split into two streams with Dr Cudkowicz giving a second talk, this time on clinical trials, cohort enrichment strategies based on biology, and the exciting new Healey platform trial which tests multiple potential treatments in parallel using a shared cohort of placebo participants. Updates on specific treatments and techniques were also a highlight, with sessions on antisense oligonucleotides for specific genetic mutations and stem cells.

Many areas in clinical care were addressed, with separate sessions on diagnostic and assessment techniques, clinical and genetic features of patients, nutritional and communication support, and current medical care status in Asia and Oceania. Within these, Dr Matthew Kiernan spoke on the development of the new Gold Coast diagnostic criteria which sought to improve on the current Awaji diagnostic criteria by simplifying the process, decreasing diagnostic delay, and promoting recruitment to trials.

In addition to the 46 invited speakers, 145 e-posters were submitted, and I provided an update on our group's work testing urine-based biomarkers of disease progression. Having previously identified urinary p75ECD as a marker of neurodegeneration, we are building a panel of biomarkers indicative of different disease processes. Our recent work adds to this showing urinary neopterin as a potential biomarker of inflammation throughout disease progression.

Excitingly, a wide range of other potential biomarkers are under investigation in PACTALS countries, as evidenced by the number of biomarker themed talks and e-posters. These covered for example, the techniques of neuromuscular ultrasound, hip versus wrist based actigraphy, and exercising maximum VO2; markers from biological fluids such as asymmetric dimethylarginine, microRNAs, sphingolipid-metabolising enzyme activity, neurofilament light chain, chitinase; dysregulated energy metabolism; the MND disease course in people with the SOD1Leu126Ser mutation (found only in Japan), methods to identify small genetic changes in small or reduced penetrance families, and the impact of APOE on TDP-43 spread in sporadic disease.

The conference wrapped up with the award presentations, one of which was taken home by our very own Associate Professor Brad Turner from The Florey Institute of Neuroscience and Mental Health in Melbourne – well done!

As with in-person conferences, the virtual 2021 PACTALS contained a wealth of information, and I couldn't see or hear it all. One benefit of its online presence, however, is that I could go back and watch the talks I missed!

MND Australia CEO David Ali moderating the Q&A session of the 'Patients and Care Symposium' at the 2021 PACTALS virtual conference

Rebecca Stevenson is a third-year PhD student in The School of Medicine at Western Sydney University. Her PhD research focuses on the degeneration of motor neurons in Amyotrophic Lateral Sclerosis. Rebecca has written a blog for MND Australia titled "Explainer: How an ethical approach to working with animal models helps MND research", and we have included a shortened version here. For the full version of Rebecca's blog, please visit **www.mndaustralia.org.au/animalmodels.**

Advances in scientific research[1] and greater recognition of animal rights and welfare have led to new, complex challenges for those researching motor neurone disease (MND). Preventing the unnecessary suffering of mice, the most common animal in MND research[1,2], and other laboratory animals, is a basic requirement for scientists in Australia[3] and across the world. Researchers must make sure that mice and other animals are comfortable, treated carefully and remain as healthy as possible.

One of the greatest challenges faced by mankind today is the treatment of neurological disorders such as Alzheimer's, Parkinson's and MND. The brain plays a critical role in health and disease, connecting all systems of the body. However, it is the organ we know the least about. Unlike many other organs, the brain cannot be directly examined in living humans, except in some surgical procedures. These are uncommon, however, and provide researchers with limited information. If we want to study complex organs like the brain, we must turn to animal models.

Animal models have been frequently used to mimic many aspects of human diseases. The models have shed light on disease progression, prevention, diagnosis and treatment. Many scientific breakthroughs were made possible using animal models, including life-saving vaccines, surgical techniques and many medications[4]. In MND research, mice models have been the focus of many studies, including for better understanding mutations in the SOD1 gene and the application of biomarkers and gene therapies[2]. More recently, zebrafish have helped with understanding environmentally-induced motor neuron degeneration and other aspects of the disease[2].

Before new and effective MND treatments can be developed, researchers need to understand why and how the disease progresses, and why motor neurons die. Animal models have contributed to recent advancements towards understanding the genetic factors, cellular mechanisms and the cause behind MND. This provides a 'bench to bedside' approach to developing treatments.

Animal research is a critical starting point for the development of new treatments and makes MND clinical trials possible. Only when a potential new drug is proven to be safe and effective at treating the disease in animals, will it progress to human trials. It is also important to note that not all breakthroughs obtained using animal models translate directly to humans. This is why human clinical trials are also an essential part of medical research.

There are many examples of how studying the animal nervous system has contributed to the development of better treatments for MND and other neurological diseases. One of which is PB-TURSO (Sodium Phenylbutyrate–Taurursodiol), a potential new treatment for MND which is currently undergoing clinical trials[5]. It is a combination of two compounds which reduced the decline of motor symptoms in a mouse model of MND[6] and Parkinson's disease[7].

The University of Melbourne has recently reported that genetically deleting a pathway involved in neuroinflammation in MND mitigates disease progression in both mice and cell-culture[8]. Although still in the early stages, promising results from animal studies such as these may be transferred to MND patients in future clinical trials.

As a society, we must acknowledge the sacrifice animals make in researching MND and other diseases. However, the fact remains that animal models have profoundly and positively shaped human lives in many ways. From everyday over-the-counter painkillers to significant developments in COVID-19 vaccines and MND treatments like Riluzole[9]. Ultimately, removing laboratory animals from research would hamper our understanding of health and disease.

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Dr James Hilton, University of Melbourne

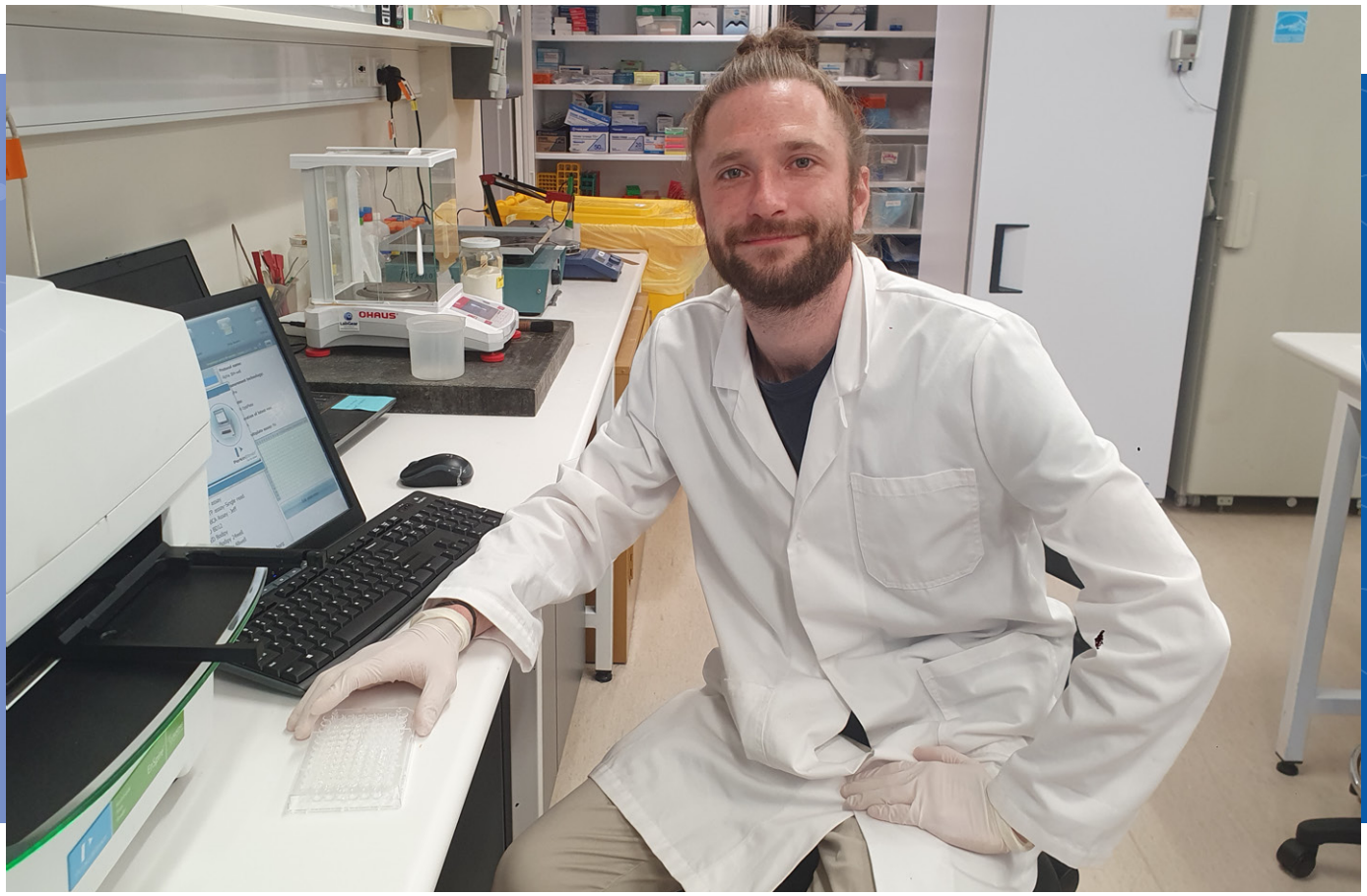
2019 - 2021 Beryl Bayley Fellowship Summary
Ferroxidase dysfunction drives glial ferroptotic stress and motor neurone death via neurotoxic A1 astrocyte conversion

While the unrelenting degeneration of motor neurons is the predominant feature in the manifestation of MND, the mechanisms that drive this are numerous and remain incompletely understood. One area of increasing interest in the neurodegeneration field focuses on the support cells of the central nervous system, called glia, and their central role in dictating neuron survival. In MND, this is perhaps best exemplified by the fact that mutant SOD1 expression in glia can create conditions toxic to motor neurons resulting in a significant impact on disease progression and survival.

Amongst the raft of adverse effects created by SOD1 mutations is disruption to how cells handle iron molecules, which is a crucial element in biology that can become pathological. Significantly, these issues are observed in both familial and sporadic human MND cases, with a prominent localisation to glial cells. These findings led me to decide to focus on how a recently characterised iron related form of cell death – coined ferroptosis – might be involved in MND through these glial support cells.

Being awarded the Beryl Bayley Postdoctoral Fellowship allowed me to follow this hypothesis which has produced multiple exciting outcomes. Research undertaken during this time has established that important markers of ferroptosis are increased in the mutant SOD1 model of MND as well as human cases of sporadic MND. In particular, these changes are most associated with glia which appear to acquire the potential for neuronal toxicity. This connection was validated using cells which showed that stressing glia to a point just short of death by ferroptosis was sufficient to coax these glia into becoming executioners of neurons. Relating back to the mutant SOD1 model, this work has found that genetically disrupting iron handling processes in glia worsens motor function, further reinforcing a role in MND. Promisingly, copper-ATSM, which is currently in clinical trials for MND, is able to rectify these iron problems and decrease markers of ferroptosis as well as restore glia back to their support state.

Outcomes produced during this fellowship have provided a greatly improved understanding of how glia can be induced to cause the death of neurons and how this might be targeted therapeutically. The complexity of this multifaceted cascade is becoming more apparent, as well as its importance to MND in terms of why motor neurons die. I am very grateful for the opportunity the Beryl Bayley Fellowship has afforded me and look forward to expanding on this research with the hope of facilitating translatable outcomes for patients and their families.



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