MND Research Network Newsletter Summer 2022

Welcome to our final newsletter for 2022! It is hard to comprehend the year is almost over. It has been a trying year for many with the ongoing effects of the pandemic, escalation of the Russo-Ukrainian War, and the cost-of-living crisis. However, in the MND research space it has been a year of many successes both nationally and internationally.

In September, the US Food and Drug Administration (FDA) made the decision to approve Amylyx Pharmaceuticals AMX0035, becoming the third FDA-approved therapy to show a slowing of disease progression in ALS/MND. Biogen's drug, Tofersen, is continuing to show promising results for the treatment of SOD1 MND. Two clinical trials were launched in New Zealand, Triumeq (Lighthouse II) and FOCUS-C9. The first Australia & New Zealand MND Research Symposium occurred, a recording of this is now available here. Professor Chris Shaw, whose research team have discovered more ALS/MND and frontotemporal dementia (FTD) genes than any other laboratory in the world, was appointed to the Hugh Green Chair in Translational Neuroscience in the Centre for Brain Research at the University of Auckland. To end the year, the first New Zealand best practice recommendations for the management and care of individuals with MND were published, available here.

In addition, there have been five New Zealand-based MND research studies this year: Costs associated with MND in Aotearoa New Zealand; the role of the MND Clinical Nurse Specialist in Canterbury & incidence of MND in Canterbury; Genetics of MND in New Zealand; Cough Assist Machine for the Prevention/Mitigation of Respiratory Infections in Neuromuscular Conditions (including MND); Role of Respiratory Function Tests in monitoring MND patients.

In October the New Zealand MND Registry reached its highest number of active participants since its inception in 2017. Recruitment for national research studies and clinical trials in New Zealand is often through the MND Registry. Anyone with MND who is interested in participating in research can sign up to the New Zealand MND Registry here.

These successes represent years of effort from a committed team of researchers, dedicated to learning more about all aspects of MND and treatment options to improve quality of life for individuals living with the condition.

The momentum and drive towards MND-related research in New Zealand continues to grow, and we are now on the international map for clinical trials. It is exciting to see what 2023 has in store! Hopefully we continue to hear more success stories. Thank you to everyone driving this movement forward.

As this is my last newsletter, I want to take this opportunity to thank you for your support in the growth of the MND Research Network. Weather you listened to one of our webinars, sent an email, sourced information from our website, read our newsletters, or followed us on our social media platforms, we are grateful. I am returning to Ireland and therefore finishing up in my position as manager of the MND Research Network and curator of the MND Registry. I have thoroughly enjoyed my time in this dual role over the past two years. I am inspired by those who are investing their time and expertise in progressing our knowledge of MND and striving for a better future for people living with MND in New Zealand. I will continue to follow the development of MND research in Aotearoa from afar.

Finally, a word from Dr Emma Scotter, Director of the MND Network.

We at the University of Auckland would like to thank Dympna for a wonderful two years in her role as NZ MND Research Network Manager. In her dual role with the Network and as curator of the NZ MND Patient Registry, she has facilitated involvement of New Zealanders with MND in many research studies, including our own Genetics Study, and in clinical trials.

She has also brought together more Network members than ever before, through webinars, newsletters, and the website. We wish Dympna all the best of luck back in Ireland. She will be dearly missed but we look forward to catching up over a Guinness!

Noho ora mai

Dympna Mulroy
(NZ MND Research Network Manager)

New Zealand Clinical Trials

FOCUS-C9 Wave Life Sciences, for patients with *C9orf72*-associated MND or FTD

Wave Life Sciences Ltd have developed an investigation drug WVE-004, and it is specifically designed for MND caused by a mutation in the *C9orf72* gene or *C9orf72*-associated frontotemporal dementia (FTD). WVE-004 uses an approach known as 'antisense', where the drug directly interferes with the faulty instructions for making a protein.

Phase 1b/2a - FOCUS-C9

New Zealand has two sites for the Phase 1b/2a study known as FOCUS-C9. This study aims to evaluate the safety and tolerability of WVE-004 in people with MND or FTD with a documented mutation in the *C9orf72* gene. This study started recruitment overseas last year and is continuing to recruit across Europe, Canada, Australia and now New Zealand. In this study, participants with FTD or MND are given either the active WVE-004 medication or placebo, administered into the fluid that surrounds the spinal cord and brain via an injection near the bottom of the back (intrathecal injection). The principal investigators for New Zealand are Professor Tim Anderson in Christchurch and Dr Julian Bauer in Auckland. Recruitment is now open to eligible participants from anywhere in New Zealand. More information is available here.

Triumeq in MND/ALS Phase 3 clinical trial (Lighthouse II)

In the last newsletter we announced that the first-ever international phase 3 MND clinical trial was approved for multiple locations across New Zealand. In the coming months, a small group of New Zealanders living with MND will begin their journey as members of this trial.

Research teams in Bay of Plenty, Wellington, Christchurch, and Dunedin have elected to participate in this trial opportunity. Dr Alan Stanley, Hawkes Bay neurologist and MND New Zealand Council member, will be the New Zealand Principal Investigator for this trial.

Laboratory research suggests that a virus, called a human endogenous retrovirus (HERV), may be the cause or trigger for ALS in some people. The particular HERV associated with MND is called HERV-K. This virus may be similar in some ways to HIV (the virus that causes AIDS). There are anti-viral medications that are very effective against HIV. This study is testing whether one of these medications, Triumeq, could also be effective in delaying progression of the disease and whether it is safe and well tolerated in patients with MND.

Phase 2 of the Lighthouse Trial showed that long-term Triumeq exposure was safe and well tolerated in the study cohort. A favourable response on HERV-K expression levels was observed, accompanied by a decline in ALSFRS-R progression rate, which indicates that Triumeq may slow disease progression in patients with MND. Phase 3, known as Lighthouse II, is a randomised, double-blind, placebo-controlled study. This study aims to determine if Triumeq improves survival in people with ALS/MND compared with a placebo. Lighthouse II is expecting to enrol 390 participants worldwide, from New Zealand, Australia, Europe and the U.K. Around 20 participants are expected in New Zealand. Although this is relatively small, it is a significant milestone in our plans to gain access to more clinical trials here.

To be able to fund this sort of research trial in New Zealand is testimony to the incredible fundraising support from across Aotearoa. It also represents years of effort by MND New Zealand, advocating for the MND community and establishing systems that connect those living with MND to the global network of researchers who are helping to fight this disease.

More information about the Lighthouse trial can be found here.

National MND Research News

Cough Assist Machines for people with neuromuscular disorders & MND

A group of researchers and clinicians at the University of Otago have just realised a report from their study that explored the use of cough assist machines across New Zealand for people with neuromuscular disorders (NMD), including motor neurone disease (MND).

Mechanical insufflation-exsufflation (otherwise known as cough assist machines- CAM) devices are recommended for many people with NMD/MND to manually assist with secretion mobilisation and clearance. However, there are no national guidelines (except the recently

released New Zealand Motor Neurone Disease Best Practice Recommendations – 2022) in place around CAM use to inform clinicians on recommended practice. Anecdotal discussion between health professionals suggested that there are discrepancies between health services in New Zealand regarding: availability of CAM devices; access to device training; provision criteria; and clinical support around ongoing patient use. Regional differences for CAM use in people with NMD/MND pose a risk of inequitable access to respiratory management.

This study had three main objectives. 1) To determine the number of CAM devices across New Zealand's district health boards for people with NMD, 2) to explore currently used guidelines and clinical criteria for provision of CAM by physiotherapists and, 3) to gain an understanding of the experience of being deemed eligible for a CAM, access to service provision, and funding of CAM by both physiotherapists and people with NMD/MND.

To read the report, including the outcomes click here. Dr Meredith Perry is keen to build on this research. If you would like to discuss this study and options to collaborate towards further research on this topic, you can email Dr Perry.

Professor Chris Shaw

On Monday 17th October Professor Chris Shaw was appointed to the Hugh Green Chair in Translational Neuroscience in the Centre for Brain Research at the University of Auckland. A recording of this lecture is available here.

Professor Shaw, who trained as a neurologist in New Zealand, is the Director of the Maurice Wohl Clinical Neuroscience Institute and established the UK Dementia Research Institute Centre at King's College London. He is also the chief scientific adviser of AviadoBio, a company developing gene therapies to target neurodegenerative disorders such as MND.

In his inaugural lecture, *"Gene therapy strategies for motor neuron disease"*, Professor Shaw discussed the remarkable progress recently achieved with a pioneering gene therapy delivery method for patients with spinal muscular atrophy (SMA). This progress has sparked a proliferation of gene therapy programmes for many neurodegenerative disorders. Professor

Shaw is involved in gene therapy trials for *C9orf72* MND/FTD, FUS-MND and the recently completed Tofersen drug trial for SOD1 MND (you can read about this trial on page 8).

His discovery of MND and frontotemporal dementia (FTD) genes has enabled gene testing for patients and at-risk family members. His research team have generated a large number of stem cell and transgenic mouse models that characterise key features of the human disease and have revealed important mechanistic insights.

At the time of his appointment to the Hugh Green Chair, Professor Shaw was interviewed by Denise Montgomery from the University of Auckland. Denise has kindly shared this publication. Click here to read the article.

Best Practice Recommendations for MND

Best practice recommendations (BPRs) for the management and care of individuals with MND were published on, 8 November 2022. These were developed over several years by a working group of New Zealand MND clinicians and health professionals around Aotearoa, who have an interest in improving care for people with MND and their whānau. Funded by MND New Zealand, these BPRs represent what specialists in MND care agree should be the standard of care for any New Zealander diagnosed with MND.

Read the NZ Best Practice Recommendations here and share them with your networks.

"This is a first and a milestone for standardising and promoting world class MND holistic clinical care across Aotearoa New Zealand"

Sir Richard Faull

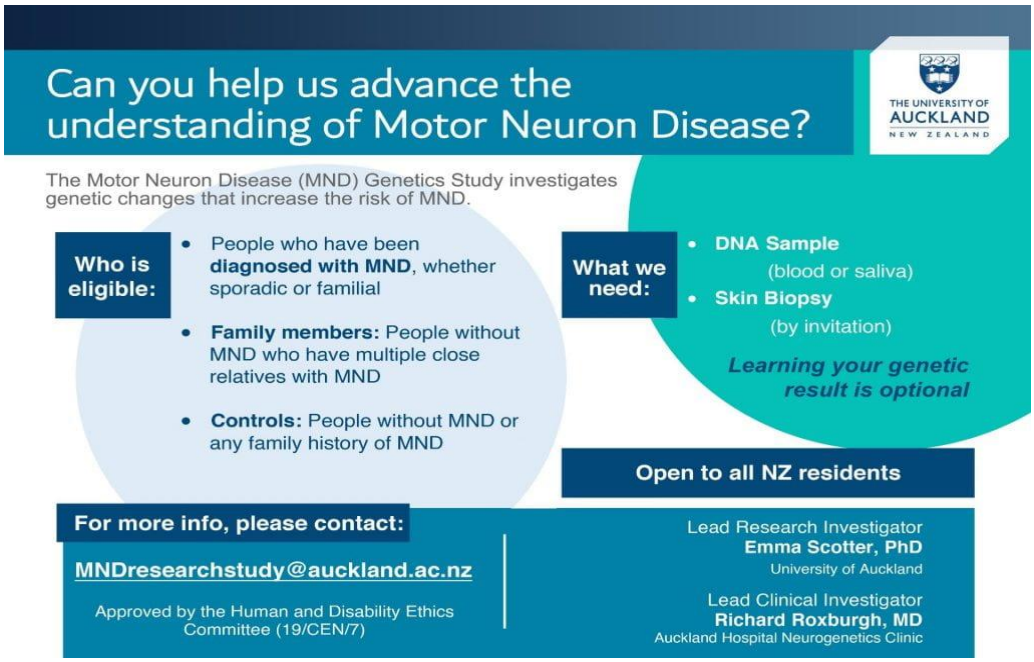
Genetic Screening in Motor Neuron Disease

There is growing discussion within the global MND community that everyone with MND should be informed of and offered genetic testing, especially as gene-based therapies are likely to be available soon or in clinical trials.

In many countries, including New Zealand, genetic testing for MND is usually restricted to patients with family members also affected by MND, or patients who do not have a family history but have symptoms starting early, under the age of 40. New research led by Prof Ammar Al-Chalabi (Director of the King's Motor Neuron Disease Research Centre in London) suggests the genetic basis of MND is being missed for hundreds of people in the UK as they do not fit the “arbitrary age limits and rules” for genetic testing.

The research estimates that nearly a quarter of people with MND have no family members with the illness yet do have a genetic link to the condition. This link goes undetected in 98% of cases because of current guidelines. With the exciting prospect of specific gene-based therapies on the horizon, and with clinical trials underway, it will become more important for people with MND to know if they have an identifiable genetic cause. You can read the findings from this study published in Brain.

In New Zealand we are currently lucky to have an MND Genetics Study. This enables all people with MND who enrol in the study to have a genetic test and receive counselling support. While this study is for research purposes and therefore cannot rapidly screen all genes, the most common MND-causing genes are been screened. This study is driving changes in the way genetic testing is offered and improving our understanding of common MND-causing genes in New Zealand.



New Zealand MND Registry

The MND Registry has continued to grow in recent months. Since its inception in 2017, 380 people have enrolled. The Registry is an opt-in registry, meaning individuals need to consent to enrol. It estimates to capture approximately 50% of the MND population in New Zealand at any one time.

The Registry aims to connect MND patients with national and international research opportunities. It has also been credited as one of the key mechanisms that captured the attention of the Lighthouse II trial team, and it is also critical to securing future research opportunities for New Zealanders living with MND.

Within the past 12 months the Registry has aided recruitment to the following six studies.

Studies approved	Sponsor
Mechanical Insufflation-Exsufflation (MI-E) Devices (such as Cough Assist) for the Prevention/ Mitigation of Respiratory Infections in Neuromuscular Conditions (including Motor Neuron Disease)	Muscular Dystrophy Association New Zealand
Costs associated with Motor Neurone Disease in Aotearoa New Zealand	MND New Zealand
Psychological Aspects and Implications of Predictive Genetic Testing for MND/ALS	Macquarie University, Sydney
Genetic Screening in MND	University of Auckland
Study of WVE-004 in Patients with C9orf72-associated ALS/MND or Frontotemporal Dementia (FTD) (FOCUS-C9)	Wave Life Sciences
Triumeq in Amyotrophic Lateral Sclerosis (LIGHTHOUSE II)	MND New Zealand

International MND Research News

Tofersen (BIIB067) Biogen; Adults with symptomatic SOD1

In the previous newsletter, we discussed Tofersen, an experimental antisense oligonucleotide (ASO) designed to reduce SOD1 protein in people with MND caused by *SOD1* gene mutations.

Although results from the VALOR, Phase 3 randomized study, concluded that treatment for 6 months did not result in improvements in people living with MND, it did indicate reduced disease progression across multiple secondary endpoints.

Due to these positive results, the trial continued beyond 6 months, and everyone in the trial was given the drug. Two groups were formed: an 'early start Tofersen' group who received the drug throughout all of the study (52 weeks), and the 'delayed start Tofersen' group that first received placebo (28 weeks) but then went on to receive the drug (from 28 to 52 weeks).

Results of the phase 3 VALOR study and the combined analysis of VALOR and its open label extension study were recently published in the New England Journal of Medicine. They concluded that earlier initiation of tofersen compared to delayed initiation slowed decline in clinical function, respiratory function, muscle strength, and quality of life.

Biogen is seeking approval of Tofersen under the FDA's accelerated approval pathway, based on the use of neurofilament as a surrogate biomarker. Decision expected 25 Jan 2023.

Albrioza (AMX0035); Amylyx Pharmaceuticals

Albrioza, also known as AMX0035, has been a major topic of conversation amongst the MND research community in recent months. In the last newsletter we reported that this drug had been approved by Health Canada subject to conditions, including being dependent on the safety and efficacy data from the ongoing Amylyx Pharma Phase 3 PHOENIX trial.

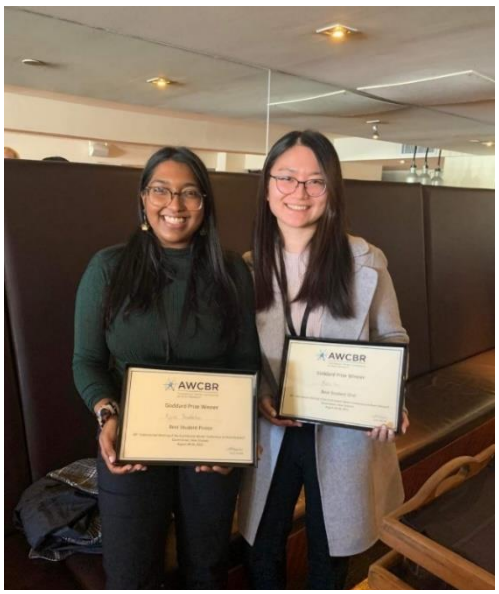
On 29th September 2022, the US FDA announced they have approved AMX0035, relabelled as RELYVRIO as a treatment for MND. Amylyx have also applied to the European Medical Agency (EMA) for AMX0035 with a decision expected to be made in early 2023. AMX0035 is a combination of two drugs, sodium phenylbutyrate (PB) and taurusodiol (TURSO /TUDCA).

The CENTAUR Phase 2 clinical trial and its extension study showed that AMX0035 significantly slowed MND patients' functional decline and reduced their risk of death. It is the first investigational therapy to demonstrate statistically significant benefit in people with MND since edaravone was approved in 2017 (this treatment has not been approved for use in New Zealand) and riluzole in 1995. Read more about the AMX0035 and the trial phases here.

Conference update

Many conferences are hybrid or online again this year. This makes global events more accessible to everyone. Click here to see a list of upcoming MND conferences/seminars.

MND New Zealand recently held a webinar, which included an update on drug trials and release of the New Zealand MND Best Practice Recommendations. Click here to listen to a recording of this webinar. Visit our website to listen to recordings of previous conferences and seminars.



L: R; Kyrah Thumbadoo and Maize Cao University of Auckland, award recipients at AWCBR.

It was great to see the return of the Australasian Winter Conference on Brain Research (AWCBR) in August. MND featured throughout the conference with five researchers presenting on topics from biomedical to patient registries.

Congratulations to Maize Cao who won the AWCBR Goddard Prize for Best Student Oral Presentation' *'Identifying TDP-43 loss-of-function markers in amyotrophic lateral sclerosis'* and Kyrah Thumbadoo who won Best Student Poster *'X marks the spot: A neuropathological signature of the X-linked motor neuron disease gene UBQLN2'.*

Upcoming virtual conferences & webinars include:

33rd International Symposium on ALS/MND | 6 – 9 December 2022

FightMND Scientific Seminar Series| 4th Tuesday of each Month 5:30-6:30pm NZT

Want to stay in the loop?

Follow us on Twitter and Facebook. If you have any questions related to MND Research or you would like to share something with the network, please contact us!

We wish you a delightful holiday with family and friends and happiness throughout the coming year.