MND Drug Trials – good news...bad news..

There has once again been considerable activity in the MND clinical trial space in the last few months.

In a first for MND, the US FDA, Health Canada and the European Medicines Agency (EMA) have all agreed to consider priority approval for Amylyx's AMX0035 MND drug based on their Phase 2 trial data. In March , a non-binding advisory panel to the US FDA voted 6-4 against approving the drug prior to a phase 3 trial, stating insufficient efficacy. Amylyx have recently released further data from their Phase 2 trial, which showed a 49% reduction of death or tracheostomy/permanent assisted ventilation and a 44% reduction in first hospitalisation over the trial and follow-up period. A decision from Health Canada regarding priority approval is imminent and we are due to hear from the FDA on June 29th. We await the final decision which may consider additional factors such as the severity of the disease and lack of treatment options.

Australian researchers, Professors Steve Vucic and Matthew Kiernan, have also been making waves with further analysis of Clene Nanomedicine's experimental medicine CNM-Au8 Phase 2 RESCUE-ALS trial, which was run in Australia. The trial was unique in that it measured whether the treatment could prevent the loss of motor neurons as measured by Motor Unit Number Index (MUNIX) scores (a neurophysiological measure that provides an index of the number of functional lower motor neurons in a muscle). They showed that in limb-onset ALS, MUNIX scores decreased by about 40% in the placebo group and a little over 20% in the CNM-Au8-treated patients. This means that the active treatment was able to slow the loss of motor neurons by about 45% over 36 weeks in this group of patients. They also showed ALS disease progression, defined as the occurrence of death, tracheostomy, non-invasive ventilatory support, or gastrostomy (feeding) tube placement declined by about 37%.

These are exciting results and we are looking forward to seeing the outcome of a larger phase 2 trial which is currently underway with 150 patients as part of the Healey Platform Trial in the US, with results due later in 2022. A 300 patient Phase 3 trial (RESTORE-ALS) is planned across several countries in 2023, including Australia.

Unfortunately, not all clinical trial news has been hopeful. In March, Biogen and Ionis announced that BIIB078, an investigational antisense oligonucleotide for C9orf72-associated amyotrophic lateral sclerosis (ALS), did not show clinical benefit and that the clinical program will be discontinued. We await more information to further understand the cause of the trial failure. This is not the only drug trial targeting patients with the C9ORF72 mutation. More positively, Wave Life Sciences announced a Positive Update to their Ongoing Phase 1b/2a FOCUS-C9 Study, which has several sites in Australia. Reductions in poly (GP), a key disease biomarker indicating drug target engagement, was observed across all treatment groups after single doses. They are now adapting the trial to ensure the drug is being used in the best possible way.

Better ways of measuring MND disease progression are still needed. Where patient follow-up studies are continued after a formal drug trial has been completed, more promising results are sometimes reported. Unfortunately, there is a very difficult compromise to negotiate between the financial pressures of running long costly drug trials versus truly proving whether a drug works. We all want treatments faster but inconclusive data helps no-one. The best way forward is more sensitive and reliable markers of disease progression (see pages 10-11 for information on biomarkers in MND). Perhaps measurements such as MUNIX will help in this regards. Many researchers in Australia are looking at better ways to measure disease changes and we are very proud to support much of this work.

▶ See inside for a report on the 2022 MND Research Symposium

Executive Director Research Report

It has been an incredibly busy and productive few months in the Australian MND research space.

The inaugural Australian and New Zealand MND Research Symposium took place from the 28-30th April in Brisbane. The meeting was jointly hosted by MNDRA and FightMND and was the largest ever Australian MND research meeting. There were many fantastic presentations, both from those with lived experience and researchers. Highlights were hearing from the Indigenous perspective of lived experience and learning about a number of large collaborative research programs that are bringing people together in the MND research space. The MND Connect session connected researchers with the wider MND community where we heard brilliant overviews of the genetic and environmental causes of MND and what's in the clinical trial pipeline, amongst other topics. Please see pages 3-5 for a full write-up of the Symposium.

Our State-of-Play webinars are continuing again this year and we have already heard about what goes wrong in nerve cells. Keep an eye out for our next episode discussing how allied health research can inform better care models on Wednesday June 22nd, during MND Week.

The MND Collective has been moving ahead and we now have a managing Board established and meeting regularly, specialist groups in the Basic Science and Allied health areas and have the MiNDAUS partnership contributing expertise in Clinical and Social Science. We have also established nodes in most states and are developing a strategic plan from the outcomes of the Summit to prioritise which resources are needed to best support the MND community.

Within our own organisation we are developing the next iteration of our research strategy for MND Australia. This will allow us to have a clear direction going forward in a rapidly changing landscape and enable us to respond to new developments. Key considerations will be how we can better communicate research outcomes and how we ensure what we do is of benefit to the MND community.

After more than two years of lockdowns and travel restrictions it has been fantastic to finally get the opportunity to travel and meet the wider MND Community again. Obviously the Symposium was an ideal opportunity to meet the research community but I have also been fortunate enough to attend some brilliant fundraising events.

The Shag Gregory Poker Run is a unique country community fundraising event in memory of "Shag" who lost his battle with MND and this was the 23rd running of this event. I was lucky enough to be able to attend the evening event in Hay, NSW for a great night with live music and a very well-stocked auction with some very generous bidders, including for the custom-built bar you can see in the picture.

A week later another regional fundraising event was underway, the "Ian Sneddon" Two Rivers Tractor Run which is a week-long "tractor trek" along the NSW/Victorian border in vintage tractors in memory of Ian Sneddon, himself a keen vintage tractor enthusiast. I attended the auction and dinner on the first night in Jerilderie, NSW where again an amazing array of items had been donated to auction and I was blown away by the generosity of the bidders.

In somewhat of a contrast, I also attended the MNDandMe Scott Sullivan Gala at the Queensland Gallery of Modern Art for a wonderful evening meeting many local donors and MND Community members including Murray Geale, who has been a prime driving force in establishing the MND Collective.

Despite the different natures of these events they all underline how powerful and uplifting community-based fundraising is and demonstrate how we can all work together to end this terrible disease. With the support of fundraisers such as these we can continue to support the brilliant research that is underpinning the new treatments and better care models current being developed and tested. Every dollar does count.

Dr Gethin Thomas,
Executive Director of Research, MND Australia

Australia & New Zealand
MND Research Symposium 2022

After many months of planning and several COVID-induced delays the inaugural Australian and New Zealand MND Research Symposium took place from the 28-30th April in Brisbane.

The meeting was jointly hosted by MND Research Australia and FightMND. The Organising Committee was chaired by Dr Derik Steyn with Dr Fleur Garton chairing the Local Organising Committee. We would like to thank Derik and Fleur for their fantastic leadership in organising the Symposium and FightMND for partnering with us to host the event.

We were fortunate enough to obtain generous sponsorship from Clene Nanomedicine, MND Queensland, MNDandMe and several UQ Institutes and Schools. This meant we were able to keep registration costs down and provide free registration for those with lived experience of MND.

Our open invitation for anyone with lived experience to attend for no cost was recognised by the awarding of a Morris ALS/MND Principles accolades certificate. The Morris ALS Principles were created with the intent of breaking down silos, avoiding expensive duplication, creating a human-centric ALS landscape and encouraging valuable collaboration between ALS stakeholders.

We had ~220 in-person registrants and another ~40 online attendees. This is by far the biggest ever national MND research meeting in Australia and represents how keen our research community was to re-connect after 2+ years of COVID disruption.

Professor Ian Blair on the complex genetic and environmental triggers that may contribute to MND

The Symposium opened with a very moving "yarn" from Mel Syron, telling us about her father's MND journey from a First Nations perspective. This is a perspective we do not hear enough from. The opening session had a strong focus on collaborative research programs with overviews of the MND Collective, the MiNDAUS Partnership, the MNDNZ Research Strategy, the MNDSA Clinical Pathway and Referral Network and the SALSA genetics database. It was especially gratifying to have a strong NZ MND Research contingent present at the meeting and promising links have been forged to work more closely in the future. The number of well-established partnership approaches across the Australian and New Zealand MND research landscape really reflect the collaborative nature of our community.

Scientific sessions then followed focussed on the causes of MND, the role of TDP-43, treatment, development and biomarkers, clinical research and improving care. A standout feature of the talks was the outstanding quality of the research, much of which was presented by junior researchers . One key theme that arose was considering muscle as a key actor in the disease process, rather than just a consequence of motor neuron degeneration. This may present new research opportunities. A big highlight of the scientific meeting was the two "Rapid-Fire Research" sessions where presenters had 5 minutes to summarise their research findings. This format provided a very stimulating fast-moving journey through the cutting edge research being undertaken in Australia and New Zealand.

On Day 3 we hosted the MND Connect session which brought together our MND researchers and the wider MND community. The scene was brilliantly set by ex-ABC journalist Sean Dorney telling us his hopes for research with the resounding message to researchers of "Just keep going". The session then continued with Catherine Hansen introducing the MiNDAUS Registry and Partnership, highlighting how patients can enrol and contribute to research. Professor Ian Blair from Macquarie University gave a wonderfully clear overview of the complex landscape of genetic and environmental triggers of MND and finally Dr Fiona Bright, the 2022 MNDRA Bill Gole Fellow, told us why the protein TDP-43 is so critical in many aspects of MND.

Following a lunch break, Dr Colin Mahoney from the Sydney Brain and Mind Centre summarised the current clinical trial pipeline, providing much hope for the future as well as identifying a few thorny problems worth considering. Vrunda Sane, a Genetic Counsellor from Genetic Health Queensland, presented a great overview of the role of genetic counselling and some of the considerations around genetic testing. The CEO of MNDandMe, Jane Milne, then introduced the PRIZM app, which provides an easy-to-access repository for a patient's clinical and treatment information. This provided an opportunity for the community to compare the PRIZM app with the MiNDAUS Registry interface to minimise any potential confusion between the two. The final presentation was from Professor Samar Aoun from the Perron Institute in Perth who introduced their Compassionate Communities Program and how it supports rural and regional needs and palliative care.

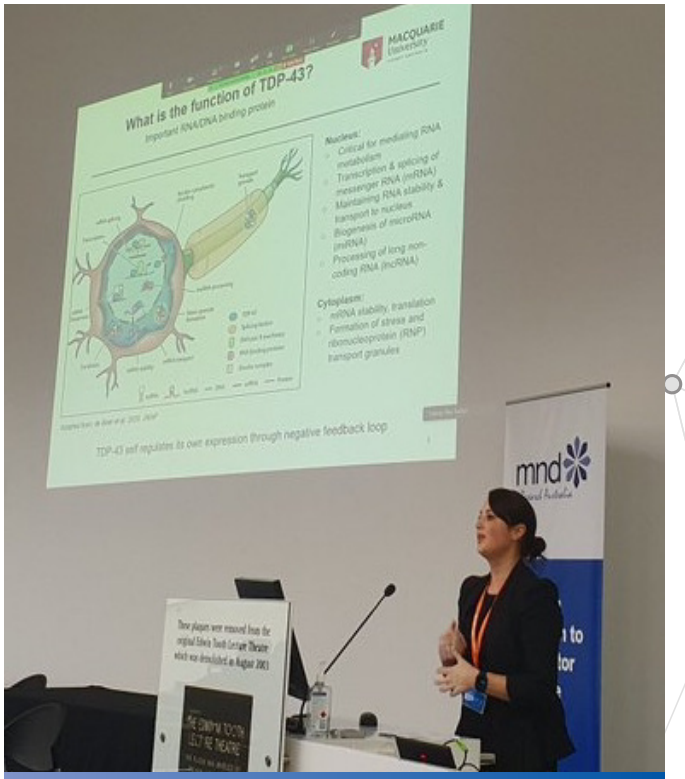
Feedback from the meeting was excellent with our research community relishing the opportunity to meet colleagues, renew connections and build new collaborations. Below are reports from two of our 2022 Research Fellows who attended the Symposium.

A key feature of the three day symposium was the opportunity for panel Q&A and discussion

Dr Marnie Graco, MNDRA Nancy Gray Fellow 2022, Implementation Scientist at Austin Health

This symposium was exactly what I needed to kick-start my 3 year early-career fellowship funded by MNDRA. I judge the value of a conference by the number of new ideas I come home with. This one was a winner! The plane trip home from Brisbane was spent talking to my colleagues about what we learnt, what we still don't know, and what else we can do.

Other conferences I have been to, in different clinical areas, have not come close to the breadth and depth of collaboration that I witnessed at the MND Symposium. Having the latest in basic science and clinical research presenting side by side, with the lived experience of MND woven throughout the symposium was a unique and inspiring experience. Not since my undergraduate days had I thought at the level of proteins and cells, and I was awed by the research presented by our Australian and New Zealand basic scientists. It was lovely to hear at the conference dinner how much they also appreciated listening to the clinical research, and of course we both agreed that hearing from those with the lived experience was what inspired, humbled, and motivated us to keep going.



Bill Gole Fellow Dr Fiona Bright

Fiona Bright, MNDRA Bill Gole Fellow 2022, Dementia Research Centre, Macquarie University

This was my first MND symposium and it was an amazing and fulfilling experience. The MND research community in Australia and New Zealand is like no other, with driven and passionate researchers who collaborate and connect directly with MND patients and families who are central to research efforts. This symposium was one of the friendliest and most engaging I have attended, with so many opportunities to engage and network with researchers, clinicians, patients and families from across the southern hemisphere.

Across the first two days of the MND symposium we heard from various researchers from around Australia and New Zealand presenting their impactful MND research spanning all aspects of the MND spectrum including but not limited to the exploration of the causes and pathogenesis of MND, preclinical studies, treatment development & clinical trials and importantly patient-focussed studies. It was particularly exciting to hear from the numerous early career researchers from various backgrounds, all of whom are dedicating their research careers to understanding the causes of and joining the fight against MND under the mentorship and supervision of esteemed senior researchers from leading research institutes around the country and from NZ.

One of the new, up and coming exciting areas of research in the MND field which was discussed at the symposium in a number of talks and posters is the use of 'human specific' models of MND utilising patient human stem cells to generate 3D human brain/spinal cord organoids. This is an area of research to watch in the coming year/s, given this novel technology will further enhance our ability as researchers to investigate the underlying causes of genetic and sporadic MND in an entirely human context.

A special highlight for me personally was the MND Connect session on day 3 of the symposium. I had the honour of presenting a talk to MND patients and families in this session discussing TDP-43, an abnormal proteinopathy contributing to pathology in the central nervous system of ~95% of MND patients. At the start of the MND Connect session I was particularly touched to hear first-hand the lived experiences and challenges directly from patients and families, something as a lab-based researcher we do not always have the opportunity to do. Some sentiments that resonated with me particularly were Sean Dorney's request to researchers to 'just keep going' and to 'share a bit more information with MND patients and tell us more about what the research is aimed at regarding the progress of research across various areas of MND', both the good and the bad news. From this session I, as I am sure many other researchers also, feel even more inspired and driven to pursue important research into understanding the causes of MND in the search for better diagnostic tools, disease modifying therapies and ultimately curative treatments.

On behalf of all of the ECRs, I would like to sincerely thank MND Australia and Fight MND for facilitating this fantastic symposium. I look forward with great anticipation to the next MND symposium and the exciting research that will come from the Australian and NZ MND research community in the coming year/s, given the high calibre of impactful research presented at this year's symposium.

State of Play in 2022

MNDRA's webinars are running again in 2022, to showcase the incredible work being undertaken by our funded researchers. In April, we kicked off with presentations from Dr Andrew Phipps and Dr Jeffrey Liddell to examine what goes wrong with nerve cells in MND. This recording, as well as previous state of play recordings from 2020-21, are available on our website at www.mndaustralia.org.au/state-of-play.

The next State of Play is scheduled for Wednesday June 22 at 7pm AEST. This webinar falls in MND week and will feature Dr Karen Hutchinson, a physiotherapist from Macquarie University, and Salma Charania, a speech pathologist from MND Queensland presenting on 'How can research in Allied Health help build better models of care?'. Registration details are available via the link above.

This webinar series is interactive and presents a unique opportunity to ask direct questions about MND research and care. At the end of the webinars we ask our presenters to stay online for approximately 20 minutes to answer questions from the audience. All of our webinars are live streamed on the MND Australia Facebook page: facebook.com/mndaustralia. If you are hearing impaired, we recommend that you watch via Facebook and ensure that captions are turned on.

We are always keen to hear suggestions regarding future topics to be covered in our State of Play webinars. Please send us an email at: research@mndaustralia.org.au to pass on any ideas.

MND Australia
International Research Update

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

Outcomes from the MND/ALS Australian National Research Conference

This article comes after the first in-person Australian/NZ MND/ALS conference since the beginning of the COVID-19 pandemic. It was wonderful to see all of the researchers present their work and how, despite the pandemic, researchers were continuing to make strides to better understand MND, provide better care and potentially treat it.

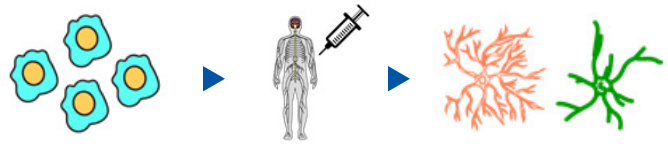
This issue of the MND International Research Update demonstrates the breadth of MND research, containing studies of why di-peptide repeats that are characteristic of the C9ORF72 mutation may be toxic, how these repeat proteins might act as biomarkers for C9orf72-associated ALS, a finding that TDP-43 accumulates in nerve axons, and a clinical trial of stem cell transplantation for ALS patients.

Hematopoietic stem cells for amyotrophic lateral sclerosis treatment

In ALS one of the major observations made is that there is excessive and widespread activation of central nervous system immune cells (microglia and astrocytes). Therefore, it is reasonable to think that deactivating or suppressing the activation of these cells may be beneficial for patients suffering from ALS. A team led by Dr Claudia Caponnetto from Genoa, Italy recently worked to mitigate the excessive activation of these immune cells in ALS patients via injection of hematopoietic stem cells into patients.

Hematopoietic stem cells?

Hematopoietic stem cells are blood stem cells capable of becoming all types of blood cells including red blood cells, platelets and white blood cells, including astrocytes and microglia. These cells are capable of being harvested from a patient, proliferated, and then reinjected into the same patient. Surprisingly, hematopoietic stem cells are capable of crossing the blood-brain barrier and also exert a suppressive effect on inflammation in degenerating central nervous system models.

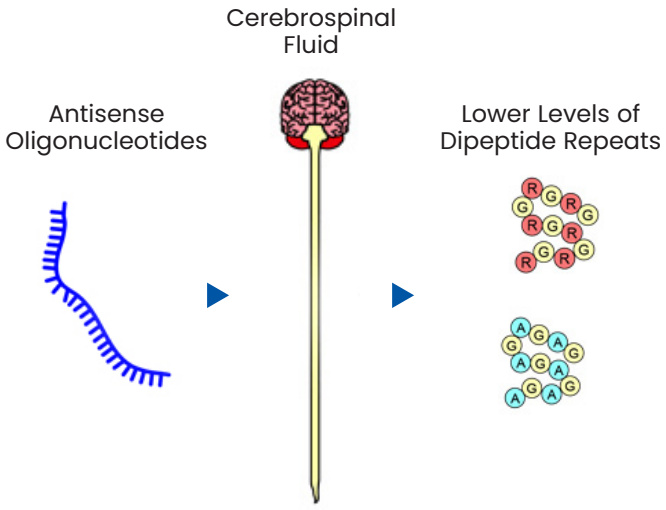


What were the outcomes of this trial?

The trial being discussed here was a phase I/IIa trial, meaning that the main outcome was treatment tolerance and safety for patients. The trial was run on a small number of patients, with only 8 of eleven enrolled patients receiving the treatment. The treatment was well tolerated and patients did not have any unexpected side effects. Unfortunately, the study was not powered (not enough patients) to adequately measure if the treatment had any beneficial effects on disease course. This being said, the major finding was that the treatment appears safe, so future studies can likely increase the treatment regime, increase patient numbers, and investigate effectiveness of the treatment. Safety in potential treatments for diseases is of the utmost importance for future success in trials.

Poly-GR and Poly-GA in cerebrospinal fluid as a biomarker for C9orf72-ALS

An ongoing problem in MND research has been the lack of useful biomarkers for diagnosis of the disease, tracking of disease progression and of the potential effect of clinical trials. Researchers from the University of Massachusetts, led by Dr Fen-Biao Gao, have recently shown that, at least in C9orf72-associated ALS cases, they can successfully use detection of poly-GR and Poly-GA dipeptide repeats as a biomarker in clinical trials for suppressing these toxic polypeptides.



Poly-GR and Poly-GA

In C9orf72-associated ALS, hexanucleotide repeat RNA is translated into repetitive polypeptides (very small proteins) composed of either glycine-alanine (GA), glycine-arginine (GR), glycine-proline (GP), proline-arginine (PR), or proline-alanine (PA). These dipeptide repeats are highly toxic to cells through several mechanisms and are unique to C9orf72 cases of ALS or frontotemporal dementia. As such, they are a potential biomarker for disease onset or progression.

Poly-GA and Poly GR as markers in cases of C9orf72 suppression

As these dipeptide repeats are unique to C9orf72 disease, they are also a potential target for therapeutic intervention. In this research, the authors used spinal fluid from patients treated with an antisense oligonucleotide (ASO) designed to prevent dipeptide repeats from being synthesised in cells. The researchers found that in cases where patients were treated with the ASO, they were capable of tracking the decrease in dipeptide repeats, especially for Poly-GA and Poly-GR. This is important because it means that for larger clinical trials of ASOs for C9orf72-ALS, this method could be used to measure ASO effectiveness alongside other measures of patient disease progression.

Pathological TDP-43 in axon nerve bundles

Most of us are aware that TDP-43 is the major pathological marker of ALS. Specifically, phosphorylated and mislocalised TDP-43 is strongly linked with an ALS diagnosis. Researchers from Hiroshima University, led by Dr Hirofumi Maruyama, recently published a report of their findings in post-mortem tissues and patient biopsies from ALS and control patients. This team was investigating if the presence of pathological TDP-43 in axon nerve bundles is a marker exclusive to ALS.

TDP-43 and its role in axons

Axons are the long extension of a nerve cell that leads from the cell body to the axon terminal, where axon terminals are the parts of motor neurons that connect to and direct signals into muscles. In some cases, the distance from the cell body to the axon terminal can exceed one metre, which on a scale for proteins is an extremely large distance to travel. TDP-43 is a protein that helps carry important RNAs to the axon terminals. If TDP-43 gets stuck in axons or the axon terminal, nerve cells die due to the lack of important molecules making it to where they need to be.

Post-mortem vs pre-mortem

Much of our understanding of ALS comes from post-mortem examination. This is due to the central nervous system being difficult to interrogate in living people and animals. The researchers here asked an important question as to whether they could measure pathological TDP-43 pre-mortem. This is possible due to axon terminals being found in connection with muscles, which are far more amenable to biopsy than the spinal cord.

Findings in this work

Most interestingly, the research team found that they were capable of detecting pathological TDP-43 in axon-muscle biopsies from living people. Some of these patients were not currently diagnosed with ALS via normal criteria. These patients were later diagnosed with ALS, whereas patients that showed no pathological TDP-43 in their axons were not diagnosed with ALS. This makes this method a potentially useful marker for diagnosing and following ALS progression.

Back to the dipeptide repeats and why they are toxic

It has become apparent that not all dipeptide repeats in C9orf72-ALS are equally toxic to cells. Poly-GR and Poly-PR peptides are the only dipeptide repeats that significantly decrease protein synthesis in cells. Researchers, led by Andrei Korostelev at the University of Massachusetts, have shown that poly-GR and poly-PR are capable of getting stuck in ribosomes and stopping them from working properly.

Ribosomes are the site of protein translation

The central dogma of biology is that DNA is transcribed into RNA which is followed by the translation of RNA into proteins. A key component of this in cells is the ribosome. Ribosomes are large structures composed of several different proteins which function to read RNA and facilitate the synthesis of proteins. If ribosomes stop working properly, then cells do not function properly because they can no longer make new proteins.

How do poly-PR and poly-GR affect other proteins

You might ask why only these two dipeptide repeats seem to affect ribosomes. The answer is found in their sequence. The arginine (R) amino acid in poly-PR and poly-GR is the answer. Arginine is a large and positively charged amino acid, making the poly-GR and poly-PR peptides extremely positively charged. This high level of positive charge means they are likely to interact with negatively charged proteins.

Cryo-electron microscopy shows poly-GR poly-PR in ribosomes

The authors of this study used cryo-electron microscopy (a very high-powered form of microscopy) to directly observe that the poly-PR and poly-GR peptides were strongly binding to areas on ribosomes that were negatively charged, thus blocking ribosomes from working properly. More interestingly, the authors found that erythromycin was capable of stopping the poly-PR and poly-GR from binding and restored the ribosomal function.

MND Research Shorts

Chaperone proteins exist to help cells deal with misfolded and aggregated proteins. In most cases, chaperone proteins appear to interact with specific types of misfolded or aggregated proteins. Work by Dr Iris Lindberg from the USA has shown that a chaperone called proSAAS can sequester toxic TDP-43 fragments away from the rest of the cell and is potentially protective in models of TDP-43 aggregation.

Hyperexcitability of motor neurons is one of the key markers of ALS. Hyperexcitability can occur due to influx of positive ions into neurons. Dr Richard Wade-Martins and his team from the UK have recently shown that in very young iPSC (Induced Pluripotent Stem Cells) derived from C9orf72 motor neurons, hyperexcitability is driven by calcium influx. This is important because we may be able to block calcium ion-channels selectively to alleviate disease.

Mutations in the SOD1 protein prevent correct folding of the protein and lead to its accumulation and aggregation in ALS. Dr Kay Double and her team from Australia published a very interesting article that reports misfolded SOD1 in sporadic ALS cases. They suggest that a common biochemical pathway that destabilises SOD1 may be occurring in most ALS cases.

MND patients suffer with breathing as the disease progressively worsens. Detecting problems with patient respiration earlier would lead to better outcomes for non-invasive ventilation. Dr Nathan Staff and his team carried out a test to compare methods to measure respiration to see which test could earliest detect alterations to respiration. They found that measuring overnight oximetry to detect small changes in oxygen levels was the most sensitive manner of determining early respiration issues in ALS patients.

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Betty and John Laidlaw
MND Research Prize 2021-22

Associate Professor Yazi Ke from Macquarie University was the recipient of the prestigious 2021-22 Betty and John Laidlaw MND Research Prize. *Her project is titled Novel therapeutic strategies targeting TDP-43 in Motor Neuron Disease and she has provided us with a summary of her research project below.* It is great to see how the generous support of our donors translates directly into research that aims to find better treatment options for people with MND.

Motor neuron disease, as we know it, is a relentless disease with degeneration of motor neurons being the central feature, leading to progressive muscle weakening, atrophy and ultimately paralysis. To date, there is only one treatment approved for use in Australia for MND; and that has limited efficacy. As such, there is an unmet and desperate need for more treatment avenues. This, however, requires more detailed insights into basic disease mechanisms. Inclusions and deposits of the TAR-DNA-binding protein 43 (TDP-43) are present in over 97% of all MND brains with the protein being mislocalised from the nucleus of cells as a key unifying feature. The underlying mechanism(s) contributing to this shift in localisation of TDP-43 has been subject of intense research over the years. We and others have previously shown that removing abnormal TDP-43, especially after disease onset, allows for the recovery of some deficits in MND animal models. This provides hope that targeted clearance of any unwanted TDP-43 is a viable therapeutic avenue worth exploring in MND.

This project is based on my team's novel identification of another molecule that interacts with TDP-43 and contributes to MND pathology. We aim to characterise this novel interaction and understand the conditions and basis for this interaction, especially in the progression of disease. More importantly, we hope to translate this increased knowledge into therapeutic strategies aimed at targeting pathological TDP-43 in MND. My team has devised two therapeutic avenues using a combination of peptide chemistry and gene therapy, and will explore their preclinical potential in a range of MND animal models as part of this grant.

Being awarded this prestigious Betty and John Laidlaw Research Prize has enabled my team to advance and accelerate this hypothesis that targetingTDP-43 beyond disease initiation can ameliorate cognitive impairment in MND. More importantly, it allows us to retain key expertise and personnel to ensure the continuity and momentum of this project. I am very grateful for this support from MNDRA and look forward to expanding on the outcomes of this work into viable therapeutic options for patients and their families.

Associate Professor Ke in her Macquarie University lab

Supporting emerging MND Researchers

MND Research Australia supports researchers to move into the challenging and rewarding field of MND research through the award of three year PhD top-up grants to promising young Australian researchers. In 2022, four PhD scholarship top-up grants were awarded by MNDRA to researchers at the beginning of their MND research careers. We are delighted to be able to support these researchers and are grateful to the incredible support of our donors, whose generosity has allowed us to provide this early-career support.

Jeryn Chang, University of Queensland

Decoding the loss of appetite and pathophysiology of the brain in motor neuron disease

The loss of appetite is observed in patients with MND. This is clinically important, as energy deficits and weight loss are associated with faster disease progression and earlier death. My studies aim to identify the impact of MND on the hypothalamus, a small area of the brain that regulates appetite, and how this may contribute to functional deficits throughout the brain. Studies aim to provide a biological basis for the loss of appetite in patients with MND, which will enhance understanding of disease, and provide insights to better manage care strategies aimed at improving quality and duration of life.

Sean Keating, University of Queensland

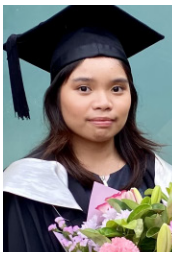
TDP-43 and protein clearance in the pathogenesis and treatment of MND

In MND, toxic clumps of proteins accumulate within the brain and spinal cord, leading to neurodegeneration. Using human MND tissue, neurons grown in a dish, and genetically modified MND mice, I aim to investigate how dysfunctional cellular "waste removal" systems cause protein clumping in neurons. I also aim to discover new ways to effectively stimulate these "waste removal" systems with drugs and gene therapies, and determine whether this can increase the break-down of toxic protein clumps and protect against disease. By stopping protein clumping, we aim to extend neuron survival as a therapeutic strategy to treat people living with MND.

Katherine Lewis, University of Melbourne

Characterising Myelin Changes in Motor Neuron Disease

Despite garnering much deserved attention and funding, the primary causes underlying MND onset and progression remain elusive. This, in part, may be due to most MND research being conducted with a neuroncentric focus. We know that motor neurons are encased in a lipid-rich sheath termed myelin, which is essential for neuronal health and survival. We also know that the cells that produce the myelin have been shown to exhibit MND pathology. However, the exact role of myelin-producing cells in MND remains unclear and it is unknown to what degree their dysfunction contributes to MND onset and progression. Thus, this PhD project aims to comprehensively characterise myelin changes in MND over the course of disease, using clinically relevant mouse models, complemented with sophisticated stem cell derived 'mini brain' model systems. By understanding the role of myelin in MND, we can provide insight into new treatment avenues and therapeutic targets to preserve motor neuron health and function.



Jianina Marallag, University of Queensland

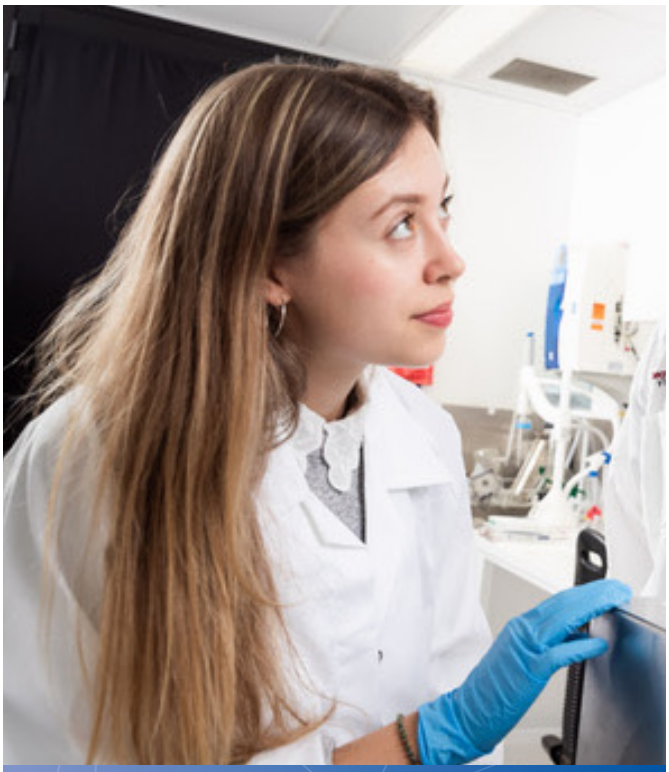
The potential role of CXCR2 activation in motor neuron disease

Excessive activation of the immune system has been found to result in motor neuron death in MND. CXCR2 is a cellular receptor that is gaining interest for its involvement in recruiting immune cells to the site of injury. Inappropriate activation of this receptor may contribute to the progression of MND. This project will utilise a drug that blocks CXCR2 in mouse models of MND and patient samples to investigate if it is able to protect motor neurons by reducing immune system activity. The results will help determine if CXCR2 can be used as a therapeutic target for MND patients.

Biomarkers in MND: What are they and how do they advance understanding and treatment for MND?

By Rebecca Stevenson, University of Western Sydney

This article is an excerpt from an MND Australia blog, which is available in full at www.mndaustralia.org.au/articles/biomarkers



Rebecca Stevenson from the University of Western Sydney in her lab

What is a biomarker?

A biomarker allows scientists and doctors to measure what is going on in a cell or a living organism at a particular point in time. Specifically, a biomarker (short for biological marker) is an objective medical sign used to detect or measure the presence or progress of a disease. This is different to symptoms, which are signs reported by a patient.

Biomarkers include a huge range of measurements from body temperature, to detecting disease associated proteins in the blood or changes on magnetic resonance imaging (MRI) scans. A biomarker is a very useful diagnostic tool that can alert a patient of disease before symptoms set in, and changes in biomarkers can help clinicians track disease progression.

How do we develop biomarkers?

Biomarkers are often developed and refined in clinical trials, before being approved by governing bodies, such as the TGA in Australia. Reliable and effective biomarkers have the potential to be used widely in clinical settings.

A good biomarker must be reproducible between patients, easy, cost-effective and safe to carry out, reliable and responsive to treatment

Many neurodegenerative diseases share similar features (such as inflammation in the brain) and it is therefore important to develop disease-specific biomarkers. A biomarker which can detect disease at different stages may also be useful for clinicians when considering treatment options. For example, a biomarker which can detect a disease in the pre-symptomatic stage may suggest benefit from preventative treatments, as opposed to a biomarker which indicates mid-stage disease.

Several biomarkers exist for neurodegenerative diseases. For example, MRI scans of the brain can be used to track the deterioration of neurons in the brain (neurodegeneration). The MRI will calculate the volume of certain brain areas which, if reduced in volume and grey matter, will indicate the level of neurodegeneration.

Biomarkers go beyond simply providing diagnostic information, they also give patients the opportunity to join clinical trials, playing a crucial role in drug development. Both early and late phase clinical trials are increasingly taking advantage of biomarkers to identify populations, monitor therapeutic response and identify and screen for side-effects of potential new drugs. All these factors can help to make trials more efficient, reducing the time to get drugs to market.

Despite a large amount of MND research, only a handful of potential biomarkers have emerged. At present, there is no single test to diagnose the disease, rather other conditions must be excluded. MND patients normally wait 12 months between the appearance of symptoms and a diagnosis (1). This, combined with the rapid progression of symptoms, means finding new biomarkers for MND is vital.

Presently, the process of MND is tracked using the Revised ALS Functional Rating Scale (ALSFRS-R). As MND symptoms progress due to the degeneration of neurons in the brain, researchers are trying to find a biomarker in the blood, urine or cerebrospinal fluid which will track neurodegeneration more directly than the ALSFRS-R.

Biomarkers under investigation in MND

1. Protein-based biomarkers

- Neurofilament proteins (such as neurofilament light) can be measured in cerebrospinal fluid and blood and their presence indicates that axons (long connecting fibres in the brain) are damaged. As neurons are damaged in the brain and symptoms progress, scientists can detect higher levels of neurofilament in the blood and cerebrospinal fluid. This allows the stage of MND to be estimated (2). However, increases in neurofilament are also present in Alzheimer's and frontotemporal dementia, meaning that neurofilament is not suitable as a standalone biomarker for MND.

- Biomarker research in MND has led to the identification of the protein p75ECD in urine, demonstrating people with MND show significantly higher levels compared to those without MND (3). This biomarker showed promise in the preliminary stages and is currently undergoing further research.

- Signs of inflammation such as the C-reactive protein (CRP) can also be used to identify disease. Studies show people with MND have increased CRP in the blood and the protein is being investigated as a biomarker for inflammation. However, as inflammation is present in many other conditions, CRP may not be a reliable biomarker for MND.

2. Oxidative stress

- Oxidative stress is an imbalance of free radicals and antioxidants in the body, which can lead to cell and tissue damage. High levels of oxidative stress are associated with MND. In fact the drug Edaravone, which was recently approved for use in the USA and Japan, targets oxidative stress in MND. As such, oxidative stress biomarkers are currently being researched in cerebrospinal fluid, urine and blood.

3. Muscle testing

- Measuring changes in the electrical activity of muscles affected in MND can tell us if the nerves controlling the muscles are damaged. This is usually carried out using electromyography (EMG) which involves a small needle being inserted directly into the muscles and the electrical activity is recorded. However, this process can be invasive and painful for patients.

The future of biomarkers in MND

The fundamental goal is to find a biomarker that could detect and track MND with a simple and easy test. As we develop new and more sensitive technology, new biomarkers and patient tests will emerge. Future biomarkers may allow us to develop personalised medicines. For example, genomic biomarkers may help to identify different subtypes of disease which will help clinicians to recommend the best-suited therapy for the individual.

Biomarkers enable us to better understand diseases like MND and may in the future allow us to detect and intervene before symptoms begin. Even though MND currently has no cure, the earlier we catch the disease the better the outcome for those diagnosed . The ultimate goal is to develop a biomarker which will allow clinicians to intervene before irreversible damage is done.

References

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