Real Hope

Having had only two treatments available for many years, in the space of just 6 months we have doubled the potential treatments for MND. As well as Relyvrio that was approved last year, the treatment specifically targeting patients carrying SOD1 mutations, tofersen (now known as Qalsody), was approved by the FDA in April. We hope that Qalsody will just be the first of a number of genetic therapies targeting genes we know to be key in developing MND, with several already being tested.

With so many other trials underway and many positive reports coming out, what does this mean for the Australian MND community? At first glance this suggests we are entering a period of rapid advancement and great hope. And indeed, that is the case, however there are also a few considerations that need to be taken into account.

In this edition of Advance, we cast the spotlight on the journey of a treatment from early research to becoming available to Australian MND patients (see pages 6-7). Unfortunately, the pathway from approval in other countries is not always fast and direct to Australia. A key role that MND Australia can play however, is to engage with the companies producing these new treatments to work with them to come to Australia as soon as possible and see how we can support the application process.

A key aspect of the Qalsody approval was the acceptance of using neurofilament light (NfL) as a biomarker for disease progression. The FDA were happy that decreases in NfL (which measure the death of nerve cells) measured in the spinal fluid of patients was an indication of improvement in disease. This is a first for MND. As we continue to develop promising treatments, the need for better measurement of disease increases in urgency. NfL is one such biomarker but more are needed to measure different aspects of disease. Australia is a powerhouse in developing such disease measurements, with many projects funded by MNDRA. We will keep making sure we support projects that have a real chance of contributing to bringing new treatments to patients.

I have again had the honour and pleasure of attending a number of fundraising events over the last few months. Two events close to my Wagga home were the Shag Gregory Memorial Poker Run in Hay and the Stomp for David Debutante Ball in Young. Both of these fundraisers have been running for a number of years providing fantastic support to MND research and are completely community based. I can very much attest that the communities fully engage in these events and have a great time raising money for this critical cause. You may notice from the photos though, that the dress codes were somewhat different....

The MND Collective

It has been two years since our initial MND Summit and the MND Collective that spun out of that meeting is now well established and starting to strengthen communication and collaboration within the Australian and New Zealand MND community.

It was therefore time to look back and reflect on our progress and to look forward to the future directions of the Collective. In May, we hosted a 2-day workshop which provided the opportunity for the wider MND Collective group to discuss the research landscape, critical gaps and areas of opportunity for collaboration and to identify priorities for the Collective moving forward. We brought together the Discovery Research and Clinical Care Expert Advisory Groups as well as an equal number of people with varied lived experience.

Some of the issues we discussed were:

- What does the MND Collective actually do, and why is this important?
- What problems do we see and experience in MND research?
- What could be the impact of solving these problems, and for who?
- What role is the MND Collective best positioned to play in each solution? How? When? What will you need?

Some of the attendees at the MND Collective workshop, including MND Australia's Dr Gethin Thomas and David Ali.

Professor Samar Aoun receiving her Western Australian of the Year Award

Professor Samar Aoun Named WA Person of the Year

Samar Aoun has been named the 2023 WA Australian of the Year in recognition of her work in research and advocacy for end-of-life care, bereavement and grieving. We are fortunate to have Professor Aoun serving as our current President of the MND Australia Board as well as President of MND WA. Professor Aoun's research focuses on under-served population groups, such as people with MND, and she strongly advocates for person-centred health and social care. Her work on supporting family caregivers at end-of-life has informed policy and practice at the national and international levels. It is fantastic for an MND researcher to be recognised at such a high level.

As always, we are very grateful for the support of our donors which allows us to continue to fund vital research into MND in Australia.

Dr Gethin Thomas
Executive Director, Research

PhD Scholarship Top-Up Grants

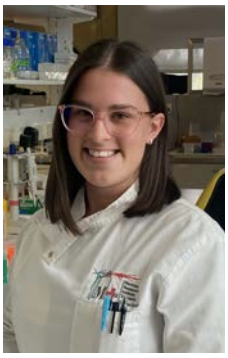
Each year, MND Research Australia awards PhD scholarship top-up grants to promising early career researchers in the field of motor neurone disease. These grants help to encourage early researchers to focus their talents on developing cures, treatments and better models of care for people living with MND.

Commencing in early 2023, MND Research Australia is delighted to support the work of three PhD scholarship top-up recipients. These grants would not be possible without the committed support of our donors.

Elise Kellett, Queensland Brain Institute, University of Queensland

The role of post-translational modification of TDP-43 in disease pathology

MND is characterised by the aggregation of proteins in upper and lower motor neurons. The main aggregating protein, TDP43, is changed chemically in several ways in disease. While initially believed to drive disease progression, recent findings question whether these changes may instead be protective. My research investigates the role of chemical alterations of this protein in disease pathology by identifying upstream proteins that regulate the alterations and exploring downstream consequences. My aim is to improve our understanding of MND pathology and identify new processes for therapeutic targeting to help people living with MND.



Kathryn Maskell, University of Tasmania

Do upper and lower motor neurons need different treatments to effectively stop neurodegeneration in ALS?

ALS involves degeneration of both the upper motor neurons in the brain and lower motor neurons in the spinal cord, but we still don't understand how degeneration starts and spreads between them. Upper and lower motor neurons have different characteristics and reside in different local environments. New evidence suggests that they are differentially vulnerable to disease mechanisms in ALS. Importantly, the two populations may need different therapeutic support to prevent disease progression. This research aims to investigate the vulnerabilities of upper and lower motor neurons to disease mechanisms of ALS and will inform our approach to treating patients suffering from ALS.

Aida Viden, University of Melbourne

Investigating the anatomical origins of MND

MND is caused by the death of both brain and connecting spinal motor neurons (MNs). Importantly, transmission of disease amongst MNs occurs in a cascade. Our current understanding of the mechanism and direction of pathological spread between brain and spinal MNs is limited. This PhD project aims to determine the primary site of disease initiation in MND with the use of a gene-editing approach targeting brain and spinal MNs individually in a clinically relevant MND mouse model. By understanding which MNs transmit disease and how, we can inform new therapeutic interventions targeting brain and/or spinal MNs to prevent further spread.

State of Play in 2023

STATE OF PLAY 2023

MNDRA is continuing to run monthly 'State of Play' webinars to showcase the wonderful work being undertaken by our funded researchers around Australia. Topics covered so far in 2023 include 'New and Old Treatments in MND', 'Can we target the muscle to develop treatments for MND?' and 'Identifying and targeting disrupted systems in MND'.

The State of Play webinar series is interactive with time allocated for questions at the end. This presents a unique opportunity for our audience to hear from and ask questions of experts in the MND research community. All of our webinars are recorded and you can view previous episodes at: www.mndaustralia.org.au/stateofplay Registration for upcoming webinars is also available via this link.

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.

Overview of TDP43 in MND

By Dr Fiona Bright, MNDRA Bill Gole Postdoctoral Research Fellow

Dementia Research Centre, Macquarie Medical School, Macquarie University

In humans, our genes influence everything from our eye and hair colour to our temperament and the likelihood of us developing disease. Our genes are made from our DNA which instructs our billions of cells to create proteins that are the building blocks of all life and our bodily functions. In disease, either caused by genetic mutations or unknown environmental factors, our proteins can become abnormally aggregated within cells and tissues, disrupting the function of the proteins and affecting the balance of the body's systems. A particular protein implicated in Motor Neuron Disease (MND) is called TDP43 (scientifically; TAR DNA binding protein 43). A gene called TARDBP is responsible for providing instructions for making this protein. Within the TDP43 protein, there are several parts (regions) that perform different roles contributing to the function of the protein. TDP43 has an N terminal, two RNA/DNA binding domains (RRM1, RRM2), a nuclear localisation signal (NLS) and a C-terminal (Figure 1).

What is the function of TDP43 within the brain and spinal cord?

The TDP43 protein is expressed throughout the human body, however in the context of MND, we focus on its expression within the brain and spinal cord (regions predominantly affected by MND). The complete function of TDP43 is yet to be fully determined, however, to date, it has been identified to have important roles in the processing and maintenance of RNA (scientifically, ribonucleic acid). RNA is crucial for the transfer of genetic information from our DNA to proteins. In addition, TDP43 is involved in many important steps of protein production and is therefore able to influence various functions of a cell. The presence of TDP43 within our cells is therefore very important for normal functioning.

Within the brain and spinal cord, the TDP43 protein is predominantly located within the centre of cells (scientifically termed the 'nucleus'). Structurally, TDP43 has a region called the NLS (nuclear localisation signal) that allows TDP43 to shuttle in and out of the nucleus to the outside of cells (scientifically termed the 'cytoplasm'), conducting its important cellular functions. Another important aspect of the TDP43 protein is that it self-regulates its own production. It is important that future research uncovers more about the complex functions of the TDP43 protein and its interactions within the brain and spinal cord.

Better understanding of TDP43's 'normal' function in healthy cells will assist researchers in understanding why things go wrong with the TDP43 protein in diseases such as MND and how best to overcome, prevent and treat these abnormalities.

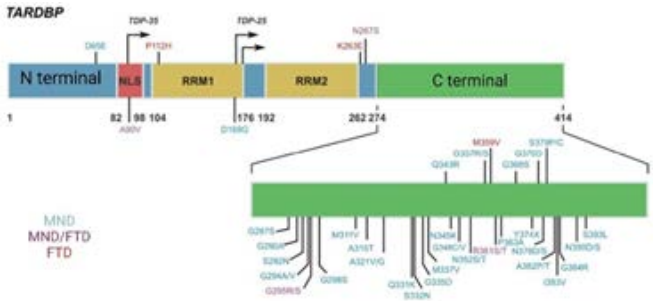


Figure 1. Adapted from Bright et al 2021, The structure of TDP43 protein: TDP43 is encoded by the TARDBP gene. Structurally TDP43 contains an N terminal (blue), two RNA/DNA binding domains (yellow-RRM1/2), a nuclear localisation signal (red-NLS) and C terminal (green). Small, coloured text refers to the location of various genetic mutations identified in the TARDBP gene linked to MND and FTD.

What goes wrong with TDP43 in the Central Nervous System (CNS) in MND?

In the early 2000s, researchers discovered that abnormal misfolding and aggregation of TDP43 proteins were present in the cytoplasm of motor neurons within the brain and spinal cord in MND patients. These abnormal aggregations of TDP43 were identified to have significant alterations in their structure and function (scientifically, the abnormal TDP43 proteins were hyperphosphorylated, ubiquitinated and cleaved into fragments). Essentially, in MND, TDP43 loses its structure and function and is abnormally redistributed from the nucleus to the cytoplasm of cells (Figure 2), where it abnormally accumulates and causes the cell to die. Pathological studies of brain and spinal cord tissue from MND patients have enabled researchers to determine that abnormal TDP43 is present within the brain and spinal cord of 95% of MND patients. Further studies by researchers have also determined that abnormal TDP43 in MND can, in some cases, be caused by known genetic mutations in certain genes linked to MND (e.g. TARDBP, C9orf72). Within the 'C terminal' of the TDP43 protein a number of genetic mutations have been identified to date, many of which are linked to MND (Figure 1).

The main genetic cause of TDP43 pathology has been identified to be mutations in a gene called C9orf72 (scientifically chromosome 9 open reading frame 72). While these known genetic mutations causing TDP43 pathology have enabled more research into the genetic causes of MND, unfortunately these known genetic mutations account for only a small percentage of MND patients. Therefore, the majority of MND patients who do not have a known genetic mutation causing TDP43 pathology have what is termed 'sporadic' TDP43 pathology. This means that there is no known cause and the TDP43 pathology could be linked to undetermined environmental factors.

The precise mechanisms that underlie the abnormal changes to the TDP43 protein within the CNS in MND remain unknown. Research that aims to understand this is critical for the development of better tools to diagnose disease, measure progression and responses to treatments, and ultimately for finding treatments and a cure for MND. To begin addressing these unknowns, research must focus on answering the following:

- **How abnormal aggregates of TDP43 can be cleared from affected cells within the brain and spinal cord while maintaining unaffected cells**
- **How to prevent or reverse the misfolding and abnormal aggregation of TDP43 within cells in the brain and spinal cord**
- **How to interfere with TDP43's self-regulation to disrupt the imbalance of the protein's steady-state within the brain and spinal cord, in order to understand how and why the transport of TDP43 between the nucleus and cytoplasm is disrupted in MND**

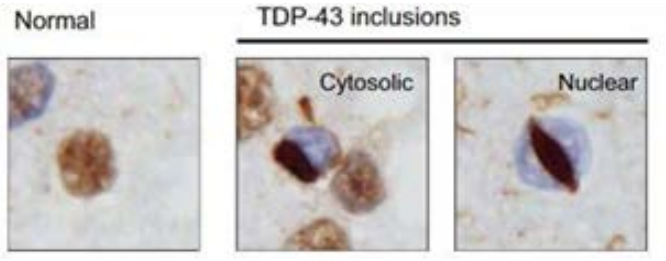


Figure 2. Adapted from Ederle & Dormann 2017 FEBS, The abnormal mislocalization of TDP43 in MND pathology. Within the brain and spinal cord. Normally TDP43 is localised to the nucleus and is able to shuttle in and out of the cell to perform its functions in processing and maintaining RNA. However in MND, TDP43 becomes lost to the cytoplasm where it abnormally aggregates. This abnormal aggregation can also be seen in the nucleus.

How my research is tackling the 'unknowns' about TDP43 pathology in MND

Supported by the MND Research Australia Bill Gole MND Postdoctoral Fellowship, my research aims to investigate a specific region of the TDP43 protein that is yet to have been fully investigated. As mentioned previously, the focus of research into the TDP43 protein has been on the 'C terminal' which is where the majority of genetic mutations have been identified. However, the 'N terminal' of the protein contains some important structures (NLS, RRM1/2) (Figure 3) that are critical for TDP43's transport between the nucleus and cytoplasm of cells.

Unfortunately, there is very little research to date that focuses on the N terminal of TDP43 and there is significantly more to be learned about the movement of TDP43 between the nucleus and cytoplasm in both healthy and diseased states. It is likely that there are regulators of TDP43 transport that involve interaction with the N-terminus specifically that are yet to be discovered. Therefore, the overall objective of my research is to address the significant gap in our knowledge regarding the understudied N terminal of TDP43 and to discover novel regions and molecular pathways of this region of TDP43. I aim to determine the precise mechanisms underlying TDP43's movement between the nucleus and cytoplasm and how this becomes disrupted in MND.

We believe this research holds the key to understanding what goes wrong during MND pathogenesis and the 'how and why' of TDP43 mislocalisation and aggregation in cells within the brain and spinal cord. Ultimately, if we can define and uncover unexplored regions, molecular pathways and novel regulators of the TDP43 protein, we are in a prime position to utilise this information to determine the mechanisms underlying the cause of TDP43 pathology in MND. This will enable us to pave the way for future research towards manipulation of these mechanisms in order to sooner and better diagnose MND, develop targeted treatments for TDP43 pathology specifically and ultimately find a cure for MND.

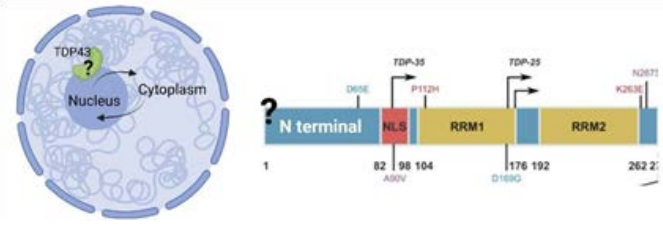


Figure 3. Schematic drawing of the N terminal region of TDP43 that has had limited research to date. It is likely there are unknown regions located in the N terminal or interactions partners with this region of the TDP43 protein that could play critical roles in the regulation of TDP43's transport in and out of cells and its disrupted transport in MND.

How research and the medical system develop medicines for Motor Neurone Disease (MND) in Australia – and what can help

By MND Australia's Ben O'Mara, Information Resources Development Manager, and Dr Gethin Thomas, Executive Officer Research

According to research, the medicine Riluzole can prolong life with Motor Neurone Disease (MND). Riluzole is the only medicine for treatment of the disease available in Australia.

By contrast, people living with MND in the United States of America (USA) can access three medicines: Riluzole, Edaravone and Relyvrio and just this month, Qalsody (previous Tofersen) which can all slow the progress of MND. But currently Australians cannot access Qalsody, Edaravone and Relyvrio through our medical system.

Why don't people living with MND in Australia have access to medicines like Edaravone? And how can scientists develop medicines sooner?

We looked at what helps a medicine progress from scientific experiments to doctors being able to prescribe it for MND in Australia. With better access to medicines, more people with MND can have greater choice over living with such a terrible disease.

How do we find a new medicine?

Research is fundamental for developing new medicines and treatments for MND or any other disease or condition. Research is where a medicine for MND begins.

Scientists must rigorously test any potential treatment before its use by patients. First steps in testing often involve seeing if the new treatment works in "pre-clinical models". Models include lab grown neurons from patients, and animal models of MND. If everything looks good after these early steps (also known as pre-clinical testing) the organisation developing the treatment may consider it for clinical trial.

Clinical trials are major research projects. Therefore, starting a clinical trial for a potential treatment requires approval. The organisation developing a treatment (usually a pharmaceutical or biotechnology company) is termed the "sponsor" and decides if they think the potential treatment is promising enough to take to trial. They then apply for approval to the regulatory authorities in the country or countries where they want to run the trial. In Australia, for example, it is the Therapeutic Goods Administration (TGA). In the US it is the Federal Drug Agency (FDA).

Clinical trials consist of phases. Usually, in Phase 1 or Phase 1/2 of a trial, testing determines treatment safety and that it won't cause harm. Scientists may also study what medicine dose might be best (the exact amount taken at one time) as part of the trial.

Phase 1 of a trial is usually very small. The trial will not involve sufficiently higher numbers of participants to provide information on the effectiveness of a treatment. In fact, scientists often run Phase 1 trials on healthy volunteers rather than actual patients. A Phase 2 trial begins after Phase 1 research shows a medicine is safe.

Phase 2 trials mainly aim to finalise the best plan for medicine doses. Trials can also provide some provisional information on the potential effectiveness of a treatment. Scientists often design Phase 2/3 trials to help start understanding treatment effectiveness. Phase 2 trials are larger than Phase 1, especially if they are Phase 2/3, as they gather more data.

It is worth noting: it is not just the decision of the sponsor determining if a treatment progresses to a clinical trial and through all its stages. At each stage data must be presented to the local regulatory authority to show whether the treatment merits progression through the clinical trial pathway.

Phase 3 trials are the final phase of the clinical trial pathway. The trial is the last stage before a sponsor seeks approval to make the treatment available to the public. Scientists specifically design Phase 3 trials to show whether a drug works. The trials need to be much larger than Phase 1 or 2 trials. The reason for the larger size is to establish statistical certainty for definitively saying whether a medicine works or not.

Phase 3 of trials are very expensive (often in the 100s of millions of dollars). In addition to the cost, the trials can take well over 12 months. Trials must be set-up, participants recruited for treatment and analyses conducted. The time and cost are necessary to try and make sure medicines actually work and are safe to use.

From research to pharmacy shelves: making a new treatment available to patients

Once a treatment has been through the clinical trial pipeline and found to be safe and effective, what happens next? How do patients access medicines?

Unfortunately, it is not an automatic progression from trial success to availability to patients. Often, at first glance, the outcomes of clinical trials may appear to be positive. But on closer analysis trial results may indicate that the benefits were not as great as first thought. Conversely, there may have been confounding reasons that resulted in a trial outcome appearing worse than it really was.

To best determine the quality of trial outcomes a local regulatory authority requires the trial sponsor to submit an application for medicine approval. The application allows the authority to objectively and independently review the data. The authority makes their own decision on the benefit of a particular treatment. Such assessment will involve a number of experts in clinical trials, statistics and the disease area in question. Assessments are very involved considerations and can often take 6 months or more. As well as considering the effectiveness and safety profile of the treatment, the process considers how medicines are scheduled for prescribing by doctors and whether they are listed on the Pharmaceutical Benefits Scheme (PBS), which helps make medicines available at a lower cost.

Currently, the TGA grants initial approval based purely on whether the evidence shows a treatment is safe and effective. The TGA offers very limited opportunity for input into their approval decisions by advocacy organisations such as MND Australia. The organisation sponsoring development of the medicine completes the application. Some organisations keep applications confidential, making it hard to even know an application is underway. However, in the MND community, which tends to work collaboratively whenever possible, it would be unlikely for an application to proceed without the MND community knowing.

What can help make more medicines available for MND

Clinical trials and regulatory authority approval can take quite a long time. But there are ways to make more MND medicines available sooner.

Ongoing investment in the work of MND scientists in Australia and across the world is critical. Research is best for finding safe and effective medicines that benefit people with MND. Donations, fundraising campaigns and other opportunities to support MND research remain vital for research into medicines.

Beyond research, working with organisations sponsoring medicines can influence the process of TGA approval in Australia. MND Australia and others can and do work with sponsors when they are preparing their submissions.

MND Australia provides data and brings the experiences of those with lived experience to the table. Sharing data and experience helps to increase the likelihood of approval for a submission.

Working to persuade sponsors to come to Australia, help them understand our system and offer support helps too. Some companies developing new treatments do not have deep resources making targeting multiple countries simultaneously for approval is difficult. This is the case for Amylyx, the company who developed Relyvrio, which was recently approved for MND treatment in Canada and USA. They need to build up their manufacturing capacity to service the USA and Canada which will establish a steady income stream so they can then look to expand their reach. MND Australia is already scoping how we can best support companies considering applying for medicine approval with the TGA.

In addition to medicine approval, MND Australia and other organisations can help with making medicines more affordable. The application process for subsidised treatment through the PBS does provide an opportunity for organisations to lobby for change. Lobbying normally takes the form of an organisation completing a written submission about the need for a treatment and its benefits.

Organisations submit applications to the TGA review committee. The testimonials of people with or affected by MND can support submissions because they help to share the experiences of daily life from living a terrible disease like MND and why an affordable medicine is so important.

MND Australia are also lobbying for greater involvement of people with MND in TGA decision making more broadly. MND Australia is participating in the review of Australia's Health Technology Assessment. The review seeks to help reduce the wait times for patients wanting to access new and innovative medicines.

Stay informed

Creating a world without MND, through the search for better medicines, and a cure, is a complicated and difficult challenge. Work is underway though and there are many opportunities to improve access to medicines and life with MND. It can help to stay informed about what the TGA is considering for MND medicines. Being aware of medicines already available, including Riluzole and medicines for pain relief is important.

- MND Australia website and social media (mndaustralia.org.au or @MND_RIA or @mndaustralia)
- Prescription medicines: applications under evaluation (TGA) (https://www.tga.gov.au/prescription-medicines-applications-under-evaluation)
- MND Info Line (1800 777 175)
- Riluzole, Breathing and MND and Pain Management and MND fact sheets: https://www.mndaustralia.org.au/mnd-connect/information-resources
- Pain management with MND.

Doctors, neurologists and other members of the healthcare team for a person living with MND can advise on how to access and use Riluzole and other medicines.

To see references for this article please see the online version: www.mndaustralia.org.au/medicineblog

MND Research Australia relies on the generous support of donors to maintain its important MND research grants program. Please fill in the form below or visit **www.mndaustralia.org.au/donatetoresearch**

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Have you seen our new monthly research update?

Research Directions is a new monthly series, written by MND Australia's Executive Research Director, Dr Gethin Thomas. Each month Gethin will explore a selection of the latest MND research, both in Australia and internationally. This publication will be available monthly on the MND Australia news section (go to our homepage at www.mndaustralia.org.au) and will also be shared on the MND Australia Facebook page (https://www.facebook.com/mndaustralia).

Bequests

Your will can provide an important way of making a gift that can have lasting influence on MND research and give hope for the future. If you would like to consider MND Research Australia in your will by providing a bequest from your Estate, please contact your solicitor or get in touch at research@mndaustralia.org.au or 02 8287 4989 for more information.

Save the date!

The 2nd Australian and New Zealand MND Research Symposium will be taking place in Wollongong on Friday 17th and Saturday the 18th of November. The two day symposium provides a unique opportunity for MND researchers and those with a lived experience of MND to collaborate and share knowledge. More details will be available on the MND Australia website and social media over the next few months.

We wish to thank Snap Printing, North Ryde, NSW, for their generous support in printing this newsletter.