mnd Research Australia

Advance

June 2024

MND Research Report

Firstly, I would like to welcome our new CEO, Clare Sullivan, who commenced earlier this year. Clare has considerable experience in advocacy, leadership and organisational transformation across the not-for-profit, government and private sectors.

As often happens in the MND world, the last few months have seen a mixed bag of outcomes.

Radicava (Edaravone), which was approved by the Therapeutics Goods Administration earlier this year, has now been recommended by the Pharmaceutical Benefits Advisory Committee for inclusion on the Pharmaceutical Benefits Scheme (PBS). Although not a game-changer, Radicava provides another treatment option for MND patients and benefit for some individuals. Inclusion on the PBS provides a cheaper option for those currently accessing it privately.

Relyvrio unfortunately failed its pivotal Phase 3 trial and the drug has been withdrawn from the US and Canadian markets where it had been approved on the basis of Phase 2 data. There was much hope around this therapeutic but also reservations around the reliability of the Phase 2 data. Going forward we must recognise that true hope comes from strong data and well-designed studies.

A great outcome has been achieved for Qalsody, a gene therapy produced by Biogen specifically targeting mutations in the SOD1 gene. Previously known as Tofersen, this drug has now been approved in the US, Canada and Europe and we understand Biogen will soon be applying for approval in Australia. In the meantime, it is available through their compassionate access program. Qalsody is a great outcome from a well-designed phase 3 trial.

We are rapidly approaching the 10-year anniversary of the Ice Bucket Challenge. This viral internet event raised the profile of MND and brought in millions of dollars for research and care around the world. Many trials underway today stem from ice-bucket funding as do many of the large-scale data collection initiatives, including the Australia genomics database, SALSA. Keep your eye out for events celebrating this incredible phenomenon.

Congratulations to Julian Gold for his award as a Member (AM) in the general Division in the 2024 Australia Day Honours. Julian has been the driving force behind testing a combination anti-retroviral therapy (Triumeq) in patients with MND – known as the Lighthouse Trials.

I have had the privilege of attending some great fundraising events. The Shag Gregory Memorial Poker Run was run for the 25th time which I think makes it the longest running MND research fundraising event in Australia. It was a fantastic day out with well over 100 very large and loud motorbikes touring around the Hay countryside. My thanks to Tracey and her family and the town of Hay for continuing to run this iconic event.

It seems the awareness and profile of MND continues to rise and this is reflected in the ongoing success of these long-running events and the fantastic fundraising outcomes they achieve. Even in tough economic times, the impact of MND strikes through to reveal the generosity of spirit in our MND community, which I feel honoured to be a part of.

Dr Gethin Thomas
Executive Director Research

For an extended version of this report go to mndaustralia.org.au/researchnews

What causes MND?

By Dr Gethin Thomas and Melissa Fagan

The question invokes the concept of "known knowns, known unknowns, and unknown unknowns". Though often associated with the former United States Secretary of Defence Donald Rumsfeld, the idea has been around a lot longer. In terms of MND, and what causes it, the concept highlights the critical role scientific research plays.

Known knowns

With MND there are very few "known knowns" when we look at the causes. The only confirmed causes for MND are mutations in the genes that have been identified, SOD1, c9ORF72 and FUS. And we have seen recently that gene therapies that target SOD1 and FUS have shown efficacy in slowing or even stopping disease progression.

Known unknowns

The list of "known unknowns" is much longer. These "known unknowns" are the possible causes of MND that are not yet established. The list includes head trauma, vigorous physical activity, exposure to toxic chemicals, smoking and blue-green algae. The hard evidence supporting any of these potential causes is limited. However, there is a large amount of information, particularly online, that claims to provide solid evidence to demonstrate their causative roles in MND.

What do we know?

A mathematical analysis by Ammar Al-Chalabi's group in London has shown six steps are required to develop MND. Up to four of these steps can be contributed by genetic mutations, but 80-90% patients (those with 'sporadic' MND) don't have those mutations. This tells us there is no single cause and multiple "hits" are needed. How do we find out what these are?

Blue-green algae – a case study

Many possible causes of MND have been suggested. An example is the theory that exposure to blue-green[1] algae causes MND. This theory came about due to a high incidence of an MND-like disease in Guam's Indigenous population, the Chamorros, whose diet includes cycad seeds and fruit bats. These contain high levels of the BMAA toxin.

Higher incidences of MND have been reported in areas with elevated levels of blue-green algae. Like cycad seeds and fruit bats, blue-green algae has high levels of BMAA. Hence the hypothesis that blue-green algae causes MND. However, areas with high levels of blue-green algae are often areas with intense agricultural activity and other factors may come into play, such as manual labour and exposure to fertiliser and pesticides. Proving BMAA is the causative factor means other factors must be ruled out.

Correlation is not causation: the role of evidence

You need more than a clever idea and a few (possibly coincidental) correlating circumstances to demonstrate a causative effect. Robust statistical evidence is needed to prove the role of a causative factor. Unfortunately, sensationalist reporting and misinterpretation of available data can lead to misinformation[2].

Well-designed research studies are the only way to accumulate sufficient data to provide true insights into the causes of MND. These studies need to have clearly defined objectives with specific variables being tested. Studies must also be large enough to demonstrate definitive outcomes.

Data, data, data

Two key pillars are critical to understanding what causes MND: biological research and data. We need researchers to be able to test at the biological level how factors identified from data drive disease. In Australia we are extremely well set up for the lab-based studies with our world-class researchers.

Underpinning this research is population level data. The enables researchers to see where MND is occurring and to identify the characteristics of those developing the disease.

To collect the data, we have established a strong framework with the MiNDAUS Registry and SALSA database collecting clinical and genetic data on MND patients in Australia. However not every patient is currently captured and longer-term financial support for these initiatives needs to be established. MND Australia is currently working with other partners in the MND community to ensure we have a comprehensive and sustainable data collection framework in place that captures every MND patient in Australia.

References:
1. www.ncbi.nlm.nih.gov/pmc/articles/PMC3194113/?tool=pmcentrez&rendertype=abstract
2. www.mndaustralia.org.au/articles/what-does-buying-a-new-car-have-to-do-with-mnd

Leaving no stone unturned – applying new methods and technologies in sporadic MND

By Dr Fleur Garton, recipient of the 2022 Scott Sullivan MND Research Fellowship, funded by MND&Me, in partnership with MNDRA

Just like most human traits or disease, MND has both a genetic and environmental contribution. For individuals without a family history, the genetic component is typically a combination of small effects, which can be studied by examining DNA. DNA, the set of instructions contained in nearly every cell in our body, plays a pivotal role in shaping who we are. Looking at the letters, but also the way it is folded and marked, we gain valuable insights into disease mechanisms.

The Scott Sullivan fellowship has provided me with a remarkable opportunity to develop a translational research program specifically dedicated to understanding the molecular aspects of Motor Neuron Disease (MND). By analysing human blood samples and existing human data, it is helping us better understand what causes/contributes to MND and how we can sensitively track these processes. Collaborating with the Sporadic ALS Australia - Systems Genomics Consortium (SALSA-SGC) - we have accessed an incredible national resource allowing us to overlay clinical, biological and lifestyle data to carry out our studies effectively in the necessary large sample sizes required.

Our research has unveiled intriguing findings regarding cell-free DNA fragments in the blood, which we found are elevated in individuals with MND. Cell-free DNA is released when cells die. Fragments from individuals with MND carry distinctive marks suggesting a common cellular origin. This discovery holds promise for developing a simple blood test to aid in diagnosis and monitoring of MND, supported by a new grant from the US Department of Defence. The technology is already used widely in prenatal testing - and together with our co-investigators at the University of California - we are excited to see where this can go.

We would like to extend our gratitude to all those who have so generously contributed to MND research – individuals with MND, their families, and all those involved in making SALSA-SGC possible. The information it has generated is critical and provides significant information to support many researchers and research questions. Thank you to MND and Me and MNDRA for creating and supporting the Scott Sullivan fellowship and MNDRA, MND and Me, FightMND for the on-going project support.

To read an expanded version of this story, and to find out how to get involved with SALSA-SGC visit mndaustralia.org.au/researchnews

Let's Talk MND

Jane Simpson, Chair of the MND Collective Lived Experience Expert Driving Team, has created a podcast, "Let's Talk MND", to share some of the many stories of people touched by MND. Jane has interviewed people with lived experience of MND, researchers, neurologists and allied health professionals. This podcast is honest, inspiring, funny and sad all at once, and Jane does an incredible job of sharing the stories of those in the MND world. It can be accessed via lots of podcast services including Spotify, Apple and Audible.

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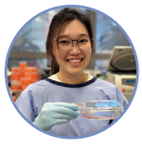
2024 PhD Scholarship Top-Up Grants

For over ten years, MND Australia has awarded PhD top-up grants to promising early career researchers in the field of motor neurone disease. These grants are a fantastic way to encourage these up-and-coming researchers to focus their talents on developing cures, treatments and better models of care for people living with motor neurone disease.

We are delighted to support the three researchers listed below and wish them well throughout their PhD programs. These PhD grants would not be possible without the support of our donors – thank you for allowing us to continue to support these talented individuals as they commence their MND research careers.

Andrew Quattrocchi, The University of Melbourne
Understanding and modelling the neurovascular niche in health and Motor Neurone Disease

Stephanie Howe, University of Queensland
Characterising the spatio-temporal landscape of neuroinflammation and metabolism in ALS



Flora Cheng, Macquarie University
Identification and characterisation of RNA-protein interaction in pathological aggregates of TDP-43 in MND

To read more about these projects, and all of the research that MNDRA funds, visit mndaustralia.org.au/currentresearch

Lived experience project by Julie Labra

MND Australia is currently running a project funded by FightMND that will develop and implement a national lived experience framework for people living with MND in Australia. In mid-2024, we will launch the new "NATIONAL MND LIVED EXPERIENCE NETWORK". This will provide a new way to connect network members who have lived experience of MND, with professional groups who are requesting lived experience input, Australia-wide. We will also be appointing 'MND Australia Ambassadors' who will work together with us to increase awareness of this challenging disease, influence systemic change, and support research. We would like to thank the people with lived experience who have worked closely with our staff on this project over the past 6 months, including: Phil Camden, Peter Chambers, Julie Colebrook, Jenne Hartmann, Keith Malpress, Peter Russo, Jane Simpson and Leanne Sklavenitis. Please keep an eye out for upcoming advertisements.

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 mndaustralia.org.au/donatetoresearch

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