

Feeding the MND treatment pipeline

The Motor Neurone Disease Research Institute of Australia (MNDRIA) is the research arm of MND Australia. MNDRIA was established in 1984 as a national organisation to promote and fund medical and scientific research into MND.

MNDRIA funds research in four key areas:

1. To better understand the cause and underlying biology contributing to MND
2. How to better measure disease progression and responses to treatment
3. Developing and testing potential new treatments
4. Improving current care models through evaluation and innovation.

In this Advance, we highlight how your donations have helped take two experimental new treatments through to clinical trials;

CuATSM:

Associate Professor Peter Crouch at the University of Melbourne has received a number of grants from MNDRIA since 2007 to develop CuATSM as a potential treatment. These initial studies, alongside further funding from government and other sources, enabled A/Prof Crouch to develop a safe and effective formulation of CuATSM that could be used for clinical trials. Following a successful Phase I clinical trial, CuATSM is now entering a Phase II/III trial which will give a clear indication of its potential to affect MND.

For the CuATSM clinical trials, funding has come from Collaborative Medicinal Development, LLC (CMD), a privately-held US/Australian based “early-stage” pharmaceutical group, in collaboration with other funding bodies. This is a great example of how MNDRIA’s early investment has been leveraged to bring in significant industry funding which is vital to take new drugs through the very expensive clinical trial process.

Triumeq:

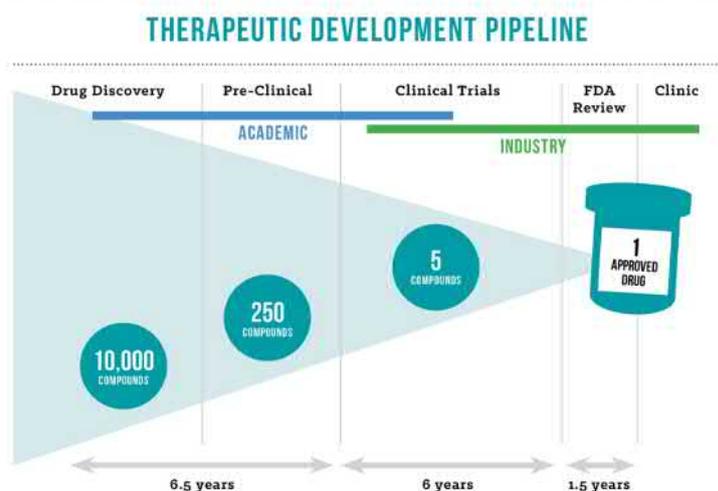
Another study where MNDRIA has played a significant role in bringing a potential new treatment closer to the clinic is in repurposing the anti-retroviral drug Triumeq. Triumeq is used in HIV patients to suppress the virus and has already been approved for use in humans. It has been shown that MND patients have high levels of retrovirus DNA suggesting retroviruses may be contributing to disease development. The “Lighthouse” Phase II trial, led by Professor Julian Gold and partly funded by MNDRIA, showed promising results. These results have led to a Phase III trial due to commence soon and which will again attract funding and support from a wide range of organisations and pharmaceutical companies.

Although results from these early studies are encouraging, a continuing pipeline of potential new treatments is still very much required. Many drugs fail to progress through the clinical trial pipeline (see figure) and MND to date has been particularly intractable to many previous new approaches. Although we are fortunate to be in a time of great hope with many potential treatments currently being tested, it is likely a range of treatments will be required to target the heterogeneous nature of MND.

By continuing to support a diverse pipeline of new approaches we will ensure we have the best opportunity to bring a full battery of treatments to the clinic to maximise our chances of improving the lives of people living with MND.

In the recently announced round of funding for 2020 MNDRIA is continuing to feed this pipeline with a number of projects targeting development of new treatments.

Additionally, we are also supporting studies looking at ways to better target drugs to the brain and the development of a platform that will specifically screen for new drugs that target microglia, important immune cells in the brain that are intimately involved in MND pathology. Our other objectives of supporting understanding of the causes of MND, better measurement of disease progression and transformative care models will also be boosted in 2020 with a number of projects. Full details of all projects funded for 2020 are available later in this edition of Advance.



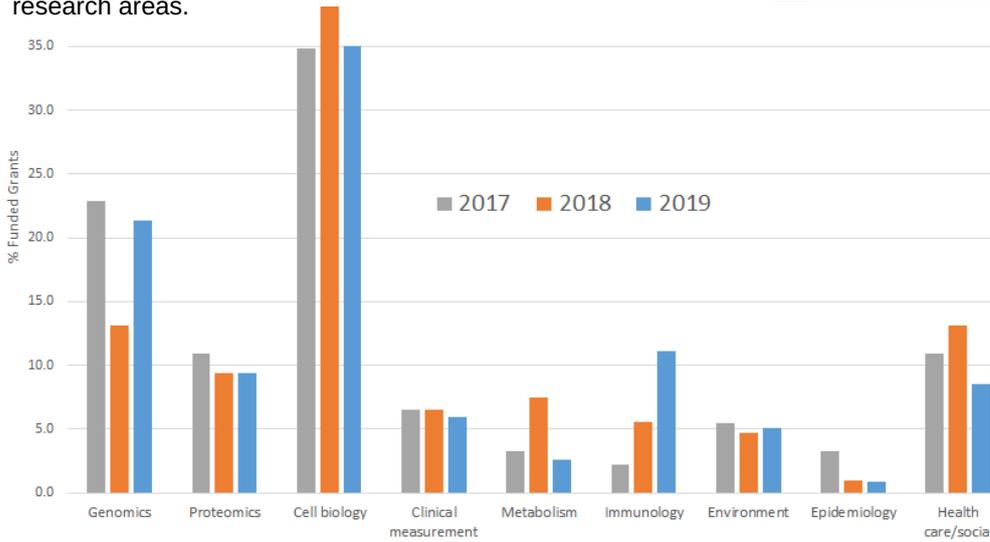
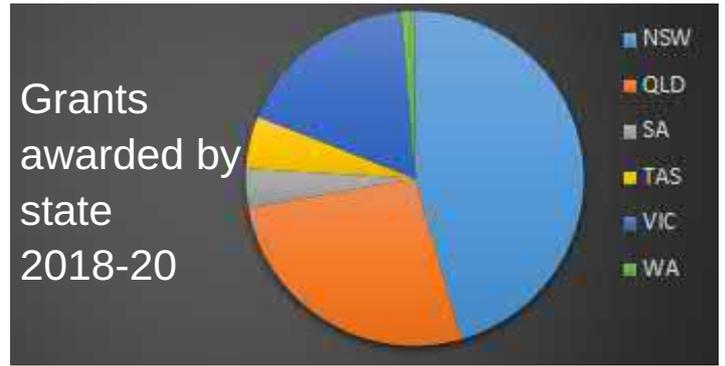
An infographic demonstrating the number of initial drug discoveries that progress to pre-clinical and clinical trials, and subsequent approval and use in patients, highlighting the need for a continuous flow of potential MND therapeutics.

Source: Nationwide Children’s Hospital

MNDRIA grants in 2020

MNDRIA has continued to build Australian MND research capacity with the 2020 grant funding round bringing MNDRIA's contribution to close to \$32M since the first grant was awarded in 1987, 32 years ago.

For 2020, MNDRIA allocated almost \$3M across 23 projects, made up of the Betty Laidlaw Prize, two postdoctoral fellowships and 20 Innovator Grants. We have recently taken a look at what we have been funding over the last three years and where that funding has gone. Over the three years we received 256 applications and funded 79 grants. As might be expected with two large MND research groups at Macquarie University and the University of Sydney Brain and Mind Centre, NSW received the largest share. As you can see from the bar graph, we fund projects across a broad spectrum of MND research areas.



Much of our funding supports the cell biology area which looks at the underlying biology of MND. We also fund a number of studies looking at the genetic causes of MND. Interestingly, over the last three years, only one area, Immunology, has seen a consistent change in support. We have seen a marked year-on-year increase in funded research in this area. This very much reflects the rapidly burgeoning interest in the role of the immune system in neuroinflammation and mediating neuronal cell death, and the growing number of immune-targeted therapies currently being tested.

Betty Laidlaw MND Research Prize

Dr Shyuan Ngo, University of Queensland



For the first time this \$250,000 prize will be awarded over 2 years. Dr Ngo's project is titled "From the nucleus to the powerhouse: investigating how TDP-43-mitochondrial interactions wreak havoc in MND" and will investigate how mitochondria (the powerhouse of the cell) might be affected by the TDP-43 protein clumps that are a common pathological feature of MND. If mitochondria function is disrupted this might be a key factor in motor neurone death.

Dr Ngo receiving her BLP medal with former Executive Director Research, Janet Nash.

Charcot Grant

A/Prof Brad Turner, Florey Institute of Neuroscience and Mental Health



The Charcot Grant is awarded to the top ranked Innovator Grant application. Dr Turner's project is titled "Development of a novel splice-switching molecular therapy for MND" and will investigate a novel therapy using powerful genetic DNA designer drugs which can target and 'turn off' the SOD1 gene in those patients carrying the MND-causing SOD1 mutation.

Beryl Bayley MND Postdoctoral Fellowship 2020 – 2022

Dr Mehdi van den Bos, Westmead Hospital



Dr van den Bos's project is titled "Deep learning as a tool to advance the diagnosis and pathophysiological understanding of ALS" and will use advanced neurophysiological methods (probing brain function with magnetic brain stimulation and brain wave recordings) together with artificial intelligence (the technique of deep learning) to identify early disease-related changes and improve early diagnosis.

Bill Gole MND Postdoctoral Fellowship 2020 – 2022

Dr Luke McAlary, University of Wollongong



Dr McAlary's project is titled "Targeting Prion-Like Strains of TDP-43" and will look at the exact nature of the toxic TDP-43 protein clumps found in the brains of MND patients. This information will enable better targeting of potential drugs to this intractable aspect of MND.

Innovator Grants for 2020

In addition to the Charcot Grant, a further 19 Innovator Grants were awarded. These grants ranged across the MND research spectrum with a number of grants looking at the basic mechanisms underlying the disease so we can better understand what might cause MND and drive disease progression thus identifying novel preventative or therapeutic approaches. Projects looking at how we can better measure disease progression and severity were also funded, either using biochemical markers that can be measured by blood or urine tests or advanced imaging and computational approaches. As described earlier, several new therapeutic approaches are also being supported. Finally, two key projects have been funded to look at improving care models. The first looks at whether substituting inpatient admissions and sleep studies when commencing non-invasive ventilation (NIV) with home implementation and telehealth results in equivalent usage but a better patient experience. The second study aims to understand how easy or difficult it is for people with MND to find, understand and make use of information about managing their life with the disorder and what help do these people, together with their families or carers, need to make the decisions which are best for them.

Research Area 1: To better understand the cause and underlying biology contributing to MND

Peter Stearne Familial MND Research Grant

Prof Julie Atkin, Macquarie University, NSW

New disease mechanisms in MND: Investigating the role of the actin cytoskeleton - the network of filaments that help to maintain cell shape

Jenny Simko MND Research Grant

Dr Samantha Barton, Florey Institute of Neuroscience and Mental Health, VIC

Could the structure of the insulating sheath that normally maintains healthy motor neuron function be altered in MND and could this be contributing to motor neuron dysfunction and death?

MNDRIA Innovator Grant

Prof Pamela McCombe, University of Queensland, QLD

Looking in the blood of MND patients for toxins produced by gut bacteria

MonSTaR MND Research Grant

Dr Marco Morsch, Macquarie University, NSW

Is the "navigation system" that directs protein aggregate to different parts of the motor neurone dysfunctional in MND?

Benalla Act to d'feet MND Research Grant

A/Prof Lezanne Ooi, University of Wollongong, NSW

Testing drugs and genes that target motor neuron communication in order to prevent cell death

MNDRIA Innovator Grant

A/Prof Trent Woodruff, University of Queensland, QLD

Understanding how our immune cells alter disease in patients with MND.

Robert Turnbull MND Research Grant

Dr Kelly Williams, Macquarie University, NSW

Measuring changes in gene activity to uncover why certain regions of the central nervous system are protected from MND

MNDRIA Innovator Grant

Dr Fiona McKay, The University of Sydney, NSW

Characterising "natural killer cells" of the immune system in ALS: do they protect or damage motor neurones, and can they be used to treat MND?

NTI MND Research Grant

A/Prof Anthony White, QIMR Berghofer Medical Research Institute, QLD

Obtaining a new understanding of how the brain's specialist immune cell is impaired in MND and targeting drugs to improve the function of these cells.

Research Area 2: How to better measure disease progression and responses to treatment

MNDRIA Innovator Grant

Dr Mary-Louise Rogers, Flinders University, SA

Measuring a protein present in the urine of people living with MND that can help to determine stage of disease for clinical trials

Run MND NSW Research Grant

Dr Kara Vine, University of Wollongong, NSW

Improving the delivery of drugs to the brain and spinal cord using focused ultrasound.

MonSTaR MND Research Grant

Dr Sicong Tu, University of Sydney, NSW

Developing new tools to monitor disease progression in MND by studying changes in brain connections using advanced imaging and artificial intelligence modelling

Research Area 3: Developing and testing potential new treatments

Fat Rabbit MND Research Grant

Dr Frederik Steyn, The University of Queensland, QLD

Tipping the Scales on MND: Preclinical testing of a compound with multiple actions to slow disease progression in MND

Col Bambrick MND Research Grant

Dr Richard Gordon, The University of Queensland, QLD

New tricks for old drugs - testing an approved blood cancer drug as a potential new treatment for MND.

MNDRIA Innovator Grant

Dr Albert Lee, Macquarie University, NSW

Investigating a new therapy to clear the toxic TDP-43 protein from neurones.

MNDRIA Innovator Grant

Dr John Lee, University of Queensland, QLD

Investigating a part of our immune system called CXCR2 as a potential drug target to protect motor neurones

Research Area 4: Improving current care models through evaluation and innovation

Mavis Gallienne and Graham Lang MND Victoria Research Grant

Prof David Berlowitz, Austin Health/University of Melbourne, VIC

Testing whether machine-assisted overnight breathing can be successfully initiated in the homes of people living with MND, as a way of reducing hospital admissions.

Superball XI MND Research Grant

Dr Susan Mathers, Calvary Health Care Bethlehem/Monash University, VIC

Identifying and responding to the health literacy needs of people living with MND/ALS – a coordinated national approach

MNDRIA Travel Grants

Ten PhD students and early career researchers have been awarded Jenny and Graham Lang Travel Grants to attend the International Symposium on ALS/MND in Perth in December 2019. The Jenny and Graham Lang Travel Grants are funded by MND Victoria and provide \$1500 for each recipient toward their travel costs to attend the Symposium. The supported researchers will be presenting a range of exciting research, from studies in telemedicine and lung function through to novel therapies, providing an ideal platform to demonstrate the world-class MND research being undertaken in Australia.

Kelly Atkins, Monash University, VIC

Meaningful contributions to ALS patient care via telehealth;
Efficacy of a group-based mindfulness program for people with motor neurone disease and their family caregivers

Britt Berning, The Queensland Brain Institute, QLD

Golgi dysfunction is an early event associated with TDP-43 pathology formation in ALS

Jayden Clark, Nuffield Dept of Clinical Neurosciences, University of Oxford, UK

Single copy expression of mutant TDP-43 increases microglial reactivity and motor neuron vulnerability to inflammatory stimuli

Dzung Do-Ha, University of Wollongong, NSW

Investigating changes in neuronal excitability using iPSC-derived motor neurons from ALS patients

John Lee, University of Queensland, QLD

A protective role for complement C3aR activation in ALS

Katherine Lewis, Menzies Institute for Medical Research, TAS

Targeting ALS cortical excitability dysfunction through nasal delivery of neuropeptide Y

Luke McAlary, University of Wollongong, NSW

ALS-associated mutations in the TDP-43 low-complexity domain have variable effects on its liquid-liquid phase separation properties

Nicole Sheers, University of Melbourne, VIC

Respiratory function and infections in people with MND; The physiological effects of a single session of lung volume recruitment in people with MND.

Sicong Tu, The University of Sydney, NSW

Subcortical abnormality is a prominent indicator of evolving cortical dysfunction in ALS

Amanda Wright, Macquarie University, NSW

A nanoparticle-based strategy for treating neuroinflammation in MND.

Building a truly national resource for patient research data collection

The Sporadic ALS Australia Systems Genomics Consortium (SALSA-SGC), the brainchild of Professor Naomi Wray at the University of Queensland and Professor Ian Blair at Macquarie University, continues to go from strength to strength.

Initially funded by the MND Australia Ice Bucket Challenge Grant in 2016, the SALSA-SGC project aimed to establish systematic and uniform data and biological sample collection in the major Australian MND clinics. The long-term goal was integration of genomic and clinical data to build a more complete picture of the complex genomic causes and consequences of MND/ALS. The initial 3-year project succeeded in collecting clinical data and DNA on close to 600 MND/ALS patients. Having established this unique resource, however, the next challenge was how to keep supporting it and further develop its huge potential.

This next stage was accomplished by the securing of a 5 year \$750,000 NHMRC Partnership Grant, commencing in 2018, titled "*Motor Neurone Disease: Patient centred care for a progressive neurological disease - evidence driving policy*" led by Professor Matthew Kiernan. This project integrated the genomics and sample collection focus of SALSA-SGC into a wider care-focused model incorporating multidimensional assessment, symptom management and care-planning to improve care and coordination, research and enrolment in clinical trials. The ultimate aims are to provide supporting data for policy development and translation of evidence into practice. This partnership project included integration with the Australian MND Registry, a well-established clinical database.

Further, as part of the patient-centric approach a "patient-app" for mobile devices is being developed to streamline patient and carer data collection and also enable expansion beyond the clinic. With the continued development of the program, it has now been branded as the MiNDAUS Partnership Project, reflecting its true national reach. As partners in this project, MND Australia and MNDRIA are contributing over \$500,000 of funds and in-kind support.

However additional funding was still needed to maximise the projects huge potential, especially in terms of specialised support staff to ensure good data collection. FightMND are now participating and will be funding some of the researchers involved in this program. Additionally, they have provided funding for research nurses in a number of centres that are running FightMND-supported clinical trials. These nurses will then also work with the MiNDAUS program. This will support better data collection and importantly expand involvement to those patients/carers living more regionally.

With this additional parcel of funding the project is set to fulfil the initial vision and reach its true potential. This presents a fantastic example of how MNDRIA-initiated projects can grow and develop into larger high profile programs that draw in stakeholders across the country and attract further funding from government and other philanthropic organisations.

**MiNDAUS
PARTNERSHIP**



Farewells.....



A big hole in the Australian MND landscape was left in September following the sad passing of generous donor and supporter of MND research John Laidlaw AO. Since 2015, John has funded the Betty Laidlaw MND Research Grant and the Betty Laidlaw Research Prize, a magnificent total contribution of \$2M that made a significant contribution to the development of CuATSM, described earlier, and other vital research. The grant and prize were named after Betty Laidlaw, John's wife. Betty has been living in Melbourne with primary lateral sclerosis (PLS), a slowly progressive form of MND, for over thirty years. We are enormously grateful for both John and his daughter, Melissa's, passion and interest in supporting high quality research to accelerate and advance understanding of MND.

John Laidlaw (centre) pictured with MND Australia President David Ali, daughter Melissa Duggan, The Hon. David Gillespie MP, and MND Australia CEO Carol Birks

In August we said farewell to Janet Nash who, after 25 years with our national network of MND associations, finally started her oft-delayed and very well-earned retirement. Janet initially joined MND NSW in 1995 as their first Care Coordinator where she established the equipment loan pool, developed information services and championed MND research. In 2005, she took on the role of Executive Officer for the MND Research Institute of Australia (MNDRIA) and, following the amalgamation of MND Australia and MNDRIA in 2010, became the Executive Director, Research.

Over the last 15 years Janet has overseen the growth in funds from 10s of 1000s of dollars to the millions we see today and has been integral to MNDRIA's support of research excellence. We thank Janet for her significant contribution to the MND community and wish her well in her retirement.



MND Australia CEO Carol Birks with Janet Nash

And welcomes....

A new Chair for the Research Committee

After 5 very successful years as Chair of the Research Committee, Professor Matthew Kiernan is stepping back. During this period MNDRIA's research budget has grown many-fold and provided funding that has greatly grown the capacity of the MND research workforce. He has overseen development of a Research Strategy and funding of significant clinical developments as well as the Ice Bucket Challenge-funded SALSA Systems Genomics Consortium and lead the successful application for a \$2.5M NHMRC Partnership grant.

Stepping into the role as an independent Chair of the Research Committee is Professor David Burke. Professor Burke was the first medical Chairman of MNDRIA (1995-1998), following inaugural Chair Dr Dawn Thew who founded the Institute in 1984. David has a distinguished career as a clinician-researcher and has served as President of the Australian & New Zealand Association of Neurologists 2005–2007, is a member of the Executive Committee of the International Federation of Clinical Neurophysiology, and has served on committees of the World Federation of Neurology and the Royal Australasian College of Physicians. We welcome David on board and very much look forward to benefiting from his immense experience and knowledge of MND.

New CEOs for MND Victoria and MND Queensland

Kate Johnson and Ian Landreth recently commenced as CEO for MND Victoria and MND Queensland respectively. Both come with strong backgrounds in the health and not-for-profit sectors and we look forward to building on our strong relationships with the states to support MND research. MND Australia and its members, the State MND Associations, form the only national network focused on improving the lives of all Australians living with MND. We welcome Kate and Ian and look forward to working with them both.

Gold Coast Consensus Meeting: Towards an earlier diagnosis of ALS/MND 27-29 September 2019

MND Australia was honoured to be invited to attend this potentially historic meeting as a representative of ALS/MND Associations. Supported by the International Federation of Neurophysiologists, World Federation of Neurologists, the ALS Association and the MND Association of England, Wales and Northern Ireland and organised by Professors Matthew Kiernan, Ryuji Kaji and David Burke, this meeting involved leading neurologists and neurophysiologists from 11 countries, as well as MND Australia, and patient and carer representatives from Australia, Sean and Pauline Dorney.

The aim of the Gold Coast Consensus Meeting was to improve the ability to diagnose ALS/MND earlier and when clinical symptoms are minimal to give current and future therapies the best chance of success in stopping, or even reversing, the disease process in the very early stages.

Participants were tasked with looking at methods for demonstrating upper motor neuron (UMN) involvement and developments over the last 10 years that have enhanced the diagnostic value of current Awaji criteria which can be included in patient assessments. The Awaji criteria were published in 2008 and focus solely on lower motor neuron (LMN) features in assisting clinicians to make a diagnosis of ALS/MND and along with the El Escorial Criteria, remain the gold standard for the diagnosis of ALS/MND. With the Awaji Criteria now over 10 years it is definitely the time to review whether advances in techniques to measure UMN involvement should be included in diagnostic criteria and whether LMN criteria can be further refined.

The desperate need for more effective treatments remained front and centre over the two-day meeting. All agreed on the need to accelerate testing of new therapies and in order to do that reliable and objective biomarkers to supplement clinical outcome measures such as the ALS FRS are vital. Lively debate ensued regarding the merits, and otherwise, of different approaches. There was consensus that all clinical trials should also be testing the various biomarkers currently available. There was acute awareness that over the next five years there could well be a therapy available for some types of ALS/MND and it will be vital to ensure people have access as early as possible in the disease process.

Discussion on Day 1 progressed to review what a clinician can do with routine diagnostic equipment and the effectiveness of new methods in assessing and measuring LMN involvement and fasciculations. The final session on genetics highlighted the acceleration in discovery of disease causing mutations and increased understanding of the many variants which may or may not lead to a person developing ALS/MND.

The final word on Day 1 went to Sean Dorney, ABC Foreign Correspondent to PNG for over 17 years, who expressed his admiration for the robust debate. He encouraged everyone present to keep fighting on to increase understanding of this very complex disease, keep researching and keep discussions going to help accelerate solutions.



Attendees at the 2019 Gold Coast Consensus meeting

Day 2 discussions focused on upper motor neuron changes and whether ALS/MND should be classified as a brain disease. The diagnostic equipment available to support assessment of UMN involvement were reviewed and discussed. Some interesting questions were posed and hotly debated:

1. Is ALS a clinical syndrome rather than a disease?
2. Does ALS have a focal clinical onset?
3. Is spread in ALS non-random?
4. Is lower motor neuron predominant ALS a better term than progressive muscular atrophy (PMA)?

These discussions questioned whether we should unify behind the term ALS as a unique clinical syndrome and what, if any, benefits there would be in selecting patients for clinical trials from an ALS syndrome point of view as opposed to a clinical phenotype point of view.

The next stage of these discussions is to develop consensus paper(s) to enable wide uptake of the outcomes of the meeting to improve earlier diagnosis and meet the needs of future clinical trials.

MNDRIA on social media

Social media is a great way to keep up to date with MND research, as well as information on upcoming events and the important advocacy work undertaken by MND Australia.

MND Australia on Facebook

Follow the MND Australia Facebook page for regular updates on advocacy, events and research.

Twitter

Both MND Australia and MNDRIA have their own twitter accounts: @mndaust and @MND_RIA

MND Australia newsletter

To receive monthly updates, via email, on activities, events, advocacy, research and other information, sign up to the MND Australia newsletter. Go to www.mndaust.asn.au to sign up.

Spotlight on MND

MND Australia regularly updates its blog with information on advocacy, living with MND, and research. The latest blog piece looks at recent research into repetitive head injuries associated with contact sports and their relationship to developing motor neurone disease. Go to the MND Australia home page (www.mndaust.asn.au) and follow the links to Spotlight to read this and other interesting blog pieces.



Get Involved

The ALS/MND Connect Event, which has previously been known as the Ask the Experts forum, will be LIVE streamed on the MND Australia Facebook page from 5-7:30pm AEDT (2-4:30pm Perth time) on Monday 2 December. You don't require a Facebook account to login, simply search for the MND Australia Facebook page and watch the event live. There is also an opportunity to submit your questions for an MND researcher to answer during the international symposium. Head to the MND Association form at <https://www.mndassociation.org/symposium-2019-your-questions-answered/> to submit your questions.

Donations

Research funded by the MND Research Institute of Australia is dependent on donations. To contribute to this vital work, please send your gift to:

MND Research Institute of Australia
PO Box 117, Deakin West, ACT 2600

Donations can be made by cheque (payable to MNDRIA). Visa or MasterCard donations can be made via phone (02 8287 4989) or online (mndresearch.org.au)

All donations of \$2 and over are tax deductible and every dollar of your donation is spent on funding research into motor neurone disease.

ABN: 46 789 710 580

Governance

MND Australia is the principal member of the MND Research Institute of Australia.

The governance and operations of both organisations are the responsibility of MND Australia.

Directors

The board of MND Australia consists of an independent elected President and a nominated representative from each member MND Association board, the chair of the MNDRIA Research Committee and up to three independent directors.

Research Committee

The MNDRIA Research Committee reviews research grant applications and determines the distribution of available funds within the set policies and criteria for scientific assessment.

Research Committee Members

Chairman: Professor Matthew Kiernan, NSW
Professor Samar Aoun, WA
Professor Ian Blair, NSW
Professor Tracey Dickson, TAS
Professor Simon Foote, ACT
Professor Glenda Halliday, NSW
Dr Susan Mathers, VIC
Professor Pamela McCombe, QLD
Dr Shyuan Ngo, QLD
Professor Dominic Rowe AM, NSW
Professor Dominic Thyagarajan, VIC
Associate Professor Bradley Turner, VIC
Professor Steve Vucic, NSW
Professor Naomi Wray, QLD

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 the MND Research Institute of Australia in your Will by providing a Bequest from your Estate, please contact your solicitor.

For more details on how your bequest can help MND research email research@mndaust.asn.au

Thank you

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