JUNE 2018

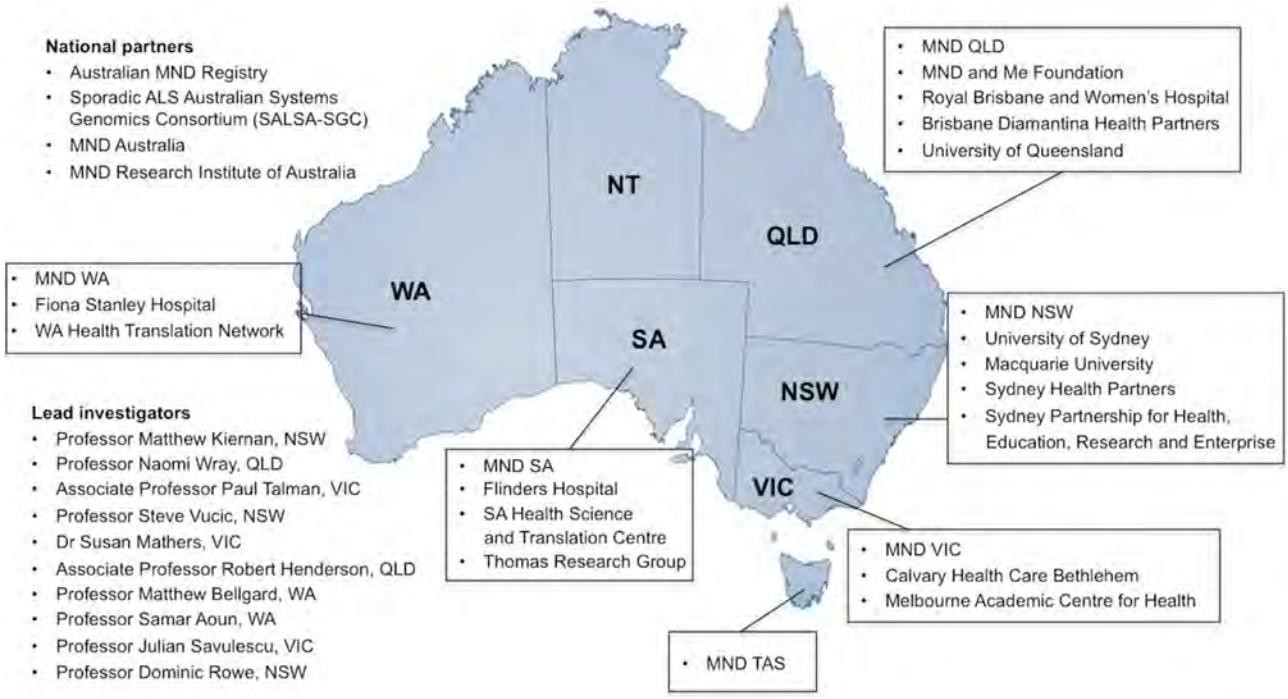
ADVANCE

$2.5 million for MND patient-centred care initiative

The MND Research Institute of Australia (MNDRIA) is proud to be part of a consortium of research organisations, clinical groups, specialist MND clinics, patient-centred organisations and care providers who have won funding from the National Health and Medical Research Council (NHMRC) to collect real-time data to inform best practice services, research and enrolment in clinical trials.

The consortium was awarded an NHMRC Partnership Grant *"MND: Patient-centred care for a progressive neurological disease - evidence driving policy*" in April this year as part of a competitive application process. The NHMRC funding together with contributions from all stakeholders amounts to an investment of more than $2.5 million into patient-centred care over five years. MNDRIA's investment into the project will be leveraged more than four-fold.

The initiative is led by MNDRIA Research Committee Chair Professor Matthew Kiernan, co-director of the Brain and Mind Centre, University of Sydney. Importantly, the partnership recognises people living with MND and their families as being best placed to inform policy development and service design through their lived experience of a rapidly changing condition.



MND: Patient-centred care for a progressive neurological disease brings together stakeholders from across Australia to create partnerships among clinicians, service providers and policy makers.

The Partnership Project has three themes:

Theme 1. *Empowering MND patients and their carers*
This theme will deliver an app for mobile devices, which has the dual-purpose of improved patient-centred care while recording data needed for evidence-based policy. The app will be designed to capture personal health and well-being data and support needs.

Theme 2. *Unification and integration of data collection in MND*
Different data collection systems will be brought together under one umbrella, making data collection more patient-focused and providing better feedback to patients, carers and clinicians. A clinical trials registry will help to quickly identify appropriate participants for future clinical trials.

Theme 3. *Integration of evidence to inform policy*
Data will be used to provide an evidence-base to create national policies. This includes uniform national policies for patient-centred multidisciplinary care, and policies that enable national and international collaborations for linking genomic research and sharing clinical data.

mnd Research Institute of Australia

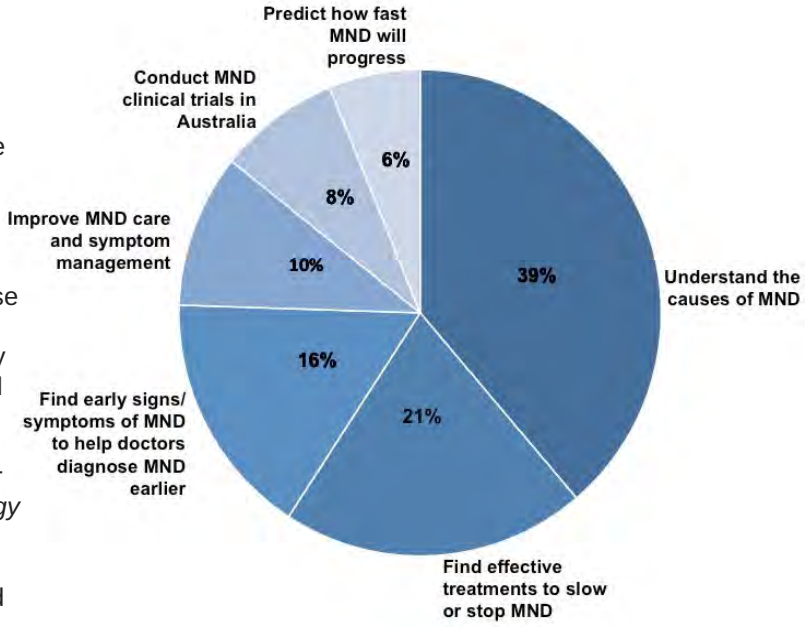
From the Executive Director Research

The past year has seen some significant progress in our understanding and treatment of MND. Research supported by MNDRIA was featured in 31 papers published in peer-reviewed journals in 2017. The discoveries of a new gene implicated in causing MND in some people (page 5) and a potential neurotoxin found for the first time in algal blooms in Australia (page 4), are just two of many recent research findings funded by MNDRIA. Earlier this year, research led by Drs Derik Steyn and Shyuan Ngo from the University of Queensland revealed increased energy use or metabolism in people with MND is linked to faster disease progression and reduced lifespan. Exactly why this happens is unclear. The researchers hope this discovery will help to manage disease progression in the clinic and open up new avenues for improving patient outcomes through treatments that specifically target energy use. Research published by Associate Professor Brad Turner and colleagues in the prestigious journal *JAMA Neurology* in March investigated neuroinflammation in ALS/MND. The study found cells in the immune system known as regulatory T cells have a protective effect and concluded strategies aimed at enhancing the regulatory T cell population could prove therapeutically useful. More about Associate Professor Brad Turner can be found on page 7 of this *Advance* newsletter.

The May Federal Budget committed $241 million to list the drug nusinersen (marketed as Spinraza) on the Pharmaceutical Benefits Scheme (PBS) from 1 June for the treatment of a particular type of MND known as spinal muscular atrophy (SMA). SMA is the number one genetic cause of death in infants, affecting 1 in 6,000 children. Abnormalities in the *SMN1* gene cause motor neurones in the spinal cord and brainstem to die. Spinraza is the first and only treatment of its kind to be listed on the PBS for Type 1, Type 2 and Type 3a patients under the age of 18. Notably, MNDRIA's Beryl Bayley Postdoctoral Fellow Dr Michelle Farrar from the University of NSW played a key role in establishing an expanded access program to enable patients with the most severe type of SMA access to the unapproved treatment while it was under review by the Therapeutic Goods Administration. The Budget also included an investment of $20 million for pre-conception screening for rare and debilitating birth disorders including SMA. This will provide funding and support for patients who face difficult choices in starting a family. Importantly, we hope this will extend to people with a family history of MND looking at starting a family.

We are very grateful to everyone who took the time to complete the *MND Australia Research Priorities Survey*. This consultation fed into the development of MND Australia's new research strategy for 2018 - 2021 *Investing in innovation, Partnering for progress*. We certainly learned a lot from participants. Overall, we found MND Australia's current research strategy aligned well with the views expressed in the survey. A comprehensive research program has supported a range of research from understanding the causes of MND, to finding potential treatments, improving diagnosis,

Projects supported by MND Australia in 2017, by research goal



conducting clinical trials and improving the healthcare of people with MND (see figure above). We noted strong community support for promoting collaboration and will be increasing our focus on strategic partnerships where we can while continuing to encourage innovation and building the capacity of the MND research workforce. The success of the NHMRC Partnership Grant application *MND: Patient-centred care for a progressive neurological disease - evidence driving policy* is hopefully the first of many strategic partnerships (see cover story). People with MND and their families are front and centre of the initiative, which will connect important clinical information and inform policy.

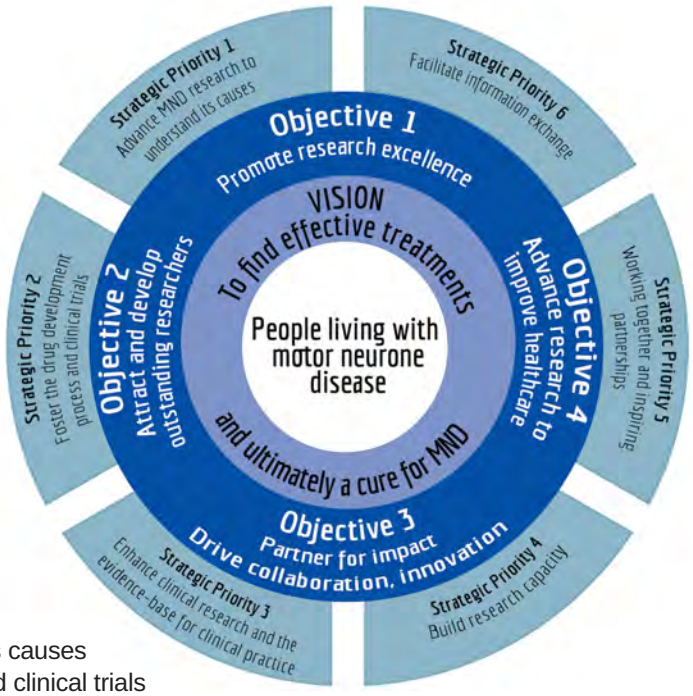
An analysis of MNDRIA's achievements to date was an essential part of developing MND Australia's new research strategy. MNDRIA was extremely proud to launch the *$25 Million, 25 Milestones: Changing the future of motor neurone disease* report at the *13th MND Australia Research Conference* in November 2017. This landmark report detailed 25 high impact, MNDRIA-funded advancements. Each milestone is another step forward in defeating MND.

We cannot thank enough our donors, supporters and volunteers who enable MNDRIA to support world-class high quality MND research. Because of you, MNDRIA is making a significant difference. Every dollar of each donation goes to research. Continued investment in Australian scientists at the forefront of MND research is vital to understanding the causes, developing effective treatments and finding a cure for MND. Our new research strategy is in place and our vision is as clear as ever. Slowly but surely we are turning the tide on MND. Together, we will prevail.

Dr Stephanie Williams
Executive Director Research
MND Australia

Investing in innovation, partnering for progress

MND Australia was pleased to announce its new research strategy for 2018 – 2021 *Investing in Innovation, Partnering for progress* in May. People with MND and their families are at the centre of the new strategy developed following analysis of the current research environment, and extensive consultation with researchers, health professionals, community and MND Australia's State MND Association members.



The Strategy's vision is of course to find effective treatments and ultimately a cure for MND. There will be an increased focus on strategic partnerships while continuing MND Australia's commitment to innovation and developing the MND research workforce.

To date, MNDRIA has invested more than $5.3 million in a range of postdoctoral fellowships since 2002. Most fellowship recipients continue to work in MND and/or neurological diseases, with several rising to be among the world's leading MND researchers. Over 30 years, more than $25 million has been invested in a comprehensive research program from discovery, to testing potential treatments, clinical research, clinical trials and healthcare.

From 2018, MNDRIA will support new ground-breaking research through Innovator Grants. Applications must meet at least one of three strategic priorities:

- Strategic Priority 1. Advance MND research to understand its causes
- Strategic Priority 2. Foster the drug development process and clinical trials
- Strategic Priority 3. Enhance clinical research and the evidence-base for clinical practice.

A total of 567 people responded to the *MND Australia Research Priorities Survey* earlier this year, providing feedback on MND research and the many challenges faced by people with MND and their families. The survey results helped to develop MND Australia's research strategy.

87% of survey participants felt that "find effective treatments" was a very high priority and 71% saw "understand more about the causes of MND" as a very high priority for the future.

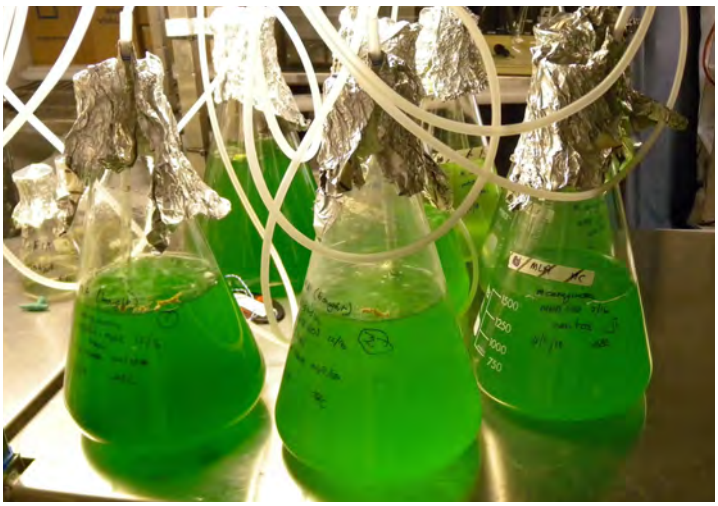
Feedback has also enabled MND Australia to gain a better understanding of MND management and care research important to the MND community. The following ten topics were found to be the highest MND management and care research priorities:

1. Breathing problems and respiratory management
2. Swallowing problems
3. Speech and communications
4. Walking and mobility
5. Pain management
6. Hand function
7. Upper limb function
8. Depression
9. Cognitive function
10. Nutrition.

There was significant support for "palliative care research" and "research into support for carers and family members", with 57% and 54% of survey participants respectively ranking them as a very high priority. Conducting clinical trials was a popular research topic and goal. Importantly, while many survey participants with MND felt very strongly that clinical trials were a very high priority, they were well aware of the limited knowledge of what causes MND and the urgent need to understand more to help find new treatments.

Blooming toxic: potential neurotoxins in Australian waterways

Research led by Associate Professor Ken Rodgers at the University of Technology Sydney (UTS) has found the presence of two suspected neurotoxins, known for short as BMAA and 2,4-DAB, in 16 surface scum samples from waterways in rural and urban NSW.



Single blue-green algal species grown in the laboratory

The research, supported by MNDRIA, found BMAA in 10 out of the 16 samples (60%) and 2,4-DAB in all (100%) of the samples. The compounds are produced by blue green algae or cyanobacteria, which, when conditions are favourable, can form blooms and scums on waterways around the world. This is the first time BMAA has been detected in bloom samples from Australian waterways.

Cyanobacteria produce a variety of toxins ranging from liver toxins, skin irritants to neurological toxins. Multiple state agencies monitor Australia's waterways and issue alerts when there are algal blooms. Research has shown BMAA can directly damage nerve cells and epidemiological studies have identified a link between regular exposure to algal blooms and an increased incidence of MND. At present, safe exposure levels to BMAA are not known and further research into its toxicity is required. The new study also highlights the need to include BMAA in regular water quality testing.

A combination of environmental and lifestyle factors interacting with genes likely contribute to the development of MND. Only about 10% of MND runs in families. Sporadic MND accounts for about 90% of people with MND, where only one person in a family has the disease and the causes are unknown. Conclusively identifying environmental factors linked to complex diseases like MND is very difficult to do but is clearly important.

Associate Professor Rodgers and his team will focus future research on tracking and monitoring algal blooms for the presence of BMAA, and determining how long BMAA remains in the ecosystem after these blooms have occurred. In collaboration with Associate Professor Simon Mitrovic at UTS, they are growing bloom samples in the laboratory to identify which cyanobacterial species produce the toxins and what conditions favour toxin production. The researchers hope this knowledge will help to reduce human exposure to BMAA.

Unlike many known toxins, BMAA is thought to be a slow toxin and its damaging effects are not seen until many years after exposure. The researchers are currently examining ways in which BMAA damages neurones so that protective therapies can be identified. They found BMAA competes with the natural nutrient L-serine leading to damage to critical proteins in neurones. Subsequently, L-serine is now in clinical trials in the US for the treatment of MND.

A blue-green algal (cyanobacterial) bloom in Central NSW

At present, safe exposure levels to BMAA are not known and further research into its toxicity is required...

Photos: Dr Anne Colville

New protein transport gene implicated in MND

Macquarie University researchers supported by MNDRIA are part of a global team that has found a new gene associated with MND. The gene known as *KIF5A*, which stands for kinesin family member 5A, makes a protein involved in moving materials along motor nerve cells or neurones.

Professor Ian Blair and Dr Kelly Williams

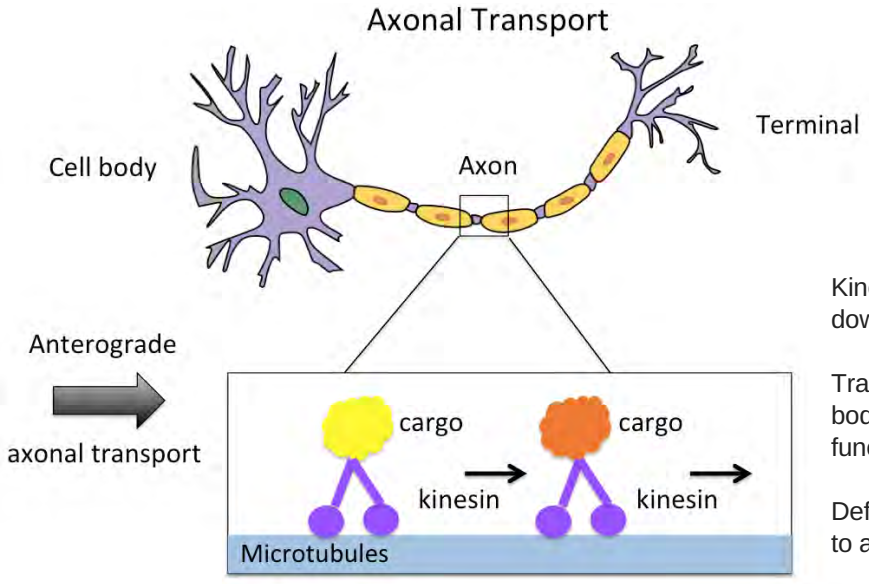
This latest discovery was published in the journal *Neuron* in March. Professor Ian Blair and his group are among 200 authors from five different countries and nine consortia across Europe, Australia and the US, including Project MinE.

Looking for MND genes is like looking for a needle in a haystack and requires investigation of large numbers of people to find them. In this case, the researchers used two approaches to find the new gene. Firstly, they compared 20,806 ALS cases to 59,804 controls and then using a different technique, they investigated 1,138 familial ALS cases and 19,494 controls. Professor Blair's team contributed genetic data from over 90 Australian families with a history of MND as well as data from Australian sporadic MND patients as part of Project MinE.

While rare genetic variants can only be detected in large numbers of samples, it does not follow they are less important than more commonly occurring mutations such as those found in *SOD1* which accounts for about 10% of familial cases. Each discovery contributes to a better understanding of what causes MND and provides new insights into disease mechanisms. The identification of *KIF5A* provides a new target and pathway in the search for potential treatments and drug development.

Motor neurones are elongated cells, up to one metre long. They require a highly efficient system to transport proteins and other factors within the neurone in order to function properly. When proteins like KIF5A fail, they contribute to the development of MND by disrupting normal transport processes. The researchers found 12 different MND-causing mutations in the tail end of the *KIF5A* gene (known as the C-terminus). They also found people with ALS/MND who had these mutations had a relatively early age of onset and longer survival (onset 45 years old, survival 10 years) compared to typical MND prognosis (average onset 65 years old, survival three years).

Notably, mutations predominantly at the other end of the gene, known as the N-terminal motor domain of *KIF5A*, have been previously found to be causative for two neurodegenerative diseases known as hereditary spastic paraplegia and Charcot-Marie-Tooth type 2. Taken together, these results broaden our understanding of how defects in the *KIF5A* gene are involved in neurodegenerative diseases and shed more light on the pathogenesis of ALS/MND.



Kinesin (purple) transports materials (cargo) down the nerve cell.

Transport of materials between the cell body and the synapse is essential for the function and survival of neurones.

Defective axonal transport has been linked to a range of neurodegenerative diseases.

Supporting emerging researchers

As part of its remit to build capacity and develop MND researchers in Australia, MNDRIA awards PhD Scholarship Top-up Grants and Travel Grants each year through a competitive process. Two MNDRIA PhD Scholarship Top-up Grants and two Travel Grants were awarded in March this year.

MNDRIA PhD Scholarship Top-up Grant

Britt Berning
Queensland Brain Institute
Sub-cellular dysfunctions associated with pathological TDP-43 in MND: disease mechanisms and therapeutic relevance

Britt Berning aims to discover molecules that could be targets for new MND treatments by investigating the machinery in motor neurones that maintain protein transport and function. She is combining a mouse model of MND with studies in cell culture and human brain and spinal cord samples. Manipulating key pathways related to subcellular movement may prevent neurone death and help remove the toxic aggregates that are a hallmark of MND. These studies will determine whether defects in motor neurone transport machinery contribute to the onset and progression of MND.

MNDRIA PhD Scholarship Top-up Grant

Camille Paynter
University of Melbourne
A longitudinal study of involvement in healthcare decision-making in MND: Patient and caregiver perceptions, impact of communication and swallowing difficulties, and quality of life

Camille Paynter's research explores the facilitators and barriers for effective involvement in healthcare decision-making in MND particularly focusing on the impact of a communicating impairment. Interviews will be conducted over 12-18 months to uncover how decision-making changes with MND progression. Improved involvement in healthcare decision-making for people with MND who have a communication impairment, will result in improved individualised care, increased empowerment and reduced burden for carers.

Susie Harris Travel Fellowship 2018

Dr Fleur Garton
University of Queensland
A novel biomarker for insight into amyotrophic lateral sclerosis (ALS) disease mechanisms and progression

Dr Fleur Garton will visit the University of California to develop a new MND biomarker called cell-free DNA (cfDNA). When cells die, DNA is released into the bloodstream. cfDNA is already used around the world as a cost-effective biomarker in both cancer and non-invasive pre-natal diagnosis. Dr Garton has pilot data to support the idea that a detectable profile of cfDNA will be specific to ALS and correlate with disease progression. If successful, this research will lead to the development of a rapid, efficient, sensitive cfDNA-based test for ALS diagnosis and progression. The outcomes of this visit will be presented at the International Symposium on ALS/MND in Glasgow in December.

Jenny and Graham Lang Collaboration Travel Grant 2018

Dr Shu Yang
Macquarie University
Assessing the pathogenic role of novel MND candidate genes

Dr Shu Yang will visit Stanford University in California to develop a test to verify new potential MND genes as causing MND. MND-linked gene mutations have helped researchers to understand disease mechanisms and provided targets for animal model and therapeutics development. It is often difficult to prove genes are involved in MND given the complexity of the disease.There is a pressing need to develop a rapid, efficient, and cost-effective screening strategy to discriminate true causative gene mutations from natural variants often seen in genes.

Meet Associate Professor Brad Turner, Molecular Neurobiologist

It was a book recommended in a second year genetics lecture that sparked Brad Turner's interest and course to a career in MND. He was studying for a medical science degree at the University of Melbourne at the time. *Deadly Feasts* by Richard Rhodes is a thrilling tale that follows tribal cannibalism in the highlands of Papua New Guinea in the 1950's to the emergence of mad cow disease in the United Kingdom in 1986. The gripping medical detective story introduced Associate Professor Turner to a degenerative disease of the brain, much like MND.

"I was instantly hooked by the brain and its degeneration which began my fascination with this complex organ. It steered me to an Honours project in Alzheimer's disease, followed by a PhD in MND," he says.

Fifteen years on, Associate Professor Turner is an NHMRC Dementia Research Leadership Fellow and heads up the MND Laboratory at the Florey Institute of Neuroscience and Mental Health in Melbourne. His group is particularly interested in understanding the molecular makeup of motor neurones long before there are even any symptoms of MND.

"We aim to understand the biological mechanisms and pathways driving selective vulnerability of motor neurones in MND. If we can unlock the reasons why some motor neurones are affected and fail in MND, then we can devise meaningful and disease-modifying interventions."

Associate Professor Turner sees working on MND as a lifelong commitment. His primary motivation is the people who battle MND daily; the patients, families and carers, as well as support Associations he has met and worked with over the years.

"Their individual stories, bravery, determination and hope for a world without MND in the face of their odds inspires me," he says.

Contributing to the ever growing knowledge space of MND, training the next generation of scientists and thinkers, and waiting for those rare eureka moments in the laboratory are all rewarding aspects of research life.

"My lab members' enthusiasm, curiosity and productivity energises me. It's an exciting time and privilege to be doing medical research with recent advances in stem cell models, gene editing tools, "remote controlling" nerve cells, gene therapies and robots, which also keeps me surprised and engaged.

"Medical research can be a slow grind. Part of this results from being meticulous and careful in our scientific approaches and interpretations, so we absolutely take the most worthwhile ideas and drug targets and candidates forward. There is no short-term reward or product in medical research and we are committed to the long haul," he says.

Associate Professor Brad Turner with his team

Get involved

MND Connect 2018

The 4th MND Connect brings together the community, researchers and clinicians to discuss MND research.
When: Saturday, 10 November 2018
Where: The Florey Institute of Neuroscience and Mental Health, Melbourne

Annual MND Australia Research Conference

Now in its 14th year, this conference is open to MND researchers and the community.
When: Friday, 9 November 2018
Where: The Florey Institute of Neuroscience and Mental Health, Melbourne

Participate in research

For more information about clinical trials and how to participate in research, visit the MND Australia website.

SALSA-SGC

Onset and progression of MND (nationwide)

People living with MND and their carers are invited to participate in this Australia-wide project looking to understand the onset and progression of MND. Both sporadic and familial MND will be studied. Contact Anjali Henders: a.henders@uq.edu.au, 07 3346 6474 or your local clinic participating in SALSA: hsu.imb.uq.edu.au/contact

Research project targeting swallowing exercises and diet change (Sydney)

Professor Vicki Flood from the University of Sydney is currently recruiting people living with MND to take part in a pilot study running from Westmead Hospital in Sydney. The study will evaluate the effects of an extra virgin olive oil enriched diet and active swallowing exercises on swallowing ability, speech, and weight status of people with MND. More information: vicki.flood@sydney.edu.au

Do regular breathing exercises help breathing function? (Melbourne)

Respiratory physiotherapist Nicole Sheers from the Victorian Respiratory Support Service is currently seeking volunteers to take part in a randomised controlled trial at Austin Health in Melbourne. This three-month study will evaluate whether performing daily breathing exercises helps breathing symptoms and lung function of people living with MND. More information: nicole.sheers@austin.org.au

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 David Berlowitz, VIC
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

MND Fact
More than 2,000 people have MND in Australia of whom 60% are male and 40% are female

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 430, North Sydney, NSW 2059

Donations can be made by cheque (payable to MND Research Institute of Australia). Visa or MasterCard donations can be made via phone (02 82874989) or online (mndresearch.org.au)

All donations of $2 and over are tax deductible.

ABN: 46 789 710 580

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
Phone Janet Nash, Executive Officer Research, on 02 8287 4989 or email janetn@mndaustralia.org.au

Thank you