mnd Research Institute of Australia

Advance

NEWSLETTER OF THE MND RESEARCH INSTITUTE OF AUSTRALIA

June 2016

Founded in 1984, the **Motor Neurone Disease Research Institute of Australia** aims to promote, support and fund the best research that has the greatest chance of realising the vision of a world without MND. Our research strategy aims to build the research workforce as well as promote collaboration and partnerships. We use a stringent review process that ensures only the best research applications are funded.

This June edition of Advance provides feedback on the grants that supported research in 2015. MNDRIA provided $2.57 million to fund 25 new grants in 2015 in addition to continuing to support nine grants from previous years. We are proud to report here the steady progress researchers are making. Research supported by MNDRIA in 2015 is helping to find new genes involved with MND, improve our understanding of MND biology, develop new animal models to better mimic MND as well as come up with new ways to detect MND early and monitor disease progression. The development of a decision support tool for people with MND and their families to use in conjunction with health professionals was a significant outcome for MND healthcare research.

We are indebted to the generosity of our donors and supporters who make all of this possible. A better understanding of MND through research is the only way we will be able to find treatments for this devastating disease. And together we are truly making a difference. MNDRIA scholarships and fellowships foster the best and brightest individuals working on MND in Australia. MNDRIA grants support a broad range of research areas given to only the most outstanding applicants. MND is complex and therefore it must be tackled on many fronts. Every dollar of every donation received by MNDRIA is spent on research.

Planning is well underway for the 2016 Annual MND Australia Research Meeting, which will be held at The Queensland Brain Institute in Brisbane on Friday 21 October *(see page 12).* Researchers with MNDRIA grants in 2016 are invited to present the outcomes of their funded research to their peers. A community research meeting "MND Research Connect" is scheduled for the following day, Saturday 22 October 2016, and whilst primarily for people with MND and their families, researchers are strongly encouraged to attend. Details of how to register will be available later in the year. We hope to see you there!

Betty Laidlaw MND Research Grant

Generously sponsored by John and Betty Laidlaw, the award of the Betty Laidlaw MND Research Grant was announced at a meeting on 9 May 2016 at the University of Melbourne. The three-year grant has been awarded to Dr Peter Crouch and collaborators for their project "Copper malfunction in MND: a therapeutic target for sporadic MND".

(more on page 2)

Dr Peter Crouch in his laboratory at the Department of Pathology, University of Melbourne with (L to R)
John Laidlaw
Melissa Duggan
Sarah Laidlaw
Jenny Michelmore
Mark Laidlaw

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Betty Laidlaw MND Research Grant

John and Betty Laidlaw generously donated $1 million to MNDRIA for a special grant for a collaborative and innovative three-year research project that aims to translate laboratory findings to an effective treatment for MND in humans.

Following independent peer review of applications by international reviewers, the Betty Laidlaw MND Research Grant has been awarded to University of Melbourne neuroscientist Dr Peter Crouch, to lead a multi-centre team working on copper-ATSM as a potential treatment for MND. Copper-ATSM has shown therapeutic potential in MND animal models by protecting motor neurones in the spinal cord, improving MND-like symptoms, and extending lifespan.

Dr Peter Crouch[1], Dr Blaine Roberts[2], Dr Dominic Hare[2,3], Associate Professor Anthony White[4], Professor Joe Beckman[5], Associate Professor Paul Donnelly[1], Professor Catriona McLean[6,7]

1. University of Melbourne 2. Florey Institute of Neuroscience and Mental Health
3. University of Technology Sydney
4. Queensland Institute of Medical Research
5. Oregon State University, USA.
6. Alfred Hospital 7. Monash University

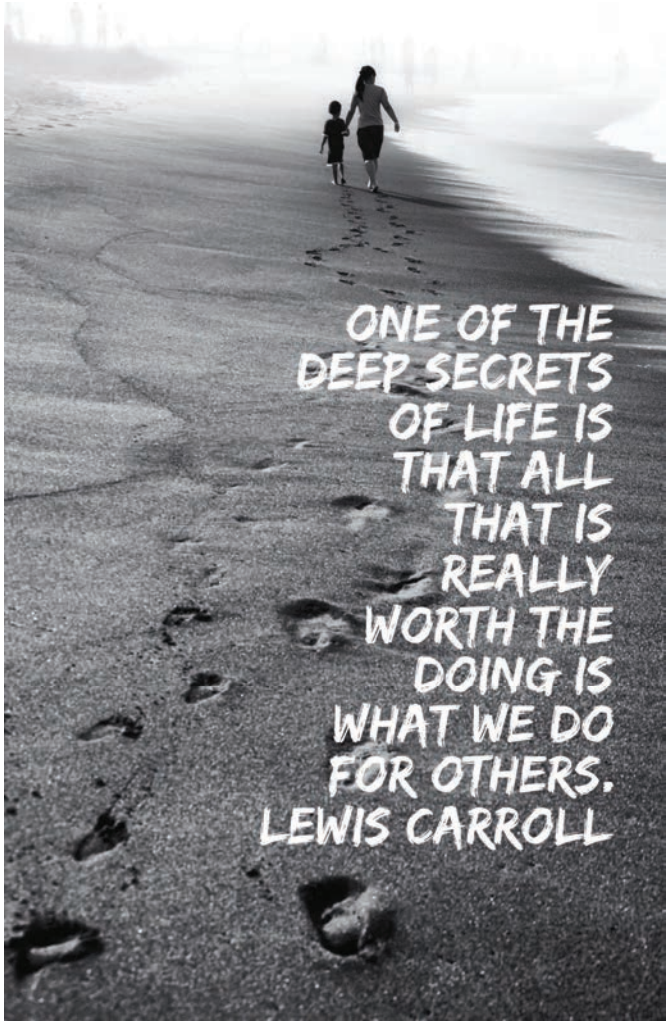
Copper malfunction in motor neurone disease: a therapeutic target for sporadic MND

We have developed the compound copper-ATSM as a treatment option for MND. Based on our outcomes from testing in animal models of MND and via our partnership with Collaborative Medicinal Development, Phase 1 clinical testing of the drug (for safety and tolerability) in Australian MND patients is due to start in 2016. As the initial stages of clinical testing commence, our current work in the research laboratory aims to broaden our understanding of the mechanistic relationship between copper-ATSM and the disease – the more we know about how the drug relates to the biology of MND, the more we'll know about who may be more responsive to the drug and when to give it to them.

We are currently investigating ways to monitor the drug's activity when given to people with MND and changes to proteins which we predict are related to the drug's activity. This new project will focus more on the fundamental biology underpinning the causes of MND. Specifically, we intend to obtain a better understanding of which drug-related processes fail in MND and when they fail relative to symptom progression. This work will generate the new information that can support further progression of copper-ATSM towards the efficacy stages of clinical testing.

Dr Peter Crouch and Betty Laidlaw MND Research Grant collaborators with John Laidlaw and family members and Janet Nash, Executive Director Research and David Ali, President, MND Australia.

Thank you



Thank you to all our donors!
All the research reported in this June edition of *Advance* is possible because of your generosity. With your help we are making a difference in understanding the causes and researching potential treatments and better care for people with MND.

Dr Stephanie Williams
Research Manager, MND Australia

Thanks to the generosity of the community, the past decade has seen an incredible growth in donations for research and therefore the number of researchers and projects MNDRIA is able to fund. To help with the additional tasks this increased support brings, we welcome Dr Stephanie Williams in a new role as MND Australia's Research Manager. Stephanie manages MNDRIA's grant application processes, annual research meeting, fundraising and communications, together with Janet Nash.

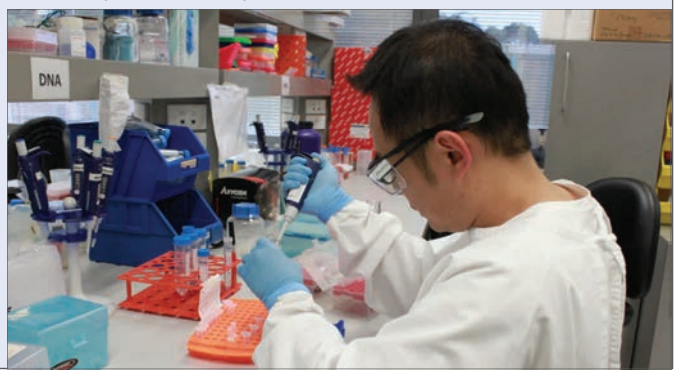
Stephanie has more than 20 years experience in health and medical research, advocacy, senior management and science communications. She began her career as a cancer researcher. After studying journalism, Stephanie moved into science communications and not-for-profit management.

Additional grants awarded by MNDRIA for 2016

Applications for this year's funding round for new grants commencing in 2017 will close on 26 August. The full range of grants offered and application details will be available at www.mndresearch.asn.au in June. We can only hope that donations received this year will fund similar quality and quantity of MND projects as has been possible for 2016.

PhD grants and travel grants are awarded later than the MNDRIA annual funding round which always closes at the end of August. August is too early for these grants; for travel it is difficult to make plans so far in advance and university and NHMRC scholarships are not confirmed until December or January.

The recipients of two travel awards as well as two PhD top-up grants and a co-funded NHMRC/MNDRIA PhD postgraduate award were announced by MNDRIA earlier this year. These grants are in addition to grants awarded at the MNDRIA Grants Allocation Meeting in November 2015.



NHMRC/MNDRIA co-funded Postgraduate Award 2016 - 2017

Dr Nidhi Garg University of Sydney

Clinical phenotypes and novel neurophysiological and immunological biomarkers in inflammatory neuropathy and neurodegeneration

The aim of this project is to gain a better understanding of inflammatory and degenerative neuropathies, such as chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and motor neurone disease (MND). At times it can be difficult to differentiate immune-mediated motor neuropathies from MND. The identification of specific antibody markers and neurophysiological parameters will aid in diagnosis of inflammatory neuropathies and differentiation from motor degenerative disorders such as MND. While we have treatment available for the inflammatory neuropathies (such as intravenous immunoglobulin or IVIg), no such treatment is yet available for patients with MND. Identification of novel biomarkers will allow for more accurate diagnosis, prognostication and better treatment planning for patients.

MNDRIA PhD top-up Grant 2016 - 2018

Dr Thanuja Dharmadasa
University of Sydney

Motor neurone disease: site of origin and patterns of disease spread

Motor neurone disorders are one of the most rapidly progressive age-related diseases known to man. However, poorly understood disease factors limit the development of adequate treatments. This clinical study will use examination findings, nerve studies, brain imaging and genetic testing to try and differentiate the various subtypes of MND, develop markers of disease, and identify the site of onset and the spread of disease. The goal of this clinical research will be to enable an early diagnosis, improve patient assessment and management, and provide new knowledge regarding nerve function in these patients. This overall insight will hopefully be able to advance the development of new treatment strategies.

MNDRIA PhD top-up Grant 2016 - 2018

Emily McCann Macquarie University, NSW

Investigating the genetic and epigenetic basis of ALS

There is currently no cure or effective treatment for MND, and genetic mutations are the only proven cause. Approximately 10% of MND is hereditary, and only two thirds of these cases are accounted for by known genetic mutations, leaving the cause of most MND unsolved. We aim to uncover further genetic variants and patterns of DNA chemical modifiers (epigenetic markers) that underlie MND by interrogating samples from MND patients and their families. Identifying such signatures of MND will provide greater insight into the molecular physiological processes underlying disease. As such, our research has great potential to identify targets for future MND therapeutics, particularly epigenetic markers that are reversible and targeted by many currently available drugs.

Susie Harris Travel Fellowship

Dr Rebekah Ahmed University of Sydney

Eating behaviour and cognition in the ALS-FTD spectrum: effect on survival

This grant will allow Rebekah to work on her project 'Eating behaviour and cognition in the ALS-FTD spectrum: effect on survival' with collaborators at the Institute of Metabolic Sciences, Cambridge, UK, and to present the findings of her work at the International ALS/MND Symposium in Dublin, Ireland, in December 2016. The Susie Harris Travel Fellowship is awarded in memory of the late Susie Harris. It is funded by the Susie Harris Memorial Fund and managed by MND Australia. The Fellowship aims to promote overseas activities that will enhance the quality of services, management or research for people living with MND.

Jenny & Graham Lang Collaboration Travel Grant

Dr Frederik Steyn University of Queensland

Re-evaluation of hypermetabolism and the assessment of endogenous adipose as a modifier of ALS/MND progression

This travel grant will support Frederik's work on 'Re-evaluation of hypermetabolism and the assessment of endogenous adipose as a modifier of ALS/MND progression'. Frederik will visit the laboratories of Professor Leonard van den Berg in the Netherlands and Professor Pierre-Francois Pradat in France. The grant will enable Frederik to strengthen and expand his research to help define patients most likely to benefit from metabolic-directed therapies. The Jenny and Graham Lang Collaboration Travel Grant is provided by MND Victoria to support travel and associated costs in 2016 for a postdoctoral fellow or final year PhD student to investigate and establish a collaborative project with other ALS/MND researchers.

Reports on outcomes of research projects funded by MNDRIA in 2015

Every research grant that is awarded by MNDRIA has been reviewed as part of a competitive process and endorsed by the MNDRIA Research Committee to ensure only the best research is funded.

MNDRIA predominantly funds grants-in-aid to seed innovative projects, as well as PhD scholarships and fellowships. From time to time, when funds are available, special grants are provided to support major initiatives. The MND Australia Leadership Grant 2013 – 2016 and the MND Australia Ice Bucket Challenge Grant 2015 – 2017 are two such special grants that support exceptional and established researchers.

The MND Australia Leadership Grant acknowledging Australia's leading mid-career researcher was awarded to Associate Professor Ian Blair in 2013 to build an MND research team at Macquarie University's Australian School of Advanced Medicine. The grant has supported Ian's progress in discovery of new MND genes and investigation of how defects in these genes lead to the death of motor neurones.

As a response to the overwhelming influx of funds from the MND Ice Bucket Challenge in 2014, the $1.05 million MND Australia Ice Bucket Challenge was awarded to support the SALSA (Sporadic ALS Australian) Systems Genomics Consortium led by the University of Queensland's Professor Naomi Wray and Macquarie University's Associate Professor Ian Blair. This is the largest collaborative MND research project ever to be funded by MNDRIA.

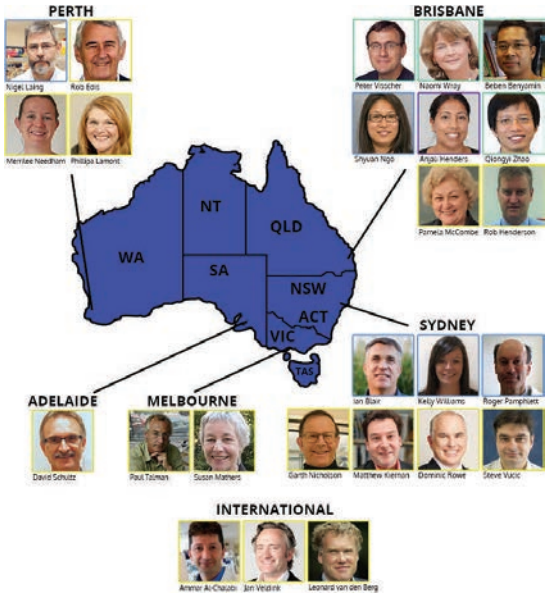
MND Australia Ice Bucket Challenge Grant 2015–2017

Professor Naomi Wray et al Queensland Brain Institute

Sporadic ALS Australian Systems Genomics Consortium (SALSA SGC)

The long-term aim of SALSA-SGC is to undertake genomics analyses of longitudinally collected biological samples as a tool to understand genetic and epigenetic factors contributing to risk and progression of sporadic ALS, a goal that requires high quality data.

Hence, our first aim was to share and harmonise protocols for optimised collection of clinical data and biological samples collected in ALS research clinics across Australia. Following dialogue with the collaborating clinicians we have developed a bespoke, online data collection platform and detailed sample collection protocols. Onsite training is in process with full roll-out expected over the next 6 months. A training workshop for research nurses in Brisbane is planned for August. Our protocols will benefit any in-clinic research conducted in Australia.

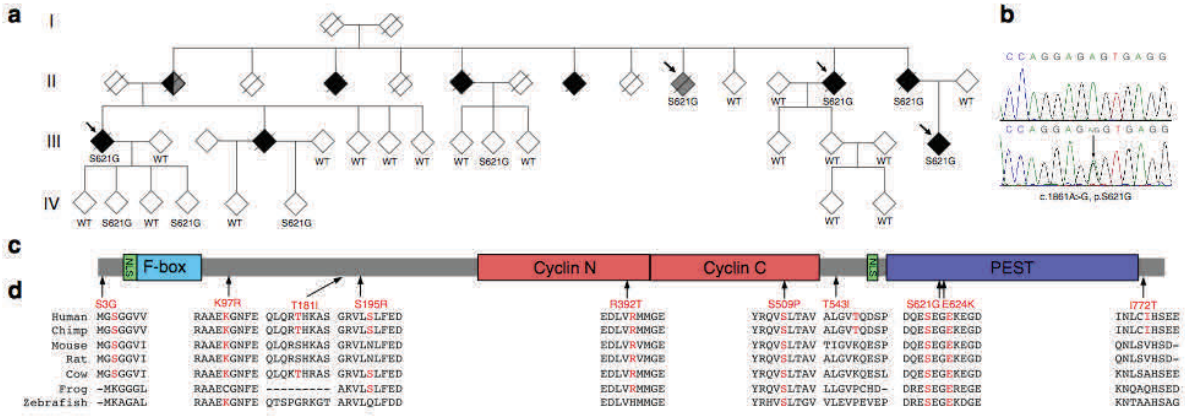


MND Australia Leadership Grant 2013–2016

Associate Professor Ian Blair Macquarie University, NSW

Investigating the pathogenic basis of familial ALS

There is an urgent need to better understand the causes of MND to develop more effective diagnostic tools and treatments for MND. Together with international collaborators, my group has identified recently described gene defects in Australian familial and sporadic MND patients (ERBB4, SS18L1, TUBA4A, TBK1). Our most recent gene discovery, CCNF, is responsible for disease in a subset of MND families from Australia, Canada, Spain, Italy, Japan, the UK and USA. Our research helps to gain a better understanding of MND biology and adds to the existing genetic testing regimes and looks for new therapeutic targets. As new genes are discovered, they can be used for the development of tests for use in prognosis and in monitoring drug trials in mice and ultimately in clinical trials.



CCNF mutations in ALS-FTD identified following genetic linkage analysis and exome sequencing

Reports from postdoctoral fellows funded by MNDRIA in 2015

Postdoctoral fellowships are awarded to outstanding Australian postdoctoral scientists with a track record in areas of neuroscience related to MND and who have no more than three years postdoctoral research experience.

These three-year awards enable early career researchers to focus their interest on MND as they become established and work towards independence.

Bill Gole MND Postdoctoral Fellowship 2015–2017

Dr James Howells University of Sydney

Hyperexcitability of the lower motor neuron in ALS

The loss of motor neurons in ALS leads to the re-innervation of denervated muscle fibres by the surviving motor axons. This research project aimed to test if the excitability of re-innervated motor units is altered because this may provide a peripheral mechanism for selective vulnerability of lower motor neurons. Research results support the hypothesis that the excitability of large single motor units is altered in ALS, with an increase in their excitability compared to recordings from normal controls. Mathematical modelling is underway to assist in the interpretation of these excitability changes.

Beryl Bayley MND Postdoctoral Fellowship 2015–2017

Dr Parvathi Menon Westmead Hospital, NSW

Insights into ALS pathophysiology from patterns of disease progression

My project aims to clarify the site of disease onset and patterns of progression underlying the development of neurodegeneration in ALS. The hypothesis is that cortical changes will be a primary event in ALS, preceding the development of muscle weakness and wasting. I am studying patients with ALS and recording responses from representative muscles from different body regions to assess for changes in brain responses, which may signal the onset of disease and to determine if these changes occur in normal appearing regions in patients before evidence for obvious changes in the muscle. In addition, I am following patients at regular intervals to establish the best prognostic measurements to help patients have a clearer understanding of their disease course as well as find the best markers to determine if a trial medication makes a difference to disease outcome.

Bill Gole MND Postdoctoral Fellowship 2014–2016

Dr Jacqueline Leung University of Tasmania

Investigating the role of oligodendrocytes in ALS

My project involves the investigation of the role of a non-neuronal cell type, called the oligodendrocyte, in disease progression in ALS. The role of oligodendrocytes is to form myelin, an insulating sheath around the neurons to allow rapid signal transduction. So far, I have examined these cells in a mutant SOD1 mouse model of ALS and identified an alteration in how these cells develop, suggesting that these cells cannot become mature and form myelin around the nerve fibres. I am now investigating how other proteins are involved in ALS. My preliminary studies have identified an increase in branching complexity in oligodendrocytes that have TDP43 protein introduced. However, these findings need further confirmation. Overall, results demonstrate that these cells have possible roles in ALS disease progression and may lead to novel therapeutic avenues targeting oligodendrocytes and myelin formation.

Bill Gole MND Postdoctoral Fellowship 2013–2015

Dr Kelly Williams Macquarie University, NSW

Investigating the molecular basis of ALS

We have used state-of-the-art genetic technologies to find a new defective gene, *CCNF*, which causes both familial and sporadic MND in diverse range of locations. The discovery of defects in *CCNF* will add to existing genetic diagnostic testing in MND families and provide further opportunities to investigate the causes of motor neuron degeneration in both familial and sporadic MND. In Australian MND patients with known causative gene defects, the course of disease varies among patients, including variable age of disease onset and duration of disease, even among those with identical gene mutations. This suggests the presence of disease modifiers. We have used an extensive cohort of Australian MND patients that are discordant for features of the disease (e.g. patients with early or late-onset; fast or slow progression) to search for these disease modifiers to enhance our understanding of the biology of MND, and potentially lead to therapeutic discovery.

Graham Linford MND Postdoctoral Fellowship 2013-2015

Dr Sharpley Hsieh The University of Sydney

Seeing the Future in MND

MND not only results in disabling motor impairments but about half of all patients show non-motor changes, which affect how patients think, behave and feel. This fellowship funded three studies into aspects of cognition, which have been little investigated in MND: (1) self-awareness of dysexecutive behaviour; (2) syntactical and semantic (general knowledge) impairments across the MND-FTD spectrum and (3) recollection of autobiographical memories. Findings showed that cognitive deficits in MND exist beyond the realm of executive functioning and extend through to language impairments, thus highlighting the MND-FTD disease continuum. Some aspects of cognition such as personal memories and neurocognitive insight, are reasonably well preserved at least in the early stages of MND, which has implications for how we understand MND illness. The multidisciplinary team can capitalise on aspects of cognition, which remain relatively well preserved to improve psychological wellbeing in a terminal illness.

Reports on PhD projects funded in 2015

Scholarships support the best and brightest new and emerging researchers entering the field of MND research.

The NHMRC/MNDRIA Postgraduate award for biomedical or public health research in MND is offered through the National Health & Medical Research Council (NHMRC) and is funded jointly by the MNDRIA and NHMRC.

PhD top-up grants are awarded as an incentive to outstanding students who have been awarded a University PhD scholarship for biomedical or public health research in MND.

NHMRC / MNDRIA Postgraduate Award 2014 - 2015

Dr Nimeshan Geevasinga University of Sydney

Electrophysiological and neuroanatomical determination of patients with ALS with the C9ORF mutation

This study explores ALS disease process in a group of patients with a familial mutation that predisposes them to developing ALS (c9orf72). We utilised a combination of neurophysiological tools to assess these patients, to better understand how ALS may begin and how it develops over time. The findings of our study suggest that a unique test called 'transcranial magnetic stimulation' may allow us to characterise ALS patients at an early stage, thereby allowing treatment to be facilitated earlier, when it is available. Furthermore, we have also undertaken work on facilitating diagnosing ALS patients at an earlier stage, utilising the current diagnostic criteria.

NHMRC / MNDRIA Postgraduate Award 2015 - 2017

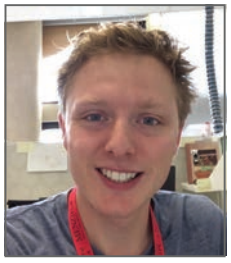
Nicole Sheers Institute for Breathing and Sleep
Austin Health, VIC

Lung Volume Recruitment in Neuromuscular Disease: Can 'breath-stacking' improve lung function, respiratory symptoms and quality of life for people with neuromuscular disease?

This project is also known as "Breath-stacking in Neuromuscular Disease" and started in February 2015. It looks at whether performing particular breathing exercises every day for three-months improves people's breathing function, cough effectiveness and quality of life. Much background work has been completed to get this clinical trial running, including purchasing and testing equipment so that breathing function can be measured in people's homes. Participant recruitment started in August 2015 and ten people with neuromuscular conditions have volunteered for this research so far. The focus this year is on recruiting interested people into the trial and collecting more information about the effect these breathing exercises may have.

PhD Top-up Grant 2013 - 2015

Jayden Clark
University of Tasmania



Axonal protection in ALS

Neuromuscular junctions (NMJs) are structures that signify and facilitate the connection between the nervous system and muscle, allowing for voluntary movement. We have recently identified that the processing of certain NMJ proteins is dysfunctional in a SOD1 mouse model of ALS. This suggests that mutant SOD1 can impede the incorporation of certain proteins into the NMJ. We also identified that the shape of the NMJ changes over time, becoming more immature as the disease course progressed. Whilst still not well understood, these alterations may benefit disease identification through biomarkers or via microscopy methods, as well as offer future therapeutic targets.

PhD Top-up Grant 2013 - 2015

Rosie Clark University of Tasmania

Interneurons dysfunction in amyotrophic lateral sclerosis: A new target for potential therapeutics?

Burgeoning research suggests an imbalance of excitation and inhibition exists in the brain of MND patients, prior to symptom onset. This imbalance may be central to disease progression. However, as yet, the cellular basis for this remains unknown. Our research has currently identified two distinct cell groups, called interneurons, which may underlie these alterations in the brain. Currently, we are hoping to determine why these cells are susceptible in MND, and what outcome their alteration will have on the cortical motor circuitry that becomes dysfunctional in patients. In doing so, we hope to identify future therapeutic targets for intervention.

PhD Top-up Grant 2013 - 2015

Jennifer Fifita Macquarie University, NSW

Examining the role of novel molecules causing motor neurone disease

The aim of my PhD was to identify novel gene mutations causing MND in Australian families. I began by sequencing the entire section of our DNA that encodes proteins in individuals with MND and members of their families. Using this data I identified a potential novel gene mutation causing MND. To determine if, in fact, this mutation can cause MND, I completed various functional analyses on the mutant protein and determined this mutation had a detrimental effect, and produced known aspects of MND pathology in neuronal cells models. My project strongly implicates this new gene as a cause of MND, though further work must be done to determine its role in MND both genetically and pathologically.

PhD Top-up Grant 2014–2016

Dr Rebekah Ahmed University of Sydney

Eating, autonomic and sexual dysfunction in FTD and ALS

It is recognized that frontotemporal dementia (FTD) and MND represent different spectrums of the one disease. Change in eating patterns is a major criterion for the diagnosis of FTD and is present in over 60% of patients. This work is the first to observe the eating habits of FTD patients in a test meal approach and to examine the effects that these eating changes have on metabolism. In MND there is increasing evidence that metabolic changes may affect disease progression, with factors such as hyperlipidemia and insulin resistance potentially being protective. In FTD we have established that there are similar metabolic changes to those seen in MND, raising the possibility that these factors may also be protective in FTD, offering the potential to examine specific interventions to modify prognosis.

PhD Top-up Grant 2015 - 2017

Victoria McLeod Florey Institute of Neuroscience and Mental Health, VIC

Androgen receptor dysregulation in ALS

The androgen receptor is a protein mediating the effects of the male hormone testosterone. It has been found to have an important support role in motor neuron health and survival as well as playing a role in Kennedy's disease, which renders motor neurons uniquely vulnerable to death, in cases often mimicking the symptoms of ALS. We have identified the androgen receptor as a potential protein, which may have implications in mediating disease progression and vulnerability of motor neurons in both the $SOD1^{G93A}$ and $TDP\text{-}43^{A315T}$ mouse models of ALS. The androgen receptor blocking drug, flutamide, has been shown to be successful in ameliorating disease progression in several mouse models of Kennedy's disease. A study is currently underway in which we are delivering flutamide to block androgen receptor signaling in $SOD1^{G93A}$ mice to determine the functional role of this receptor in ALS. An outcome of the impact of this drug on disease progression, survival, motor neuron and muscle pathology is anticipated in the near future.

Jenny & Graham Lang Collaborative Travel Grant 2015

This grant is awarded to support travel and associated costs for a postdoctoral fellow or final year PhD student to investigate and establish a collaborative project with other ALS/MND researchers. This may include a period working in a research facility overseas .

Dr Emily Don, Macquarie University, NSW

Generation of individualized zebrafish models of MND

An ongoing problem with MND research is the lack of animal models in which to explore the biological triggers that cause MND and trial new therapeutics. This has sadly led to a lack of effective treatments for patients suffering from MND. With this grant, I travelled to the laboratory of Professor Stephen Ekker at the Mayo Clinic, USA, where I was trained in world-leading gene editing techniques. In addition to forming new collaborations, I now have the knowledge to apply genome-editing technology to a unique animal model, the zebrafish, and will pass on this training to others in Australia. This precision genome editing will allow for more accurate animal models of MND. I would like to thank MNDRIA for the award of the Jenny and Graham Lang Collaboration Travel Grant to provide this amazing opportunity that I truly believe will aid the establishment of rapid, robust, high-throughput animal models, which will be individualised to a patient and used to seek a cure for MND

Susie Harris Travel Fellowship 2015

This grant is awarded in memory of the late Susie Harris. It provides funds for attending the International Symposium on ALS/MND and visiting a laboratory, hospital or care centre for training in new techniques, acquisition of knowledge or participation in collaborative research valuable for MND.

Dr Nimeshan Geevasinga, University of Sydney

Novel diagnostic algorithm for ALS and cortical excitability insights into Riluzole and ALS

I am grateful to MNDRIA and the Susie Harris Memorial Fund for the award of this grant which enabled me to attend the 'Ozdinler' Laboratory in Northwestern University, Chicago to meet with Professor Hande Ozdinler. Whilst I was at her laboratory, I was introduced to the molecular changes of ALS utilising novel mice models. Furthermore, interestingly some shared patterns of neurodegeneration were evident in the mice models, comparable to neurophysiological findings that we have identified in our human ALS patients. Going forward, we are hoping to collaborate with a view of undertaking ALS proteomics in her laboratory, in collaboration with our neurophysiological 'transcranial magnetic stimulation' technique. This would be a very important and cutting edge approach to evaluate the pathophysiology of ALS and monitor changes at a molecular, clinical and neurophysiological level.

Reports on nineteen grants-in-aid funded by MNDRIA in 2015

Grants-in-aid provide funding for one year to seed research that is innovative and has a clear relationship to the causes, treatments and cures of MND or the support of people living with MND. These development grants help researchers to initiate projects they can grow to attract more funding from large granting bodies such as the National Health and Medical Research Council. Named grants can be sponsored by donors raising $50,000 or more.

Angie Cunningham Laugh to Cure MND Grant

Associate Prof Julie Atkin Macquarie University, NSW

Optimising the protective activity of protein disulphide isomerase in motor neurone disease

We have identified that a 'chaperone' protein prevents abnormal protein clumps from forming in ALS/MND, and it is protective against the death of motor neurons. Whilst this chaperone is protective, it cannot be used as a new drug because it is too large to be delivered to the brain. Also, it was unknown which of the many functions of this chaperone are responsible for protection. Therefore, in this study we investigated which features are responsible for its protective ability, so that new drugs can be designed based on these features. We found that 'oxidase activity' is responsible for almost all the protective functions in ALS/MND. We are currently designing new drugs based on this oxidase activity. This study has found a new type of activity that is necessary to prevent motor neurons from dying in ALS/MND, which will form the basis of strategies to develop new drugs in the future.

MND Ice Bucket Challenge Grant-in-aid

Associate Prof Ian Blair Macquarie University, NSW

Next-Generation Sequencing of Australian sporadic MND patients to identify genetic risk factors

This research has launched Australia's role in a bold international initiative called Project MinE, the largest effort to-date to identify the genetic determinants of risk to ALS. We undertook whole genome sequencing of 35 Australian sporadic MND patients, which resulted in a huge list of gene variations that can only be understood in the context of thousands of similar sequences from those with, and without, MND. We are therefore collaborating with other large international initiatives to identify the genetic factors that confer risk to developing MND. The Australian data is under statistical genetic analysis to identify potential MND risk variants and has already been used to help another study internationally. This project has fostered greater collaboration between Australian groups and helped us to make a case for further funding to become a major contributor to Project MinE.

MNDRIA Grant-in-aid

Dr Catherine Blizzard University of Tasmania

Synaptic dysfunction: An early mechanism of TDP-43 pathogenesis in ALS?

ALS can be pathologically characterised by the accumulation of aggregated proteins in neurons, most commonly TDP-43. Normally, one of TDP-43's functions is to actively regulate synapses in neurons. This project aimed to determine how alterations in levels of TDP-43 protein lead to disruptions in synapses, and ultimately neuronal decline in ALS. To date, we have found that synaptic alterations are an early disease-causing event in a mouse model of ALS. Furthermore, using primary neuronal cultures, my research team has found that whilst TDP-43 does not affect neurite outgrowth, it significantly alters the formation of dendritic spines, indicating that the spine loss observed in the animal model is an intrinsic neuronal mechanism. We are currently trying to pinpoint the earliest changes in synapses in ALS in both inherited and sporadic forms of disease, using novel mouse models. Results obtained will provide a pathway for appropriately trialing a suite of new clinically relevant molecular targets as potential therapeutics.

Mick Rodger Benalla MND Research Grant

Professor Roger Chung Macquarie University, NSW

Proteomic studies to identify the defects in protein-protein interactions and cellular signalling pathways caused by mutations in a newly identified familial ALS gene

We have been investigating how newly discovered mutations in the *CCNF* gene cause ALS. The *CCNF* gene encodes for the Cyclin F protein, which is involved in tagging dysfunctional proteins for degradation. We have found ALS-causing mutations in Cyclin F increase this activity, leading to an accumulation of tagged proteins that are not able to be appropriately cleared by motor neurons, which we think ultimately leads to their degeneration. We have identified the proteins that inappropriately accumulate inside motor neurons expressing the ALS-mutations in Cyclin F, which indicates specific biochemical processes that have become dysfunctional in these neurons. This information is important, because it starts to identify potential targets for therapeutic intervention. Because the inappropriate accumulation of proteins within motor neurons is associated with all forms of ALS (not just those with *CCNF* mutations) we believe this discovery is important for all ALS cases.

Mick Rodger MND Research Grant-in-aid

Associate Prof Tracey Dickson University of Tasmania

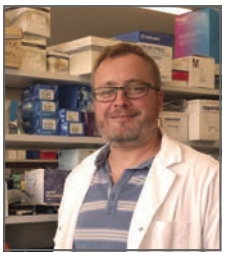
Inhibitory regulation of motor neurons: a new target mechanism for ALS?

There is evidence from many areas of medical research that in MND motor neurons may be dying due to a toxicity that is triggered from their overactivity – known as excitotoxicity. We and others have

new evidence that this toxic cascade may initially be triggered by the death or dysfunction of another type of neuron in the brain – the interneuron. Interneurons are critical regulators of motor neuron activity and modulators of the balance that is essential for normal brain function. We have developed a method of specifically growing interneurons and/or motor neurons, derived from transgenic mice developed to model MND, in primary culture. This highly specific 'brain in a dish' approach will allow us to determine if the presence of abnormal or pathogenic interneurons can lead to abnormal motor neuron function and pathology. These studies will provide important insight into the mechanisms responsible for ALS, and provide a high throughput model for later assessing potential therapeutic interventions.

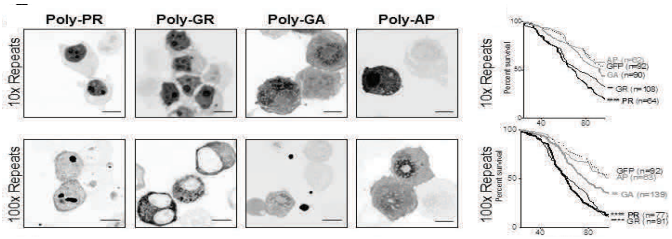
Peter Stearne Familial MND Research Grant

Dr Danny Hatters University of Melbourne



Determining the mechanism of toxicity of C9ORF72 RAN translation products

We made five different "junk" proteins that are known to accumulate in human tissue in the C9ORF72-forms of MND and investigated whether and how they damage simple cell culture models of MND. Three of the five proteins were found to be potently toxic to cell health and survival. Two of the most toxic proteins formed clusters tightly associated with the cellular DNA in the nucleus. Using a method called proteomics, we have determined which proteins in the cell stick to the various junk proteins. These results have unearthed candidate mechanisms for how the junk proteins cause toxicity. We plan to continue this research to more completely understand these details and unmask the mechanisms.



Graham Lang Memorial MND Research Grant

Dr Robert Henderson UQ Centre for Clinical Research

Blood Biomarkers in ALS: Translation into clinical practice of pNfH and search for additional biomarkers using proteomics

In 2015, our testing of 766 MND patient samples collected from 100 individual MND patients during their illness indicated a link between levels of neurofilament proteins in the blood of MND patients and the rate at which their illness progressed. In 2016, we are doing experiments to compare different ways of testing for neurofilaments to develop a standard test that helps give patients with MND some idea of how fast their illness is progressing and to help establish neurofilament testing as a measure of the effectiveness of clinical trial treatments. Neurofilament testing potentially offers people with MND an indication of how fast their disease is progressing and encourages faster development of drug treatments for MND.

MND Victoria Grant

Dr Anne Hogden Macquarie University, NSW

Decision support tools for MND multidisciplinary care

A journal article describing the protocol used in this study has been published in *British Medical Journal Open*. The paper is significant for two reasons. It is the first peer-reviewed publication to define the need for development of decision support tools to assist people living with MND. While these tools are well known in chronic disease and cancer care, this is the first time a suite of tools will be developed specifically for MND. Secondly, the process of tool development is innovative in MND healthcare research. Extensive consultation with expert panels of patients, carers, health professionals, researchers and representatives from MND Australia and MND NSW forms the basis of tool development. This comprehensive process will ensure that the tools developed are useful to patients and families, and relevant and feasible for MND clinical care.

MNDRIA Grant-in-aid

Professor Lars Ittner University of NSW

Novel MND mouse models

The aim of our study was to understand the role of profilin 1, a factor interacting and regulating the cytoskeleton in cells, in development and progression of MND. Mutations in the profilin 1 gene have been identified in three independent families with MND history. Experiments to understand profilin 1 have been limited to cultured cells because there was no animal model available. We have closed this gap and developed a novel MND mouse model based on profilin 1. Accordingly, we have generated genetically modified mice expressing profilin 1 together with mutations found to cause MND in patients. We found that already during the development of the central nervous system, differentiation of motor neurons in the developing spinal cord was compromised. These defects were functionally compensated initially, but as mice aged, they showed muscular deficits and poorer performance during motor function testing. Therefore, our data suggest that in people with profilin 1 mutations, problems during neuronal development contribute to clinical deficits that establish during adulthood.

Cunningham Collaboration Grant

Professor Pamela McCombe
UQ Centre for Clinical Research

A multicentre study of the impact of metabolic balance and dietary intake on the clinical parameters of disease progression

People with MND show a loss of fat mass throughout the course of disease. This is of clinical importance because a rapid loss of fat mass is associated with worse disease outcome. By studying the relationship between energy balance and fat mass in MND patients in

Grants-in-aid for 2015

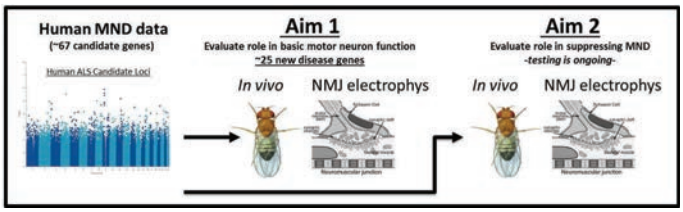
Australia, we have found that ~50% of our MND patients have increased energy needs when compared to people without MND. Our ongoing studies are tracking these changes in energy needs relative to disease progression and clinical features of disease, and we are now starting measurements in MND patients in the Netherlands.

Terry Quinn MND Research Grant

Associate Professor Greg Neely University of Sydney

Genomic approach to find new MND disease genes and drug targets

MND has been linked to failures in neuronal communication. Therefore, identifying factors and mechanisms that act at the sites of neuronal communication, the synapses, is crucial to understand the cellular hallmarks of MND. Over the past year, we have identified 161 regulators of motor behaviour, the vast majority not previously linked to synaptic architecture and function. Furthermore, by electrophysiology we have found two of these genes are novel regulators of synaptic function. Reduced expression of protein encoded by one of these candidates, Kinesin associated protein 3 (Kap3), leads to a defect in synaptic architecture. This work has significantly helped our understanding of genes involved in MND.



Bob Delaney MND Research Grant

Dr Shyuan Ngo The University of Queensland

In search of novel MND therapeutics: investigating the role of selective KATP channel activators on cortical hyperexcitability, corticospinal circuit degeneration, and cortical bioenergetics

In people with MND, increased activity of the brain cells that control movement is believed to be one of the primary factors that lead to their death. Through targeting a class of proteins that control cell activity by responding to the energy levels inside the cell, we have aimed to regulate nerve cell activity, with the view to prevent them from dying. Ongoing studies are testing multiple drug candidates to see how they may change nerve cell activity, and how they might improve survival and prevent the loss of nerve cells in the brain and spinal cord of MND mice.

MNDRIA Grant-in-aid

Associate Professor Peter Noakes
University of Queensland

The role of altered neuromuscular activity and mRNA transport in modifying the progression of MND

We have achieved our goal to establish a human neuro-motor circuit to assess motor neurone-muscle connection stability and transport of synaptic molecules in people with and without MND. Our research has found that muscle cells derived from MND patients are unable to effectively respond to motor neurone molecules to form specialised regions for motor neurone contacts. These results are exciting because they support the growing idea that a loss in the stability of connections between motor neurons and muscle is fundamental in progression of MND. We are now growing up MND and non-MND muscle to see if these differences extend across all MND derived muscles. We are also testing motor neurons that carry mutations to TDP43. This research has shown that mechanisms that drive MND can now be examined directly in human derived motor neurons and muscle. Secondly, the testing of drugs can now be screened in human derived motor neurons and muscle.

MNDRIA Grant-in-aid

Dr Rachel Tan Neuroscience Research Australia, NSW

Histopathological changes in functional zones of the cerebellum across the MND -FTD continuum

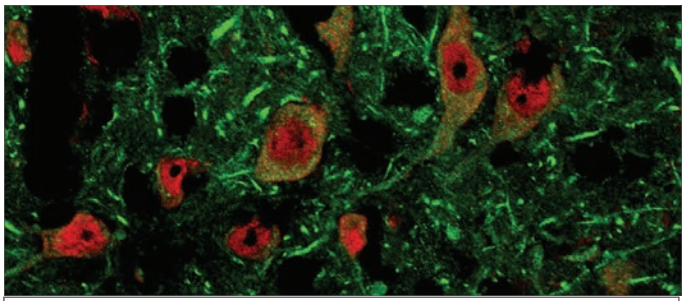
Approximately 80% of neurons in the human brain reside within the cerebellum, suggesting a pivotal role of this structure in intact neurological function. Despite this, the cerebellum remains largely overlooked in the study MND. Within the cerebellum reside the granule and Purkinje cells, which are respectively, amongst the smallest and largest neurons present in the human nervous system. Using well-established techniques, we assessed the integrity of these neurones across cerebellar functional zones targeted in MND. We found a significant and consistent loss in the 10% of ALS cases with an intermediate repeat expansion in the ATXN2 gene. No cerebellar neuronal loss was identified in patients with a C9ORF72 expansion, sporadic ALS or sporadic progressive muscular atrophy suggesting a different mechanism may therefore be involved with ALS cases that have an intermediate ATXN2 repeat expansion.

Ted Dimmick Memorial MND Research Grant

Dr Bradley Turner Florey Institute of Neuroscience and Mental Health, VIC

Androgen receptor abnormalities in MND

Genetic defects in androgen receptor (AR) signalling are seen in Kennedy's disease (KD). This project investigated the potential role of androgens and AR signalling in motor neurons in MND given the overlap with KD.



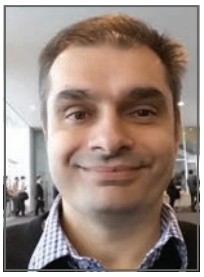
Photomicrograph of spinal cord section showing androgen receptor (green) and motor neurons (red) from MND mice.

Grants-in-aid for 2015

We have shown that AR protein is mainly found in motor neurons in the spinal cord. AR protein levels begin to progressively decline from symptom onset in spinal cords of MND mice, suggesting that loss of AR function in motor neurons may contribute to disease onset. Furthermore, AR loss occurred in motor neurons of male MND mice, but not females. These results suggest loss of AR function may be a common mechanism linking MND and KD, and could partly explain the increased incidence and severity of MND in males. Future studies will involve confirming these results and explore the therapeutic potential of AR for MND using approaches aimed at restoring or stimulating AR function in mouse models of MND.

MNDRIA Grant-in-aid

Professor Steve Vucic University of Sydney



Safety and biological efficacy of narrow-band UVB phototherapy in ALS

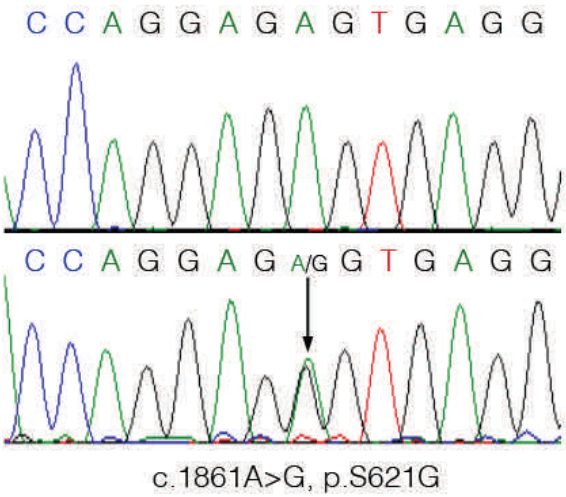
Recent evidence points to regulatory T cells of the immune system (Tregs) potentially slowing disease progression in amyotrophic lateral sclerosis (ALS). In this project we are conducting the first trial in ALS of narrow band UVB phototherapy, known to increase Treg activity. We have enrolled nine study participants with ALS in August-September 2015 from 47 potential participants; the treatment increased serum Vitamin D. A further 11 participants will be enrolled in winter 2016. Tregs will be analysed at the end of the study. Demonstration of safety and efficacy would support a larger trial examining whether UVB can slow disease progression.

Rosalind Nicholson MND Research Grant

Dr Kelly Williams Macquarie University, NSW

Epigenomic approaches to understand MND disease variability

Patients who possess identical genetic mutations can exhibit vast differences in clinical features of ALS. This demonstrates that modifiers of disease other than genetic predisposition are at play.



Sequence trace showing A to G gene mutation in the CCNF gene

We have been examining DNA samples from a large, well-characterised Australian ALS patient cohort that present with different manifestations of the disease (e.g. early onset, rapidly progressing disease, long disease duration or comorbidity with frontotemporal dementia, FTD). We are searching for physical changes to DNA that occur without altering the genetic code (epigenetic) that modify the onset and progression of ALS. Biostatistical analyses have identified epigenetic changes and patterns that differ between ALS and FTD patients. This work aims to enhance our understanding of ALS and help pinpoint potential therapeutic targets involved with disease onset and/or duration.

Charles & Shirley Graham MND Research Grant

Associate Prof Trent Woodruff University of Queensland

Therapeutic targeting of the NLRP3 inflammasome using a potent and orally active inhibitor in experimental MND

In this project, we investigated a novel component of the immune system (called inflammasomes) in the progression of MND. Our work has identified that this immune pathway is over-activated in MND mice, and increases as disease progresses. We have also shown that pathogenic MND proteins specifically activate this pathway in brain immune cells called microglia. Importantly, together with our collaborators, we have identified a potent, and orally active inhibitor of this immune pathway. We are now blocking this pathway in MND mice using this drug, and using gene-knockout techniques, to determine if we can slow disease progression. If we are successful, we hope our results will spur future MND clinical trials with this compound.

Zo-ee MND Research Grant

Dr Justin Yerbury University of Wollongong, NSW

Monitoring accumulation of ubiquitin chains in ALS: Developing a potential imaging tool for monitoring preclinical disease progression

Currently there are no effective treatments for MND. Although many drugs have showed promise in the laboratory none have translated to become symptom-slowing drugs in human trials. It has been proposed that MND may start inside motor neurons much earlier than previously thought, and potentially years before physical symptoms appear. We aim to develop an imaging molecule that would allow the detection of cellular dysfunction well before symptom onset. So far in this project we have validated specific molecule chains that accumulate in MND brain cells. This has allowed us to create a laboratory experimental paradigm that we can use to search for molecules that recognize these chains. We are almost ready to begin screening thousands of molecules to find a good candidate for this purpose. We believe that our screen and discovery of a molecule capable to bind these chains may in the future allow us to detect the disease earlier.

MND Research Institute of Australia

Office Bearers and Members June 2016

MND Australia is the principal member of the MND Research Institute of Australia.
Dr Ian Davis is a member of MNDRIA as a representative of the Cure for MND Foundation.
The operations of MNDRIA are the responsibility of MND Australia.

Directors

The board of the MND Research Institute is the same as the board of MND Australia, consisting 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 co-opted directors.

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

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Professor Dominic Thyagarajan, VIC
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Professor Naomi Wray, QLD

MND Australia Research Meeting 21 October 2016

This year's MND Australia Research Meeting will be held at the Queensland Brain Institute in Brisbane on Friday 21 October. Researchers with MNDRIA grants in 2016 are invited to present the outcomes of their funded research as oral and/or poster presentations. Submissions to present posters will also be welcomed from all researchers working in the MND field. We are looking forward to hearing progress made during 2016.

This meeting is intended for a research audience but all people with an interest in MND are invited to attend. There is no fee and refreshments will be provided.

We are grateful for the support of QBI and the University of Queensland and sponsorship from Biogen.

Queensland Brain Institute, University of Queensland
Friday 21 October 2016
9.30am—5.30pm Oral presentations
5.30pm—7.30pm Poster reception

MND Research Connect 22 October 2016

Introducing "MND Research Connect", a community meeting which will be held the day after the MND Australia Research Meeting. This meeting is intended for a community audience including people with MND and their families, health workers and others with an interest in MND.

Keynote speakers will be Professor Leonard van den Berg (University Medical Center Utrecht, The Netherlands) and Associate Professor Megan Munsie (Stem Cells Australia).

Professor van den Berg will speak about environmental factors and MND as well as the international Project MinE.

Professor Munsie will provide a stem cell research update .

Other topics will include looking at progress of clinical care research as well as an update on clinical trials in Australia.

We are most grateful to Dr Shyuan Ngo and Dr Frederik Steyn for organising this meeting.

There is no fee to attend and refreshments will be provided.

Queensland Brain Institute, University of Queensland
Saturday 22 October 2016 10.00am—3.00pm

Donations

Research funded by the Motor Neurone Disease 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 990, Gladesville NSW 1675

Donations can be made by cheque (payable to MND Research Institute of Australia) or credit card (Visa or MasterCard) or online at www.mndresearch.asn.au.
All donations of $2 and over are tax deductible.

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,
phone Janet Nash, Executive Director Research on 02 8877 0990 or email research@mndaust.asn.au.

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