mnd Research Institute of Australia

Advance

NEWSLETTER OF THE MND RESEARCH INSTITUTE OF AUSTRALIA

December 2016

The **Motor Neurone Disease Research Institute of Australia** (MNDRIA) promotes, supports and funds only the best MND research in Australia that has the greatest chance of realising the vision of a world without MND. Investment along the entire research pipeline, from the laboratory to healthcare, is integral to MNDRIA's research strategy. Funding is awarded following a transparent, competitive process and a meeting of MNDRIA's expert Research Committee to discuss applications. This year, the Institute received a record 104 applications for new projects. MNDRIA has allocated $3.75 million to support research in 2017. A total of 32 grants have been awarded, which include four healthcare projects. Two new grants were given out this year in addition to two three-year fellowships and 29 grants-in-aid: the Betty Laidlaw MND Research Prize for an outstanding mid-career researcher (story below) and the Charcot Grant, to be given annually for the highest ranking grant-in-aid application. The Charcot Grant was awarded to Queensland researcher Dr Shu Ngo for her project "Metabolic exploration in neurodegenerative disease: synergy between derangements in systemic and muscle metabolism in MND." Research funding through MNDRIA is vital in ensuring Australian researchers remain at the forefront of the global fight to stop MND. Our understanding of MND has transformed in recent years thanks to the tireless efforts of researchers, donors and supporters. We are deeply grateful to the thousands of people who have made this possible. Brief descriptions of the research to be supported in 2017 are outlined in this newsletter and demonstrate the scope of MND research in Australia. We hope you enjoy the read.

Betty Laidlaw MND Research Prize awarded

From left to right: MND Australia Executive Director Research Janet Nash, Dr Catherine Blizzard, John Laidlaw, Melissa Dugan.

The inaugural Betty Laidlaw MND Research Prize has been awarded to Dr Catherine Blizzard from the Menzies Institute for Medical Research, University of Tasmania. The Prize rewards an outstanding mid-career researcher with a demonstrated background of excellence in neuroscience research to undertake an innovative project with the potential to lead to effective treatments for MND.

Catherine received the award from John Laidlaw and his daughter Melissa Dugan at the MND Australia Research Meeting 2016 held at the Queensland Brain Institute on 21 October. Catherine's research aims to understand why nerve cells in the motor cortex of the brain are vulnerable to MND. Her project "TDP-43 misprocessing drives synaptic deficits and ALS" will investigate how defective function of TDP-43 alters nerve cell communication and how these changes lead to nerve cell death.

The Betty Laidlaw MND Research Prize will be awarded each year for another three years, thanks to the generosity of John and Betty Laidlaw. John's wife, Betty, has a slowly progressive form of MND. Catherine says the Prize will help her establish her work and give her a kick-start. "I'll be able to increase capacity, employ a few people and increase the scope of my research. I can build momentum. It's an incredible opportunity."

MNDRIA funding has played an important role in nurturing Catherine's emerging career. She completed her PhD in March 2011 and was awarded the prestigious Bill Gole Postdoctoral Fellowship (2011 - 2013) from MNDRIA to investigate the role of excitotoxicity in MND. In 2015, Catherine won an MNDRIA grant-in-aid to investigate how TDP-43 protein mutations affect nerve cells. We look forward to following her progress.

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Motor Neurone Disease Research Institute of Australia

Executive report 2015 - 2016

The past year was marked by a truly magnificent gift to the MND Research Institute of Australia (MNDRIA) from John and Betty Laidlaw. Our heartfelt thanks to the Laidlaws for their generous $1 million donation and for moving us closer to a world without MND. The Betty Laidlaw MND Research Grant was awarded to University of Melbourne neuroscientist Dr Peter Crouch in May to lead a multicentre team working on a drug called copper-ATSM as a potential treatment for MND.

During 2015 – 2016, research highlights included making inroads in understanding the genetics of MND. Research supported by MNDRIA and led by Dr Kelly Williams and Associate Professor Ian Blair at Macquarie University, found a new genetic cause of MND and frontotemporal dementia. Three new genes known as *C21orf2*, *MOBP* and *SCFD1* were linked to MND, and a fourth gene, *NEK1*, was confirmed as being associated with MND. The findings are the result of a huge international effort that was partly funded by MNDRIA.

There was also a significant advance in MND care research supported by MNDRIA. Associate Professor David Berlowitz led a study that showed non-invasive ventilation increased survival by an average of 13 months and was most useful for people with ALS-bulbar disease.

These research advances would not be possible without the generosity of bequestors and donors. Collaboration with the Cure for MND Foundation introduced the awarding of grants through the MNDRIA grant allocation process with $1.74 million contributed to 13 grants in their name. In total, MNDRIA awarded a record-breaking $5.978 million to 42 new research projects in 2015 – 2016. Eight additional grants continued in 2016.

Bequests continue to provide a significant proportion of funds each year. MNDRIA is fortunate to have the steadfast support of the State MND Associations and loyal donors who give so generously every year. Association contributions of $636,466 are the core of research funding this year, with special thanks to MND Victoria who contributed an amazing $380,000.

Congratulations and thanks also to MonSTaR Foundation whose very successful annual golf day marked 10 years of supporting MND research and achieved their first named grant in 2016.

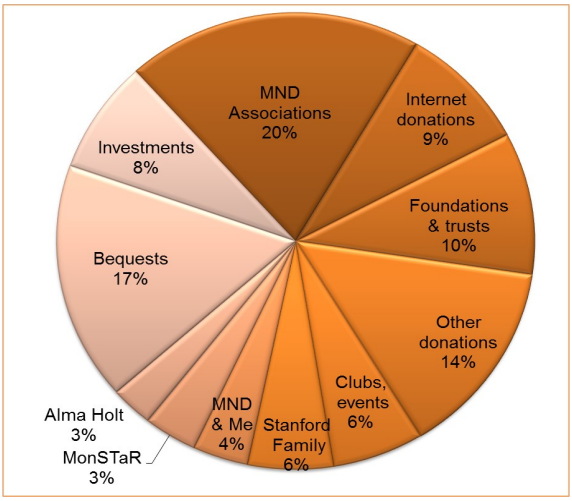
The 11th annual MND Australia Research Meeting was held at the Sydney Nursing School, University of Sydney, in November 2015. Many thanks to Professor Matthew Kiernan and his team for their assistance with arranging the meeting, and to Biogen for their generous sponsorship. The meeting is held in different states each year to facilitate attendance from a broad range of MND researchers and interested members of the MND community. Researchers funded by MNDRIA in 2015 presented the outcome of their research to an audience of over 150 people.

Thanks to the generosity of the community, the number of researchers and projects MNDRIA is able to fund has grown over the last decade. To help with the additional tasks this increased support brings, we welcomed Dr Stephanie Williams in a new role as MND Australia's Research Manager in February. Stephanie manages MNDRIA's grant application processes, annual research meeting, fundraising and communications, together with myself. Stephanie has more than 20 years experience in health and medical research, advocacy, senior management and science communications.

Alan Hauserman and Maureen Burmeister continue as highly valued volunteers, providing steadfast support. Maureen's assistance with the MNDRIA accounts before the annual audit ensure all runs smoothly.

Professor Matthew Kiernan was re-elected as Chair of the Research Committee in October 2016. I thank the Research Committee for their commitment to reviewing grant applications and ensuring only the best MND research is supported. With the ongoing dedication of our supporters, the guidance of our expert Research Committee and the ingenuity of Australia's researchers, we will continue to work unwaveringly towards changing the future of MND.

Janet Nash, Executive Director Research



Sources of MNDRIA funds for new grants in 2017

Research grants awarded by MNDRIA for new grants commencing in 2017

MNDRIA's research strategy is about building the research workforce, promoting collaboration, encouraging strategic partnerships within the research community and facilitating information flow. MNDRIA invests in the entire research pipeline from the laboratory to healthcare. We are committed to supporting high quality research and encouraging researchers at all stages of their research careers to dedicate their efforts to MND research. MNDRIA-funded researchers are involved in local and international collaborations which foster excellence.

MNDRIA supports the best and brightest students through **PhD scholarships** and **top-up grants**. After gaining a PhD, these emerging researchers are eligible to apply for a highly prized **postdoctoral fellowship**. These fellowships offer salary for three years to help early career researchers gain a track record and move towards independence. MNDRIA **grants-in-aid** provide seed funding to established researchers to initiate 12-month projects that will grow to attract major project grant funding from other sources such as the National Health & Medical Research Council.

When funds are available, special grants are given out from time to time. Earlier this year, the Institute was thrilled to be able to offer the $1 million **Betty Laidlaw MND Research Grant** for an innovative multicentre study. The three-year grant was awarded to Dr Peter Crouch at The University of Melbourne for his ground-breaking work on copper-ATSM in May 2016 (see the June 2016 *Advance* newsletter for more details). Thanks to the incredible generosity of John and Betty Laidlaw, MNDRIA was also able to offer a mid-career award this year for the first time, the **Betty Laidlaw MND Research Prize**. This award is for an outstanding mid-career researcher and aims to help an individual 5 -10 years post-PhD get established. The inaugural Betty Laidlaw MND Research Prize was awarded to Dr Catherine Blizzard based at the Menzies Institute for Medical Research in October (see below for project details).

Applications will close at the end of January 2017 for a **PhD top-up grant** and the **Susie Harris Travel Fellowship**.

Mid-career Fellowship: $250,000 for one year

Betty Laidlaw MND Research Prize

Dr Catherine Blizzard
Menzies Institute for Medical Research, University of Tasmania
TDP-43 misprocessing drives synaptic deficits and ALS

Both inherited and sporadic ALS is defined by characteristic pathology of the protein TDP-43. Our research has identified a novel mechanism for how a disease associated mutation to this protein is causing degeneration of the nerve cells of the brain. We propose that the mutant protein causes a very early breakdown in communication between nerve cells. Importantly, these changes occur before obvious symptoms, potentially giving significant insight into how the disease may start. We will investigate how defective function of TDP-43 alters nerve cell communication and how these changes lead to nerve cell death that characterises ALS.

Postdoctoral MND Research Fellowships: $100,000 per year for 3 years

Bill Gole MND Postdoctoral Fellowship (2017 - 2019)

Jennifer Fifita
Macquarie University, NSW
Investigating the molecular and pathological origins of amyotrophic lateral sclerosis

This project aims to use next-generation sequencing technologies to identify gene mutations that cause ALS, or may increase the risk of developing ALS, in patients with both familial and sporadic ALS. To understand how these new mutations cause disease, each will be studied in neuronal cell culture models, as well as in a zebrafish animal model. The identification of new ALS genes adds to DNA diagnostic testing, and provides a greater understanding of the underlying cause of ALS. New genes can be used to develop new cell and animal models, which will greatly assist in the testing and development of novel treatments for this devastating disease.

Beryl Bayley MND Postdoctoral Fellowship (2017 - 2019)

Dr Emma Devenney
Brain and Mind Centre, University of Sydney
Behaviour, cognition, eye-movements and psychiatric disease in C9orf72 MND and FTD; a cross modal-approach to facilitate early and accurate diagnosis

Firstly, this project will measure eye movements in patients with MND, FTD, and the C9orf72 expansion, and also asymptomatic carriers of the expansion. This work will identify the exact nature of eye-movement abnormalities in these conditions and determine whether they are a feature of pre-symptomatic disease. Secondly, this study will address the issue of psychiatric symptoms in the same disease cohort by determining the underlying causes of these symptoms, which will inform future management strategies.

29 new Grants-in-aid for 12-month projects in 2017 (up to $100,000 each)

Charcot Grant

Dr Shyuan Ngo
The University of Queensland
Metabolic exploration in neurodegenerative disease (MEND): synergy between derangements in systemic and muscle metabolism in MND

Our current study into energy needs in MND has shown that people living with MND use more energy than expected. We also have exciting new data that shows that skeletal muscle of MND patients becomes energy hungry, and that this might cause the overall increase in energy needs in people living with MND. We now aim to further investigate the relationship between the overall energy needs of MND patients and the energy needs of their skeletal muscle. Insights gained from this study will help us develop therapies that are personalised to match the precise energy needs of individual MND patients.

The MND Puzzle, courtesy of Shu Ngo & Derik Steyn.

MNDRIA Grant-in-aid

Associate Professor Julie Atkin
Macquarie University, NSW
Telomere dysfunction in ALS/MND

The risk of developing MND increases with age, but the reasons why are unclear. Most genetic forms of MND are caused by mutations in a protein called C9ORF72, and we have evidence that this damages DNA and binds to telomeres. Telomeres protect the ends of our chromosomes and they shorten with age. DNA cannot be replaced so damage to chromosomes can have serious consequences for the cell. Hence, in MND, loss or shortening of telomeres could lead to motor neurone death. We aim to characterise the telomeres in C9ORF72-MND, and determine whether telomere dysfunction triggers degeneration/death of motor neurones.

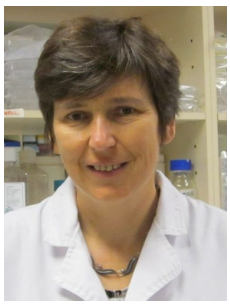
Mavis Gallienne MND Victoria Research Grant

Associate Professor David Berlowitz
Institute for Breathing and Sleep, VIC
Lung volume recruitment in neuromuscular disease

As MND progresses, the inability to breathe deeply or cough effectively becomes more distressing. Breathing complications, chest infections and respiratory failure are debilitating and contribute to early death in people living with MND. “Breath-stacking” is a simple, inexpensive therapy that helps people take deep breaths. Doing this daily may stretch the chest wall, improve lung capacity, cough strength and slow the decline in breathing. This research trial is the first in the world to test whether performing these exercises regularly improves breathing function, symptoms, cough and quality of life for people living with MND over three months.

MNDRIA Grant-in-aid

Dr Karin Borges
The University of Queensland
Triheptanoin to improve energy metabolism in MND



Recent research indicates that problems in energy metabolism contribute to disease progression in MND. Thus alternative fuel sources are a promising approach to treat MND. Triheptanoin, the triglyceride of heptanoate (a C7 fatty acid), has already been used safely for 15 years in other disorders for energy metabolism and neuromuscular disorders. In an MND mouse model, it protects against motor neurone death and delays the onset of motor symptoms. We will generate more data to show that triheptanoin targets metabolic impairments that contribute to MND. These new data will be crucial to initiate large clinical trials of triheptanoin in MND.

Mick Rodger MND Research Grant

Dr Christopher Bye
The Florey Institute of Neuroscience
Understanding disease susceptibility in idiopathic MND

Sporadic MND causes 90% of disease in patients, yet we have an extremely limited understanding of why these patients become sick, in part due to our inability to model sporadic forms of the disease. The advent of iPS stem cell technology now allows us to take cells from patients, and use them to generate genetically identical motor neurones in the laboratory. In this proposal we are using iPS cells from sporadic MND patients in a newly developed long term disease model to understand why neurones from these patients are susceptible to disease, and potentially develop new treatments.

Grants-in-aid for 2017

Graham Lang Memorial MND Research Grant

Ashley Crook
Macquarie University, NSW
Preventing motor neurone disease: barriers, facilitators, costs and benefits of genetic testing for MND in Australia

Preventing and reducing incidence of MND is only currently possible in families with a known faulty MND gene, through access to reproductive options that prevent passing on the faulty gene to future children. Little is known about how individuals from these families decide whether to have genetic counselling, have genetic testing and undergo reproductive options. We will explore what factors influence these decisions, and assess the cost-effectiveness of different genetic testing options in Australia. We will use this information to create evidence-based guidelines for MND clinics and clinicians on genetic counselling and associated genetic testing options for familial MND.

MNDRIA Grant-in-aid

Dr Peter Crouch
The University of Melbourne, VIC
Mitochondrial TDP-43

A protein known as TDP-43 is involved in the development of MND but the biological mechanisms through which it does so remain unclear. Over the past few years we have investigated if/how TDP-43 affects mitochondria – the energy-producing components that exist within all cells. We have established that TDP-43 interacts with mitochondria and, recently, an independent international team has shown that MND-causing changes to TDP-43 affect the way in which it interacts with mitochondria. The focus of our current work is to better understand the relationship between TDP-43 and mitochondria, and how this relationship may contribute to the development of MND.

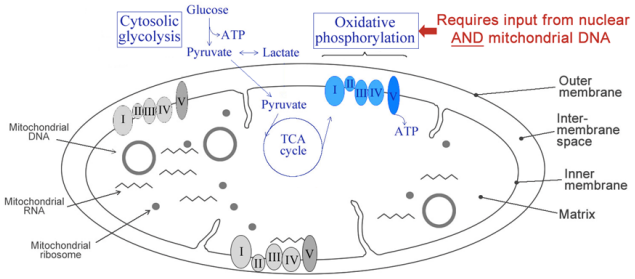


Diagram of a mitochondrion, found in large numbers in living cells. Processes take place inside mitochondria to produce energy.

Jenny Simko MND Research Grant

Professor Victoria Flood
The University of Sydney and Westmead Hospital, Western Sydney Local Health District, NSW
The effects of active exercise combined with an enriched diet on swallowing, speech function and weight in patients with MND; a randomised trial

Eating, drinking and speaking are an important part of our life and patients with MND experience a rapid decline in these functions. Research suggests that active exercise might prolong the ability to eat and drink safely and prolong the ability to speak, however no thorough research has been conducted. Other research suggests that changes in diet might slow the progression of MND, with improved maintenance of weight status and muscle function. This study will be the first to evaluate the effects of these diet changes in patients with MND combined with active exercising on swallowing function, speech and weight status.

MNDRIA Grant-in-aid

Dr Fleur Garton
The University of Queensland
Cell-free DNA and ALS; insight into disease mechanisms and Progression

The last five years have seen rapid discovery in identifying the genes that cause ALS. Parallel investigations that improve diagnosis and patient monitoring would benefit from an objective blood-based marker of disease. In this proposal, we hypothesise that levels of cell death may increase with ALS and correlate with disease progression. We will measure cell death in ALS patients, healthy individuals, and an ALS mouse by investigating levels of circulating cell-free DNA (cfDNA). Using a cfDNA test as a biomarker for ALS presents a significant opportunity for early detection of motor neurone death and hence, rapid improvements in diagnosis.

Dr Paul Brock MND NSW Research Grant

Dr Nimeshan Geevasinga
University of Sydney, NSW
Functional and structural connectivity in ALS

MND is a progressive disorder with the underlying etiology still undetermined. Recent work has suggested cortical dysfunction, with MND and frontotemporal dementia represents a disease continuum. We will use novel MRI techniques to explore changes in brain connectivity in ALS patients. Whilst there is some data on the MRI structural changes, an evolving area of neuroimaging is exploring a concept of 'Connectomics',

looking at comprehensive maps of the human brain, then identifying which areas have increased/reduced connections in ALS patients, when compared to healthy controls. Furthermore these changes will then be correlated with novel neurophysiological biomarkers and clinical demographic scales and scores.

MNDRIA Grant-in-aid

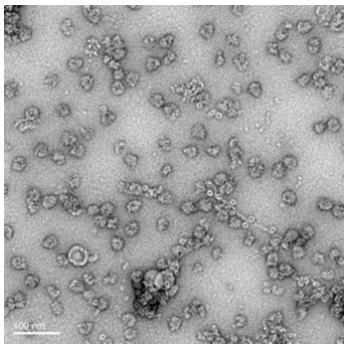
Dr Jean Giacomotto
The University of Queensland
New and innovative polygenic approach for understanding and modelling MNDs in zebrafish

ALS is a complex disease, lacking appropriate treatment. Although its cause appears to be multifactorial, there are strong evidences that genetics plays a role in some patients. Therefore, we believe that we can use genetics to understand this disorder and find therapeutics. Different forms of ALS exist, but they all share a common hallmark: motor neurone degeneration. We are using an innovative genetic approach in zebrafish to elucidate the individual and synergistic pathogenic role of risk-genes with the ultimate goal of generating an animal presenting motor neurone degeneration, paving the way to find therapeutics for all forms of the disease.

MNDRIA Grant-in-aid

Professor Andrew Hill
La Trobe University, VIC
Harnessing the power of exosomes to understand MND

The presence of aggregates of protein in the brain is characteristic of MND; however, the process by which they spread throughout the brain has eluded the MND field despite concerted efforts. We recently developed an innovative new methodology that is capable of studying protein spread in the human brain. We aim to implement this methodology in MND to discover how proteins spread from cell to cell in the diseased human brain.



Exosomes successfully isolated from the human brain. *This is a transmission electron micrograph of exosomes isolated from human frontal cortex. Scale bar = 100 nm*

Jenny Simko MND Research Grant

Associate Professor Mark Howard
Institute for Breathing and Sleep, VIC
Translation of respiratory biomarkers into MND practice

The inability to breathe is unfortunately the most common cause of death in people living with MND. Our research group reported that breathing assistance using noninvasive ventilation (NIV) increases survival by 13 months. Importantly, respiratory muscle strength appeared to identify the best time to start NIV. We propose to use 25 years of Australian Motor Neurone Disease Register data to confirm our preliminary findings. These experiments will enable clinicians to advise individual people with MND about when breathing assistance should be started to maximise benefit and assist researchers to optimise the design of therapeutic trials in MND.

Alma Grace Holt MND Research Grant

Dr Anna King
Wicking Dementia Research and Education Centre, Tas
Staying connected: determining targets to protect neuronal circuitry in ALS

Nerve cells are specialised cells which communicate with each other along long axons. MND is characterised by the nerve cells losing the ability to communicate with each other in a process called axon degeneration. Axon degeneration occurs in the motor nerve cells in the brain as well as those that control the muscles. The goal of our work it to determine the mechanisms by which axons degenerate in MND in order to find therapeutic targets to stabilise and maintain the function of these axons and their connections

MNDRIA Grant-in-aid

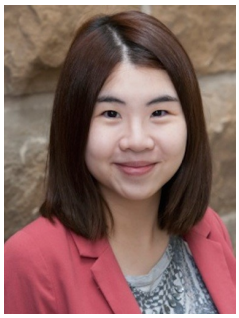
Dr Albert Lee
Macquarie University, NSW
Investigating the regulatory roles of Cyclin F phosphorylation in the development and prevention of amyotrophic lateral sclerosis

Our team recently identified mutations in a new ALS/FTD gene that encodes the protein Cyclin F. It is involved in maintaining cellular health by tagging unwanted proteins (ubiquitylation) for breakdown and recycling within the cell. Mutant versions of Cyclin F, found in ALS patients, are defective in that they lack the necessary features (addition of a phosphate molecule) needed to regulate proper function, which ultimately leads to increased ubiquitylation and accumulation of proteins.

Grants-in-aid for 2017

This project will investigate new mechanisms of regulating Cyclin F activity that will contribute to our understanding of reducing abnormal accumulation of proteins inside motor neurones.

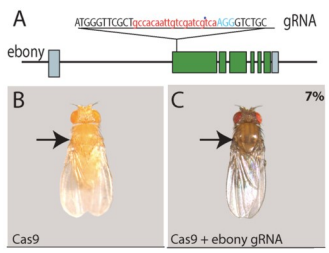
MNDRIA Grant-in-aid
Dr Jacqueline Leung
Wicking Dementia Research and Education Centre, Tas
Identifying the role of oligodendrocytes in disease onset and progression in amyotrohpic lateral sclerosis



In this project we will determine the role of a cell type called the oligodendrocyte in ALS. These cells produce myelin, a fatty layer surrounding the neurone processes that facilitates rapid signal transduction and provide structural support. Although oligodendrocytes appear to be affected in ALS with the presence of insoluble TDP-43 protein, in a similar way to the nerve cells, their role in ALS is unclear. In this project we will develop a mouse model with TDP-43 pathology in oligodendrocytes to determine its effects on nerve cells. This will provide evidence supporting oligodendrocytes as a potential therapeutic target in ALS.

MNDRIA Grant-in-aid
Dr Sean Millard
School of Biomedical Sciences, University of Queensland
Functional analysis of ALS candidate genes

To effectively treat ALS, the functions of the genes involved need to be determined so that biologically relevant therapies that modulate progression of the disease can be identified. This grant will assess whether genes associated with ALS in human genome-wide association studies function at the neuromuscular junction of *Drosophila melanogaster.* The majority of the genes for ALS identified to date are conserved in fruit flies making this an ideal platform for assessing what these genes do. These studies will enable us to assign functions to several new ALS candidate genes, laying a foundation for future therapeutic studies.

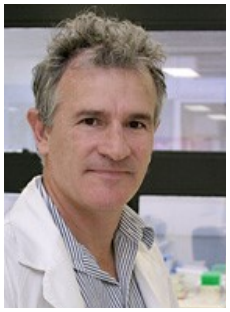


Making mutant fruit flies for example with the ebony gene. A is a diagram of the ebony gene which is cut into the genetic make up of the fly. B is a "control' fly without the ebony gene. C is an ebony mutant fly and has a dark coloured body.

MNDRIA Grant-in-aid
Associate Professor Greg Neely
University of Sydney, NSW
Functional genomic dissection of motor neuron disease

There are currently no effective therapies for treating MND and potential drug targets are desperately needed. Recent human genetics efforts to identify MND genes have been difficult, suggesting complimentary approaches may be useful. Since MND involves defects in synaptic function in motor neurones, here we will define the core synaptic machinery required for proper motor neuron function and identify synaptic targets that can suppress development of MND *in vivo*. These efforts will illuminate new conserved regulators of motor neurone function, information that can then be used to develop novel therapies for this devastating illness.

MNDRIA Grant-in-aid
Associate Professor Peter Noakes
The University of Queensland
Targeting neuromuscular stability in MND



Motor neurones attach to muscle cells in the body and make muscles work. Muscle weakness occurs in MND when the end of the motor neurone moves away from the muscle cell. We believe that there is a breakdown in the communication between the motor neurone and the muscle causing the neurone to withdraw. We will take muscle cells from patients with MND, place them in culture, and test them to see if they respond to chemicals normally released from motor neurones which make muscles work, and look at ways to stabilise the connection between them to improve muscle strength.

MND and Me Foundation Research Grant
Professor David Pow
University of Queensland Centre for Clinical Research
Discovery of EAAT5 – a protein that may stop glutamate excitotoxicity in ALS

The cause of ALS is unclear; however, much evidence suggests that toxicity from a chemical called glutamate plays a key role. Indeed, the only therapy that improves survival in ALS acts through modulating glutamate. Therefore, finding additional mechanisms to prevent glutamate toxicity is an attractive target for the treatment of ALS. This project has a new approach to this. We have identified a new protein (EAAT5) that turns off glutamate release. It also acts as a transporter to mop up glutamate, terminating the excitatory effects. Preliminary studies showed that EAAT5 is reduced in the spinal cord of an animal ALS

model. This loss of EAAT5 would cause a rise in glutamate levels and cause death of motor neurones. This study will define the anatomical and cellular distribution of EAAT5 in normal and diseased human nervous tissues, and may help identify potentially new therapeutic strategies to treat ALS.

MNDRIA Grant

Dr Mary-Louise Rogers
School of Medicine, Flinders University, SA
CSF and serum p75 extracellular domain as validation of a fluid biomarker for MND

A lack of biomarkers that can measure the effect of treatment has been identified as one of the reasons that clinical trials of treatments for MND have failed. Our group has shown a protein in urine called p75ECD is a biomarker of MND, and is the only identified so far that is a progression and prognostic marker. We now plan to validate our findings in urine by examining if serum and cerebrospinal p75ECD correlates with urinary p75ECD. This also involves collaboration with Pam Shaw's group in Sheffield, UK. This grant will enable our marker to move forward to clinical trials.

Peter Stearne Familial MND Research Grant

Dr Fazel Shabanpoor
Florey Institute of Neuroscience and Mental Health,VIC
Alleviation of C9orf72-mediated ALS: A novel bi-functional peptide-oligonucleotide strategy both suppressing gene expression and activating autophagic clearance of toxic protein

Abnormal expansion of the *C9ORF72* gene is the most common genetic cause of MND. The product of expanded region within this gene are proteins which aggregate inside a particular group of nerve cells known as motor neurones. These toxic proteins cause the degeneration of motor neurones and progressive muscle weakness. The central objective of this study is to develop dual purpose biotherapeutic molecules known as peptide-oligonucleotides as a potential therapy for C9ORF72-linked ALS. This novel therapeutic approach prevent the formation and simultaneously clear the toxic protein aggregates.

Stanford Family MND Research Grant

Associate Professor Ronald Sluyter
University of Wollongong, NSW

Establishing the therapeutic potential of the P2X7 receptor ion channel in amyotrophic lateral sclerosis

There are currently no effective treatments for MND. Findings from our group and others indicate a role for a communication pathway (termed the ATP-P2X7 pathway) between motor neurones and other cells of the central nervous system in the progression of MND. Through the use of a new drug in a classic mouse model of MND, this project will investigate whether blockade of the ATP-P2X7 pathway can prevent MND progression. This research will provide further insight into the mechanisms in MND and assist in planning possible drug trials in people with MND.

MonSTaR Foundation MND Research Grant

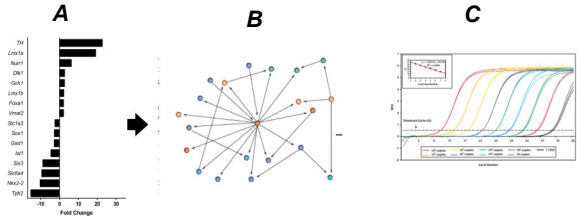
Dr Rachel Tan
Brain and Mind Centre, University of Sydney, NSW
Is ATXN2 a potential therapeutic target in MND?

The death of neurons in MND is caused by a normal protein called TDP-43 becoming toxic. Cell and animal models have shown that another protein, called ataxin-2 (ATXN2), may be involved, a concept that appears more certain as genetic variability in the *ATXN2* gene increases the risk of getting MND and also shortens survival. This study will assess whether variability in the *ATXN2* gene impacts on protein levels (different forms of ATXN2 and toxic TDP-43) and neuronal integrity in patients with MND in order to provide critical information on whether therapeutic strategies for MND should target ATXN2.

Benalla Act to d'Feet MND Research Grant

Dr Bradley Turner
Florey Institute of Neuroscience and Mental Health, VIC
Profiling the gene expression pathways of motor neuron vulnerability early in development of MND

While MND typically presents in mid to late-life, the seeds for development of MND may be sown years or even decades before symptom onset. This implies the pathological processes of MND may start early in life. Using gene profiling technology, this project will identify the earliest genetic changes occurring in motor neurones in a mouse model of MND for the first time. Identification of the earliest genetic changes in motor neurones may provide new insights into potential critical players responsible for triggering motor neurone vulnerability and therefore highlight relevant gene targets and pathways for effective intervention in MND.



Work Flow: (A) Genes switched on in early life will be identified and (B) analysed. (C) Another technique will be used to confirm the results.

Grants-in-aid for 2017

Stanford Family MND Research Grant

Dr Mehdi Van den Bos
Westmead Hospital and University of Sydney, NSW
Pathophysiological mechanisms underlying ALS: insights from novel cortical functional techniques

A growing body of evidence has provided support for a "dying forward" model of MND and is centered on excessive excitatory activity ("glutamate excito-toxicity") at the cortical level initiating a degenerative cascade. Whilst recent work at a cellular level has provided dramatic insight into this process, a translational demonstration in humans is awaited. Our project will provide direct neurophysiological evidence of increased cortical excitation in humans, demonstrate how the disease spreads from this cortical excitatory origin, and is likely to provide a critical earlier biomarker by which treatment efficacy may be judged.

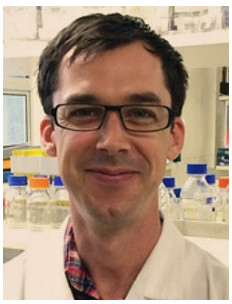
MonSTaR Foundation MND Research Grant

Dr Adam Walker
Macquarie University, NSW
New proteins and pathways contributing to TDP-43-mediated neurodegeneration

In almost all patients with MND, a protein known as TDP-43 misbehaves in the brain and spinal cord. I have created genetically modified mice that develop TDP-43 pathology and disease very similar to human patients, to allow the analysis of brain and spinal cord tissues at early stages of disease development. In collaboration with other researchers, my team is using advanced biochemical analyses to narrow down the biochemical changes involved in disease in these mice. This project will characterize the role that newly identified proteins play in disease, with the goal of identifying new ways to treat MND.

Fat Rabbit MND Research Grant

Associate Professor Trent Woodruff
The University of Queensland
Therapeutic inhibition of HMGB1 to slow disease progression in MND



In MND, there is death of nerve cells. As yet there is no way to stop these cells from dying and new approaches are thus needed. We are studying the role of the immune system in MND. We have evidence that activation of the immune system contributes to the progression of disease. In particular, we have been studying a group of proteins called the toll-like receptor (TLR) system. We suggest that the therapeutic targeting of this system could slow the progression of MND. We will investigate this further, using a novel therapeutic drug to treat MND mice. If successful, we will then perform a trial of our novel drug, which acts on this TLR pathway.

MNDRIA Grant-in-aid

Professor Naomi Wray
The University of Queensland
Genome-wide association study data for SALSA-SGC

The 2015 MNDRIA Ice Bucket Challenge Grant has provided funding to establish the Sporadic ALS Australia Systems Genomics Consortium (SALSA-SGC). The consortium has established common clinical data and biological sample collection protocols and online sample tracking systems, which are being rolled out to all major ALS clinics in Australia. This harmonised resource of patient data will underpin many future studies. We will now take the SALSA-SGC samples forward through to scientific discovery by generation of basic genome-wide genetic data, contributing to international collaborative efforts in a paradigm proven to work in providing new leads for research.

Two special awards made at the MND Australia Research Meeting 2016

Left: Philanthropist John Laidlaw accepts his award from Professor Matthew Kiernan. Right: Professor Matthew Kiernan, Professor Dominic Rowe, Janet Nash.

Two special presentations were made at the MND Australia Research meeting in Brisbane. An award in recognition of exceptional philanthropy was presented to Australian Philanthropist John Laidlaw by MNDRIA Research Committee Chair Professor Matthew Kiernan. John and Betty Laidlaw have donated $2 million to MND research. A $1 million donation last year led to the Betty Laidlaw MND Research Grant, which was awarded to Dr Peter Crouch from the University of Melbourne in May. Dr Crouch is leading a multicentre team working on "copper malfunction in MND: a therapeutic target for sporadic MND." A second $1 million commitment has enabled the establishment of four mid-career awards to be given out over four years. A special award was also presented to Professor Dominic Rowe AM in recognition of his exceptional leadership of the MNDRIA Research Committee over ten years 2005 - 2014. On accepting the award from MNDRIA Research Committee Chairman Professor Matthew Kiernan and Executive Director Research MND Australia Janet Nash, Professor Rowe reflected on research progress over the last few years and how much things have changed. Research has transformed our understanding as we work together towards a world without MND.

MND Connect 2016, Saturday 22 October, Queensland Brain Institute

MND Connect 2016 brought together the community, researchers and clinicians in an interactive forum to discuss MND research in Australia at the Queensland Brain Institute on Saturday 22 October. We welcomed some of Australia's best and brightest MND experts who covered topics from gene discovery to clinical trials, and the current status of stem cell research. Personal stories and panel discussions were integrated into the program. Wayne Patterson shared his experience of living with MND. Proceeds from Wayne's book "Fat Rabbit" are going towards MND research. Associate Professor Megan Munsie outlined how stem cells are being used to understand MND, what is happening with MND stem cell clinical trials, and the dangers of going overseas for unproven stem cell therapies. Professor Julian Gold spoke about the Lighthouse Project to investigate whether retroviral DNA in our genetic make-up could play a role in MND for some people. Associate Professor Paul Talman presented the Australian Motor Neurone Disease Registry and how data gathered can be used to help further the understanding of MND. To find out more about how to get involved visit www.mndregistry.org.au

Huge thanks to meeting sponsors: MND Queensland, MND and Me Foundation and VWR. Special thanks also to Dr Derik Steyn and Dr Shu Ngo for their hard work in putting the MND Connect program together to make such a fabulous day. Conversations between community, clinicians and scientists provided valuable insights and dialogue on possible research questions for the future. Presentations can be found online at www.mndaustralia.org.au/mndconnect2016.

Grants continuing in 2017

MND Australia Ice Bucket Challenge Grant 2015 - 2017
Professor Naomi Wray , Queensland Brain Institute. Sporadic *ALS Australian Systems Genomics Consortium (SALSA-SGC*

Betty Laidlaw MND Research Grant 2016 - 2018
Dr Peter Crouch, The University of Melbourne. *Copper malfunction in MND: a therapeutic target for sporadic MND*

Beryl Bayley MND Postdoctoral Fellowship 2016 - 2018
Dr Michelle Farrar, University of NSW. *MNDs in children and young people—understanding pathophysiology and developing treatment approaches*

Bill Gole MND Postdoctoral Fellowship 2016 - 2018
Dr Fleur Garton, University of Queensland. *Identification of novel genetic loci and pathways associated with ALS through interrogation of multiple integrated genomics data sets*

MNDRIA Postdoctoral Fellowship 2016 - 2018
Dr John Lee, University of Queensland. *The role of C3aR signalling in slowing down the disease progression of MND*

NHMRC/MNDRIA co-funded Postgraduate Scholarship 2016 - 2017
Dr Nidhi Garg, University of Sydney. *Clinical phenotypes and novel neurophysiological and immunological biomarkers in inflammatory neuropathy and neurodegeneration*

MNDRIA PhD top-up grant 2016 - 2018
Dr Thanuja Dharmada, The University of Sydney. *Motor Neurone disease: site of origin and patterns of disease spread*

MNDRIA PhD top-up grant 2016 - 2018
Emily McCann, Macquarie University. *Investigating the genetic and epigenetic basis of ALS*

Bill Gole MND Postdoctoral Fellowship 2015 - 2017
Dr James Howells, University of Sydney**.** *Investigating the role of oligodendrocytes in ALS*

Beryl Bayley Postdoctoral Fellowship 2015 - 2017
Dr Parvathi Menon, University of Sydney**.** *Insights into ALS pathophysiology from patterns of disease progression*

NHMRC/MNDRIA co-funded Postgraduate Scholarship 2015 - 2017
Nicole Sheers, Austin Health, VIC. *Breath-stacking in neuromuscular disease*

MNDRIA PhD top-up grant 2015 - 2017
Victoria McLeod, Florey Institute of Neuroscience & Mental Health. *Androgen Receptor dysregulation in ALS*

The NHMRC/MNDRIA Postgraduate Scholarship award for 2017 - 2019 will be announced early in 2017.
The MNDRIA PhD top-up grant and Susie Harris Travel Fellowship will be awarded in early 2017.

12th MND Australia Research Meeting

Queensland Brain Institute, University of Queensland, 21 October 2016

The national MND Australia Research Meeting is held each year following the annual MNDRIA Grants Allocation Meeting. The objectives of the MND Australia Research Meeting are:

- To promote sharing of expertise amongst MND researchers in Australia
- To enable interaction of researchers to foster the development of research collaborations
- To provide feedback to a wide audience about the latest developments in MND research
- To demonstrate the value of the funded research to donors to encourage their continuing support.

This event has been held annually since 2005 at venues in Sydney, Melbourne and Brisbane to facilitate participation for researchers in different states. The 2016 meeting was kindly hosted by Professor Pankaj Sah and the Queensland Brain Institute. The conference was generously sponsored by Biogen.

Researchers who presented the outcomes of their 2016 MNDRIA-funded projects with Research Committee members

MND Australia President David Ali updated the audience on the year's achievements

More than 130 passionate researchers gathered at the Queensland Brain Institute in sunny Brisbane on Friday 21 October to attend the MND Australia Research Meeting 2016. This year's meeting included 21 speakers reporting on the outcomes of their research projects supported by MNDRIA in 2016 and 35 stimulating poster presentations.

The theme of the first session was new models in research to understand the causes of MND. We heard about studies in fruit flies, zebrafish and mice from A/ Professor Greg Neely, Dr Nicholas Cole, and Dr Adam Walker respectively. Each model organism has its own advantages and together they provide an array of techniques for researchers to test new therapeutic strategies. We heard about the effects of cellular stress in motor neurones and the possible involvement of structures called "paraspeckles" from Western Australian researcher Dr Archa Fox while A/Professor Julie Atkin shared her work on the potential role of DNA damage in MND.

The accumulation and deposition of pathological proteins is a common hallmark of MND and was a common theme of the next session. Dr Danny Hatters is developing a tool to measure protein homeostasis in cells grown in culture in the laboratory. Similarly Dr Shu Yang is aiming to do the same thing using skin cells donated by MND patients and by focusing on one aspect of protein homeostasis – protein removal (or degradation). Cellular systems of protein removal are likely to be dysfunctional in MND; Dr Darren Saunders and Dr Albert Lee both provided evidence that this is the case. Dr Marco Morsch provided striking evidence that protein aggregates can travel from one cell to another in a living zebra fish brain.

In the afternoon session, research focusing on potential therapeutic treatments under study and drug delivery approaches was discussed. Dr Peter Crouch updated the audience on his research on the effect of copper malfunction in MND. Metal ions like copper are essential for the activity of proteins and enzymes in our cells. Dr Crouch's research is supporting a preliminary clinical trial to test a potential therapeutic named copper-ATSM, which aims to correct this mineral malfunction in MND. Meanwhile, A/Professor Peter Noakes has been studying another drug, PMX205, in a mouse model of MND. This drug has shown a therapeutic effect in mice when administered before or shortly after the onset of symptoms. On a different tack, Dr Sandy Shultz is investigating the link between traumatic brain injuries and MND in rodent models, which may provide alternative pathways for drug development. To improve the delivery of therapeutics to motor neurones, a common hurdle in drug development for MND, Dr Mary-Louise Rogers and Dr Bradley Turner are developing "immunogenes" while Dr Justin Yerbury presented a liposome-based approach. Both strategies use specific antibodies chosen for their ability to direct the delivery of a gene therapy or drug from circulation to motor neurones, the site of the disease.

Continued on page 12

MND Australia Research Meeting 2016 *continued from page 11*

The final session wrapped up the day of talks at the clinical end of the research spectrum. A/Professor Tracey Dickson and Dr Catherine Blizzard are studying why neurones in the cortex of the brain are overactive. It may be because the usual mechanisms to inhibit neuronal overactivity are dysfunctional in MND or that protein aggregates of TDP-43, the major MND-associated protein, disturb neurone-to-neurone communication. In line with A/Professor Dickson's finding, Dr Nimeshan Geevasinga reported that in people with C9ORF72-familial MND and those with sporadic MND, the normal inhibitory neuronal activity of the motor cortex is reduced. This work tells us that these two different cohorts of patients share a common physiological abnormality that causes cortical hyperexcitability. Exercise researcher Dr Michael Lee told us that patients can maintain what they're currently doing for exercise, but not to exercise to fatigue. Instead, intermittent exercise below the level of maximum exertion can be beneficial as it helps to restore neurone activity to normal levels. In terms of energy requirements, Dr Derik Steyn emphasised that no two MND patients are the same and their energy needs vary greatly, but hypermetabolism and weight loss are universally detrimental to disease progression. A patient's intake of energy from their diet alters the course of disease: energy supplementation slows disease progression while energy restriction accelerates it. So a calorie-rich diet as well as whatever low-moderate amounts of exercise one is capable of are two ways a person with MND can actively help themselves out and improve their quality of life.

The evening poster session was held together with a drinks reception to close the research meeting. The Poster Committee reviewed twelve student posters and the prize for best poster was awarded to PhD student Andi Lee from The University of Queensland for her poster 'Mutation of TDP43 leads to disrupted transmission and morphology at neuromuscular junctions'. It was great to see the next generation of researchers in the field present their outstanding work.

By Clare Watson, Isabella Lambert-Smith, Justin Yerbury, University of Wollongong.

MND Research Institute of Australia

Office Bearers and Members December 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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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 430, North Sydney NSW 2059

Donations can be made by cheque (payable to MND Research Institute of Australia) or credit card (Visa or MasterCard) or online at www.mndresearch.org.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 8287 4989 or email research@mndaustralia.org.au.

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