mnd Research Institute of Australia

Advance

NEWSLETTER OF THE MND RESEARCH INSTITUTE OF AUSTRALIA

December 2014

The MND Research Institute of Australia, established in 1984, aims to promote 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. MNDRIA has the responsibility of distributing all funds received from donations each year through the peer review process. Every dollar received is spent directly on research and the MND Research Committee, after scrutinising all applications, ensures that the available funds go only to the best research with the greatest chance of achieving significant results.

Since the first MNDRIA research grant was awarded in 1987 there has been a steady increase in MNDRIA funds available each year and the number of people in Australia focussing their research on MND. This increase has been remarkable in the last ten years due to the many new discoveries that have stimulated hope and a focus on MND research. When research produces results, donors respond as they see their gift has been well spent so MNDRIA can now offer larger grants with a marked increase in the quality of applications received.

This year, MNDRIA has again achieved a new record with $2.57 million awarded for 25 new grants commencing in 2015, including two postdoctoral fellowships *(page 10)* and 19 grants-in-aid *(pages 4-9)*. Two travel grants, a PhD scholarship co-funded with the National Health and Medical Research Council of Australia (NHMRC) and a PhD top up grant will be allocated early in 2015. Scholarships and fellowships encourage emerging scientists to establish their career in MND research. Grants-in-aid are development grants which provide a lifeline for dedicated MND researchers who aim for more significant project grants from major funding sources such as the NHMRC. This has recently been successfully demonstrated with NHMRC awarding over $4 million to new MND projects whose recipients acknowledge the MNDRIA support for their preliminary research as the key factor in achieving major government funding.

MNDRIA is acknowledged as a major contributor of research funds with listing on the Australian Competitive Grants Register.

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The MND Ice Bucket Challenge

came out of nowhere and the worldwide response was amazing. Social media brought it to Australia in August and within a few short weeks there can't have been too many people who had not heard about the devastating condition called motor neurone disease (or MND or ALS) and the need to do something about it. The challenge is to say a few words about MND, douse yourself with a bucket of ice and water, post the video on Facebook and challenge three others to do the same thing and/or to make a donation to the MND charity of their choice. The challenge spread through the community of sports people, celebrities, media, politicians, billionaires, corporations, MND Associations, researchers, schools and everyone else. In particular, people living with MND and families remembering relatives lost to MND embraced involvement in spreading the word about the need for change.

Menzies Research Institute's MND Research Group braved the cold of winter in Tasmania to take up the MND Ice Bucket Challenge

The outcome for the MND Research Institute of Australia has been an influx of about $1.3 million. Some of this has already been allocated as the *MND Ice Bucket Challenge Grant-in-aid* to kick-start Australia's involvement in Project MinE, an international collaboration which will be the largest genetic study ever proposed for MND *(page 4)*.

Most of the balance will fund a major three-year team project, something that has never been possible for MNDRIA before. The *MND Australia Ice Bucket Challenge Grant* will go to Australia's best team of researchers with an aim to understand the causes of sporadic MND in humans and lead the way to a potential treatment.

Internationally more than one hundred million dollars have been contributed to support MND care and research as a response to the ALS/MND Ice Bucket Challenge.

There is no doubt that 2014 will be remembered as the turning point for motor neurone disease.

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Professor Dominic Rowe AM has been leading the MND research committee since he took over the role of Chair of MNDRIA at the end of 2004. Following amalgamation of MNDRIA with MND Australia in 2010, Dominic was elected by research committee members to continue as Chairman of the research committee of MND Australia and MNDRIA and as a director on their Boards. During the past ten years of working with Dom we have seen enormous change and exponential growth of MND research in Australia. With Dom's drive for discovery of cause, better care, control and cure of MND, the past ten years have brought ever increasing donations to MNDRIA to help achieve these aims. Dom has ably led the Research Committee through review and discussion of research proposals to ensure that funds available are appropriately distributed each year. Dom's passion to encourage young researchers to investigate MND has seen the introduction of funding for PhD scholarships and top-up grants and annual awards of early career postdoctoral fellowships. His determination to award grants-in-aid for only the very best proposals has seen an upward spiral in the quality of applications from established researchers with a resultant increase in discoveries and publications. His vision for continued growth has seen the introduction of the first major four-year grant to reward and support Australia's best mid career MND researcher and, thanks to the MND Ice Bucket Challenge, a major project grant for Australia's best MND research team will be awarded in 2015. On stepping down after ten years, Dom leaves MNDRIA in a very strong position to make a significant contribution towards the international race to stop MND.

Other changes in the MND research committee this year are the retirement of Professor James Vickers (Tasmania) after serving on the committee for eight years and the appointment of Associate Professor Tracey Dickson as the new representative for Tasmania. With increases in the number of grant applications received each year, the role of committee members becomes more demanding. It takes considerable time to carefully assess all grant applications to ensure that the available funds go only to the proposals with the greatest relevance and the most likely chance of providing benefit for people with MND. This time is given freely by research committee members who are the leaders in their various fields of MND research in Australia.

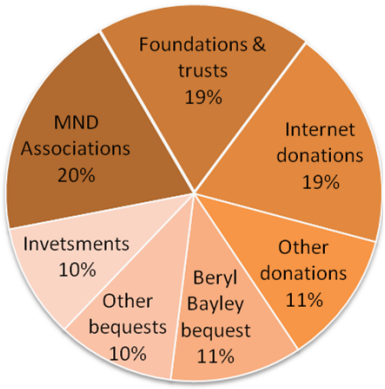
Funds awarded for new grants commencing in 2014 totalled $2.17 million. It was noted that this allowed funding of about 50% of the many excellent applications received. In the calendar year 2014 a total of $2.37 million has been paid by MNDRIA for 20 grants-in-aid, five concurrent postdoctoral fellowships, one PhD scholarship (co-funded with NHMRC), five PhD top-up grants, one travel grant and the MND Australia Leadership Grant. MNDRIA is now well established as a major force in driving MND research with successful outcomes, particularly in the fields of genetics and cell biology research.

Support was provided in 2014 for the Bill Gole and Graham Linford Postdoctoral MND Research Fellowships, the Charles and Shirley Graham Grant, the Graham Smith Grant, the Peter Stearne Familial MND Research Grant, the Rosalind Nicholson Grant and the MND Australia Leadership Grant. Another six grants were funded by MND Victoria and its supporters: the Graham Lang Memorial Grant, the Mick Rodger Grant, the Mick Rodger Benalla Grant, the MND Victoria Grant, the Zo-eè Grant and the Jenny and Graham Lang Collaborative Travel Grant.

The majority of funds available for MND research grants come from bequests and donations. People who are not necessarily able to give during their lifetime certainly can make a difference with provision for research in their Will. Bequests in 2013/14 account for 51% of total funds received during the year. Most of this came from the estate of the late Beryl Bayley whose magnificent gift of $2.3 million will provide for the Beryl Bayley Postdoctoral MND Research Fellowship for many years to come.

New major research supporters this year include CommBank (Wake up after Winter), Pat and Angie Cunningham (Laugh to Cure MND) and Kim Evans (Devil'n Me around Ozee).

Funds available for distribution for new grants commencing in 2015 have come from bequests (21%), MND Associations (20%), foundations and trusts (19%) and internet donations, including supporters' campaigns (19%). Major donors, special fundraising events and MND associations continue their generous sponsorship for named grants. Other grants are funded by unsolicited gifts and donations so generously given each year by regular supporters (11% of funds available).



Sources of funds for grants commencing in 2015

The MNDRIA newsletter *Advance* continues to provide feedback to donors about how their donations have been used with announcement of awards for new projects and reports on the outcomes of completed projects. Hard copies (5,000) are distributed nationally through the MND associations and a link is provided to all email news subscribers and to members of the International Alliance of ALS/MND Associations. On the MND Australia website, the greatest number of news hits go to the brief quarterly MND Australia International Research Report which this year has been produced by Wollongong University PhD student, Isabella Lambert-Smith.

The 9th annual MND Australia Research Meeting was held at Macquarie University, Sydney in November 2013 with generous support from the University and Sanofi. This is now a significant national MND meeting and provides the opportunity for networking and exchange of ideas. It is primarily intended for researchers currently funded by MNDRIA to present the outcomes of their research to one another, but all interested people are invited to attend. The poster session at the conclusion of the meeting was strongly supported by PhD students. The record attendance of 120 researchers and supporters, many from interstate, demonstrated the success of this first full day symposium and laid the foundation for future meetings.

Janet Nash, Executive Director Research

Professor Matthew Kiernan: Chairman MND Australia Research Committee

At the MND Research Committee Meeting on 26 November 2014, Professor Matthew Kiernan was elected by the members of the committee as their new Chairman. Professor Kiernan takes over this role from Professor Dominic Rowe and will also act as a Director on the board of MND Australia representing research.
Professor Kiernan has a distinguished career as a clinician and researcher. We are proud to welcome him to guide the MND Research Institute of Australia through the next stage of its growth in the quest to control and defeat MND.

Professor Matthew Kiernan
Bushell Chair of Neurology
University of Sydney.
Professor Kiernan's clinical research unit is located at the Brain and Mind Institute. He was appointed Professor of Neurology, Royal Prince Alfred Hospital (RPAH) in 2013 and Senior Staff Specialist RPAH. He is also a Senior Scientist at Neuroscience Research Australia. Professor Kiernan is the head of the Clinical Neuroscience research group comprising a 20-strong team of clinicians, scientists, biomedical engineers, doctoral and postdoctoral students with focus on neurological disease. His research team's focus is clinical neurology, in particular disease pathophysiology and treatment strategies of frontotemporal dementia and motor neurone sydnromes. Currently his team is investigating the mechanisms and the possible prevention of neurodegeneration in motor neurone disease; frontotemporal dementia; chemotherapy-induced neurotoxicity; stroke; Machado-Joseph disease; spinal muscular atrophy and other inherited neuropathies. They are also involved in clinical trials investigating potential drug treatments for motor neurone disease, multiple sclerosis and chronic inflammatory demyelinating polyneuropathy. His team's research is intrinsically linked to the provision of clinical services, particularly the ForeFront Multidisciplinary Motor Neurone Disease and Fronto temporal Dementia Clinic and diagnostic neurophysiology clinics. Professor Kiernan is the Editor-in-Chief of the Journal of Neurology, Neurosurgery and Psychiatry (BMJ Publishing Group) and Vice President of the Australian Brain Foundation.

A big thank you from MNDRIA to:

- More than 60,000 people in Australia who donated and many more who participated in the MND Ice Bucket Challenge and contributed to changing the profile of MND forever.
- The state MND associations which are the reason we exist as MNDRIA provides the appropriate way to allocate donations that have been given to, and raised by them for research.
- The major donors, organisations and foundations whose significant contributions have promoted MNDRIA as a driving force for MND research in Australia.
- Our regular donors who, with their dedication to MND research, provide a valued source of funds each year.
- The people who had the foresight to include MNDRIA as a beneficiary in their Will.
- All those who choose MNDRIA for in memoriam tributes in memory of a relative or friend.
- The many people who have their own fundraising events to support MNDRIA or who set up their own fundraising page at www.gofundraise.com.au and ask all their friends and associates to contribute to their cause.
- Our loyal volunteers Maureen Burmeister and Alan Hauserman who are always there for us when we need special help.
- The members of the MND Research Committee who give an ever-increasing amount of time to the vital task of reviewing grant applications.
- The many dedicated MND researchers around Australia who are determined to succeed in making the breakthrough that leads to an effective treatment for motor neurone disease.

(continued from page 1)

This means that Universities undertaking research funded by MNDRIA will receive more than 20% in addition to the funds received from MNDRIA as Research Infrastructure Block Funding.

Named grants have been an inspiration in encouraging donors to raise their targeted level of support to give a close connection with the research they are supporting. Initiated by the Bill Gole MND Postdoctoral Fellowships and rapidly followed by MND VIC and their supporters, MNDRIA has awarded 16 named grants for 2015. These include new grants: the Beryl Bayley Postdoctoral Fellowship, the Angie Cunningham Laugh to Cure MND Research Grant, the Bob Delaney MND Research Grant, the Cunningham Collaboration Grant and the Ted Dimmick Memorial MND Research Grant.

Too late to be included in this year's funding round but the new Jenny Barr Smith MND Research Grant will be awarded next year thanks to the fantastic fundraising efforts of the Watts MND Bike Challenge admirably led by Andrew Kaye.

None of this would be possible without the extraordinary philanthropic endorsement of the many contributors who are collectively paving the way to make MND a treatable disease.

Grants-in-aid for MND research in Australia in 2015

Grants-in-aid support start-up research projects. These development grants help established researchers to initiate projects with the hope they can 'grow' to produce data that will attract more significant funding from granting bodies such as the National Health and Medical Research Council of Australia (NHMRC). This year five MND researchers have attributed their success in attaining NHMRC funding for new projects to commence in 2015 to their preliminary work funded by MNDRIA.

MNDRIA has awarded nineteen grants-in-aid for new projects for 2015 in four Australian states: ten in NSW, five in Queensland, two in Victoria and two in Tasmania. These projects cover many aspects of MND research including genetics, cell biology, clinical measurement and health care.

Six of the grants-in-aid awarded this year come from MND Victoria with a requirement of attendance at the International ALS/MND Symposium in Orlando, Florida in 2015. This MND Victoria initiative has introduced many researchers to the annual Symposium and the opportunity to share new research and establish collaborations. Australian researchers have long been involved in major breakthroughs and are at the forefront of world MND research.

MND Ice Bucket Challenge Grant-in-aid

This special grant, awarded from donations received from the MND Ice Bucket Challenge, provides start-up funding for Australia's participation in Project MinE. This international collaboration will be the largest genetic study ever proposed for MND.

A/Prof Ian Blair

Australian School of Advanced Medicine, Macquarie University

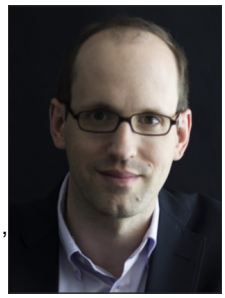
Next-Generation Sequencing of Australian sporadic MND patients to identify genetic risk factors

Around 90% of MND cases have no known cause. There is strong evidence that this sporadic MND is caused by the combination of genetic factors (genetic variations that confer risk to MND) and environmental exposure. Indeed, current evidence indicates that genetic factors and environmental factors contribute about equally to the development of sporadic MND. Our aim is to identify genetic factors that predispose to MND or change the pattern of disease, such as age-of-onset, disease spread and duration. In general, common gene variations only contribute a small amount to the risk of disease, while rare variations contribute a lot. The identity of these genetic variations can help us understand the mechanisms underlying MND and therefore lead ultimately to rational therapies.

Dramatic advances in technology mean that we can now search for rare gene variations using a technique called Next-Generation Sequencing. This method determines the entire genome sequence of each patient. The result is 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 in which large-scale Next-Generation Sequencing data will be collected from thousands of individuals, and shared across countries and research groups to identify the genetic factors that confer risk to developing MND.

MNDRIA Grant-in-aid

Prof Lars Ittner



Dept of Anatomy
University of NSW

Novel MND mouse models

The aim of the proposed study is 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 recently been identified in three independent families with MND history. Experiments in cultured cells showed that the disease -causing mutations in profilin 1 compromise its ability to maintain cytoskeleton integrity and thereby contributing to functional impairments. However, these studies are limited to cell cultures, since there is no animal model to perform *in vivo* experiments. This application will close this gap and develop a series of novel MND mouse models based on profilin 1. Experiments in these mice will be complemented by live cell culture studies. Professor Ittner has extensive experience with the generation of genetic mouse models of neurodegenerative diseases. It is anticipated that this project will significantly enhance the understanding of principle mechanisms that lead to MND and further will provide novel mouse models for the development and testing of new therapies.

Terry Quinn MND Research Grant

Dr Greg Neely

Garvan Institute of Medical Research

Genomic approach to find new MND disease genes and drug targets

There are about 350,000 MND patients in the world. Currently, there are no effective therapies. Therefore, identifying potential drug targets for treatment of MND will help us address a large unmet medical need. MND involves a strong genetic component, although much of the genetics of MND remain to be identified. Recent genome-wide association studies (GWAS) have revolutionized

G E N E T I C S

our search for MND susceptibility loci, but these results are correlative and require functional validation to pinpoint bona fide MND disease genes and new drug targets.
In this proposal, human association efforts will be combined with functional target validation in *Drosophila melanogaster* (Fruit Fly) to evaluate all candidate human MND genes (~430 candidate MND disease genes). Specifically, the expression of each gene will be knocked-down in neurons and MND-like phenotypes such as basic motor coordination and lifespan will be evaluated *in vivo*. Since defects in synaptic development and function have been linked to MND, candidate genes will be further examined for their synaptic function and ultrastructure using a broad set of synaptic assays that combine electrophysiology, high-resolution imaging and electro -microscopy. Additionally, we will identify genes that are capable of stopping MND disease when targeted in humanized fly models of MND.
On completion of this project, we will have identified and functionally validated genes that can either cause or stop MND disease progression. Our results may lead to new strategies for early diagnosis and treatment of MND.

Rosalind Nicholson MND Research Grant
Dr Kelly Williams

ASAM, Macquarie University
Epigenomic approaches to understand MND disease variability

The only known causes of ALS are gene mutations, which account for only a small proportion of ALS cases. Patients with ALS experience very different diseases courses, with variable age of onset, clinical progression and duration of disease. Most interestingly, patients who possess identical genetic mutations can exhibit vast differences in these clinical features. This demonstrates that modifiers of disease other than genetic predisposition are at play. We have a unique opportunity to examine 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 or long disease duration). We will search for physical changes to DNA that occur without altering the genetic code (epigenetic) that modify the onset and progression of ALS. Biostatistical analyses of these epigenetic changes aim to find specific epigenetic patterns that discriminate between the different subtypes of ALS and correlate with disease duration. If these disease modifiers can be identified, we will be well positioned to not only enhance our understanding of the biology of ALS, but to pinpoint potential therapeutic targets that may be able to enhance quality and duration of life for ALS patients.

Mick Rodger Benalla MND Research Grant
Prof Roger Chung

ASAM, Macquarie University
Proteomic studies to identify the defects in protein-protein interactions and cellular signalling pathways caused by mutations in a newly identified familial MND gene

Our team has recently identified new mutations in a gene responsible for ALS in an Australian family, and through international collaborations has identified mutations in this gene in Canadian, US and European ALS patients. This represents a new major discovery in ALS genetics. This ALS gene encodes a protein that is directly involved in protein degradation and recycling in motor neurons, and our preliminary studies indicate that ALS mutations in this gene lead to abnormal accumulation of proteins within the cell, leading to neurodegeneration. This project will use a series of experimental techniques to precisely identify the specific proteins and signaling pathways that are impaired in motor neurons expressing mutations in this new ALS gene. Because abnormal protein degradation and the inappropriate accumulation of proteins inside motor neurons is observed in all forms of ALS/MND, the outcomes of this project will lead to greater understanding of the molecular causes of the disease.

Angie Cunningham Laugh to Cure MND Grant
A/Prof Julie Atkin

ASAM, Macquarie University
Optimising the protective activity of protein disulphide isomerase in motor neuron disease

ALS/MND is a devastating disease and currently there is no effective therapeutic treatment, hence there is a great unmet need to identify new treatments that address the underlying pathology. One pathology common to the diverse forms of ALS/MND is the formation of abnormal protein clumps or ‘inclusions’ in affected motor neurons. We have identified a type of protein called a ‘chaperone’ that prevents these abnormal clumps from forming, and is protective against multiple other pathological events that occur in motor neuron cells in ALS. Whilst this chaperone is protective, it cannot by itself be used as a new drug because it is a large molecule and cannot be efficiently delivered to the brain. Hence in this proposal we aim to identify which specific features of this protein are responsible for its protective ability, so that new, drug-like molecules can be designed, based on its protective features. Secondly we will also characterise the protective

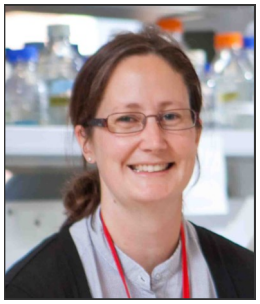
activity of this protein in new disease models based on zebrafish, so that in the future, screening for new drugs can be performed in these animals, based on this chaperone protein. This study therefore aims to develop novel treatments for ALS/MND.

MNDRIA Grant-in-aid
Dr Catherine Blizzard

Menzies Research Institute, University of Tasmania
Synaptic dysfunction: an early mechanism of TDP-43 pathogenesis in ALS

Amyotrophic Lateral Sclerosis (ALS) is a devastating disease that is caused by the death of motor neurons. There is a desperate need to discover new therapeutic ways to stop this neuron death, ideally targeted at early changes in the disease to prevent the majority of cell loss. Synapses are specialised structures that allow neurons to communicate with each other. Disturbances in neuronal synapses may be one such early event that potentially leads to neuronal dysfunction and then death. Changes in synapses can have serious effects on neurons' activity levels and if not controlled can cause neuron death.
Mutations in the DNA editing protein TDP-43 causes a genetic form of ALS. TDP-43 has recently been shown to be involved in maintaining synapses between neurons; regulating the number and maturation of spines. It is feasible that an early disease-causing event in ALS may be changes to synapses. We will investigate how different mutations of the TDP-43 protein determines the number and composition of synapses *in vitro* using specialised compartmentalised primary neuronal cultures. This novel research program addresses an important gap in the current understanding of how synaptic changes can lead to neuron death in ALS and may open up a new target for drug intervention in this devastating disease.

Mick Rodger MND Research Grant
A/Prof Tracey Dickson



Menzies Research Institute, University of Tasmania
Inhibitory regulation of motor neurons: A new target mechanism for ALS?

There is considerable evidence from many areas of clinical and basic medical research that in MND motor neurons may be dying due to a toxicity that is triggered due to their over activity – 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. Not only would these studies provide important insight into the mechanisms responsible for ALS, but they would also 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

In 2011, mutations in the C9ORF72 gene were discovered to be the commonest cause of inherited forms of MND accounting for 40% of all inherited cases. In addition, the mutations are found in 7% of sporadic cases as well as familial and sporadic forms of the closely related disease Frontotemporal Dementia. Recent discoveries have suggested that the mutations cause the gene to turn on the production of junk proteins that are not normally ever meant to be produced. These junk proteins accumulate in the brain of MND patients and have been postulated to be toxic to the neurons. Our research is aimed at determining how these junk proteins interfere with the normal functioning of cells and the extent to which they might be toxic. This knowledge is expected to inform the development of therapeutic strategies targeting the mutant C9ORF72 gene.

MNDRIA Grant-in-aid
A/Prof Peter Noakes

School of Biomedical Sciences University of QLD
The role of altered neuromuscular activity and mRNA transport in modifying the progression of MND

There is evidence that abnormalities in the connections between motor nerves and muscle occur early in MND. Recent research has revealed three alterations in communication between motor

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neurons and muscle that are likely early modifying factors in MND. They include: ***i***) alterations in the transport of important mRNAs from the motor neuron's cell body within the spinal cord, to the motor nerve ending within muscle. These mRNAs make specific proteins needed for motor neurons to effectively contract muscle; ***ii***) a decline in the signalling between motor nerves and muscle that stabilizes their connections; and ***iii***) abnormally increased motor neuron activity.
To investigate how these alterations trigger MND, we propose to re-construct the human neuromuscular circuit in culture from cells derived from MND and control patients. Skin cells from MND and control patients will be differentiated into muscle and motor neurons and subsequently co-cultured to form motor neuron-muscle connections.
By assessing the movement of mRNAs and their RNA binding proteins within the motor neuron and its nerve terminal ending, measuring the stability of neuromuscular connections over time, and artificially altering the activity of motor neurons in this culture system, we will be able to gain unprecedented insight into the causes of MND.
In the process, we will also establish a novel drug-screening platform for MND, which could have therapeutic benefits for improving the muscle function in MND.

Ted Dimmick Memorial MND Research Grant
Dr Bradley Turner

Florey Institute of Neuroscience and Mental Health
Androgen receptor abnormalities in MND

Androgens such as testosterone are important factors for proper development and survival of motor neurons. Androgens act on the androgen receptor (AR) to carry out their function. There is increasing evidence that androgens may play a role in MND, including the higher incidence of MND in males, abundance of AR in motor neurons and AR defects link to another motor neuron disorder, Kennedy's disease. We have new evidence that AR protein levels are lower in spinal cords of MND mice. Furthermore, AR loss occurs specifically in motor neurons in MND mice. We now wish to determine how early AR abnormalities occur in Petri dish and mouse models of MND. We will also establish the primary mechanism responsible for AR loss in MND. This may provide important insights into the potential contribution of AR to MND and whether AR presents a new disease player and potential therapeutic target for MND.

zo-ee MND Research Grant
Dr Justin Yerbury

IHMRI, University of Wollongong
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. This project will build the foundations of an imaging molecule discovery pipeline allowing for the development of an imaging technique to detect the accumulation of specific targets in MND. It is possible that detecting the disease earlier may give the drugs that work in the lab setting more of a chance to work in people living with MND.

Bob Delaney MND Research Grant
Dr Shyuan Ngo

School of Biomedical Sciences, University of QLD
In search of novel MND therapeutics: investigating the role of selective K_{ATP} channel activators on cortical hyperexcitability, corticospinal circuit degeneration, and cortical bioenergetics

In people with MND, brain cells that are involved in controlling movement have increased activity. While the only drug that is available for the treatment of MND (riluzole) works by controlling cell activity, it only provides a modest improvement in survival. Because increased cell activity is believed to be one of the primary factors that lead to the death of these brain cells and their connections, the identification of compounds with improved efficacy over riluzole is critical as this may greatly improve the effectiveness of current treatment strategies.
We will investigate a class of proteins that control cell activity by responding to the energy levels inside the cell. Substantial evidence suggests that in MND, changes in how the body uses energy contributes to the progression of disease. We therefore believe that the brain cells involved in controlling movement are unable to produce enough energy to sustain their

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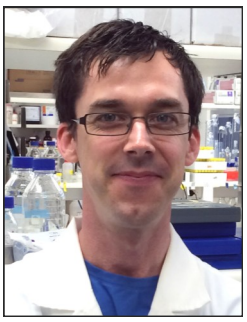
survival. We also believe that the energy sensitive proteins on these cells do not respond to the energy deficit in the right way. Because of this, they are unable to assist in controlling cell activity, and this would contribute to the death of the cell. Using a mouse model of MND, we will test the effect of a novel compound that has been found to act on these energy sensitive proteins. We believe that by helping these proteins to function in the right way, this compound will normalise cell activity, and prevent the loss of these brain cells and their connections.

Cunningham Collaboration Grant
Prof 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 change in fat mass in MND is of clinical importance as a rapid loss of fat mass is associated with worse disease outcome. The underlying cause for the loss of fat mass appears to be linked to an increase in metabolism, which drives an increase in energy demand from the body. Interestingly, it has been reported that MND patients who receive high protein, high carbohydrate, or high fat supplements in their diet are able to maintain or increase their body weight. This in turn has been associated with improved outcome. Whether the benefits associated with dietary supplements in MND patients is due to an improved ability to meet energy demands because of the availability of excess calories remains unknown. Thus, this project aims to conduct a multicentre study that will assess relationship between metabolic balance and dietary intake, and the impact of this relationship on disease progression in MND patients. By identifying ways in which we can help the body to sustain optimal energy needs, we hope to develop metabolic strategies that have the potential to improve prognosis in MND.
This project will also develop collaboration between the RBWH/UQ MND group and the Netherlands MND centre in Utrecht.

Charles & Shirley Graham MND Research Grant
A/Prof Trent Woodruff



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

Inflammation is a key process in the body's natural defence against infection. However, when chronically activated in the absence of infection, it can also lead to progressive tissue damage. In the late 1990's a new mechanism was identified which could regulate inflammatory damage in the brain. Our laboratory, and several other groups, have preliminary evidence that this inflammatory pathway is activated in MND. We hypothesise that over-activation of this pathway in MND brains leads to death of motor neurons, which accelerates disease progression. Our group has identified a novel, orally active drug, which can block this inflammatory pathway. In this study, our goal is to investigate the therapeutic potential of this drug in a preclinical mouse model of MND. We will also examine this pathway in the blood of MND patients, and also in brain samples of patients who have died of MND. This will provide vital proof-ofconcept data that therapeutic targeting of this inflammatory pathway may slow MND in humans. If our project is successful, it will pave the way for future clinical trials of drugs that target this inflammatory pathway in MND patients. Our group, consisting of experienced pharmacologists, medicinal chemists, neurologists, and immunologists, are well positioned to carry out this work.

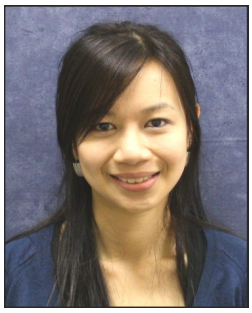
MNDRIA Grant-in-aid
A/Prof Steve Vucic

Westmead Millenium Institute, University of Sydney
Safety and biological efficacy of narrow-band UVB phototherapy in ALS

ALS is unknown, recent evidence points to an important role for immune dysregulation in ALS pathogenesis. In particular, a role for the suppressive arm of the immune system, directed primarily by regulatory T cells (Tregs), may slow disease progression. In this project we will conduct the first trial in ALS of a specific immune therapy, narrow band UVB phototherapy, known to increase Treg activity.
For this, a team has been assembled with all relevant expertise. It is led by a clinician scientist with a long track record in ALS research and clinical care. Narrow band UVB phototherapy is a simple, safe and non-invasive treatment used routinely to suppress damaging immune reactions in other conditions such as psoriasis. We will determine whether UVB phototherapy is safe in ALS and whether it induces regulatory T cells. If effective, this would support a larger trial examining whether UVB phototherapy can slow the progression of disease.
Slowing disease progression using phototherapy would be a major advance for a devastating disease. If phototherapy has no effect on disease progression but can increase regulatory T cells it may be useful in combination with other neuron-regenerating

treatments that are in development, by reducing immune-mediated neuron damage. The study proposed here will expand our knowledge of the role of the immune system in ALS and highlight the potential to harness its regulatory arm to slow disease progress.

MNDRIA Grant-in-aid
Dr Rachel Tan



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

The human cerebellum comprises 10% of total brain volume and is home to more neurons than any other brain region. The sheer enormity of this structure suggests a pivotal role in intact neurological function yet little is known about the cerebellum in MND. Recent findings in healthy humans demonstrate crucial cerebellar involvement in motor, cognitive and neuropsychiatric processes. Given that approximately 14% of patients with MND demonstrate cognitive and neuropsychiatric symptoms characteristic of behavioral variant frontotemporal dementia (bvFTD), these findings have cumulated to position the cerebellum at the centre of the MND-FTD continuum. We recently examined structural changes in cerebellar subregions across the MND-FTD continuum and demonstrated consistent cerebellar involvement, which impacts on motor, cognitive and neuropsychiatric processes. Histopathological analyses are required to determine the underlying changes that subserve regional cerebellar atrophy identified with these neuroimaging methodologies.
The goal of the proposed research is to identify specific neuronal populations targeted and characterise the pattern of protein accumulation in cerebellar subregions associated with the various MND -FTD syndromes. The outcomes of this study will provide crucial knowledge that will progress research into targeted disease-modifying agents for the treatment of MND and bvFTD syndromes.

MND Victoria Research Grant
Dr Anne Hogden

Australian Institute of Health Innovation,
Macquarie University
Decision support tools for motor neurone disease multidisciplinary care.

People with MND and their families face many decisions for symptom management and quality of life. Patients and their family members value information about MND from sources they trust, such as MND associations, MND clinics and research-based websites. However, many people report feeling overwhelmed by the amount of information needed to manage their condition, and the confronting nature of that information. We know that difficulties coping with the impact of MND can cause patients to delay healthcare decisions, putting their safety and quality of life at risk.
An effective way to present patients with specific, research-based information is through the use of decision support tools. Decision support tools have been used in chronic disease and cancer care to help patients make healthcare decisions as their condition deteriorates. The tools summarise the best practice options for symptom management, and inform patients of the risks and benefits associated with these options. Patients are then able to make informed decisions, and discuss the available options with family and health professionals. Currently, there are no decision tools designed to guide MND patients through treatment decisions.
This project aims to develop MND-specific tools to support major treatment decisions, including: use of riluzole; assisted ventilation; artificial feeding and hydration; end of life care; and saliva management. Additional tools, including equipment use and advance care planning, will be developed as the study progresses. The study team will produce paper and electronic tools, and investigate the development of phone app formats.

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 MND, a biomarker that can predict disease severity and measure disease progression is needed for assessment of individual patients and also for clinical trials. There is no existing marker and using survival as a marker is flawed. A marker needs to be practical, applicable to all stages of disease and able to be applied equally in different MND centres. In this study we will expand on our preliminary work that appears to show that pNfH measured in the blood has potential to be a useful marker. We need to prove this in a prospective study, by comparing with other markers and in a larger number of subjects. A second part of the study will be to look for other biomarkers using mass spectrometry of plasma from subjects with MND. One important by-product of this project is that the blood samples are available for other MND research at 3 different centres in Qld and NSW.

Postdoctoral MND Research Fellowships

These early career fellowships provide the help needed by researchers who have recently obtained their PhD and want to establish a career in MND research. After three years they are firmly entrenched in their commitment to MND. This year two new postdoctoral fellowships have been awarded. Dr James Howells will be the 14th Bill Gole Fellow and Dr Parvathi Menon has been awarded the new Beryl Bayley MND Postdoctoral Fellowship.
Both will be working in the field of clinical measurement.

Bill Gole MND Postdoctoral Fellowship
2015 - 2017
Dr James Howells
Brain and Mind Research Institute, University of Sydney
Hyperexcitability of the lower motor neuron in ALS

Involuntary twitching of muscles (fasciculations) are characteristic of MND. Fasciculations are spontaneous ectopic motor unit discharges that arise predominantly in the distal parts of the peripheral nervous system. Recent evidence indicates that they are the earliest detectable abnormality in ALS, preceding by several months evidence of degeneration. Despite their importance it is not clear how fasciculations are generated or how they are related to motor neuron degeneration. This research program will focus on the membrane properties of lower motor neurons in ALS, and in particular changes responsible for altered excitability and ectopic activity. We hypothesise that:
1. The characteristic fasciculations of MND are driven by early pathological alterations in the 'excitability machinery' of peripheral motor axons and that these changes can be profiled using noninvasive excitability testing techniques.
2. That the diminution of fasciculation in patients with advanced MND is due to the preferential degeneration of the larger and faster axons and thereby may be a marker of those motoneurons at greatest risk.
We aim to characterize the excitability and variability of lower motor neurons in MND and in doing so improve the accuracy of the motor unit scan (an essential indicator of disease progression).

Beryl Bayley MND Postdoctoral Fellowship
2015 - 2017
Dr Parvathi Menon
Westmead Hospital, University of Sydney
Insights into ALS Pathophysiology from patterns of disease progression

The aim of my project is to better understand patterns of spread of MND and the mechanisms underlying it, specifically a phenomenon called cortical hyperexcitability which in previous studies has been shown to be an early disease feature and to precede the onset of clinical disease in people with a genetic predisposition. Disease spread has been studied earlier though mostly by patient examination and usually by retrospective analysis. The unique feature of my project will be prospective follow up of patients and supplementation of clinical examination by sensitive testing techniques for brain and nerve function. Disease onset in a body region is well known to precede obvious weakness raising the need for special functional diagnostic tests to supplement our examination techniques. Understanding the mechanisms underlying disease onset and progress would help identify better treatment targets. Identifying cortical hyperexcitability as an early diagnostic marker of MND would reduce the current diagnostic delay and enable earlier introduction of treatment measures including recruitment of eligible patients into available treatment trials.
Overall, the aim of my project is to improve understanding of the disease processes underlying MND thereby working towards better treatment options in the near future and cure in the longer term.

Ongoing postdoctoral fellowships awarded in previous years

Bill Gole Fellowship
2014 - 2016
Dr Jacqueline Leung
U Tasmania
Investigating the role of oligodendrocytes in ALS

Graham Linford Fellowship
2014 - 2016
Dr Sharpley Hsieh
NeuRA, NSW
Seeing the future in MND

Bill Gole Fellowship
2013 - 2015
Dr Kelly Williams
Macquarie, NSW
Investigating the molecular basis of ALS

Bill Gole Fellowship
2011 - 2015
Dr Rachael Duff
Perkins IMR, WA
Application of new generation genetic techniques to MND

PhD Scholarships

PhD Scholarships will be announced in January 2015. One new MNDRIA/NHMRC co-funded PhD Scholarship and one MNDRIA PhD Top-Up Grant will be awarded.

Scholarships from previous years continue in 2015 for:
Dr Nimeshan Geevasinga, Westmead Hospital, MNDRIA/NHMRC PhD Scholarship:
Electrophysiological and neuroanatomical determination of patients with ALS with the C9ORF72 mutation.

PhD Top-Up grants continue in 2015 for:
Dr Rebekah Ahmed, Neuroscience Research Australia: *Eating, autonomic and sexual dysfunction in MND and FTD*
Jayden Clark, University of Tasmania: *Axonal protection in ALS*
Rosie Clark, University of Tasmania: *Interneuron dysfunction in ALS: A new target for potential therapeutics?*
Jennifer Fifita, Macquarie University: *Examining the role of novel molecules causing MND*

MND Australia Research Meeting

The Florey Institute of Neuroscience & Mental Health, University of Melbourne, 27 October 2014

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 researc
- To demonstrate the value of the funded research to donors to encourage their continuing support

Current recipients of MNDRIA grants are invited to report on the outcome of their funded project to an audience comprising their peers, MND Research Committee members, other leading MND scientists and researchers and the wider MND community. This event has been held annually since 2005 at venues in Sydney, Melbourne and Brisbane to facilitate participation for researchers in different states. The 2014 meeting hosted by the Florey Institute was generously sponsored by Biogen Idec. Attendees were welcomed by MND Australia President, David Ali and Professor Philip Beart, Head of Neurodegeneration at the Florey Institute. This report on the meeting was written by Dr Justin Yerbury, University of Wollongong for the *ALS/MND Research and Care Community Blog (ReCCoB)*.

The annual MND Australia Research Meeting for 2014 was held at The Florey Institute of Neuroscience and Mental Health, University of Melbourne. There was an air of excitement at the meeting due to the recent world wide phenomenon of the MND/ALS Ice Bucket Challenge, which has not only raised vital funds to allow much needed research into MND but has also significantly raised the profile of MND in the Australian community. Fittingly, on this particular Monday morning, Melbourne decided to open its skies and hold its own version of the ice bucket challenge with huge thunderstorms crashing across the city resulting in train and tram line failures and more than a few meeting attendees arriving soaking wet.

The meeting was bigger and better than ever with 21 platform presentations, 27 posters and over 100 people registered to attend. The meeting was opened with the announcement that the MND Australia Research Committee Chair Professor Dominic Rowe AM had stepped down after ten years. Prof Rowe, of Macquarie University, has led the MND research committee since he took over the role at the end of 2004. During those ten years, funding for MND research in Australia has expanded to encourage the full spectrum of researchers from PhD students through to well-established researchers. The position of MND Research Committee Chair has been taken up by Prof Matthew Keirnan, Brain & Mind Research Institute, University of Sydney, who certainly has some big shoes to fill.

Prof Philip Beart, head of neurodegeneration at the Florey Institute gave the opening address and kicked the day off by speaking about protein misfolding and aggregation and the need to “take out the trash” using protein degradation machinery. His insights into neuron specific processes set the tone.

On the subject of protein misfolding, Prof Ken Rodgers, University of Technology Sydney, provided evidence that the blue green algae toxin BMAA can be misincorporated into growing polypeptides which may cause protein misfolding and aggregation. It was proposed that non-proteinogenic amino acids such as BMAA may accumulate in misfolded proteins throughout life and result in MND. One way of degrading such misfolded proteins is autophagy and Dr Brad Turner of the Florey Institute presented his work outlining small molecule activation of autophagy and its consequences on accumulation of misfolded and aggregated proteins. It seems the effectiveness will depend on which specific autophagy pathway is targeted.

While there have been many recent discoveries outlining genetic causes of MND there is still a significant amount of inherited forms of MND in which a genetic defect is not identified. As a result, genetics of MND is still a hot topic and A/Prof Ian Blair, and Dr Kelly Williams from Macquarie University spoke on the use of next generation sequencing and epigenetics in the study of MND respectively. In addition, Beben Benyamin from the University of Queensland spoke about his work on genomic and epigenetic changes in the Chinese population. Studying specific populations seems important due to the differences in inheritance such as the lower age of onset in the Chinese population compared to the European population and the lower frequency of c9orf72 expansions. It appears that as we move forward with genetic studies we may have to move towards studying polygenic analysis of common SNPs. Importantly, we were reminded that the discoveries made in the genetics arena feed into the study of molecular and cellular biology and provide more

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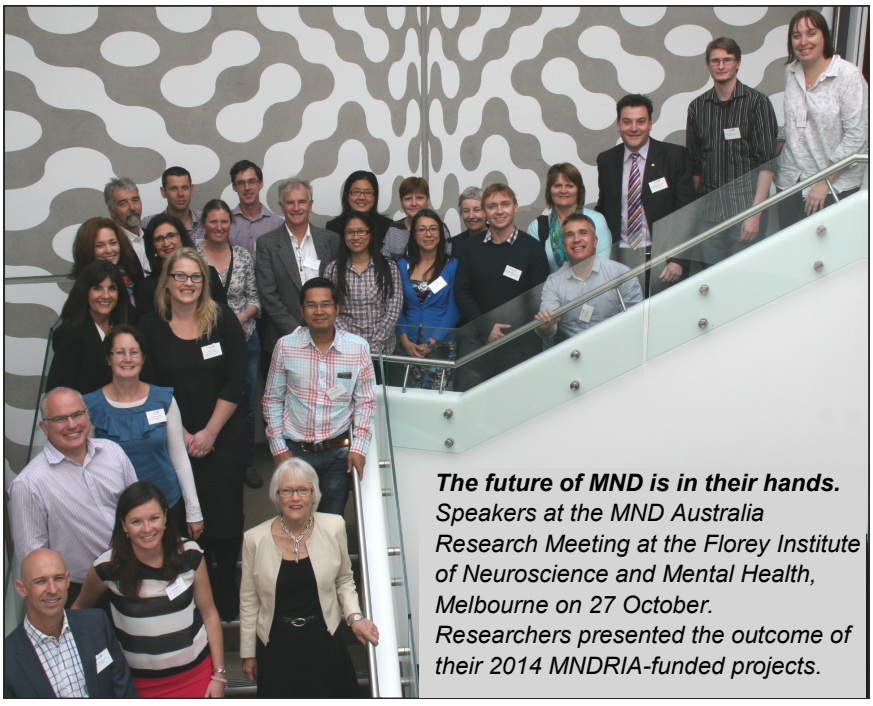

The future of MND is in their hands. *Speakers at the MND Australia Research Meeting at the Florey Institute of Neuroscience and Mental Health, Melbourne on 27 October. Researchers presented the outcome of their 2014 MNDRIA-funded projects.*

MND Research Institute of Australia

Office Bearers and Members December 2014

MND Australia is the principal member of the MND Research Institute of Australia.
The operations of both organisations 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 special tenure directors.

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Associate Professor Steve Vucic, NSW

MND Australia Research Meeting

(continued from page 11)

pieces to the puzzle. This lead directly to the construction of model systems to study these genetic discoveries such as the zebra fish presented by Dr Nick Cole, Macquarie University, and the iPSC derived motor neurons generated in the laboratory of Dr Lezanne Ooi, University of Wollongong. Importantly, Dr Ooi's models were generated with mRNA so as not to change the DNA of the patient cells and the models recapitulated major MND phenotypes such as increases in phosphorylated TDP-43.

Prof Peter Noakes, University of Queensland, advocated for the use of human tissue in the study of MND and showed some breathtaking images of neuromuscular junctions from human muscle biopsy. ALS NMJs were significantly fragmented, withdrawn, and showed terminal sprouting.

Dr Catherine Blizzard, University of Tasmania, presented work to suggest that TDP-43 plays an important role in the maintenance of the synapse through delivery of vital mRNA. While the cytoskeleton, was shown to be important to trafficking of TDP-43 into axons by the work of Dr Anna King, also of the University of Tasmania.

Cellular signaling also was a prominent theme in the presentations with Dr Marie Mangelsdorf, University of Queensland, presenting her work on the EphA4 protein, its splice variants and its role in speed of disease progression. Further, Dr Jeff Liddell presented work to show that the copper containing drug used in his laboratory at the University of Melbourne activated the Nrf2 pathway possibly leading to beneficial effects. Lastly, Dr Aaron Russell, Deakin University, presented his work showing that mitochondrial health and thus motor neuron survival may be promoted by suppressing specific micro RNA that control mitochondrial gene expression.

The poster session followed and was a hive of activity, with many discussions around the interesting work being presented. By then the clouds had parted and we could all make our way home and reflect on how fast the field is growing, what the year 2014 has delivered and what major challenges lie ahead.

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.

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