Motor neurone disease (MND) is a devastating fatal condition for which, as yet, there is no cure. There are an estimated 1,900 people living in Australia with MND today. Their average life expectancy from the time of diagnosis is only two to three years. In 2011, 790 people with MND died in Australia - that’s more than two people every day. The latest data from the Australian Institute of Health and Welfare show that the MND death rate is increasing. We don’t know why this is happening but the only way we can hope to change this is through research.

The Motor Neurone Disease Research Institute of Australia (MNDRIA), the research arm of MND Australia, has been promoting MND research in Australia for almost thirty years. Established in 1984, MNDRIA has grown steadily since the award of its first grant-in-aid in 1987. Now, with the allocation of a record $2.17 million for new grants commencing in 2014, there is no doubt that the Motor Neurone Disease Research Institute of Australia is a major force in driving MND research in Australia.

Twenty-two new grants have been awarded to emerging scientists and established researchers who are seeking to understand the causes, provide better care, control the symptoms and find a cure for MND. Together with 11 grants continuing from previous years (the MND Australia Leadership Grant, 4 post-doctoral fellowships, 3 PhD scholarships and 3 PhD top-up grants), MNDRIA will be supporting 33 MND research projects spanning all Australian states in 2014.

This is all made possible by growing support from the Australian community of MND supporters who provide all of the funds distributed each year by MNDRIA. The awarding of MNDRIA research grants is a comprehensive process to ensure that donations and bequests fund only the best research that will have the greatest chance of providing benefit for people with MND. Every dollar received is spent directly on research.

There have been so many recent research discoveries that we can now really hope that early diagnosis and an effective treatment are not far away and that we will eventually have a world free from MND.

We thank each of the many donors whose combined effort is helping to achieve this goal.
The past year has been a groundbreaking year for the MND Research Institute of Australia. Not only were more funds than ever before distributed by MNDRIA, but also a major project grant was awarded for the first time.

**Bequests and donations**
The majority of funds available for MND research grants come from bequests and donations. Although bequests are received as an unexpected windfall, they have played a significant part in boosting available research funds to record high levels. We are grateful for gifts of several bequests in 2012/13 which account for 24% of total funds available for distribution this year.

Family trusts and foundations (including MND and Me and the Scanlon Foundation) provided 26% of donations, and MND Associations another 23%. The MND Associations provide the link to the wider MND community and contribute donations they receive for research to be allocated through the MNDRIA peer review process.

Major donors, special fundraising events and MND Associations continue their generous support for named grants. Support was provided in 2013 for the Bill Gole and Graham Linford Postdoctoral MND Research Fellowships, the Peter Stearne Grant for Familial MND Research, the Rosalind Nicholson MND Research Grant, the Charles & Shirley Graham Grant and five grants funded by MND Victoria and its supporters: the MND Victoria Grant, the Zo-eè Grant, the Mick Rodger Benalla Grant, the Mick Rodger Grant and the Susie Harris Memorial Fund Grant. Other grants are funded by unsolicited gifts and donations so generously given each year by the many regular MNDRIA supporters (14% of income).

**Research Grants**
Grants awarded for new grants commencing in 2013 totalled $2.014 million. In the calendar year 2013 a total of $1.75 million has been paid by MNDRIA for 15 grants-in-aid, five concurrent Bill Gole Postdoctoral Fellowships, two PhD scholarships (co-funded with NHMRC) and four PhD top-up grants. These grants are not only providing substantial support for established researchers, but also encouraging young researchers to dedicate their career to MND. With no other funds awarded by the National Health and Medical Research Council for new MND research projects in 2013, MNDRIA is now a major force in driving MND research in Australia.

**MND Australia Leadership Grant**
A further $150,000 has been paid to the Australian School of Advanced Medicine (ASAM), Macquarie University, NSW for the first of four annual instalments of the MND Australia Leadership Grant. The inaugural MND Australia Leadership Grant commencing in January 2013 was awarded to Associate Professor Ian Blair to investigate the pathogenic basis of familial ALS. Ian and his team of researchers focus on the genetics of MND, but they are just one team of the collaborative program at the new MND Centre at ASAM, officially launched in June 2013, with expertise in cell biology, biochemistry, proteomics, and mouse and zebrafish disease models.

**MND Research Committee**
Long-serving MND Research Committee Member, Emeritus Professor John Pollard OA, has stood down after 19 years of providing wisdom and guidance in determining allocation of funds available for research grants. We are grateful for the countless hours that he and other research committee members have given each year in rigorous assessment of all grant applications to ensure that the available funds go only to the best proposals with the greatest relevance and the most likely chance of providing benefit for people with MND. The time that this task requires is given freely by research committee members who are the leaders in their various fields of MND research and represent most Australian states.
Meetings
The annual MND Australia Research Meeting which provides the opportunity for researchers funded by MNDRIA to present the outcome of their work to their peers and to MNDRIA members was held at the Queensland Brain Institute in November 2012 with generous support from both QBI and Sanofi. Record attendance of 75 researchers and supporters, many from interstate, provided a stimulating forum for interchange of ideas. Future annual meetings will be extended to full day symposia to accommodate both oral and poster presentations from the increasing numbers of MND researchers in Australia. The first of these will be held at Macquarie University on 18 November 2013 (see report on page 11).

Information
The MNDRIA website has been integrated into the new MND Australia website www.mndaust.asn.au. MNDRIA retains the same web address www.mndresearch.asn.au which goes directly to the research pages on the MND Australia site but it is also easy to navigate to research from the MND Australia home page.

Regular research newsletters give information about MND research in Australia to the MND community and also provide feedback to the many donors who provide the funds for the research. Advance, the bi-annual newsletter of MNDRIA, has a circulation of 4,500 copies. The MND Australia International Research Update is a brief quarterly report produced by MND Australia and funded by MND Victoria. Both newsletters are distributed nationally with the help of state MND Associations and internationally through the International Alliance of ALS/MND Associations.

Paula Trigg, former Honorary Secretary of MNDRIA and member of the MND Research Development Committee has stood down after nine years of service. Paula played an enormous part in developing policies and procedures to ensure transparency of the Institute.

MND research has come a long way since the establishment of MNDRIA by volunteers in 1984. Dr Graham Lang, who died in January 2013, had a significant role in development of the highly regarded Research Institute we have today. He attended the 2012 grants allocation meeting and witnessed the record breaking award of over $2 million. Graham’s contribution has been recognised with the award of the Graham Lang Memorial MND Research Grant for 2014 and the Jenny and Graham Lang collaboration Travel Grant. He would have been proud to know that we have now officially raised the bar to provision of at least $2 million every year and this has been achieved again in 2013.

Janet Nash, Executive Officer Research

A big thank you from MNDRIA to:

- 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 the driving force for MND research in Australia.
- Our regular donors who, with their dedication to MND research, provide a reliable flow 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 to contribute to their cause.
- Our loyal volunteers: Maureen Burmeister, Libby Gole 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 paves the way to a better life for people with MND.

Devil n Me around Ozee
Kim Evans, with his dog Devil, set out from Lismore, NSW in May to cycle around Australia as an ambassador for MND research. The challenge was too much for Devil, but four months later Kim arrived triumphantly home after cycling 15,500 km, meeting up with MND research groups in Brisbane, Perth, Adelaide, Melbourne and Sydney and almost $70,000 in the bag for MNDRIA and the Bob Delaney MND Research Grant. A fantastic tribute to his friend. Thank you Kim.
Scholarships awarded for MND research commencing in 2014

The Bill Gole MND Postdoctoral Fellowships have been sponsored anonymously since 2005 and are now widely recognised as a very successful program encouraging our best emerging scientists to focus their attention on motor neurone disease. The three-year fellowships are hotly contested with an increasing number of applications received each year. This year’s fellowship has been awarded to Dr Jacqueline Leung who is the thirteenth person to be awarded this prestigious fellowship and the fourth Bill Gole Fellow from Tasmania.

The new Jenny and Graham Lang Collaboration Travel Grant provides for an extended travel period for the investigation and establishment of a collaborative project with other MND researchers.

The MNDRIA PhD scholarship top-up grant will be announced early in 2014.

Bill Gole MND Postdoctoral Fellowship
2014 - 2016
Dr Jacqueline Leung
Wicking Dementia Research & Education Centre, University of Tasmania
Investigating the role of oligodendrocytes in ALS.
Amyotrophic Lateral Sclerosis (ALS) is characterised by the progressive loss of motor neurons in brain and spinal cord. The axons (longest processes of neurons) of the motor neurons are mostly wrapped by the oligodendrocytes that produce myelin, an insulating layer that allows rapid conduction of the neuronal signal. The oligodendrocytes have also recently been identified to play an important role in providing metabolic support to these axons. Recent evidence in ALS research has suggested that oligodendrocytes might have an active role in both disease onset and disease progression in ALS. This study will focus on understanding the role of oligodendrocytes in ALS and allow us to uncover specific mechanisms in the involvement of oligodendrocytes in ALS. The results collected from this study will contribute to a greater understanding of disease processes in ALS, as well as establishing new therapeutic targets in ALS treatments.

Jenny & Graham Lang Collaboration Travel Grant
Dr Rebecca Sheean
Florey Institute of Neuroscience & Mental Health, VIC
Development of survival motor neuron (SMN) gene therapy for MND.
SMN is an essential factor required to support motor neurone growth and maintenance. SMN loss causes the childhood disease SMA and reduced SMN gene copy number is a proposed risk factor for MND. We recently identified that SMN protein levels are critically low in motor neurones of MND patients and mice. This suggests that supplementing SMN could be beneficial in MND. We confirmed this by genetically engineering MND mice with extra SMN gene copies which slowed symptom onset and protected motor neurones. We now wish to extend these findings by developing and evaluating a form of gene therapy which can be injected and specifically targets and delivers SMN to motor neurones. We will examine the effects of SMN gene therapy on disease signs, brain and spinal cord pathology in mouse models of nerve injury and MND. With this travel grant I will be able to work with both my laboratory and the laboratory of Professor Kevin Talbot at the University of Oxford to test SMN gene therapy in multiple mouse models of MND. If SMN gene therapy is effective in MND mice, then this approach, which is readily amenable to administration in people, may have clinical potential for MND.

Ongoing postdoctoral fellowships awarded in previous years

<table>
<thead>
<tr>
<th>Fellowship Type</th>
<th>Name</th>
<th>Institution</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bill Gole Fellowship</td>
<td>Dr Kelly Williams</td>
<td>Macquarie University, NSW</td>
<td>Investigating the molecular basis of ALS.</td>
</tr>
<tr>
<td>Graham Linford Fellowship</td>
<td>Dr Sharpley Hsieh</td>
<td>Neuroscience Research Australia, NSW</td>
<td>Seeing the future in MND.</td>
</tr>
<tr>
<td>Bill Gole Fellowship</td>
<td>Dr Shyuan Ngo</td>
<td>University of Queensland</td>
<td>Investigating mechanisms underlying defective energy metabolism in MND.</td>
</tr>
<tr>
<td>Bill Gole Fellowship</td>
<td>Dr Rachael Duff</td>
<td>West Australian Institute for Medical Research</td>
<td>Application of new generation genetic techniques to MND.</td>
</tr>
</tbody>
</table>
Grants-in-aid for MND research in Australia in 2014

Grants-in-aid support MND projects. These are development grants which help established researchers to initiate projects with the hope they can ‘grow’ to produce data that can attract more significant funding from granting bodies such as the National Health and Medical Research Council.

Twenty new projects around Australia have been awarded grants-in-aid for 2014: seven in Queensland, five in NSW, four in Victoria, two in Tasmania, one in South Australia and one in Western Australia. These projects cover many aspects of MND research including genetics, cell biology, biomarkers and quality of life.

Five of the grants-in-aid awarded this year come from MND Victoria with a requirement of attendance at the International ALS/MND Symposium in Brussels in 2014. This MND Victoria initiative has introduced many researchers to the annual Symposium and the opportunity to share new research and establish collaborations. This year 30 percent of all oral and poster presenters at the Symposium in Milan are from Australia. Australians have long been involved in major breakthroughs and are at the forefront of world MND research.

Graham Lang Memorial MND Research Grant

Professor Samar Aoun

Curtin University, WA

Best practice in breaking the news of an MND diagnosis: A survey of patients, family carers and neurologists.

Communicating a diagnosis of MND is challenging for clinicians and for patients. This project consists of an Australia wide survey on breaking the news of an MND diagnosis from the perspectives of patients, family carers and neurologists. The feedback from the 3 groups will assist in describing the experience of when and how the diagnosis was provided, in assessing the current practice of clinicians in breaking bad news, and in making recommendations for Australian MND specific guidelines.

MNDRIA Grant-in-aid

Dr Mark Bellingham

School of Biomedical Sciences, University of QLD

Respiratory motor dysfunction and treatment in an animal model of motor neuron disease.

Despite the fact that death in MND is usually due to respiratory failure, and that respiratory function is one of the best predictive factors for disease progression, we know very little about how dysfunction develops in the neural control of breathing movements in MND. In particular, effective treatments for respiratory dysfunction are sadly lacking. The planned outcome of this research will be the first comprehensive characterization of the neural control of breathing movements and its progressive dysfunction in a commonly used mouse model of MND. This characterisation will range from the cellular to the systems level, from functional and structural changes in single respiratory motor neurons to breathing movements and responses to common breathing stimuli in the whole animal.

We will also test two novel therapeutic strategies – prophylactic early treatment with riluzole at a time when changes in motor neurons controlling breathing movements are already starting to occur, and the induction of enhanced breathing output (respiratory long-term facilitation) in both the early stages of disease, and in the dysfunctional adult breathing motor system. The outcomes of these treatment strategies will provide invaluable insights into how and when to treat breathing dysfunction in human MND.
Mick Rodger Benalla MND Research Grant  
Dr Beben Benyamin  
Queensland Brain Institute, University of QLD  
Trans-ethnic and trans-omic statistical analyses to identify new ALS risk variants.  
Elucidating the aetiology of ALS/MND is the key to its treatment and cure. Genetic factors are a major cause of ALS even in apparently sporadic cases (i.e. no family history of ALS). Currently, the known ALS genes explain a small proportion of sporadic cases. Except for age and sex, there are no specific biomarkers and environmental factors known affecting ALS. Using state-of-the-art genomic technologies, such as genome-wide association study, exome sequencing and epigenome-wide association study in ALS patients and controls, we aim to discover novel genes affecting ALS and to dissect their biological functions in ALS. To achieve these aims, we will use rich data from ~4,000 Chinese ALS case-control samples and summary GWAS data from the largest European ALS samples (ALSGEN Consortium). To our knowledge this will be the first large-scale trans-ethnic meta-analysis for ALS. We expect to identify novel genetic risk variants affecting ALS disease status or age of onset across ethnic populations and to understand their roles in ALS. An association between locus or genome-wide epigenetic states and ALS disease status or age of onset may lead to the discovery of novel pathways.

MNDRIA Grant-in-aid  
Dr Catherine Blizzard  
Menzies Research Institute, University of Tasmania  
Synaptic alterations in ALS: A novel therapeutic target?  
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. Disturbances in neuronal synapses may be one such early event that potentially leads to neuronal dysfunction and then death. Synapses are specialised structures that allow neurons to communicate with each other. Changes in synapses can have serious effects on neurons’ activity levels and if not controlled can cause neuron death. In dendrites, the large structures that relay information to the neuron’s cell body, these synapses are present on small protrusions known as dendritic spines. Mutations in the protein, transactive response DNA-binding protein 43 (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 TDP-43 protein mutation determines the number and type of synapses on motor neurons in the brain and how these changes lead to dendritic spine alterations in ‘real time’ through a unique mouse model and sophisticated imaging techniques. 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.

Peter Stearne Grant for Familial MND Research  
Dr Nicholas Cole  
Australian School of Advanced Medicine, Macquarie University, NSW  
Modeling the ALS-linked C9ORF72 hexanucleotide repeat expansion in zebrafish. Despite many years of research on amyotrophic lateral sclerosis (ALS), there is little understanding of the basic biology that results in a person acquiring ALS, and no effective treatment. We therefore need successful research models of ALS to help us understand the mechanism of the disease. Several genetic faults that cause ALS have been identified from patients. We can put these same faulty genes into zebrafish, enabling us to create zebrafish that develop ALS-like features in order to help us understand the biology of the human disease. In this way, zebrafish become a powerful research model of ALS. This is possible because we share common biology with zebrafish. For example, the same genes and proteins that make motor neurons develop and function in humans also direct these processes in zebrafish. Recently, a repetitive sequence within the genetic code of a gene called C9ORF72 has been identified as the most common cause of familial ALS. It is thought that this repetitive DNA sequence makes a toxic protein. These ALS patients have more of this repeat sequence in their genetic code than healthy people. In this project, we will create the first
animal model with this significant ALS-causative mutation by making zebrafish that have different lengths of this repeat inside them. We will use this fish model of the human disease to study and understand the basic biological processes that result in motor neuron degeneration. We can then use the fish to investigate potential treatments.

**MND Victoria MND Research Grant**

**Dr Anne Hogden**

Centre for Clinical Governance, Australian Institute of Health Innovation, University of NSW


Multiple and diverse symptoms characterise motor neurone disease (MND). In addition to physical deterioration, many patients are known to experience changes to their cognition (such as problem solving and memory) and behaviour (such as apathy). Yet, unlike physical status, cognition and behaviour are not routinely assessed in MND multidisciplinary clinical practice. The aim of this study is to improve patient care by assessing these changes, and their impact on patients and carers. We will trial a purpose-designed package of assessments to measure cognitive and behavioural change, patient wellbeing and carer burden. We will then evaluate the feasibility of these assessments for use in MND multidisciplinary clinics, and the contribution assessment results make to patient care. The insights gained from this study will: assist service planning; inform patient and carer decision-making; and allow clinicians to proactively tailor care to patients’ varied and complex needs.

**MNDRIA Grant-in-aid**

**Dr Anna King**

Wicking Dementia Research and Education Centre, University of Tasmania

ALS/FTLD (frontotemporal lobar degeneration) proteins in axon function and role in disease.

In the last five years there have been great increases in our understanding of the genetic basis of ALS and links have been drawn between ALS and FTLD. A number of proteins have been implicated in playing a role in these diseases. In particular one protein, TDP-43, is involved in over 90% cases of ALS. This protein is expressed in all the cells of the body and therefore its particular role in the degeneration of the nervous system is puzzling. Nerve cells are very specialised cells with a number of unique functional parts including the long nerve processes, which are responsible for transmitting the nerve signals from one part of the nervous system to another. There is accumulating evidence that TDP-43 and other ALS/FTLD associated proteins are involved in maintaining these long nerve processes. ALS is characterised at early stages by extensive loss and degeneration of nerve processes, resulting in disconnection of the motor nervous system. We currently don’t know how these proteins work to maintain the nerve processes or even if they are present in them. To address this we will use genetic techniques to alter the levels of these proteins in the nerve cells and also to make them pathologic. We will then examine how these proteins are involved in the function of the nerve processes in both animal and primary cell culture models. In particular we will focus on whether they play a role in maintaining or modifying the structural cytoskeletal proteins of the axon.

**MNDRIA Grant-in-aid**

**Dr Jeffrey Liddell**

Department of Pathology, University of Melbourne, VIC

Induction of Nrf2 by neuroprotective CuII (atsm) in SOD1-G37R astrocytes.

More effective therapeutics are urgently needed for the treatment of MND. Using genetically modified mice that recapitulate the symptoms of MND, we have found that a metal complex known as CuII(atsm) elicits striking beneficial effects: the compound delays the onset and progression of symptoms and improves survival of the mice. Importantly, CuII(atsm) still elicits these disease-attenuating effects even when administered after the onset of symptoms, which is a critical characteristic for a therapeutic agent. However, it is unknown exactly how the compound is working. I have recently deduced an exciting mechanism which may explain how CuII(atsm) is acting. However, my experiments to date have been performed on cells isolated from the brains of normal mice; the compound may act very differently in cells that model MND. Thus this project seeks to determine the effect of CuII(atsm) in cells isolated from the brains of genetically modified mice that develop symptoms analogous to MND in humans. This will help
determine whether this compound could be a new, more effective therapeutic for the treatment of MND. In addition, we may also learn if certain aspects are impaired in cells from these mice that could contribute to the underlying disease process.

**MNDRIA Grant-in-aid**  
**Dr Marie Mangelsdorf**  
Queensland Brain Institute, University of QLD  
**Targeting EphA4 as a treatment for MND.**

In mammalian cells a single gene can produce multiple different proteins each with a different cellular function. Around 95% of human genes produce multiple proteins in this fashion. This project will examine one gene, **EPHA4** that has recently been shown to modulate disease progression in motor neurone disease (MND). We have targeted EPHA4 in a mouse model of MND and have seen a moderate effect on disease onset. Only one known protein is produced from the **EPHA4** gene. Our initial analysis has suggested that there are indeed many EPHA4 proteins. This project will investigate all of the protein products produced from the **EPHA4** gene, and the roles they each play in MND. EPHA4 is being targeted as a novel MND therapy and targeting all isoforms, or alternatively specifically avoiding some, may be required for effective treatment. We aim to improve targeting of EPHA4 in the development of an MND treatment.

**Graham Smith MND Research Grant**  
**Professor Pamela McCombe**  
University of QLD Centre for Clinical Research, QLD  
**Investigating the consequences of increased fat catabolism in motor neurone disease.**

People with MND who show rapid loss of fat mass have worse disease outcome. The loss of fat mass appears to be due to the rapid use of fat as an energy source to satisfy increased energy demand from skeletal muscle. Using an animal model of MND, we will investigate the consequences of the loss of excessive fat mass. By understanding the cause and consequences of decreased fat mass we will provide essential information for the development of strategies to slow the progression of disease.

**MNDRIA Grant-in-aid**  
**Dr Diane Moujalled**  
Department of Pathology, University of Melbourne, VIC  
**The role of hnRNP RNA binding proteins in motor neuron degeneration.**

Transactivation response DNA-binding protein-43 (TDP-43) is a major constituent of the mass of protein that are characteristic of two types of brain diseases; amyotrophic lateral sclerosis (ALS) a type of MND, and frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U), a sub-type of dementia, commonly found in patients with ALS. The mechanism by which changes in TDP-43 promote the loss of brain cell function and structure in ALS and FTLD-U remains elusive. In the current literature there is growing evidence that suggests that certain proteins referred to as hnRNPs play significant roles propagating brain diseases and are therefore considered candidates in propagating TDP-43 associated brain diseases. Our studies have shown that mutations in TDP-43 have robust effects on hnRNP expression, which may be a key factor to drive TDP-43 related brain diseases. It is well known that hnRNP proteins play a pivotal role in coordinating vital cellular processes. However, the molecular mechanism of which hnRNPs contribute to disease progression in ALS is unknown. This research aims to identify the molecular mechanism that drives changes in these proteins and reveal novel therapeutic strategies to treat clinically relevant diseases that affect the brain and spinal cord.

**Charles & Shirley Graham MND Research Grant**  
**Associate Professor Peter Noakes**  
School of Biomedical Sciences, University of QLD  
**The role of altered neuromuscular signalling in ALS: factors that modify the course of MND.**

Despite recent advances in understanding the genetic cause of motor neurone disease, the reason why motor neurones die is still unknown. In this application, we will be pursuing abnormalities in the signalling between motor neurones and muscle. This aspect of MND has not been systematically studied, and the loss of motor neurone to muscle connections is a key early event in this disease. In this study, we will collect muscle samples from MND patients and controls. These samples will be used to perform cellular and
molecular analyses of nerve-muscle connections in early-diagnosed MND patients and to examine changes to gene expression in the muscle during the early stages of MND. We believe that abnormalities of the neuromuscular junction and muscle are found in MND and could be targets for development of new therapies.

MNDRIA Grant-in-aid
Dr. Lezanne Ooi
Illawarra Health and Medical Research Institute, University of Wollongong, NSW

Examining the role of protein degradation in iPS cell models of ALS.

Our major goal is to understand how and why motor neurons die in MND. Our preliminary evidence indicates that dysfunctional protein degradation and the formation of inclusion bodies are important pathogenic pathways in MND. We have found that the pathways by which inclusion bodies are formed are unique in different patients and are unlikely to cause toxicity via the same mechanism. To identify causal mechanisms of motor neuron death we need to develop robust means to interrogate the chronology of pathological events in cells from MND patients. Drawing on our recent developments in stem cell technology, we will generate and bank skin-derived induced pluripotent stem cells from MND patients. These cells will then be used to generate motor neurons that represent the complex genetic background of individual MND patients. The motor neurons will be utilised to examine the role of protein degradation dysfunction in MND pathology and neuronal death. By moving beyond mouse and other cell models currently used to study MND, our approach using induced pluripotent stem cells will be better suited to understand the complex two-hit (or potentially more) genetics that is currently coming to light in MND pathogenesis. Additionally, our novel methods of generating induced pluripotent stem cells, motor neurons and other cell types involved in MND pathology bring us a step closer to using patients’ own cells to replace those lost in this devastating disease.

MNDRIA Grant-in-aid
Dr. Ken Rodgers
Medical and Molecular Biosciences, University of Technology Sydney, NSW

Studies investigating the non-protein amino acid BMAA, as an environmental trigger for MND.

In the majority of patients with motor neurone disease (MND) no genetic cause can be identified, suggesting that environmental factors are involved. The South Pacific Island of Guam is one of the few places in the world in which a very high incidence of an MND-like neurodegenerative disease has been reported. The disease affected people from diverse genetic backgrounds living on Guam and occurred at 50 to 100 times the rate of MND in the general population suggestive of an environmental link.

We have recently demonstrated that a toxin made by blue green algae (called BMAA) and found in cycad seeds which were consumed by the people living on Guam, can be incorporated into human proteins in place of L-serine, rendering them toxic to cells. This mechanism may explain the long observed spatial association between BMAA exposure and increased risk of contracting MND. Importantly, our recent studies also identified that the human amino acid L-serine is protective against toxicity caused by BMAA in human cells. We now wish to expand these studies to examine whether exposure to BMAA exacerbates toxicity in in vitro and in vivo models of genetic MND. Cyanobacteria are ubiquitously distributed in terrestrial, fresh water and marine environments and all five known morphological groups of cyanobacteria produce BMAA. With increasing global temperatures, human exposure to BMAA is increasing, which in turn has been linked to an increased risk for contracting MND. We propose BMAA might be a trigger for sporadic MND in susceptible individuals, thus our finding that BMAA toxicity can be blocked with serine provides clues for a preventative or therapy.

Rosalind Nicholson MND Research Grant
Dr. Mary-Louise Rogers
Human Physiology, School of Medicine, Flinders University, SA

A biomarker to track progression of motor neuron disease in humans and MND mice.

There are no effective treatments or biomarkers to track motor neurone disease progression. We have found a protein shed from affected nerves that can be detected in urine and blood. Our aim is now to show this marker can be used to track disease in
symptomatic and asymptomatic people and also mice with MND that are used to test possible new drugs. The significance of this is that a biochemical marker will be available to identify the effectiveness of new treatments for this devastating illness and to assist neurologists detect the disease much earlier than is currently possible.

**Mick Rodger MND Research Grant**

**Associate Professor Aaron Russell**

School of Exercise and Nutrition Sciences, Deakin University, VIC

Inhibiting microRNA-23 as a therapeutic strategy to treat motor neurone disease.

Amyotrophic lateral sclerosis (ALS), the most common adult-onset motor neuron disorder, has no cure and death from respiratory insufficiency occurs within 3-5 years after diagnosis. We identified that microRNA-23a (miR-23a) is elevated in ALS and inhibits important proteins that normally protect muscle and neurons for death. We will block miR-23a in ALS mice and expect this to prevent neuron death and significantly delay disease progression. This will provide a major advance in understanding the mechanisms involved in the development and progression of ALS and identify novel pre-clinical therapeutic strategies to prevent the development or delay the onset and severity of ALS.

**Zo-ee MND Research Grant**

**Dr Bradley Turner**

Florey Institute of Neuroscience and Mental Health, VIC

Therapeutic targeting of autophagy in MND.

One common feature of MND is the accumulation of protein deposits inside nerve cells which leads to their death. Although the factors responsible for accumulation of these proteins deposits remain unclear, strategies that reduce the load of damaged proteins in MND represent a rational approach for potential disease intervention. We have identified a potent drug which enhances autophagy, a protective process which breaks down protein deposits inside cells. We have shown that this autophagy enhancer efficiently clears protein deposits linked to MND in the Petri dish. We propose to treat MND mice with this autophagy enhancer and predict that it will slow disease signs, preserve lifespan and protect nerve cells by reducing the burden of protein deposits in the brain. If our proposal is supported, then this study will encourage future use of autophagy enhancers for potential treatment of MND.

**MNDRIA Grant-in-aid**

**Dr Trent Woodruff**

School of Biomedical Sciences, University of QLD

Innate immune complement signalling in peripheral immune cells during the progression of MND.

There is death of nerve cells in MND. 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 the complement group of proteins. We suggest that the therapeutic targeting of complement could slow the progression of MND. In this study we will investigate this further, using blood samples from people with MND as well as animal models of MND. If this study is successful, we will then be able to perform a trial of our novel drug, which acts on this complement pathway.

**MNDRIA Grant-in-aid**

**Associate Professor Naomi Wray**

Queensland Brain Institute, University of QLD

Whole exome sequencing of sporadic MND.

Recent studies show that genetic factors account for more than half of the risk of developing MND, even in subjects with so-called “sporadic” MND. A number of causative genes have been identified for familial MND and some of these are found in subjects with apparent sporadic MND. In some subjects there is very obvious inheritance of disease and in other families the inheritance is less clear-cut. To understand this further we need systematic studies of the genetics of sporadic and familial ALS. Local studies then need to be combined with studies from other investigators to increase power. We have a cohort of well-characterised subjects with MND, who have already been screened for the presence of the more common genes implicated in causing MND. We now wish to perform whole exome sequencing of all the genes in these patients and controls.
Over 100 researchers gathered at Macquarie University for the Motor Neurone Disease Research Institute of Australia (MNDRIA) annual meeting held 18th November 2013. The importance and purpose of the work about to be presented was crystallised by Chair of the MNDRIA Research Committee, Professor Dominic Rowe, in his introduction. As we all know too well MND is a terrible and incurable disease leading invariably to death. Prof Rowe pointed out that it is only through the work of those in the audience, and colleagues around the world, that we will find a treatment or cure.

The meeting is a showcase of research that has been funded by MNDRIA over the past 12 months. Significantly, the work being conducted spans clinical electrophysiology, biomarker discovery, cognitive deficits, energy metabolism, genetics, and importantly cell and molecular biology of axon degeneration, protein homeostasis and protein degradation. Regardless of the explosion of genetic discoveries over the last few years, genetics remains a hot topic in MND research. In Australia there is still about 30% of inherited MND to be explained. The genetics workflow, and the discovery of a new MND/ALS gene was described by Professor Ian Blair and his postdoctoral researchers Dr Kelly Williams and Dr Shu Yang, Macquarie University. The identity of the gene is not yet published, but hints were given as to the pathways it might contribute to. Prof Blair described how many of the MND-causing genes can now be functionally categorised into either RNA metabolism (TDP-43, FUS, TAF15, EWSR1) or protein degradation pathways (UBQLN2, VCP, p62). The Blair group spoke at length about a new genetic discovery that falls within the protein degradation pathways and argue that this discovery adds more weight to the argument that protein degradation pathways are dysfunctional in MND.

The dying forward and dying back debate continued to rage on during the meeting with Dr Parvathi Menon, University of Sydney, presenting work suggesting that cortical hyperexcitability may explain split-hand symptom of MND. Adding to this was Dr Neil Simon, Neuroscience Research Australia, who presented work suggesting that upper motor neuron involvement may be clinically assessed by H-reflex measurements. In rodents both Dr Anna King, University of Tasmania, and Dr Catherine Blizzard, University of Tasmania, presented evidence that excitotoxicity causes a dying back phenotype and that this effect is only seen when the toxin is presented to cell bodies, consistent with a dying back mechanism. Importantly, Dr King presented data that showed that treating with the anti-cancer drug taxol that stabilises microtubules prevented this toxin-induced die back.

The topic of biomarkers was also a popular one, with a number of talks around the discovery and use of biomarkers. This area has obvious and important clinical and eventually treatment consequences. pNFH was put forward as a biomarker by Dr Rob Henderson, University of Queensland, but it was pointed out that there is a large subpopulation of patients for which this is not a robust measure. Dr Henderson presented work to suggest that measuring motor unit number was still an accurate measure of disease progression, but this is not a viable marker available for long term use. Interestingly, a much less invasive marker was suggested by Dr Mary-Louise Rogers, Flinders University. The extracellular domain of p75 receptor was found in urine of both MND mice and patients suggesting that this may be a useful marker for disease.

While genetic discoveries are increasing our list of known causes of MND, the actual mechanisms that cause motor neurone death resulting from the discovered mutations are still to be determined. Protein homeostasis is the concept that the proteome must be maintained in the correct 3D structure, at the appropriate concentrations and in the desired location in the cell to be functional. Much work is being conducted around the inappropriate accumulation of MND-associated proteins in various regions of the cell or even outside cells. The most common example of which is the cytosolic accumulation of TDP-43. Dr Diane Moujalled, University of Melbourne, presented work that indicated that C-Jun N terminal kinase controls TDP-43 accumulation in stress granules. However, whether the formation of stress granules is favourable or detrimental is yet to be determined. In addition, while SOD1 is normally a cytosolic protein, it can be found outside cells. Dr Julie Atkin, La Trobe

(Continued on page 12)
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.

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

**Research Committee Members**

**Chairman:** Professor Dominic Rowe, NSW  
Professor Perry Bartlett, QLD  
Dr David Berlowitz, VIC  
Associate Professor Ian Blair, NSW  
Professor Nigel Laing, WA  
Professor Matthew Kiernan, NSW  
Dr Susan Mathers, VIC  
Professor Pamela McCombe, QLD  
Professor Dominic Thyagarajan, VIC  
Professor James Vickers, TAS  
Associate Professor Steve Vucic, NSW

---

**MND Australia Research Meeting**  
(continued from page 11)

University presented work to show that SOD1 outside cells could be taken up by neurones and that this uptake of aggregated SOD1 activates the unfolded protein response, inhibits ER-Golgi transport and promotes golgi fragmentation. Continuing on with SOD1, Dr Brad Turner, University of Melbourne, presented his work demonstrating that expression of mutant SOD1 produced enlarged endosomes. This correlated with an increase in endosome markers Rab5 and Rab11 in cells and in MND patients. Collectively the work presented would suggest that modifying protein homeostasis pathways may be an effective treatment strategy for MND.

The meeting finished with a great poster session that touched on topics as diverse as end of life issues, diagnostic utility of threshold tracking TMS, stress granule formation, T-cell involvement in disease progression and the misincorporation of the toxin BMAA into human proteins just to name a few.

The MND research community in Australia has grown substantially in the last 5 years and with it the MNDRIA meeting has gone from a small room in Gladesville and around 20 researchers and an afternoon of talks, to a 150 seat auditorium filled with researchers listening to a full day of talks followed by a poster session. To top this off the MNDRIA announced $2.2 million in funding for MND in 2014. It was clear by the end of the day that we are gaining momentum in the fight against MND.

---

**Donations**
Research funded by the MND Research Institute of Australia is dependent on donations.  
To contribute to this vital work, please send your gift to:  
MND Research Institute of Australia  
PO Box 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, MNDRIA Executive Officer on 02 8877 0990 or email research@mndaust.asn.au.

---

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