

December 2011

**The Motor Neurone Disease Research Institute of Australia (MNDRIA)**, as the research arm of MND Australia, allocates funds for MND research in Australia. Annual grant applications are reviewed by the national MND Research Committee. All funds available for distribution come from donations and bequests to the Institute and to MND Associations. It is not such a long time since few people knew about MND but, as awareness has grown, more funds have been contributed to support the research that is the only way of changing the future. As the funding has grown, so too has the quality of the research projects.

It is rewarding to announce that funds totalling \$1.357 million have been awarded by MNDRIA to new grants commencing in 2012 (see pages 4 - 7). Three scholarships have been awarded to encourage new researchers to the field of MND. Twelve grants-in-aid will fund projects that approach MND from many angles that seek to understand the causes, provide better care, control the symptoms or find a cure for MND. These grants help to retain established researchers as they continue their quest to fight MND.

The MNDRIA grants-in-aid pave the way to approach government sources for larger project funding using data gathered from the start-up projects. This year \$2,665,500 has been awarded by the National Health & Medical Research Council to MND projects in 2012. With the exciting research breakthroughs presented recently at the International ALS/MND Symposium in Sydney (see story below), the race is on to see who can be the first to make the leap that leads to finding the cause and a cure.

**\$4,022,500 has been provided for new MND research grants commencing in Australia in 2012.**

## The 22nd International Symposium on ALS/MND

*Over 600 international researchers and care providers met in Sydney to attend the inspiring concurrent scientific and clinical sessions. Unfortunately it was not possible to be in two places at the same time so Dr Brad Turner, University of Melbourne, describes only the highlights from the scientific sessions.*

The Symposium kicked off with two excellent presentations outlining the clinical and genetic differences seen in MND. John Ravits (USA) reminded us that MND is not a single disease, but probably a spectrum of disorders, striking down nerve cells almost simultaneously in the brain and spinal cord, that starts randomly at a discrete location e.g. left leg, spreading to the opposite location e.g. right leg, and eventually other body regions e.g. arms and finally invading the respiratory system. He emphasised that the spread of damage - propagation - is the defining feature of MND and understanding the key factors responsible may unlock the mystery of MND.

Garth Nicholson (NSW) provided a nice overview of genes involved in MND. While hereditary MND only accounts for 10% of patients, he urged that the commoner sporadic MND could be partly caused by addition of many rare DNA mistakes that could be masked in small families. Garth came up with this equation that may help explain MND:

*MND = single gene defect + rare gene defect + environment*

Garth effectively illustrated this by replaying "ping-pong rat trap"

footage where a ping-pong ball launched into a field of primed rat traps caused massive devastation. One interpretation from this analogy is that motor neurone loss once triggered (ball) causes sudden damage that becomes amplified and irreversible (rat trap). This suggests that the complex genetic makeup of people determines their lifetime risk for MND and that genes provide practical targets for potential treatments.

Stan Appel (USA) shared new insights into the dialogue between the brain and immune system in MND. Motor neurones do not exist alone, but rather interact with many cell types including immune cells in nature and MND. In particular, he focused on white blood cells called T-cells. Eliminating T-cells in MND mice made the disease worse, while transplanting T-cells into MND mice prolonged lifespan, arguing that T-cells may actually protect motor neurones. In an exciting development, Stan showed that these protective T-cells are lost in

MND which can be measured in blood which could provide a powerful tool or "biomarker" to monitor the progress of MND, especially in clinical trials. His studies reveal new roles for the immune system in MND and potential targets for drug therapy.

MND belongs to a family of diseases which attack motor neurones. In a session devoted to other types of MNDs, we learnt about updates in Kennedy's disease and childhood SMA. I also presented new studies from our laboratory (backed by MNDRIA) blaming a new culprit molecule in MND.

*(continued on page 2)*



I eagerly guided the audience through our findings that loss of the SMN protein may drive MND. Before I knew it, my 12 minutes of "fame" was over and I fielded questions, stage-dived and scored good feedback and a couple of collaborations afterwards.

Bob Brown (USA) launched the session on "RNA biology" pointing out that many MND genes like TDP-43 and FUS are involved in "quality control" of RNA, aka genetic message, inside cells. For some unknown reason, motor neurones appear to be at risk to bad quality control and accumulate genetic flaws in MND. New data from the Cleveland lab provided some insights into this, showing that TDP-43 and FUS "bind" and control 50% of all genes, particularly those involved in brain connections that may strike out motor neurones. A number of emerging MND mice with TDP-43 or FUS gene defects were also presented which may provide more relevant models to tackle MND in the laboratory.

A session devoted to MND in Guam followed the next day. Paul Cox (USA) recounted the story of an unusually high incidence of MND in Guam in the 1950s which was linked to exposure of an unknown environmental toxin. One enduring hypothesis was that consumption of a toxin called BMAA found in cycad plants and fruit bats in native Guamanians was responsible. It was also proposed that BMAA is produced by cyanobacteria which are found everywhere in fresh water and oceans which has potential public health implications beyond Guam, which was illustrated by a case study in Southern France, and may help to explain the commoner sporadic MND. The highlight of the session was Ken Rodgers' presentation which showed that BMAA attacks nerve cells by causing the wrong incorporation of building blocks into proteins which leads to misshapen and faulty proteins which clump together. Abnormal protein clumps inside motor neurones are a signature of disease in MND and these data provide an important link between BMAA exposure and MND pathology. The significance of BMAA in the cause of MND, if any, remains hotly contested and may require more hard evidence from lab animals exposed to BMAA which is lacking at present.

Julie Atkin (VIC) continued the misshapen protein theme in a session about cell stress in MND. Every cell accumulates protein clumps throughout life and uses clever mechanisms to manage or dispose of this load. A compartment known as the "ER" inside cells mainly handles protein load and responds to this stress appropriately. Julie's team over the years have shown that the ER is defective in MND leading to abnormal stress, but the actual cause of ER stress remains unclear. She presented compelling evidence showing that a transport block in the ER is responsible for stress and protein overload. Most exciting was the finding that correcting this block spared motor neurones from death, suggesting that blocked ER transport is an early and central culprit in MND which opens up a new potential drug target.

Teepu Siddique (USA), perhaps considered the Godfather of MND genetics, opened a session dedicated to new MND genes. The last few months have seen discoveries of three new MND genes elegantly called UBQLN2, SQSTM1 and C9ORF72. The first 2 are involved in the "kiss of death" of proteins that targets them for disposal inside motor neurones. Not surprisingly, these two decorate protein clumps found in MND brains suggesting defective protein disposal. This points towards another dominant theme in MND: quality control of protein handling, recycling and disposal. This was reinforced by Peter Schofield (NSW) who presented data on another potential candidate gene in MND called SIGMAR1 also involved in protein quality control.

In a segment allocated to therapeutic developments in MND, Peter Crouch (VIC) reported promising findings that a copper binding drug improves survival in a second mouse model of MND.

Mary-Louise Rodgers (SA) presented efficacy data on a "gene delivery system" for motor neurones. Unlike previous systems using viruses, this version exploits the natural uptake mechanisms by motor neurones and could be used to deliver large therapeutic molecules which are otherwise excluded from the brain.



Kevin Eggan (USA), an international superstar on the stem cell front, spoke about ground-breaking momentum and application of stem cell technologies for MND. He demonstrated how simply skin cells could be transformed into stem cells and then motor

neurons in the petri dish. Importantly, motor neurons grown in this way from MND patients showed key aspects of MND pathology including abnormal electrical activity and shrinkage. These stem cell-derived motor neurons in theory provide an infinite and powerful resource to test disease hypotheses and treatments in MND because they are tailored to patients, especially people with the commoner sporadic MND without known causes. To me, it is foreseeable that programmed stem cells could replace traditional MND mouse and rat models in the next 5 years because they are the disease, rather than a model. Despite an IT glitch in his presentation, Kevin remarkably unfazed proceeded to deliver one of the best talks in my opinion.

In the closing session, Bryan Traynor (USA) gave an exuberant account of how two international research teams hunted down the largest known genetic cause of MND to date. The C9ORF72 gene was abnormally expanded in about 40% of hereditary MND cases, making it twice as common as the first MND gene discovered called SOD1. C9ORF72 shows overlap with TDP-43 and FUS, and is believed to affect quality control of genetic message in motor neurones and now laboratory models are eagerly awaited. To end on a high note, Kevin Talbot (UK) outlined the major challenges of MND and how medical researchers are equipped to tackle them head-on in the 21st century. In the past, diagnostic delay was costly for patients, but now new potential blood markers of disease activity are emerging. Previously, the high level of clinical and biological complexity of MND hampered disease models, but now significant and common genetic causes and links such as C9ORF72 are surfacing. Lastly, inadequate animal models for MND have resulted in disappointing clinical trial outcomes, but now more relevant models of TDP-43 and FUS have been generated and need validation, in addition to stem cell-derived motor neurons that may possibly revolutionise the drug development pipeline. With the explosion of discoveries in the MND field these past 3 years in terms of fingerling culprit genes, molecules and dominant themes such as genetic message and protein quality control in motor neurone biology and vulnerability in MND, I sensed a real air of excitement and optimism heading out of this Symposium and looking forward to strides achieved in the Chicago 2012 meeting.

*Bradley Turner, Florey Neuroscience Institutes*

# Motor Neurone Disease Research Institute of Australia

## Executive report July 2010 – June 2011

### The year in review

A record \$1,395,000 was awarded for new grants commencing in 2011 – double the amount awarded for 2010.

The Australian Competitive Grants Register lists schemes that provide competitive research grants to Universities. The income Universities receive from schemes listed on the ACGR is used in determining the allocation of the Australian Government's Research Block Grants. Research Block Grants contribute to infrastructure costs associated with the funded research projects. When a research project is funded by an organisation that is listed on the ACGR, the government contributes an additional amount, presently about 35 cents (50 cents in 2013) per dollar, to support the project. To be eligible for listing on the ACGR, MNDRIA must provide a minimum level of funds for grants each year. This level was previously set at \$200,000 but has now been raised to \$1 million. Fortunately MNDRIA is able to meet the requirements for ACGR listing this year but this new level is one more incentive to ensure that we provide at least \$1 million for grants every year.

### Research grants

The MND Research Committee members continue in their important role of reviewing grant applications and determining how the available funds will be allocated. In the calendar year 2011 a total of \$1,351,590 has been provided for twelve grants-in-aid, five concurrent Bill Gole Postdoctoral Fellowships, one PhD scholarship and support for the MND Research Tissue Bank. Since inviting applications for grants-in-aid up to a maximum of \$100,000 for projects for grants commencing in 2011, the quality of applications received has risen to a new level. An application for a grant-in-aid now more closely resembles a full 12 month project rather than a grant-in-aid of a project.

### Information

*Advance*, the bi-annual newsletter of MNDRIA, has a circulation of 4,800 copies that are distributed nationally. This report not only gives information about MND research in Australia to the MND community, but also provides feedback to the many donors who provide the funds for the research. An International MND Research Report that is funded by MND Victoria and written quarterly by Bill Gole MND Research Fellow, Dr Justin Yerbury is sent to all MND Associations for distribution to their members. Both of these publications are also distributed internationally through the International Alliance of ALS/MND Associations.

### Meetings

The annual MNDRIA Research Meeting provides the opportunity for researchers funded by MNDRIA to present the outcome of their work to their peers and to MNDRIA members. The last MNDRIA Research Meeting was held at Monash University in Melbourne in November 2010. This special meeting attracts researchers from most Australian States who take the opportunity to meet one another and discuss collaborations. There was no MNDRIA meeting in 2011 as most grant recipients attended the International ALS/MND Symposium in Sydney in December. There they contributed to and shared in the new discoveries that provide real hope that a better future is within reach.

### Donations & bequests

Major donors continue their generous support for named grants. New named grants this year are the Rosalind Nicholson MND Research grant and the Susie Harris Memorial MND Grant (MND VIC). Special fundraising events have provided the Graham Smith Grant and the Connie Steps Forward for MND Research Grant.

Simon Eldridge (NSW) held a hugely successful fundraising event that not only gave an enormous boost to funds for MND research, but also to funds for MND care. We are grateful for continued support for the Bill Gole Postdoctoral MND Research Fellowship (anonymous), the Peter Stearne Grant for Familial MND Research (the Stearne family), the Roth Charitable Foundation Grant, the Charles & Shirley Graham Grant (MND Queensland) and four grants funded by MND Victoria and its supporters: the MND Victoria Grant, the Zo-eè Grant, the Mick Rodger Benalla Grant and the Mick Rodger Grant.

Bequests are received as an unexpected windfall and in 2010/2011 bequests accounted for 17% of all donations received. The major proportion of this came from the Estate of the late Terry Quinn (SA) as a share portfolio to be invested as a capital fund to provide income for the Terry Quinn Grant to be awarded each year. Notification was received that \$1,000,000 from the Estate of the late Graham Linford (WA) has been bequested as a capital fund to provide funds for an ongoing postdoctoral fellowship.

Increased contributions were received from all MND Associations, accounting for an incredible 42% of all income for the year. Noteworthy increases came from MND VIC (total \$310,000) and MND WA (total \$65,283).

We give thanks to the many loyal MNDRIA supporters who contribute regularly each year. A bi-annual appeal letter produces a steady income stream and also acts as a way of staying in touch with regular supporters and providing feedback about the research results that have been achieved through past donations. Unsolicited donations, frequently in memory of a loved one, are becoming more common. Donors are making increased use of the internet (via the MNDRIA website at [www.mndresearch.asn.au](http://www.mndresearch.asn.au) or people setting up their own MND research webpage at [GoFundraise.com.au](http://GoFundraise.com.au)).

This fantastic support helped to push research funds up over the one million dollar mark for the second consecutive year – a fantastic result for MND research in Australia. Grants totalling \$1,357,000 have been awarded for new MND research projects commencing in 2012.

### Volunteers

Voluntary help is given in many ways by many people to boost MND research in Australia. These include: the research committee members who review all the grant applications and make sure that funds are appropriately allocated, people who organise or participate in special fundraising events, and regular volunteers who willingly help whenever they are needed, particularly Maureen Burmeister, Paula Trigg, Libby Gole and Alan Hauserman.

We continue with our goal of having at least one million dollars available for MND research every year and the vision of **a world free from MND**.

Janet Nash  
Executive Officer

## Grants awarded for MND research in Australia in 2012

### Bill Gole Postdoctoral Fellowship for MND Research 2012 - 2014

#### Dr Shyuan Ngo

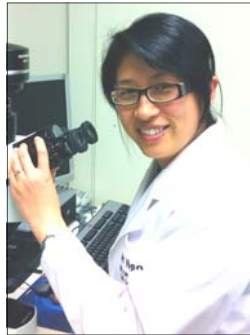
University of Queensland Centre for Clinical Research and School of Biomedical Sciences

*Investigating the mechanisms underlying defective energy metabolism in motor neuron disease.*

Motor neuron disease (MND) is an adult onset neurodegenerative disease. In MND, the irreversible loss of cells in the brain and spinal cord causes muscle weakness, and leads to death within 3-5 years of diagnosis.

To date, the cause of MND remains unknown. However, it is known that the production and use of energy is disrupted in subjects with MND. This occurs before the onset of muscle weakness and muscle loss, and may therefore contribute to the onset and further development of the disease. By understanding the cause and consequences of this change in the production and use of energy, we may be able to better understand this disease.

This project will be the first comprehensive investigation of the impact of altered energy metabolism on the pathogenesis of MND. The identification of metabolic factors that contribute to the onset and progression of MND will not only provide greater understanding of the processes that cause MND, but could lead to therapeutic interventions to correct defective energy metabolism, thereby possibly slowing disease progression, improving quality of life and alleviating the suffering of MND patients.



### MNDRIA/NHMRC co-funded PhD Scholarship 2012 - 2014

#### Dr Neil Simon

Neuroscience Research Australia, NSW  
*The distribution and spread of motor system dysfunction in early motor neurone disease.*

The exact nature and mechanisms of spread of the underlying pathology are currently unclear in ALS. Understanding the pathogenesis of ALS is necessary in order to develop sensitive biomarkers to permit early diagnosis of the disease, and to allow for investigation of targeted novel therapies. Currently, treatment options for ALS remain limited, in part because diagnosis is often delayed owing to diagnostic uncertainty in the early stages of the disease. The aim of this proposed research project is to clarify the pathogenic mechanisms of ALS by serial detailed clinical assessments of patients with early MND combined with novel neurophysiological and neuroimaging technologies. This research will lead to the development of optimum early diagnostic paradigms and will contribute to the search for novel targeted therapies.



**PhD top-up grant 2012 - 2014** To be announced soon.

## Grants-in-aid

MND research fellowships and scholarships support the *person* and aim to encourage emerging scientists to develop a specific interest in MND research.

Grants-in-aid support MND *projects*. Grants-in-aid help established researchers to get new projects going with the hope they can 'grow' to produce data that can attract more significant funding from granting bodies such as the NHMRC. Twelve new projects have been awarded grants-in-aid for 2012: six in NSW, three in Victoria, two in Queensland and one in South Australia.

### Susie Harris Memorial Fund Grant

#### Dr Julie Atkin

La Trobe University, VIC  
*Failure of ER-Golgi trafficking as a central mechanism of toxicity in motor neuron disease.*

The diverse forms of MND all have similar symptoms and pathology. Despite many studies into possible molecular mechanisms underlying neurodegeneration, definition of the primary mechanism still remains elusive. We have exciting new evidence that the death of motor neurons occurs by the same basic cellular processes in different forms of MND. This proposal aims to identify the initial trigger of these common disease mechanisms in MND. Understanding these processes will enable the development of more effective therapies in the future.



### Peter Stearne Grant for Familial MND Research

#### Dr Ian Blair

ANZAC Research Institute, NSW.  
*Identifying and establishing the role of new MND genes in familial and sporadic cases.*

The only proven causes of MND are gene mutations that lead to motor neuron death.

The fact that more than one MND gene has been identified to-date suggests that the disease involves multiple biological mechanisms. These mechanisms remain elusive, with most genes yet to be identified. Our preliminary studies indicate that we have identified mutations in new familial MND genes. The aim of this proposal is to determine the broader contribution of these genes to MND and the role of the mutations. Each new gene offers a unique opportunity to discover the mechanism leading to MND. Any new MND gene or protein will potentially be a new therapeutic target. It will also add to existing genetic testing regimes (MND diagnostic laboratories, including ours, currently test SOD1, TDP-43 and FUS in MND but these only account for about 2% of cases) and be available for the development of tests for use in prognosis and in monitoring drug trials in mice and ultimately in clinical trials.



### Mick Rodger Benalla MND Research Grant

#### Dr Tim Karl

Neuroscience Research Australia, NSW

*A novel mouse model for motor neuron disease.*

Motor neuron disease (MND, also known as amyotrophic lateral sclerosis, ALS) is a devastating neurodegenerative disorder caused by death of the nerve cells controlling the voluntary muscles. MND patients experience a series of emerging symptoms including progressive limb muscle weakness, speech and swallowing difficulty and eventually respiratory failure. The disease is often fatal within 2-5 years of diagnosis. The majority of MND patients are sporadic, but approximately 10% of the patients have a family history. The mechanism underlying MND is unknown. Some environmental factors, such as prolonged exposure to neurotoxins and head injuries, have been proposed. To date, gene mutations are the only proven causes. The protein TDP-43 was identified as a major component of the protein clusters found in MND patient brains and spinal cords. Blair and colleagues found several mutations in the *TDP-43* gene from both sporadic and familial MND patients. However, it remains unclear how these mutations cause MND. Current studies suggest that these mutations may cause the protein TDP-43 to become toxic. Our preliminary results suggest that introducing these mutations into nerve cells reproduces features seen in MND patients. Mutated *TDP-43* caused more nerve cell death than the normal *TDP-43* gene. We are now proposing to investigate the neuro-behavioural effects of one of the mutations (i.e. TDP-43<sup>M337V</sup>) in mice. This will enhance our knowledge regarding TDP-43 function and its role in MND and answer the question why the mutation leads to selective toxicity in motor nerves. Importantly, these mice can serve as a model for the development of diagnostic tools and treatments.



### Charles & Shirley Graham MND Research Grant

#### Dr Pamela McCombe

The University of Queensland Centre for Clinical research

*MND: not a simple disease.*

Patients with motor neurone disease vary in their clinical features, such as the site of onset of weakness and whether they have predominantly mixed or upper or lower motor neurone signs, and in the rate of progression of disease and in their length of survival. We have developed precise measures of the rate of loss of upper and lower motor neurones, as well as blood biomarkers of neuronal death. We will use these techniques to look in detail at a group of subjects with MND, to look at the relationship between loss of



upper and lower motor neurones, the pattern of spread of disease from one site to another and factors such as the immune response and gender that could influence the rate of progression of disease.

### MND Victoria Research Grant

#### Dr Eneida Mioshi

Neuroscience Research Australia, NSW. *Cognitive and behavioural changes in MND: relation to clinical phenotypes and impact on carer burden.*



MND was described as a pure motor syndrome in the past. More recently, studies have shown that

unfortunately this is not the case, with a great proportion of patients developing also cognitive (such as memory, judgement and problem solving) and behavioural (such as apathy, which is a type of lack of motivation not related to depression) problems. These cognitive and behavioural changes seem to relate to worse prognosis, and the combination of these changes and physical disability compound to high levels of burden for carers. We aim to investigate which MND presentations (limb or bulbar) are likely to cause changes in cognition and behaviour, which will help health professionals in making accurate prognosis and deliver tailored care. We also aim to investigate the underlying changes in the brain behind these deficits, which could be addressed in drug treatments in the future. Finally, we will study the contributions of physical, cognitive and behavioural changes to carer burden, in order to identify the main factors behind burden and address them adequately in services, websites and informative leaflets.

### Graham Smith MND Research Grant

#### Professor Garth Nicholson

ANZAC Research Institute, University of Sydney

*Sporadic MND: the contribution of genes, biomarkers & metabolites.*

Finding the cause of the common sporadic form of MND is proving extremely difficult. Association studies involving thousands of sporadic cases has not found a cause. However the study of MND families has been fruitful as a number of genes have been implicated and various mechanisms causing the death of MND neurones have been found. The relevance of familial MND gene variations to sporadic MND now has to be determined. Most of these gene variants cause only a small proportion of sporadic MND. We propose that sporadic MND has many causes made up of particular gene variations which when strong cause rare familial cases and when weak, cause sporadic cases. This application aims to find whether new gene variations that cause familial MND also cause sporadic MND. To do this we wish to collect sporadic MND samples and test them for gene variations found in families with MND.



The project will also collect plasma samples to study the BMAA toxin and kynurenin pathway toxic catabolites in collaboration with MND researchers at the University of NSW and the University of Technology. This work aims to continue the collection of vital blood samples for future research from sporadic motor neurone patients, commenced by Associate Professor Roger Pamphlett's DNA bank which ceased sample collection this year.

### **Roth Foundation MND Research Grant**

**Dr Mary-Louise Rogers and Professor Robert Rush**

Flinders University, South Australia

*Improving targeted down-regulation of SOD1G93A in MND mice.*



MND is an illness of nerves controlling muscles, which results in a creeping paralysis and death; there is no effective treatment. We have developed a technology called

immunogenes to enable antibodies to deliver genes into nerves. We have also found that an antibody can increase the life span of the transgenic mouse that models MND. The project combines this novel antibody and our immunogene technology to test the agent as a potential drug for the treatment of MND in mice. Successful outcomes will encourage development of targeted treatments for MND in humans.

### **Mick Rodger MND Research Grant**

**Dr Bradley Turner**

Florey Neuroscience Institutes, Victoria. *Exploring the therapeutic potential of survival motor neuron protein for MND.*

Survival motor neuron (SMN) is an essential protein required by motor neurons and its loss causes the childhood disease SMA. We recently showed that SMN levels were low in laboratory models of MND and patients with MND. Treatment of MND mice with SMN was shown to prevent motor neuron loss, suggesting that SMN could have a protective role in MND. We now wish to determine whether SMN is also effective in different animal models of MND looking at nerve injury and newly available TDP-43 mice. These studies will help confirm whether SMN should be considered an important player in MND and a potential target of interest for treatment approaches.



### **Connie's Step Forward for MND Research Grant**

**Assoc Prof Steve Vucic**

Westmead Millennium Institute, University of Sydney  
*T cells: a vehicle for neuroprotection in ALS?*

Amyotrophic lateral sclerosis (ALS) is a progressive, fatal, neurodegenerative disease with most affected patients dying of respiratory compromise and pneumonia after 2 to 3 years; although occasionally individuals may survive for many years.

Recently, purification and injection of a specific type of immune cell was shown to delay disease onset and slow progression in an animal model of ALS. Moreover this cell type appears to be dysregulated in human ALS. These findings open up a new and exciting direction for potential treatment of ALS. The goals of this study are to determine how the function of these immune cells relates to human ALS and its progression; and to determine whether a recently described treatment that boosts this cell type can delay disease progression in the animal model of ALS.



### **Zo-è MND Research Grant**

**Dr Robyn Wallace**

Queensland Brain Institute  
*Analysis of TDP-43 target genes in C. elegans.*

Protein tangles that aggregate in affected nerve cells are a pathological hallmark of MND. Studies of MND patient cells have demonstrated that TDP-43 protein is a principal component of these nerve cell aggregates. Genetic mutations associated with MND have also been identified in the TDP-43 gene. However, the role of TDP-43 in the pathogenesis of MND remains unclear. TDP-43 is involved in gene regulation and we have recently identified a number of genes that bind to TDP-43. The aim of this project is to study the genes that are regulated by the TDP-43 protein in a living organism. The nematode worm is widely used in neuroscience research because its well-characterised and less complex nervous system facilitates rapid analysis of nerve cell function. The nematode will be used to analyse the role of TDP-43 target genes in motor neuron function. These studies will improve our understanding of how abnormal TDP-43 causes MND and highlight cell processes that could be targeted for the future development of new therapies.



### **Terry Quinn MND Research Grant**

**Dr Anthony White**

University of Melbourne  
*Targeting kinases to control TDP-43 and FUS accumulation in motor neuron disease.*

Motor neuron disease (MND) or amyotrophic lateral sclerosis (ALS), is a group of fatal adult-onset illnesses in which the function of motor neurons in the spinal cord and brain progressively deteriorates leading to death in 1-5 years. Little is known about the cause of MND and there are no effective long term treatments. Recently, the RNA-binding proteins known as TDP-43 and FUS have been found to cause most cases of genetic



MND and are likely to have a critical role in sporadic cases. In brain and spinal cord of MND patients, these proteins leave their normal location in the nucleus and accumulate in the cytoplasm causing neuronal cell death. However, there is little understanding of how this abnormal process occurs. Recently, using new cell culture models generated through generous support from the MNDRIA we have been able to recapitulate these processing changes in neuronal cells. Our key finding has been that cell signaling kinases such as JNK and ERK have a critical role in controlling cytosolic accumulation, abnormal processing and aggregation of TDP-43 (initial steps in neuronal death). In the present study, we will investigate how activation of key cell signaling kinase pathways control cytosolic accumulation and toxicity of both TDP-43 and FUS in neurons and identify novel targets for inhibition of abnormal protein accumulation using kinase inhibitors. These studies will open up a completely novel area of therapeutic treatment for MND and related neurological diseases.

### Rosalind Nicholson MND Research Grant

#### Professor Mark Wilson

University of Wollongong

*Protein aggregation and chaperones: key players in MND.*



The motor neurone disease amyotrophic lateral sclerosis (ALS, hereafter simply referred to as MND) is a currently untreatable disease that attacks nerves controlling voluntary muscles. It usually occurs in adults and has an appalling prognosis, commonly leading to loss of muscle control and rapid death within a few years of onset. Current evidence

strongly suggests that inappropriate aggregation of protein molecules is a primary contributor to MND pathology, however there is very limited understanding of the molecular processes involved and the role of chaperones (the usual defence against protein aggregation). This current application forms a part of a larger project and will (i) identify and quantify proteins in the insoluble protein deposits found in human MND spinal cord tissues, thereby identifying new genes important in MND, and (ii) screen the effects of a range of chaperones on the aggregation and toxicity of TDP-43 (one of the proteins already known to be present in MND deposits and implicated in causing disease), both *in vitro* and in cell models. The larger project will also screen the effects of these chaperones in transgenic *Drosophila* (fruit fly) expressing TDP-43, where we have already shown that expression of a chaperone can protect against loss of locomotor activity and extend life. The new knowledge this project generates will be critical for the future development of new diagnostics and effective therapies for MND.

### Five postdoctoral fellowships awarded in previous years continue in 2012 for:

**Dr Catherine Blizzard**, Menzies Research Institute, Tasmania  
**Bill Gole Postdoctoral Fellowship 2011 - 2013**  
*Investigating the cause of site-specific excitotoxicity in ALS.*

**Dr Rachael Duff**, Centre for Medical Research, WA  
**Bill Gole Postdoctoral Fellowship 2011 - 2013**  
*The application of new generation genetic techniques to motor neuron disease.*

**Dr Shu Yang**, ANZAC Research Institute, NSW  
**Bill Gole Postdoctoral Fellowship 2010 - 2012**  
*Investigating the role of recently identified mutant genes in MND pathogenesis.*

**Dr Justin Yerbury**, University of Wollongong, NSW  
**Bill Gole Postdoctoral Fellowship 2009 - 2011**  
*Probing molecular mechanisms of microglial and astrocyte activation in ALS.*

**Dr Jennica Winhammar**, Neuroscience Research Australia, NSW  
**Bill Gole Postdoctoral Fellowship 2008 - 2010** (period extended due to maternity leave).  
*Clinical trial to assess the neuroprotective properties of a sodium channel blocking agent in motor neurone disease.*



*The line up of Bill Gole Fellows are making their mark in MND research. Dr Shyuan Ngo (page 4) will be Bill Gole Fellow No. 11 in 2012. Five more were present at the International ALS/MND Symposium: (L to R): Former BG Fellows Dr Ian Blair (No.3) and Dr Anna King (No.5) and current BG Fellows Dr Shu Yang (No.8), Dr Justin Yerbury (No.7) & Dr Catherine Blizzard (No.9).*

### National Health & Medical Research Council MND research grants (\$2,665,514) for 2012

#### Project grants were awarded to:

- Dr Julie Atkin, La Trobe University, Vic: \$419,925
- Prof Philip Beart, University of Melbourne, Vic: \$604,960
- Dr Nicholas Cole, University of Sydney, NSW: \$419,925
- A/Prof Roger Pamphlett, University of Sydney, NSW: \$621,175
- A/Prof Steve Vucic, University of Sydney, NSW: \$245,462

A postdoctoral C J Martin fellowship was awarded to Adam Walker from La Trobe University for his project *Investigating mechanisms of dementia and motor neuron disease.*

**We are all working together to make sure that emerging scientists and established researchers have the support they need to drive them onwards in their mission to unlock the mysteries of motor neurone disease.**

# MND Research Institute of Australia

## Office Bearers and Members 2011

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.

#### DIRECTORS

**President:** Ralph Warren  
**Vice President:** David Ali, VIC  
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#### Special Tenure Directors

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**EXECUTIVE OFFICER:** Janet Nash

**AUDITOR:** C M Pitt & Co

#### RESEARCH COMMITTEE

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

#### Research Committee Members

**Chairman:** Professor Dominic Rowe, NSW  
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Dr Susan Mathers, VIC  
Assoc Prof Pamela McCombe, QLD  
Professor John Pollard, NSW  
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Professor James Vickers, TAS

## MND Australia Research Update

The MND Australia Research Update is sponsored by MND Victoria. For three years, Bill Gole Postdoctoral Fellow, Dr. Justin Yerbury, has been writing this popular quarterly report as an easy-to-understand interpretation of the latest scientific publications of worldwide MND research results. Back issues can be found at [http://www.mndresearch.asn.au/International\\_news.htm](http://www.mndresearch.asn.au/International_news.htm). Justin's inaugural role in writing this quarterly update has allowed him to develop a style of communication that is not normally easy for a scientist. He has done an excellent job and we are sorry to lose him but, as his Bill Gole Fellowship term is coming to an end, it is time to pass on the baton to a newer Bill Gole Fellow. Dr Catherine Blizzard from the Menzies Research Institute at the University of Tasmania has agreed to take on the task and will produce her first Research Update in March 2012. This role provides an excellent training opportunity for a young scientist to learn to communicate research findings to an interested audience who may not have in depth scientific understanding. Catherine comes well-armed with an impressive writing style which will be demonstrated in the next issue.



**Handing over the baton**  
*Outgoing Research Update author, Dr Justin Yerbury, and incoming author, Dr Catherine Blizzard, who both attended the International ALS/MND Symposium in Sydney in December 2011*

### 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](http://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 [info@mndresearch.asn.au](mailto:info@mndresearch.asn.au).

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