mnd Research Institute of Australia

Advance

NEWSLETTER OF THE MND RESEARCH INSTITUTE OF AUSTRALIA

June 2013

The Motor Neurone Disease Research Institute of Australia (MNDRIA), the research arm of MND Australia, is endorsed as an approved research institute by the Australian Taxation Office. The ATO guidelines for an approved research institute ensure that

- all donations for research are paid into a research fund and can only be used for research
- applications for grants from this fund are scrutinised by an expert panel whose members are approved by the National Health & Medical Research Council of Australia (NHMRC) as being suitably qualified to assess health research
- results of research financed from the research fund must be available and wherever possible published in the scientific press.

The MND Australia Research Committee is the expert panel whose members are approved by NHMRC. They are the great strength of the MNDRIA research granting process, giving their time to ensure that donations and bequests received go only to the best research that will have the greatest chance of making a difference for people with MND. The Research Committee comprises eminent clinicians and scientists from all over Australia. Their combined expertise covers all fields of motor neurone disease research.

Each year, new MNDRIA grants in both biomedical and health care research are advertised nationally with closing date for applications at the end of August. Each committee member reviews all grant applications received. Applicants must include reports on previously funded projects to show their results and to demonstrate that previous funds have been used in accordance with the approved grant. Without this reporting requirement there would be no way of knowing how previous grant awards have been spent. Final decisions about new grants are made at an annual Grants Allocation Meeting in November, where members of the Research Committee meet in person and/or by teleconference to discuss the relative merit of applications competing for the available funds.

Profiles of MND Australia Research Committee members are provided below. They demonstrate the wealth of knowledge and experience that is brought together to select only the best research projects with the greatest chance of success.

Go to pages 5 to 11 to read brief reports on projects funded by MNDRIA in 2012.

Chair of the MND Australia Research Committee 2013

Professor Dominic B Rowe AM

B.Sc(Med), MBBS, FRACP, PhD (UNSW)

Dominic Rowe is the Inaugural Professor of Neurology at the Australian School of Advanced Medicine, Macquarie University. He studied biochemistry and medicine at the University of Sydney, and then completed training in internal medicine and neurology in Sydney before completing neurology training at Queen's Square and Newcastle Upon Tyne, UK. His doctoral studies in the pathogenesis of Parkinson's disease were performed at Baylor College of Medicine and completed at the University of New South Wales. Since returning from the USA in 1998, he has worked clinically as a neurologist and as an academic with research focus on the mechanisms involved in Parkinson's disease and motor neurone disease.

He has been the Chairman of the Research Committee of Motor Neurone Disease Australia since amalgamation with the MND Research Institute of Australia in 2010. Prior to that he was the Chairman of MNDRIA from 2005 to 2010.

Research committee profiles continued on page 2

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Members of the MND Australia Research Committee 2013

Professor Perry Bartlett, QLD
Director of the Queensland Brain Institute, Foundation Professor and Inaugural Chair of Molecular Neuroscience at the University of Queensland and a Fellow of the Australian Academy of Science. Professor Bartlett was the first to demonstrate the existence of a resident population of stem cells in the embryonic brain. He later found the same to be true in the adult, and identified the existence of quiescent populations of cells in the hippocampus that could be activated to produce new neurons. At the Queensland Brain Institute, Professor Bartlett and his team have shown that experiences such as learning and memory can stimulate the activation of one subset of hippocampal cells and antidepressant treatment can trigger another. He has also identified that in the adult brain, the rate of normal neuron production decreases with age but increases in response to physical exercise. Professor Bartlett and his group are now working towards understanding these mechanisms of activation and the influence of new neurons on the function of the adult brain. By harnessing the capacity of the brain to generate new functional cells, there is great potential to develop therapeutics for the treatment of the ageing, diseased or damaged brain.

Dr David Berlowitz, VIC
David Berlowitz is a cardio respiratory and research physiotherapist at the Victorian Respiratory Support Service and the Institute for Breathing and Sleep at the Austin Hospital in Melbourne. His PhD examined sleep and breathing in the first year following acute quadriplegia and found that acute cervical cord injury causes obstructive sleep apnoea. David recently completed a Clinical Post-Doctoral Fellowship from the Transport Accident Commission, was recognised in 2011 as a "Difference Maker" by the Rick Hansen Foundation for his leadership in Spinal Sleep Research and is the Lead Investigator on the five year, Sleep Health in Quadriplegia research program. His other research includes chronic disease management, program evaluation and the use of non -invasive ventilation in ventilatory failure, particularly in MND and obesity hypoventilation.

Associate Professor Ian Blair, NSW
Ian Blair heads a research group investigating the molecular and cellular basis of MND at the Australian School of Advanced Medicine, Macquarie University. The aims of his research are to identify genes that either cause or predispose to MND and study how defects in these genes lead to motor neurone death. Ian's research career has focused on various neurological diseases including MND, bipolar disorder, Joubert syndrome, sensory neuropathy, Charcot Marie Tooth disorder (CMT), and the spinal cerebellar ataxias (SCA). Previously, Ian held senior research positions at ANZAC Research Institute, the Garvan Institute of Medical Research and the University of Washington School of Medicine.

Professor Matthew Kiernan, NSW
Senior Principal Research Fellow, Neuroscience Research Australia; Professor of Medicine, UNSW; Consultant Neurologist, Prince of Wales Hospital.

The focus of Matthew Kiernan's research team is clinical neurology, in particular disease pathophysiology and treatment strategies of neurological disorders. Currently his team is investigating the mechanisms and the possible prevention of neurodegeneration in MND; chemotherapy-induced neurotoxicity; stroke; Machado-Joseph disease; spinal muscular atrophy and other inherited neuropathies. His team is also involved in clinical trials investigating potential drug treatments for MND, multiple sclerosis and chronic inflammatory demyelinating polyneuropathy.
His team's research is intrinsically linked to the provision of clinical services, particularly the Multidisciplinary MND Clinic; the Hereditary Nerve and Muscle Clinics and diagnostic neurophysiology clinics.
Matthew Kiernan is the Vice President of the Australian Brain Foundation and Chairman of the Scientific Committee responsible for distributing funding towards research and medical education for the treatment and prevention of neurological disorders. Matthew is Editor-in-Chief of the Journal of Neurology, Neurosurgery and Psychiatry.

Professor Nigel Laing, WA
University of Western Australia and Western Australian Institute for Medical Research.
Professorial Fellow and NHMRC Principal Research Fellow, Nigel Laing has worked in human genetics research since 1987, is associated with the identification of 15 human disease genes, including mutations in SOD1 as the first known genetic cause of MND, mutations in slow tropomyosin as the first known cause of nemaline myopathy, mutations in skeletal muscle actin as a significant cause of severe congenital myopathies, and mutations in beta cardiac/slow skeletal myosin as the cause of Laing distal myopathy. Current research interests include using next generation sequencing (NGS) to identify further novel human disease genes, researching the use of NGS in molecular diagnostics and the implementation of population screening for neurogenetic disorders in Australia.

Members of the MND Australia Research Committee 2013

Dr Susan Mathers, VIC

Consultant Neurologist at Monash Medical Centre, and the Clinical Director of Neurology at Calvary Health Care Bethlehem, Melbourne, which provides neuro-rehabilitative and neuro-palliative services to people with progressive neurological diseases including over 200 people with MND. She is a member of the MND Research Tissue Bank of Victoria and a founding member of the Australian MND Register. Her main interests are in the management of chronic progressive neurological diseases and models of care. She is currently involved in a project to implement a state-wide integrated care service for people with progressive neurological diseases in Victoria.

Professor Pamela McCombe, QLD

Professor McCombe's research interest is in the field of neuroimmunology, both in how the immune system causes disease of the nervous system, and more recently in how the immune system might contribute to recovery from damage. Much of her work in neuroimmunology has been done in the fields of MS and in neuromuscular disorders. In MS she has been interested in the regulation of inflammation. Her interest in neuromuscular diseases led to studies of ALS, both in neurophysiology and in immunology. An overarching theme of her work has been an interest in how gender and pregnancy influence diseases of the nervous system.

Emeritus Professor John Pollard AO, NSW

Professor Pollard has an international reputation in the fields of neuropathy and multiple sclerosis. He was Bushell Professor of Neurology, University of Sydney until 2008 and remains Co-Director of the Nerve Research Foundation and a Director of the Brain Mind Research Institute. He is a member of the steering Committee of the World Federation of Neurology and a past-board member of the Peripheral Nerve Society. He remains Deputy Chairman of the Advisory Board of the National Multiple Sclerosis Society of Australia and Chairman of the MS Interest Group within the Australian and New Zealand Association of Neurology. In 2005 he was awarded an AO for his contributions to neurology and in particular to multiple sclerosis. He is also a Board member of the Institute of Neuromuscular Research at the Children's Hospital, Westmead.

Professor Dominic Thyagarajan, VIC

Professor of Neuroscience in the Department of Medicine, Southern Clinical School (Monash University) and Directory of Neurology (Monash Health), based in Monash Medical Centre, Clayton. He heads one of the largest neurology departments in Australia (22 neurologists) in a hospital network servicing about one third of Victoria's population. It has substantial undergraduate and postgraduate medical training, teaching and research activities. The spectrum of research is broad, ranging from clinical research to laboratory science.

Professor James Vickers, Tasmania

Professor Vickers completed a BSc(Hons) at the University of Tasmania, a PhD at Flinders University and was awarded a DSc in 2005 from UTAS for contributions to research into neurodegenerative disease. He completed postdoctoral studies at the Mt Sinai School of Medicine (New York), and has received NHMRC CJ Martin, RD Wright and Senior Research Fellowships. In 2003, he was appointed Professor of Pathology at UTAS and acted as Deputy Head (2007-09) then Head (2010-2012) of the School of Medicine. He is also co-Director of the Wicking Dementia Research and Education Centre. His principal areas of research focus have been on the cellular basis of the degeneration and regeneration of the nervous system, and he is involved in studies related to Alzheimer's disease, fronto-temporal dementia, MND and brain trauma using both cell culture and experimental animal models. He also has an interest in brain plasticity, neurogenetics and adaptability, with human cohort studies related to how later life learning can potentially build brain resilience to neurodegenerative studies. Other studies relate to the support of carers of people with brain conditions, health system redesign for neurological disorders and health workforce development.

Associate Professor Steve Vucic, NSW

Associate Professor of Neurology, University of Sydney and Senior Staff specialist in Neurology at Westmead Hospital. His research interest is in determining the pathophysiological mechanisms underlying the development of MND, in particular determining the site of disease onset. In order to address this issue he was part of a team that developed a novel neurophysiological technique for determining cortical function. Application of this technique to the understanding of MND has established that cortical dysfunction may be an initial event in MND. In addition to furthering the understanding of the pathophysiological mechanisms in MND, Steve's research has potentially resulted in the development of a novel test which can aid in the diagnosis of MND.

New MNDRIA scholarships announced in January 2013

Two new MNDRIA PhD scholarships co-funded with the National Health and Medical Research Council of Australia and three MNDRIA PhD scholarship top-up grants were announced in January 2013. These three-year grants aim to encourage and support our brightest young researchers to develop a specific interest in MND research.

MNDRIA/ NHMRC PhD Scholarship 2014 - 2015

Dr Nimeshan Geevasinga
University of Sydney and
Westmead Hospital, NSW
Electrophysiological and neuroanatomical determination of patients with Amyotrophic lateral sclerosis with the C9ORF72 mutation.

There have been significant advances made in the genetic understanding of ALS as well as another closely related condition, frontotemporal lobar degeneration (FTLD). An expanded hexanucleotide repeat in the C9ORF72 gene has recently been identified as a major cause of ALS and familial frontotemporal lobar degeneration. Currently little is known about the neurophysiological/neuroanatomical and cognitive properties in patients with the C9ORF72 mutation. We wish to better characterise the peripheral nervous system function in patients with the mutation, utilising a novel threshold tracking transcranial magnetic stimulation technique in conjunction with neurophysiological techniques to assess peripheral nerve function. Further to this we will perform neuropsychiatric evaluations to assess the cognitive profile of patients with the affected mutation as well as undertaking neuroimaging with magnetic resonance imaging to analyse neuroanatomical patterns and relationships.

These patients will then be followed over a period of two to three years to look for changes over time. The information when gathered will help better characterise patients with this particular mutation. We will then follow these patients over time to look for changes in their neurophysiological, neuroanatomical and cognitive domains. Understanding how these genetic mutations cause motor neuron degeneration is pivotal to improving our understanding of disease pathophysiology and to the development of more powerful neuroprotective therapies.

MNDRIA/ NHMRC PhD Scholarship 2013 - 2015

Dr Parvathi Menon
University of Sydney and
Westmead Hospital, NSW
Pathophysiology of ALS: Evidence to support the dying forward hypothesis.

Neurophysiology is the technique of recording spontaneous and induced electrical potentials in the nervous system and has been extensively used to understand the working of this system which functions as an enormous communication network in the human body and transmits information using electrical potential changes. The nervous system is the primary target of MND which commonly affects both the peripheral aspect of the motor system comprising nerve cells and nerves supplying muscles along with the central component comprising the motor neurons arising in the cerebral cortex and their connection with the peripheral pathway. There has been long standing debate on where MND begins: whether in the central or peripheral motor system or both simultaneously.

My research uses a variety of neurophysiology techniques to assess the central and peripheral motor pathways in order to detect alterations of function which might provide better understanding of the pattern of involvement of the motor system in MND. The ultimate aim of my research is to gain a better understanding of the unique nature of MND and its progression so that interventions can be targeted early to where the problem begins.

MNDRIA PhD top-up Grant 2013-2015

Jayden Clark (PhD candidate) and Associate Professor Tracey Dickson (Principal Supervisor)
Menzies Research Institute, University of Tasmania
Axonal protection in ALS.

Currently the only effective treatment for ALS is the drug Riluzole, which extends a patient's life for 3 to 6 months. Therefore there is a need for new and targeted approaches to ALS treatment.

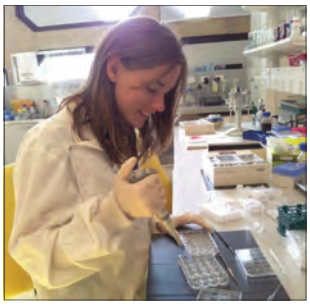
I aim to use the drug Taxol, more commonly used in cancer therapies to prevent cancer cells dividing, to help slow progression or rescue the motor neurons from cell death. Taxol works on proteins in the axons (the long processes of neurons). These proteins help with the movement and transport of other proteins and cellular machinery through the cell. As axon dysfunction is found to be one of the earliest pathologies in ALS, a targeted approach to axonal treatment may be beneficial. This work will be done using a genetic model of ALS as well as a model of sporadic ALS currently in development in the Dickson Laboratory at the Menzies Research Institute of Tasmania. Changes to behaviour/motor function and neuronal pathology will be identified.

New MNDRIA scholarships announced in January 2013

MNDRIA PhD top-up Grant 2013 - 2015

Rosemary Clark (PhD candidate) and
Associate Professor Tracey Dickson (Principal Supervisor)
Menzies Research Institute, University of Tasmania
Interneuron dysfunction in ALS: A new target for potential therapeutics?

ALS is a disease typically defined by motor neuron dysfunction and subsequent degeneration. However, increasing evidence suggests it may be considered non-cell autonomous, involving other neuronal and non-neuronal populations. The roles of various non-neuronal populations in ALS pathogenesis have begun to be investigated, yet a key regulatory population, the interneuron, remains largely overlooked. This is surprising as there is strong clinical evidence in both cortical and spinal regions to implicate reduced inhibition as a primary disease mechanism in ALS. Indeed motor neuron hyperexcitability precedes degeneration in many cases, suggesting dysregulation of excitatory circuitry may be a modifiable therapeutic target in ALS. I aim to explore this concept by firstly investigating pathological changes to the inhibitory interneuron



populations and, secondly, by assessing interneuron vulnerability under pathogenic conditions. This will enable the role that interneurons may play in altered inhibition and disease progression to be determined.

MNDRIA PhD top-up Grant 2013 - 2015

Jennifer Solski (PhD candidate) and
Associate Professor Ian Blair
(Principal Supervisor) Australian School of Advanced Medicine, Macquarie University, NSW
Examining the role of novel molecules causing MND.

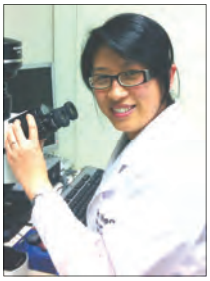
Known mutations account for 60% of familial ALS cases and less than 5% of sporadic cases in Australia. The aim of my PhD project will be to discover and examine novel genes that cause familial ALS, and determine the role of their encoded proteins in ALS. I aim to identify new ALS genes and examine newly reported genes in a large cohort of patients that are negative for all known ALS genes. I will use state-of-the-art genetic technologies to analyse DNA samples from these patients. With over 40% of families that are yet to have a mutation implicated, the discovery of new genes is significant to patients and their families on a diagnostic level. Following the identification of new ALS genes, a number of experiments will be performed to determine the role of their encoded proteins in ALS. This will include using cultured skin cells from patients and neuron-like cell lines. Zebrafish models will also be studied to see how these mutated proteins affect the animals and their relationship to ALS. This will lead to a greater understanding of the cellular mechanisms and pathology associated with disease, and provide critical information towards a treatment for ALS by providing potential drug targets or biomarkers.

Reports on fellowships and scholarships funded by MNDRIA in 2012

Researchers are asked to provide a six-monthly progress report and a final report at the end of the project. Brief overviews from the final reports from projects funded by MNDRIA in 2012 are published in this newsletter. These reports demonstrate the breadth and depth of motor neurone disease research in Australia.

Bill Gole Postdoctoral Fellowship 2012 - 2014

Dr Shyuan Ngo, University of Queensland
Investigating the mechanisms underlying defective energy metabolism in MND.

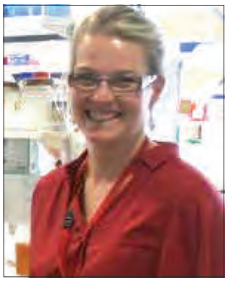


My results to date suggest that in the early stages of disease, hormones may act to prevent the loss of muscle function. I am further investigating this to determine if these same hormones may prevent motor neuron death.
Studies on energy metabolism in skeletal muscle are progressing well. I have measured many changes in the expression of molecules that are responsible for regulating energy metabolism in skeletal muscle. Interestingly, I have found that SOD1G93A animals are insulin resistant when they have muscle weakness. My results suggest that there is an increase in the breakdown of fat in the body so that it can be used by muscle as an alternative energy supply.
Studies in the TDP43 mouse have been put on hold. Recent published results show that TDP43 mice suffer from severe intestinal complications. Because this can impact metabolic state, results obtained in these mice may not properly determine whether changes in metabolism in MND are due to the disease process, or something else.
Plasma samples collected from MND patients at the Royal Brisbane Women & Children's Hospital MND clinic will be analysed in the coming months for markers of metabolism. Results from these analyses will be compared and correlated to findings from SOD1G93A mice.
I travelled to France to undertake collaborative research, learning techniques that will allow me to determine whether changes in metabolic hormones are due to changes in the brain. The observations from my ongoing studies will potentially identify molecules that may be selectively targeted to correct defective energy metabolism in MND.

Reports on fellowships and scholarships funded by MNDRIA in 2012

Bill Gole Postdoctoral Fellowship 2011 - 2013

Dr Catherine Blizzard
Menzies Research Institute, Tasmania
Investigating the cause of site-specific excitotoxicity in ALS.



The overall aim of this project is to determine the role somatodendritic excitotoxicity plays in primary degeneration in the distal axon.

This project is critically focused on determining the degenerative changes underlying ALS-like axonopathy by using site-specific insults *in vivo* to determine axonal degeneration and dysfunction. It will determine the degenerative changes underlying ALS-like axonopathy and establish links to potential excitotoxicity causative factors. MND is caused by a loss of function of the nerve cells controlling the muscles. This loss of function of the nerve cells may be due to over excitation of nerve cells, either at the muscle or at the site of the nerve cell bodies, the spinal cord. I am exploring these two possibilities on the toxic site leading to nerve cell degeneration. I have currently established a model of over excitation in the spinal cord of a mouse that causes axonal degeneration and neuronal cell death. This will enable determination of the role that over excitation of the nerve cell bodies could play in disease progression.

Bill Gole Postdoctoral Fellowship 2011 - 2013

Dr Rachel Duff, Western Australian Institute for Medical Research
The application of new generation genetic techniques to MND.

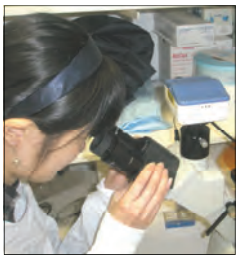
One of the main aims of this project is to determine the genetic cause of disease in people with MND. Although many genes responsible for MND have been discovered already, there are still many people with the condition who do not have a mutation in a known gene. This project uses a new technology that allows every gene in a person's DNA to be searched for a mutation (whole exome sequencing). In the last six months this test has been performed on DNA from an additional five individuals, bringing to fifteen the total number of samples tested so far in this project.

The discovery of new disease genes is an essential part of making diagnosis more accurate and to allow families to screen for MND. Identifying new genes in MND also greatly aids the researchers understanding of the condition and gives new insight into the development of treatments.

Another aim of this project is to determine why some people with a mutation in *SOD1*, known to cause MND, do not develop the condition. A new approach will be used to search for the genetic reason behind this difference in the next six months. This method is based on the successful UK research group discovery of a genetic mutation responsible for differences in disease severity in people with cystic fibrosis.

Bill Gole Postdoctoral Fellowship 2010 - 2012

Dr Shu Yang
ANZAC Research Institute, NSW
Investigating the role of recently identified mutant genes in MND pathogenesis.



One of the milestones in MND research was the discovery of gene mutations in the *SOD1* gene in 1993. More than 100 different mutations have been found in *SOD1* which cause 10-20% of familial MND cases. More than a decade later, two more disease causing genes encoding the TAR DNA binding protein 43 (TDP-43) and the fused in sarcoma (FUS) protein were identified. Our laboratory played key roles in the identification of these two genes and we continue to search for other unknown MND genes. My research aims to identify the mechanisms through which defects in TDP-43, FUS and other novel MND candidate genes cause MND, which will give insights that are relevant to other familial and sporadic MND cases. With the support of a Bill Gole fellowship, I have established experimental models using patient skin and blood cells, mouse motor neuron cells and transgenic mice. These models will serve as reliable platforms to study MND mechanisms and to test potential treatments. We reproduced MND-like cellular features in the cell models. One of the hallmarks of MND is the presence of protein aggregates, or inclusions, in their brain and spinal cord. We treated cells with different stresses, some of which induced inclusions with similar composition to those seen in MND patients. We can also examine pathologies associated with any known or novel MND causative protein using MND patient post-mortem brain and spinal cord tissues. We are currently optimising our transgenic mouse model and are using different stresses in an effort to induce MND-like features.

As part of our established exome DNA sequencing program, we have identified mutations in a new MND causative gene within a subset of patients. This gene plays a role in coordinating essential cell cycle events. We are currently studying the functional consequences of these mutations in order to identify the disease mechanisms in these patients.

Bill Gole Postdoctoral Fellowship 2009 - 2011

Dr Justin Yerbury, University of Wollongong, NSW
Probing molecular mechanisms of microglial and astrocyte activation in ALS.

The Bill Gole Fellowship has allowed me to concentrate on building a research team and gain experience in new areas. I have also been able to build a network of strong collaborators in the field of MND research. The work of my team has approached MND from many different angles of research from single proteins, growing neurons and glia in the test tube, animal models of MND and studies in humans. Our work has centred on protein aggregates, which are the junk piles of protein that are associated with all forms of MND.

We have shown that these can be toxic to the cells they grow in, but then can further damage surrounding cells if they are released. This may in part help to explain the progression of pathology in MND. We will continue to research the nature and mechanism by which proteins aggregate in motor neurons and their effect on surrounding cells with the goal of uncovering a potential mechanism to target for therapeutic benefit.

MNDRIA/ NHMRC PhD Scholarship 2012 - 2014

Dr Neil Simon, Neuroscience Research Australia, NSW

The distribution of motor system dysfunction in MND.

The exact location of onset and subsequent spread of disease in MND is still not completely understood. This project explores these issues using serially collected clinical information, combined with neurophysiological and imaging testing of the brain, spinal cord and peripheral nerves. Being able to clarify the mechanisms of disease onset and spread in MND may have significant implications for patients in that it may allow further understanding of the causes of degeneration of motor nerves, as well as guiding exploration for new disease-specific treatment modalities. So far the project has collected some interesting data exploring the relationship between the motor nerves and the spinal cord in patients with ALS, and this has resulted in the preparation of several manuscripts and two international conference presentations. In addition, promising new imaging techniques are being explored, with the aim of developing new ways to quantify peripheral motor nerve degeneration. The next phase of the project will be to consolidate the data already obtained, and finalise these publications.

Subsequent studies will focus on correlating new imaging techniques with clinical and neurophysiological information with the aim of developing new non-invasive biomarkers of motor nerve degeneration

MNDRIA/ NHMRC PhD Scholarship 2010 - 2012

Dr James Burrell, Neuroscience Research Australia, NSW

Cognition and behaviour in MND.

As MND progresses, some patients may develop changes in language, personality or behaviour that resemble those symptoms seen in patients with frontotemporal dementia (FTD). Similarly, a significant minority of patients with FTD may develop MND. Recent discoveries in pathology and genetics have reinforced the concept that MND and FTD are

two extremes of a single disease continuum. This project aimed to develop our understanding of the links between MND and FTD, using a number of clinical, neurophysiological, and neuroimaging tools. Clinical assessments included detailed motor system examination and neurophysiological assessment in patients with FTD, with results compared to patients with MND. Further testing of eye movements, which reflect underlying cognitive processes, was performed using a device specifically designed for the purpose. This testing was combined with sophisticated MRI scans to detect changes in the brain responsible for fast eye movements known as saccadic eye movements. Such testing may prove helpful in the detection of cognitive changes in the MND clinic. Another component of my project involved the description and characterisation of an isolated bulbar phenotype of MND, which appears to have a better prognosis than typical bulbar-onset MND. Neurophysiological techniques were used to help make the distinction between isolated bulbar palsy and other forms of MND. Finally, neurophysiological and neuroimaging techniques were used to better understand the links between symptoms and pathology in corticobasal syndrome, a neurodegenerative disease that shares many clinical features with MND.

A clear understanding of cognitive symptoms and the relationship of MND to FTD is crucial, not just to increase the basic understanding of MND, but also to highlight the potential impact cognitive symptoms have on patients with MND, their carers and patient management. In addition, a deeper understanding of the links between clinical symptoms and underlying pathology is necessary to help guide future trials of potential drug treatments.

MNDRIA PhD top-up Grant 2012 - 2014

Alexandra Mot (PhD candidate) and Dr Peter Crouch (Principal Supervisor), University of Melbourne, Victoria

Investigating energy metabolism in models of MND to elucidate the mechanism of action of the potential therapeutic Cu^{II}(atsm)

The development of treatments for MND is dependent on the availability of models in which to test potential therapeutics and to study the fundamental biology of the disease. The most widely used models to date involve mutations in the SOD1 gene. Our research team has demonstrated that the drug Cu^{II}(atsm) has strong protective activity in SOD1 mouse models of MND. We have recently acquired access to a new TDP43 mouse model of MND and have also tested the therapeutic potential of Cu^{II}(atsm) in these mice. Although we found some protective activity for Cu^{II}(atsm) in these mice (it potently attenuated markers of inflammation in the spinal cord tissue), the mice die prematurely due to gastrointestinal problems well before overt MND-like symptoms appear. Whether these mice represent a valid model of MND remains unclear. Through a series of in vitro experiments we have made some progress in unravelling the mechanism of action of Cu^{II}(atsm) by establishing that the compound responds specifically to conditions of impaired energy metabolism. Our current focus is on investigating the role of impaired energy metabolism in MND. We expect to generate new information to help understand how impaired energy metabolism contributes to the pathogenesis of MND and to better understand the mechanisms through which Cu^{II}(atsm) is protective in SOD1 mouse models of the disease.

Reports on grants-in-aid funded by MNDRIA in 2012

Grants-in-aid provide an incentive for successful researchers to continue to move forward in their chosen area of research. Reporting on successful outcomes from previously funded research provides a favourable track record when reviewers assess grant applications for new projects. These grants also help researchers to initiate new projects with the hope they can 'grow' to produce data that can attract more significant funding from government grant schemes.

Susie Harris Memorial Fund Research Grant

Dr Julie Atkin, La Trobe University, Victoria

Failure of ER-Golgi trafficking as a central mechanism of toxicity in ALS.

Motor neurone disease patients currently face a bleak future. Available therapies have at best a modest effect on the course of the disease with little or no benefit in terms of overall patient survival. This study investigates common mechanisms of disease in the diverse forms of MND, both sporadic and genetic forms, which lead the death of motor neurons. We have now identified a disease mechanism common to several diverse forms of MND and are currently investigating where this mechanism is initiated from. These studies will lead to opportunities to develop new therapies in the future. Thanks to the generous support of the MNDRIA the above grant also contributed to studies which comprised the preliminary data allowing us to achieve a NHMRC project grant which commenced in 2012. This project will enable us to examine in detail the molecular mechanisms responsible for the inhibition of ER-Golgi trafficking: "ER-Golgi trafficking and ALS', 2012- 2014, $419,925 CIA Atkin.

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. We have identified mutations in new familial MND genes. Together with Australian and international collaborators, we have discovered that defects of the EWSR1 gene contribute to motor neuron death. EWSR1 is closely related to the known MND gene, FUS, thereby implicating a common biological mechanism. We have also identified defects in another gene, UBQLN2, and shown that this gene interacts in cells with previously known MND genes. Again, this implicates a common biological mechanism. Most recently, we investigated a recently discovered MND gene (C9ORF72) and found that mutations in this gene are present in almost 40% of Australian familial MND patients. These discoveries have led to the development of new diagnostic tests and studies are now underway to determine how these new genes cause MND.

Mick Rodger Benalla MND Research Grant

Dr Tim Karl, Neuroscience Research Australia, NSW

A novel mouse model for MND.

The protein TDP-43 was identified as a major component of the protein clusters found in MND patient brains and spinal cords. Ian 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. We are now investigating the neuro-behavioural effects of one of the mutations (i.e. TDP-43M337V) 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.

To date, the research team has tested the motor functions in this novel genetic mouse model for MND at different ages. Mice did not develop any motor deficits up to 15 months of age. As has been reported for other disorders such as schizophrenia, researchers have now started exposing test mice to stress, as human research has shown that stress can trigger the onset of a motor phenotype in humans at risk to develop MND. In case stress induces the onset of motor impairments in genetically modified mice, the hypothesis that human disorders are mostly caused by an interaction of genetic and environmental risk factors for the disease in question would be confirmed.

It will take another six months before we will have sufficient animal numbers to actually report the outcome of this combined research strategy.

Charles and Shirley Graham MND Research Grant

Professor Pamela McCombe

University of Queensland Centre for Clinical Research

MND: Not a simple disease.

We are studying measures of disease progression in people with MND who attend our MND clinic. This is an

ongoing project and requires that we make assessments and follow people over the course of their illness. Patients are seen every three months and have clinical assessment, MRI studies, neurophysiology studies and measurements of blood markers. This is a very detailed assessment and will enable us to determine factors that influence the course of disease and to make a prognosis of the course of disease.

The MRI studies are progressing well. The basic analysis has been perfected, and the results have been published. We have now performed serial studies of people with MND and shown that MRI can measure the rate of loss of nerve fibres that run from the brain to the spinal cord. We are also looking at the differences in MRI appearances between people with different clinical features of MND.

The neurophysiology studies are also progressing well. We have shown that patients with different clinical features have different rate of loss of motor neurones from the spinal cord. We have also shown that the rate of loss of motor nerves from the spinal cord is greatest at the site of onset of weakness. We have preliminary evidence that the rate of loss of motor units is predictive of survival.

We have also measured a protein called neurofilament H in the blood of subjects with MND. In some subjects the levels are very high. We are correlating these levels with the results of the MRI and neurophysiology studies, to see if we can use the blood neurofilament results as a simple means of detecting people with rapidly progressing 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 first described as a pure motor syndrome. More recently, studies have shown that unfortunately this is not the case, with a great proportion of patients also developing 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 appear to be very common, and the combination of these changes and physical disability could compound to high levels of burden for carers.

Our project resulted in three main studies which have been published in scientific journals or presented in scientific meetings nationally and internationally. In a first study, we have shown that patients with MND who show shrinkage in some brain areas are likely to demonstrate non-motor symptoms such as the cognitive and behavioural symptoms mentioned above: apathy, difficulties in problem solving, etc. This is very relevant because this study also shows that those without these brain changes tend to have circumscribed typical MND motor symptoms.

We have found that the type of MND (e.g. limb or bulbar) does not reveal if a person will have cognitive or behavioural symptoms. Instead, we have shown that these symptoms are very common but not severe in the majority of patients. We have also demonstrated that these behavioural symptoms do not lead to worse survival of the patients.

We have also presented a new assessment tool in this study. This tool has been shown to be very good at detecting these symptoms in MND, and will be used in MND centres worldwide.

Finally, we are also doing research on the role of the different symptoms (e.g. physical, cognitive and behavioural changes) in the levels of burden in family carers. This will provide evidence for more tailored services in the community which should directly benefit families. Data for this study have been collected and analyses are underway. We hope that our findings will help in planning of services, professional training, websites and informative leaflets. While there is no cure for MND yet, we hope to establish services for those looking after the people with MND. Family carers will benefit from interventions and evidence-based support and will be better equipped with skills to support the person with MND.

Graham Smith MND Research Grant

Professor Garth Nicholson

ANZAC Research Institute, NSW

Sporadic MND: the contribution of genes, biomarkers and metabolites.

In order to determine the contribution of gene mutations to motor neurone disease, we have commenced a project to collect both families with MND and sporadic cases MND. Preliminary results indicate that we can find gene mutations in 60.6% of families with MND and in about 3.9% of cases with sporadic MND. Every year new genes are found to cause familial MND and the proportion of sporadic cases with gene mutations is also gradually increasing. Once we know all the genes contributing to sporadic MND we will be in a much better situation to determine the contribution of genes and the environment to the cause of the disease.

During 2012 we were able to collect nine new families with familial MND and 25 samples from patients with sporadic MND. Many other previously known families have been expanded and we now have a database of 277 families with familial MND. Lymphocyte transformations from MND affected individuals in families have been carried out at Genetic Repositories Australia (GRA). DNA and plasma are being stored from sporadic cases at the Molecular Medicine Laboratory, Concord.

New arrangements have been made at GRA to carry out lymphocyte transformation of newly collected sporadic MND samples where permission has been given for the samples to be used by bona fide MND researchers.

Reports on grants-in-aid funded by MNDRIA in 2012

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.

We have developed a gene therapy for MND consisting of an antibody capable of targeting specific nerves chemically linked to a gene that can prevent mutant proteins causing the disease in nerves that control movement. As a result of our own work, and also from recently published findings of others, it is becoming clear that effective down-regulation of the mutant proteins in motor neurons requires two essential criteria to be met. Firstly, a large percentage of all motor neurons must be targeted and secondly, each neuron must be transfected with sufficiently large therapeutic. By labeling the antibody used for targeting our immunogenes to motor neurons, we have been able to show that systemic administration achieves delivery to more than 90% of all motor neurons within the mouse spinal cord, from the cervical regions of the cord to the lower lumbar segments. This knowledge has encouraged us to continue to develop immunogenes that can withstand the degradative conditions within the blood.

In parallel, we have also detected a protein present in urine of mice that develop MND but not in those that do not get the disease. We are currently testing the validity of this protein as an objective and quantitative biomarker for MND, as biomarkers are urgently needed to assist assessment of potential new drugs, for earlier diagnosis and also for monitoring disease progression. If found to be a valid biomarker, we will use it to assist determination of the effectiveness of our new gene therapy.

Mick Rodger MND Research Grant

Dr Bradley Turner
Florey Neuroscience Institute, Victoria
Exploring the therapeutic potential of survival motor neuron protein for MND.

Survival motor neuron (SMN) is an important survival factor for motor neurones and there is genetic evidence that extra SMN genes are a risk factor for MND. We recently showed that SMN protein is abnormal in MND patients and the SOD1 mouse model of MND.

This project examined whether SMN is also involved in TDP-43 mice, a new model of MND. We have shown that SMN protein abnormally accumulates in motor neurones of TDP-43 mice long before symptoms start. By genetically engineering TDP-43 mice with extra SMN copies, we have shown that increased SMN hastens disease progression in these mice. This provides evidence that SMN is affected by TDP-43 and that SMN gene dosage is important for MND which opens up a new player for pathology and treatment of MND.

Connie's Step Forward for MND Research Grant

Associate Professor Steve Vucic
Westmead Hospital and University of Sydney
T cells: a vehicle for neuroprotection in ALS?

The immune system has been thought to be involved in damaging the motor neurons in MND. However, recent research has shown that certain immune cells can actually help protect the neurons in the mouse model of MND. These cells are raised in the early phases of disease but fall away in the later rapidly progressing stage of disease in this model.

In this project we have examined this type of immune cell (called a regulatory T cell) in MND patients. We used a more comprehensive typing method to assess the cells than previous human studies and found that, similar to the animal model, these cells are raised in MND patients in the early phase of disease. We have also found that higher levels of these cells are associated with slower progression of disease.

Using a novel analysis method, we have also shown that other immune cell groups (T cells, neutrophils) are present in different proportions in the peripheral blood in ALS. Our ongoing work is analysing samples collected from our 40 patients (and 40 people with no MND) to assess which immune cell genes are switched on in the blood in ALS to tell us what is the balance between damaging immune cells and protective immune cells in MND.

Ultimately we are interested in the possibility of manipulating immune cells to protect the neurons in MND. We are conducting an experiment using an immune cocktail that is known to specifically induce the protective cell type in other animal models. We will test whether this cocktail can increase the protective immune cells in the mouse model of MND, and whether this slows disease.

Zo-ee MND Research Grant

Dr Robyn Wallace, QLD 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. We have generated a model for TDP-43 pathology in the nematode C. *elegans* by expressing different ALS- causing mutations of human TDP-43 in a specific subset of neurons. C. *e/egans* have a total of 23 motor neurons, which can be visualised using a stain carrying a green fluorescent protein.

The nematode will be used to analysis 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

Associate Professor Anthony White
University of Melbourne
Targeting kinases to control TDP-43 and FUS accumulation in MND.

Understanding the processes involved in MND is critical for development of effective therapeutics. Accumulation of the protein TDP-43 in the cytoplasm of neurons in the spinal cord and brain of MND patients is thought to be an important factor in the disease process. However, little is known about the mechanisms controlling this process.

Our studies have shown that abnormal accumulation of TDP -43 may be controlled by its interaction with another protein, hnRNP K. These two proteins bind together and the latter may control the movement of TDP-43 within the cell. We have found that a protein kinase called CDK2 is able to phosphorylate hnRNP K, acting as a molecular switch and, upon this activation, hnRNP K and TDP-43 remain bound together at sites of accumulation in neurons. Blocking the action of CDK2 with chemical inhibitors reduces the amount of hnRNP K and therefore, TDP-43 accumulating in the cell. This may provide a unique opportunity to control the abnormal accumulation of TDP-43 in MND and offer the hope of a therapeutic intervention. Further testing in animal models will be required to determine if this is possible.

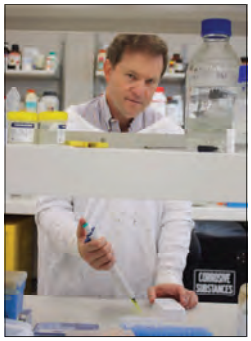
Rosalind Nicholson MND Research Grant

Professor Mark Wilson, University of Wollongong, NSW
Protein aggregation and chaperones: key players in MND.

The project worked past many technical issues to get to the point where we can reproducibly identify a population of particles released from burst cells taken from spinal cord tissues from MND patients. Specific dual labeling with antibodies allows us to identify these particles as the protein deposits implicated in the death of motor nerve cells in MND. We have physically purified these particles and have established that the yield in terms of amount of protein is low. We now know how many particles we will need in order to give us enough protein to identify the individual proteins they contain, which will give us clues as to the proteins most important in causing MND. We are accumulating more and more purified particles currently in preparation to do this. We have concurrently been developing parallel approaches to purify (more easily in large quantities) inclusions from cell models of MND.

One of the proteins already known to be in these deposits is TDP-43. We have shown that a chaperone protein (known as clusterin) can inhibit the formation of protein aggregates by TDP-43 *in vitro.* Furthermore we have shown that when expressed in a fly model of MND (in which TDP-43 is expressed in fly motor neurones), clusterin extends the life of the flies and protects them from the loss of locomotor activity normally resulting from progression of the MND-like pathology. We have also constructed cell models in which TDP-43 can be expressed either constitutively or in a regulated way. In these systems the TDP-43 can accumulate as deposits in the cytoplasm and this is associated with increased cell death. Co-expression of clusterin in these cell models results in less cell death and co-localisation of clusterin with the TDP-43.

Collectively these lines of investigation are providing exciting new insights into the molecular mechanisms that underpin the development of MND pathology. We expect to identify a list of proteins contained in MND inclusions, which will give us targets to study further (e.g. screen the genes for these proteins in MND patients to see if mutations in these genes can explain the "heritability" of MND). Furthermore, the fly model is currently being used to look at whether TDP-43 exerts different effects in different cell types and whether it can "migrate" from one cell to another in vivo, which might explain the progressive spreading of the loss of motor function in MND patients. This project will make a significant contribution towards understanding those processes that impact upon the health of motor neurons in MND patients. Improved understanding in this area will be essential to develop new diagnostics and therapies for this pernicious disease.



MND Research Institute of Australia: Office Bearers and Members 2013

MND Australia is the principal member of the MND Research Institute of Australia.
The operations of both organisations are the responsibility of MND Australia.
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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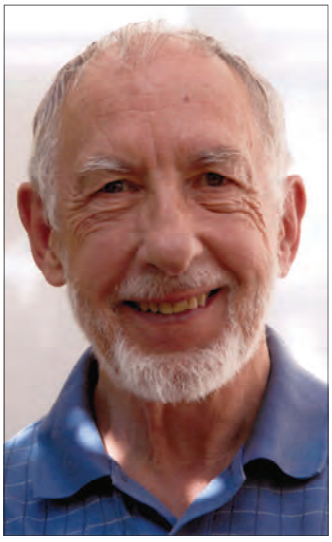
Dr Graham Lang 1933 - 2013



Dr Graham Lang died on 18th January 2013. He had long been a champion of MND in Australia, serving on the boards of both national and state MND organisations. He was a Chairman and a long standing member of the State Council of MND Victoria. He was also Chairman of the MND Research Tissue Bank of Victoria. Graham had considerable skill in attracting other well qualified people to serve on the boards of the various MND organisations with which he was involved and the membership of the boards we have today owe much to Graham for this initiative.

Nationally his roles included Chair of MND Australia and membership of the MND Research Institute of Australia. He took responsibility for the development of the MNDRIA constitution which provided the structure for the highly regarded Research Institute we have today. Graham was a member of the committee that saw the union of these two organisations in 2010. Amalgamation was effected by drawing the Research Institute into the administrative structure of MND Australia, forming a unified, national body.

Graham was a passionate advocate for research and his family share our pleasure in the announcement of the Graham Lang Memorial MND Research Grant in recognition of his contribution to the fight against MND. This grant is generously sponsored by MND Victoria.

This newsletter not only provides information about the latest results from MND researchers in Australia, but also serves as a source of feedback to the donors who provide the funds that make this research possible. We thank and applaud the many donors who have contributed to the realisation of these outstanding results and continue to provide hope that we will achieve a world free from 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:

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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.

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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 Officer Research on 02 8877 0990 or email research@mndaust.asn.au.

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