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The MND Research Institute of Australia (MNDRIA) has awarded a record $2.17 million for new MND research projects commencing in 2014. The eleven members of the MND Research Committee rigorously assessed 52 applications before awarding 22 grants to the very best applications which have the greatest chance of providing benefit for people with MND. The successful recipients were located in every state in Australia.

Among the recipients was Dr Jacqueline Leung from the University of Tasmania who received the three-year Bill Gole MND Post-Doctoral Fellowship. A new international collaborative travel grant was awarded to Dr Rebecca Sheean from the Florey Institute of Neuroscience and Mental Health, University of Melbourne, who will travel overseas to work at University of Oxford with Professor Kevin Talbot.

The remaining funds were allocated to 20 development grants to support established researchers in their quest to understand the causes, provide better care, control the symptoms or find a cure for MND.

MND Australia, through its research arm, MNDRIA is the major force driving MND research in Australia, due to the generosity of donors.

New grants awarded for projects commencing in 2014

Bill Gole MND Postdoctoral Fellowship 2014 - 2016

Dr Jacqueline Leung
Wicking Dementia Research and Education Centre, University of Tasmania
Investigating the role of oligodendrocytes in ALS.

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

Jenny & Graham Lang Collaboration Travel Grant 2014

Dr Rebecca Sheean
Florey Institute of Neuroscience & Mental Health VIC
Travel to University of Oxford to work with Professor Kevin Talbot and the Oxford Motor Neuron Disease Group.
Development of survival motor neuron (SMN) gene therapy for MND.

This project aims at investigating the therapeutics of delivery SMN in models of MND.
There are a number of factors that implicate survival motor neuron (SMN) in MND including reduced copy number of *SMN* in MND patients.. We have shown loss of SMN in motor neurones expressing MND-linked genes (SOD1, TDP43) and in spinal cords of presymptomatic SOD1G93A mice suggesting that this is an early event in MND. In addition we have shown SMN depletion in spinal cords from sporadic MND patients, highlighting that loss of SMN occurs broadly in MND and is not restricted to familial forms of the disease. Therefore, we propose that SMN upregulation may be beneficial in MND. Preliminary data from our group has shown that increasing SMN expression is protective in models of MND. Transgenic mice neuronally overexpressing SMN protein (SMN Tg) were resistant to axotomy-induced motor neuron loss using a nerve injury model. Also, we have shown by crossing SMN Tg and mutant SOD1 mice that SMN upregulation delays disease onset and is protective against motor neuron loss. In this project we aim to investigate the therapeutic effects of SMN gene therapy using an immunogene approach in mouse models of MND.

MNDRIA PhD top-up grant 2014 - 2016

This grant will be awarded after the announcement of University PhD Scholarships at the end of the year.

Grants-in aid commencing in 2014

Graham Lang Memorial MND Research Grant

Professor Samar Aoun
Curtin University WA
Best practice in breaking the news of an MND diagnosis: A survey of patients, family carers and neurologists.

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

MNDRIA Grant-in-aid

Associate Professor Julie Atkin
ASAM, Macquarie University
Identifying novel pathological mechanisms linked to C9ORF72 in amyotrophic lateral sclerosis.

Whilst many potential drugs have been trialled in ALS, to date, none have resulted in effective therapies. This reflects a lack of basic understanding of the underlying mechanisms that trigger disease. In the last two years, a mutation in a protein known as "C9ORF72" was identified as the major genetic cause of ALS, but the normal function of this protein and how the mutation causes the disease remains unknown. In this study we will investigate the disease mechanisms triggered by C9ORF72. Investigation of how this newly identified protein causes ALS is a critical step in understanding how disease develops, how motor neurons degenerate and eventually die. From these studies, effective therapeutics can be designed to treat ALS patients in the future.

MNDRIA Grant-in-aid

Dr Mark Bellingham
School of Biomedical Sciences, University of QLD
Respiratory motor dysfunction and treatment in an animal model of motor neuron disease.

Despite the fact that death in MND is usually due to respiratory failure, and that respiratory function is one of the best predictive factors for disease progression, we know very little about how dysfunction develops in the neural control of breathing movements in MND. In particular, effective treatments for respiratory dysfunction are sadly lacking. The planned outcome of this research will be the first comprehensive characterization of the neural control of breathing movements and its progressive dysfunction in a commonly used mouse model of MND. This characterisation will range from the cellular to the systems level, from functional and structural changes in single respiratory motor neurons to breathing movements and responses to common breathing stimuli in the whole animal.
We will also test two novel therapeutic strategies – prophylactic early treatment with riluzole at a time when changes in motor neurons controlling breathing movements are already starting to occur, and the induction of enhanced breathing output (respiratory long-term facilitation) in both the early stages of disease, and in the dysfunctional adult breathing motor system. The outcomes of these treatment strategies will provide invaluable insights into how and when to treat breathing dysfunction in human MND.

Mick Rodger Benalla MND Research Grant

Dr Beben Benyamin
Queensland Brain Institute, University of QLD
Trans-ethnic and trans-omic statistical analyses to identify new ALS risk variants.

Elucidating the aetiology of ALS/MND is the key to its treatment and cure. Genetic factors are a major cause of ALS even in apparently sporadic cases (i.e. no family history of ALS). Currently, the known ALS genes explain a small proportion of sporadic cases. Except for age and sex, there are no specific biomarkers and environmental factors known affecting ALS. Using state-of-the-art genomic technologies, such as genome-wide association study, exome sequencing and epigenome-wide association study in ALS patients and controls, we aim to discover novel genes affecting ALS and to dissect their biological functions in ALS. To achieve these aims, we will use rich data from ~4,000 Chinese ALS case-control samples and summary GWAS data from the largest European ALS samples (ALSGEN Consortium). To our knowledge this will be the first large-scale trans-ethnic meta-analysis for ALS. We expect to identify novel genetic risk variants affecting ALS disease status or age of onset across ethnic populations and to understand their roles in ALS.
An association between locus or genome-wide epigenetic states and ALS disease status or age of onset may lead to the discovery of novel pathways.

MNDRIA Grant-in-aid

Dr Catherine Blizzard
Menzies Research Institute Tasmania
Synaptic alterations in ALS: A novel therapeutic target?

Amyotrophic Lateral Sclerosis (ALS) is a devastating disease that is caused by the death of motor neurons. There is a desperate need to discover new therapeutic ways to stop this neuron death, ideally targeted at early changes in the disease to prevent the majority of cell loss. Disturbances in neuronal synapses may be one such early event that potentially leads to neuronal dysfunction and then death. Synapses are specialised structures that allow neurons to communicate with each other. Changes in synapses can have serious effects on neurons' activity levels and if not controlled can cause neuron death. In dendrites, the large structures that relay information to the neuron's cell body, these synapses are present on small protrusions known as dendritic spines.

Mutations in the protein, transactive response DNA-binding protein 43 (TDP-43) causes a genetic form of ALS. TDP-43 has recently been shown to be involved in maintaining synapses between neurons; regulating the number and maturation of spines. It is feasible that an early disease-causing event in ALS may be changes to synapses. We will investigate how TDP-43 protein mutation determines the number and type of synapses on motor neurons in the brain and how these changes lead to dendritic spine alterations in 'real time' through a unique mouse model and sophisticated imaging techniques. This novel research program addresses an important gap in the current understanding of how synaptic changes can lead to neuron death in ALS and may open up a new target for drug intervention in this devastating disease.

Peter Stearne Grant for Familial MND Research

Dr Nicholas Cole
Australian School of Advanced Medicine (ASAM), Macquarie University
Modeling the ALS-linked C9ORF72 hexanucleotide repeat expansion in zebrafish.

Despite many years of research on amyotrophic lateral sclerosis (ALS), there is little understanding of the basic biology that results in a person acquiring ALS, and no effective treatment. We therefore need successful research models of ALS to help us understand the mechanism of the disease.

Several genetic faults that cause ALS have been identified from patients. We can put these same faulty genes into zebrafish, enabling us to create zebrafish that develop ALS-like features in order to help us understand the biology of the human disease. In this way, zebrafish become a powerful research model of ALS. This is possible because we share common biology with zebrafish. For example, the same genes and proteins that make motor neurons develop and function in humans also direct these processes in zebrafish.

Recently, a repetitive sequence within the genetic code of a gene called C9ORF72 has been identified as the most common cause of familial ALS. It is thought that this repetitive DNA sequence makes a toxic protein. These ALS patients have more of this repeat sequence in their genetic code than healthy people. In this project, we will create the first animal model with this significant ALS-causative mutation by making zebrafish that have different lengths of this repeat inside them. We will use this fish model of the human disease to study and understand the basic biological processes that result in motor neuron degeneration. We can then us the fish to investigate potential treatments.

MND Victoria MND Research Grant

Dr Anne Hogden
Centre for Clinical Governance, Australian Institute of Health Innovation, University of NSW
Assessing patient cognition and behaviour in specialised MND multidisciplinary care: a feasibility study.

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

MNDRIA Grant-in-aid

Dr Anna King

Wicking Dementia Research and Education Centre, University of Tasmania

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

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

MNDRIA Grant-in-aid

Dr Jeffrey Liddell

Department of Pathology, University of Melbourne

Induction of Nrf2 by neuroprotective Cu^{II}(atsm) in SOD1-G37R astrocytes.

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

MNDRIA Grant-in-aid

Dr Marie Mangelsdorf

Queensland Brain Institute, University of QLD

Targeting EphA4 as a treatment for MND.

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

Graham Smith MND Research Grant

Professor Pamela McCombe

University of Queensland Centre for Clinical Research

Investigating the consequences of increased fat catabolism in motor neurone disease.

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

MNDRIA Grant-in-aid

Dr Diane Moujalled
Department of Pathology, University of Melbourne
The role of hnRNP RNA binding proteins in motor neuron degeneration.

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

Charles & Shirley Graham MND Research Grant

Associate Professor Peter Noakes
School of Biomedical Sciences, University of Queensland
The role of altered neuromuscular signalling in ALS: factors that modify the course of MND.

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

MNDRIA Grant-in-aid

Dr Lezanne Ooi
Illawarra Health and Medical Research Institute, University of Wollongong
Examining the role of protein degradation in iPS cell models of ALS.

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

MNDRIA Grant-in-aid

Dr. Ken Rodgers
Medical and Molecular Biosciences, University of Technology Sydney
Studies investigating the non-protein amino acid BMAA, as an environmental trigger for MND.

In the majority of patients with motor neurone disease (MND) no genetic cause can be identified, suggesting that environmental factors are involved. The South Pacific Island of Guam is one of the few places in the world in which a very high incidence of an MND-like neurodegenerative disease has been reported. The disease affected people from diverse genetic backgrounds living on Guam and occurred at 50 to 100 times the rate of MND in the general population suggestive of an environmental link.
We have recently demonstrated that a toxin made by blue green algae (called BMAA) and found in cycad seeds which were consumed by the people living on Guam, can be incorporated into human proteins in place

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

Rosalind Nicholson MND Research Grant

Dr Mary-Louise Rogers
Human Physiology, School of Medicine, Flinders University SA
A biomarker to track progression of motor neuron disease in humans and MND mice.

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

Mick Rodger MND Research Grant

Associate Professor Aaron Russell
School of Exercise and Nutrition Sciences, Deakin University VIC
Inhibiting microRNA-23 as a therapeutic strategy to treat motor neurone disease.

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

Zo-ee MND Research Grant

Dr Bradley Turner
Florey Institute of Neuroscience & Mental Health VIC
Therapeutic targeting of autophagy in MND.

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

MNDRIA Grant-in-aid

Dr Trent Woodruff
Biomedical Sciences, University of Queensland
Innate immune complement signalling in peripheral immune cells during the progression of motor neurone disease.

In motor neurone disease (MND), there is death of nerve cells. As yet there is no way to stop these cells from dying and new approaches are thus needed. We are studying the role of the immune system in MND. We have evidence that activation of the immune system contributes to the progression of disease. In particular we have been studying the complement group of proteins. We suggest that the therapeutic targeting of complement could slow the progression of MND. In this study we will investigate this further, using blood samples from people with MND as well as animal models of MND. If this study is successful, we will then be able to perform a trial of our novel drug, which acts on this complement pathway.

MNDRIA Grant-in-aid

Associate Professor Naomi Wray
Queensland Brain Institute, University of QLD

Whole exome sequencing of sporadic MND.

Recent studies show that genetic factors account for more than half of the risk of developing MND, even in subjects with so-called “sporadic” MND. A number of causative genes have been identified for familial MND and some of these are found in subjects with apparent sporadic MND. In some subjects there is very obvious inheritance of disease and in other families the inheritance is less clear-cut. To understand this further we need systematic studies of the genetics of sporadic and familial ALS. Local studies then need to be combined with studies from other investigators to increase power. We have a cohort of well-characterised subjects with MND, who have already been screened for the presence of the more common genes implicated in causing MND. We now wish to perform whole exome sequencing of all the genes in these patients and controls.