mnd Research Institute of Australia

Advance

NEWSLETTER OF THE MND RESEARCH INSTITUTE OF AUSTRALIA

June 2012

MND research in Australia

The National Health and Medical Research Council of Australia (NHMRC) has the traditional role of providing government funding for health and medical research in Australia. As it becomes increasingly difficult for applicants to achieve the requested level of funding from NHMRC, researchers are driven to seek funding for their projects from other sources.

This happens in a time when the Motor Neurone Disease Research Institute of Australia (MNDRIA) is more able to fill the gap and MNDRIA now has a significant role in initiation and continuation of MND research in Australia.

MNDRIA has been providing grants to MND researchers in Australia since 1987. Each year MND Research Committee experts (see page 8) determine which applications have the greatest relevance to MND and the greatest chance of making a difference (after considering the track record of the applicant and the feasibility of the project). Initially just one grant each year was offered but 25 years down the track much more is possible. Now, with over $1,000,000 available to allocate to grants in the past two years, MNDRIA has been able to offer grants up to $100,000 for each funded project. This makes a major difference from the $25,000 grants that were offered previously and the quality of the research projects funded by MNDRIA has risen accordingly. New findings, both national and international, form the basis for many of the projects being investigated in 2012.

This year, MNDRIA is funding nineteen projects in twelve institutes throughout Australia with at least one funded project in each State. Researchers are asked to provide a progress report after six months and a final report at the end of the project. Brief overviews from the final reports from projects funded in 2011 are published in this newsletter. These reports demonstrate the breadth and depth of MND research in Australia.

At the end of each year currently funded researchers are invited to present the results of their year's work at a meeting attended by their fellow researchers and other interested people. In 2011, the International Symposium on ALS/MND held in Sydney in December provided an international platform for this exchange of information and ideas and the groundbreaking work presented created a feeling of excitement and optimism. A number of Australian MND researchers will attend the 2012 International Symposium on ALS/MND in Chicago in December. The 2012 MNDRIA grant recipients will also meet at the Queensland Brain Institute on 12 November.

Rapidly advancing technology and increased funding must accelerate the research that will find the answers for MND.

We believe there is a cure. We just haven't found it yet.

The Graham Linford MND Research Fund: $1,000,000 bequest

Dr Graham Linford died from MND in May 2011 in Perth, WA. He had the foresight and the ability to leave a legacy that will drive MND research in the years to come. His bequest will be maintained to provide the Graham Linford Postdoctoral Fellowship for MND Research.

Dr Linford, with a distinguished career as a geophysicist, knew that research is the only way to make a change. His name will live on as his bequest makes it possible for MNDRIA to expand its award of postdoctoral fellowships for MND researchers.

His magnificent gift provides hope for people living with MND.

DR GRAHAM LINFORD 1940 - 2011

Donations and bequests

All MNDRIA funds come from donations. These come as gifts from loyal MNDRIA supporters, research contributions to MND Associations, memorials to a loved one and special occasion gifts. Each year more people, clubs and entire communities hold special events to fund MND grants. They not only advance the profile of MND in the community but also extend the range of grants offered. Significant contributions from major donors, private trusts and foundations all add to the wealth of support for MND research.

MNDRIA has received a number of bequests this year which will help to achieve the million dollar goal for grants to be awarded for 2013.

Every dollar donated for research is spent directly on research.

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MND Australia Leadership Grant

We are pleased to announce MND Australia's prestigious new grant to support an outstanding leader in motor neurone disease research. The MND Australia Leadership Grant aims to provide $150,000 per year over four years, commencing in January 2013.

It will enable an outstanding researcher to build a team who will seek to understand the causes, provide better care, control the symptoms or find a cure for MND.

The MND Australia Leadership Grant will be awarded to a leading Australian researcher who has demonstrated his or her passion and tenacity for MND research. It will enable MND Australia to support long term projects that are specifically focussed on MND, to retain our brightest researchers and, ultimately, to drive future MND research.

As the ability to support MND researchers has grown, it has become apparent that we must do more to support those researchers who have demonstrated their commitment particularly to MND research. It is not possible to take on long term projects without a guarantee of income over an extended period. This new grant will provide the possibility to plan ahead and to drive future research.

Information about application for the MND Australia Leadership Grant will be available at www.mndresearch.asn.au in July.

The annual MNDRIA research meeting will be held at the Queensland Brain Institute on 12 November 2012. Researchers funded by MNDRIA in 2012 will present the results of their work and meet with their peers and MND Research Committee members. All interested people are welcome to attend this research meeting. Program details will be available later in the year at www.mndresearch.asn.au

The 23rd International ALS/MND Symposium will be held in Chicago, USA on 5-7 December 2012 with parallel biomedical and clinical research sessions. The many delegates represent the dynamism of the global MND research community. The Allied Professionals Forum will be held on 4 December. Registration for both meetings is available at www.mndassociation.org with early bird rates until 15 July.

Bill Gole Postdoctoral Fellowships for MND Research
Reports from projects funded in 2011

Bill Gole died from MND in 2003. His name lives on as young scientists compete for the postdoctoral fellowship named in his memory and sponsored by a generous friend who is determined to drive MND research forward. The first Bill Gole Postdoctoral Fellowship commenced in 2005 and this year the eleventh young Australian scientist to gain this prestigious grant has commenced a career in MND research. Dr Shyuan Ngo (Bill Gole Postdoctoral Fellow 2012 - 2014) has commenced her project at University of Queensland this year. The fellowship aims to encourage young researchers to focus their interest on MND. It is directed towards postdoctoral scientists with a track record in neuroscience related to MND and is offered for a three year period.

These brief reports are from four concurrent Bill Gole MND Postdoctoral Fellows funded in 2011.

Bill Gole Postdoctoral Fellowship 2011 –2013

Dr **Catherine Blizzard**

Menzies Research Institute, University of Tasmania

Investigating the cause of site-specific excitotoxicity in ALS.

Motor neuron disease 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, which will enable the role that over excitation of the nerve cells bodies could play in the disease progression to be determined.

Bill Gole Postdoctoral Fellowship 2011 –2013

Dr Rachael Duff

Centre for Medical Research, University of Western Australia

The application of new generation genetic techniques to MND.

The majority of this project is focused on using new DNA sequencing technologies for the identification of gene mutations in familial and sporadic ALS, so an important first step has been in the successful implementation of these technologies in Perth. In January 2011, a generous philanthropist donated $1 million for a new sequencing instrument at the LotteryWest State Biomedical Facility: Genomics (LSBFG) in Perth. I have been working closely with the manager of this facility to establish the analysis requirements for this new equipment. This involved a visit to the US to attend specialised training in the computer based analysis in addition to a visit to a prestigious laboratory at Duke University in North Carolina. This laboratory has created a specialised computing tool for the identification of gene mutations in a variety of conditions. I have now implemented this software in Perth, ready for the analysis of data generated in this project.

Laboratory work has also commenced, with approximately 20 samples screened for inclusion in the study. Ten of these samples were sent for next-generation, whole exome sequencing to laboratories at Duke University and The University of Queensland. The LSBFG facility is now in the final stages of set-up optimisation and when complete we will sequence further samples. These first steps lay the foundation for identifying as yet unknown causes of MND. This will provide an opportunity for many families to test for the presence of a mutation leading to the development of MND.

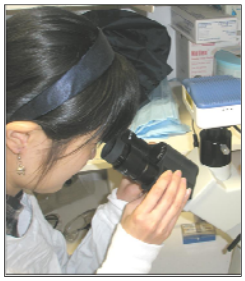
Reports on Bill Gole Postdoctoral Fellowships funded in 2011

Bill Gole Postdoctoral Fellowship 2010 - 2012

Dr Shu Yang

ANZAC Research Institute, NSW

Investigating the role of recently identified mutant genes in MND pathogenesis.



The majority of MND patients are sporadic, that is, they do not have a family history of MND. The remaining 10% of patients have familial MND with family histories indicating that there are heritable genetic defects associated with MND. One of the milestones in MND research was the discovery of gene mutations in the superoxide dismutase 1 (*SOD1*) gene. More than 100 mutations have been found in *SOD1* which cause 10-20% of familial MND cases. More than one 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 in the brain and spinal cord. We treated cells with different stresses, some of which induced inclusions with similar composition to those seen in MND patients. I found more aggregates in skin cells with a novel TDP -43 indel mutation than control cells under stressful conditions. We also identified a mutation in the UBQLN2 gene in a large MND family. Under stress, patient skin cells with the UBQLN2 mutation showed a higher incidence of aggregates that contain both ubiquilin and TDP-43. I also found that different stresses led to inclusions with different compositions. For example, a proteasome inhibitor induced inclusions containing proteins that are responsible for protein degradation, but an oxidative stress was unable to induce such inclusions. This approach helps us identify the impairment of cellular activity that is relevant to the development of MND.

Our next step is to examine whether we can dissolve the cell inclusions. This may offer a means to develop treatments. We are currently optimising our transgenic mouse model and we will use stresses in an effort to induce MND-like features. We aim to also use this mouse model to study MND biology.

Bill Gole Postdoctoral Fellowship 2009 - 2011

Dr Justin Yerbury

Centre for Medical Biosciences, University of Wollongong

Probing molecular mechanisms of microglial and astrocyte activation in ALS.

Recent evidence suggests that motor neurone degeneration is an orderly and propagating process that moves from one part of the nervous system to other nearby locations. All forms of MND are associated with piles of protein junk, (inclusions) and neuroinflammation. These protein junk piles can be found in motor neurones and another non-neuronal cell type – astrocytes. Only astrocytes that are close to motor neurones have these inclusions. I am investigating the possibility that these broken proteins in the junk pile are somehow passed on from one cell to another causing dysfunction of neurones and astrocytes. It is hoped that if we can identify the way that cell death and dysfunction is "passed on" from neurone to neurone we can design a much needed therapeutic.

MND/NHMRC co-funded PhD Scholarship 2009 - 2011

Dr James Burrell

Neuroscience Research Australia, NSW

Cognition and behaviour in motor neuron disease.

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 (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.

Reports on grants-in-aid awarded for MND research in 2011

Twelve one-year projects were supported by MNDRIA grants-in-aid in research laboratories around Australia in 2011.

Zo-eè MND Research Grant

Dr Julie Atkin

MND Research Group, La Trobe University, Victoria

Novel therapeutic agents for motor neuron disease with optimal pharmokinetic properties.

We recently showed that a cellular pathway called 'ER stress' triggers the death of motor neuron cells in MND. More importantly, we and others have shown that (i) ER stress occurs very early in the disease process, suggesting that it is an early and important part of the process that kills nerve cells in MND, and (ii) ER stress occurs in humans with the most common, sporadic form of MND.

We have exciting new evidence that a drug called BMC prevents ER stress and motor neurons from dying in both cell culture and animal models of disease. Hence this may be a novel treatment for human MND. However, this drug, whilst being effective, cannot normally enter the brain from the rest of the body. This is due to the 'blood brain barrier' (BBB), which is a type of filter which prevents some materials from the blood entering the brain. The BBB is a common problem for drugs which have the potential to cure patients with neurological disorders. However some materials are able to cross this barrier, such as those which are soluble in fats and some drugs can be made to cross the BBB by making them more fat soluble.

In this study we modified the chemical structure of our drug, and we made 5 new drugs based on BMC, which are more fat-soluble and hence more likely to cross the BBB. These drugs (RM17, RM25, RM26, RM35, RM64) are all more permeable to the BBB. Furthermore, all 5 drugs were found to be equally as protective as BMC in preventing the toxic effects of the proteins involved in MND, and two of these compounds, RM17 and RM25, were even more protective than BMC. The new drugs RM17 and RM25 have great potential for the treatment of MND, and hence our study has opened up novel and exciting therapeutic targets for human MND in the future.

Mick Rodger MND Research Grant

Dr David Berlowitz

Institute for Breathing and Sleep, Austin Hospital, Victoria

Identifying who will benefit from Non Invasive Ventilation in motor neurone disease in a clinical cohort.

The rate and pattern of weakness in MND varies within individuals but regardless of this, the inability to breathe effectively is the usual cause of death in almost all people with MND. Treatment of this breathing failure with a mask and a machine has been shown to improve survival and, in some people, quality of life. However, it is unclear whether the improvement that we see in well controlled research trials translates into the real world. This project is using the data we have been collecting at Bethlehem Hospital in Melbourne since 2002 and combining it with the national Australian MND Registry to determine how much difference to survival using a mask and a breathing machine makes in MND and who is most likely to benefit from this treatment.

So far we have analyzed the last two years of data; 150 of the approximately 800 patients in the dataset. We presented these preliminary results at the International MND meeting in Sydney in November 2011 and the international non-invasive ventilation meeting in Barcelona in March 2012. These preliminary results are interesting and not what was expected. Essentially, when we look at all people with MND who have been cared for by the Bethlehem clinic, we are not able to reproduce the statistically significant survival benefit that was seen in the randomized controlled trials. We are able to see some benefit, particularly in those with bulbar disease, but the effect is not as large as predicted. However, these are preliminary results and we need to complete the analysis on the entire patient group and control statistically for all of the other variables that can affect survival before we draw any firm conclusions.

Perhaps the most important result of the work so far is that our findings reinforce the critical importance of registries. People with MND have been very generous with their time and the clinicians working with MND around Australia have collected comprehensive information for many years. This has allowed us to examine this question in a meaningful way.

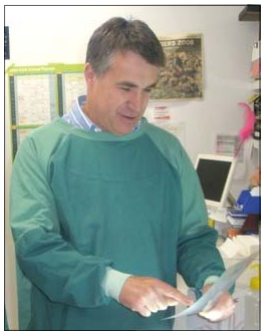
We expect that our results will add to understanding how much non-invasive ventilation assists in MND. With this information we will work with MND organizations, families and clinicians to develop information guides to assist medical and other health professionals to better answer the question "how much benefit will using a machine overnight give to a person like me?"

Peter Stearne Grant for Familial MND Research

Dr Ian Blair

ANZAC Research Institute, NSW

Using next-generation DNA sequencing strategies to identify new MND genes.



Identification of the genes that cause or predispose to MND will lead to the unravelling of the underlying biology leading to effective disease diagnosis and treatment. Our studies indicate that the defective gene is yet to be identified in 40-50% of familial MND cases. The aim of this project is to gain a better understanding of MND through identification of new genes that cause the disease.

We have used state-of-the-art ("next generation") and traditional genetic screening strategies in MND families to locate new MND genes and assess previously implicated genes. In a large collaborative study with leading MND researchers worldwide, mutations in the TAF15 gene were implicated in familial and sporadic MND. TAF15 is closely related in function to TDP-43 and FUS, genes previously shown to play causal roles in MND. This further implicates a common disease mechanism. We also identified a mutation in the UBQLN2 gene in a large MND family, thereby verifying the role of this gene as previously described by others in 2011. Several new genes have been implicated and we are now working in collaboration with other international MND groups to establish the significance and role of these defective genes. Once identified, these new disease genes will lead to development of models, which are tools for investigating the causes of MND and for evaluating proposed treatments.

Deborah Brine MND Research Grant

Dr Pamela McCombe

University of Queensland Centre for Clinical Research

Comprehensive assessment of MND patients as a means to studying progression and identifying disease subtypes.

This project is part of our ongoing effort to find new ways to measure the rate of progression of MND, and then to use these techniques to understand more about the disease process. We have recruited patients from the MND clinic at Royal Brisbane and Women's Hospital. We use three ways to measure disease. First we use neurophysiology studies to measure numbers of nerve cells. By doing this several time in the same patient, we can calculate the rate of loss of nerve cells. We also use advanced MRI techniques to measure the nerve fibres connected to motor neurons in the brain. We are about to use these studies to calculate the rate of loss of these fibres. Finally we measure the levels in the blood of a neurofilaments protein that is released from damaged nerve cells. We have completed extensive studies with our neurophysiology technique and have been able to calculate the half-life of motor nerve cells in patients with MND. We have found that there is a reduction in the nerve fibres connected to motor neurons in the brain in patients with MND and are about to investigate whether the rate of loss of these nerve fibres can be calculated. We have shown that the levels of the protein are elevated in the blood of subjects with MND. We have commenced studies and have found that the rate of loss of nerve cells differs among patients with different clinical features. In the future we will also correlate clinical features with the rate of loss of connections in the brain and the levels of neurofilament protein in the blood.

Charles & Shirley Graham MND Research Grant

Dr Peter Noakes

University of Queensland

The role of the innate immune system during the progression of motor neuron disease: the search for new therapeutic targets.

The immune system is a major component of our body's defense mechanism that protects us from infection. In recent years researchers, including our group, have discovered that selected components of the immune system are also present in the brain and spinal cord of non-infected animals and humans. These include the molecule C5a and its receptors CD88 and C5L2, and Toll-like receptors -2 and -4. C5a acting on CD88 promotes the inflammatory response that results from an infection, and/or from dying cells (such as a motor neuron) in our body. This response produces increased blood flow and movement of cells that act to destroy the infectious agents and remove dead cells. Toll-like receptors are also involved in this process; in that they cause the release of other molecules that help with movement of cells into the site of infection. In the spinal cord, we have shown that C5a's receptor CD88 is present on motor neurons and surrounding glial cells in the spinal cord of normal animals, and that these molecules increase their expression during the course of MND in animal models. We have also shown that blocking CD88 with our drug slows the progression of MND in a rat model of MND. In this project we have shown the same effect in a mouse model of MND. We have demonstrated that CD88 is required for the progression MND in our animal models. Mice that carry MND mutations and lack CD88 have more motor neurons and live longer. We expect to publish this data later this year. We also plan to extend our CD88 blocking drug studies to the new MND models which are in the process of being created. These new models of MND will carry mutations of TDP43, FUS and C9ORF72 genes. To this end we have formed collaborations with researchers in the UK and the USA.

We are examining C5a and CD88 expression levels in humans with MND. So far we have shown that in serum, C5a is increased in MND patients. We are now in the process of looking at human spinal cord tissue, and have confirmed that CD88 is increased in human lumbar spinal cord, and is present on the microglial cells that surround upper motor neurons in the brain. These upper motor neurons are the nerve cells that make direct contact with motor neurons in the spinal cord. They also die in MND.

We have also made good progress in trying to work out how CD88 contributes to the death of motor neurons within the spinal cord. We have managed to show that motor neurons are capable of releasing C5a under conditions of stress, and for C5a to connect with CD88 that is expressed on the motor neurons. This causes the expression of known death molecules within the motor neuron to cause it to die. Blocking CD88 with our drug prevents this stress-induced death. We are now working on the complete mechanism of this death response triggered by CD88. This includes using motor neuron-like cells that have been created to carry known MND gene mutations. These mutant neurons are genetically stressed and will provide a closer model to motor neurons that carry these same mutations within the spinal cord.

Our project has also been examining the expression of C5a's other receptor C5L2. We have shown that C5L2 and CD88 are increased during the middle stages of MND symptoms. Originally we thought that C5L2 was expressed prior to MND symptom onset. However these results confirm the latest findings of C5L2 actions, namely to support CD88 actions. Together this supports our idea that C5a acting on either CD88 and/or C5L2 work to accelerate the progression of MND.

For Toll-like receptors -2 and -4, we have confirmed that these receptors are increased in spinal cords of MND animals, and others have shown this for MND patients. We have demonstrated that these receptors are found on the cells that surround motor neurons (glial cells). Next, we have discovered that a key molecule (HMGB-1) that activates these toll-like receptors is released from spinal cord cells in our MND animals. We have shown that HMGB-1 is released by stressed motor neurons, which then binds to these receptors present on the surrounding glial cells. The receptors in turn act to cause the release of growth factors (e.g. cytokines) from these glial cells. These factors act to promote movement and activation of immune cells and other glial cells to assist the local inflammation response, including the removal of dying neurons.

MND Victoria Research Grant

Dr Moira O'Connor

Curtin University, Western Australia

Children's pilot study: The experiences and psychosocial needs of children who have a parent living with MND.

The aim of our research was to explore the experiences and psychosocial

needs of 11-16 year old children and adolescents with a parent with MND. The main focus of research, in the area of MND, is on the person with MND and his/her carer, and there is a distinct lack of research into the needs and experiences of children and adolescents. We also argue that children are often invisible in clinical settings. Our project asked children and adolescents what factors helped their coping and adjustment, what they needed, and what supports and information would be helpful. We hope our findings will provide a basis for much-needed support programs for children and adolescents who have a parent with MND.

We have conducted two in-depth case studies so far. Despite several recruitment strategies we have had some challenges in recruiting more young people. There are many reasons for this including the great demands and burden faced by people with MND, and their carers and families. However, our interviews revealed rich information that will provide a starting point in this area of social research. One interesting finding is that young people are clear on the positives of their situation as well as the challenges. They want to know how their parents are going and they would like to meet others in similar situations, rather than being 'protected' from the illness.

Future research could focus on professional carers and health professionals to see how they provide support for the children, adolescents and young people in the family. Parents could also be interviewed. We need to build a picture of what supports are needed and look at ways at providing such support. Then we need to trial interventions to see if they improve emotional wellbeing.

Assoc Prof Roger Pamphlett
Stacey MND Laboratory
University of Sydney
Looking for abnormal gene expression in ALS spinal cords using next-generation sequencing.

The cause of the most common form of MND, sporadic MND, remains unknown. Although sporadic MND does not run in families, many researchers think that an abnormal gene is the problem causing this disease. Since the parents of patients with sporadic MND are not affected by the disease, their genes are likely to be normal. We therefore hope to find the abnormal gene in MND patients by comparing their genes with their unaffected parents' genes.

A recent powerful technique (next-generation sequencing) means that we are now able to examine the active parts (the exons) of all the genes. Any newly-arising genetic abnormalities in the MND patients can be detected by this method. We think we therefore have a good chance of finding a genetic cause for sporadic MND.

Truly effective therapy is most likely to arise once the cause of MND is known. Any future gene therapy for MND (which has been very effective in animals models) depends on this genetic cause being found.

Roth Foundation MND Research Grant

Dr Mary-Louise Rogers and Professor Robert Rush
Human Physiology, School of Medicine, Flinders University SA
Targeted down regulation of SOD1G93A in MND mice.

We have developed a gene therapy 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 neuron 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.

Dr Lachlan Thompson
Florey Neuroscience Institutes, University of Melbourne
Development of a stem cell therapy for motor neuron disease.

This project has explored the feasibility of growing new neurons from human embryonic stem cells and transplanting them directly into the brain as a therapeutic strategy for MND. There were some very positive outcomes, with the results showing that the new, stem-cell derived neurons, possess a remarkable capacity to survive and integrate into the host brain circuitry after transplantation. The project characterised the growth properties of the grafts over time and although the grafts integrate well early, it was found there was a need to protect the grafts from immune-rejection at longer time-points. Nonetheless, the early phase after transplantation suggests that the grafts may be able to delay the onset of motor deficits in an animal model of MND. The next phase for this research will be to see if we can achieve more sustained benefits by suppressing the host immune system after transplantation.

Mick Rodger Benalla MND Research Grant

Dr Bradley Turner
Florey Neuroscience Institutes,
University of Melbourne
Are endosomal transport defects a primary cause of MND?

We recently showed that a compartment inside motor neurons called the "endosome" is abnormal in test tube and animal models of MND. The endosome is important for protein

recycling and waste management within nerve cells and its malfunction in MND could explain why nerve cells build-up junk piles of toxic protein. In this funded project, we have discovered that endosome defects are present in people with MND. Importantly, they arise very early in the disease course of MND mice, which places endosome defects early in the disease process. In particular, we have identified that signature molecules for endosomes called "Rabs" are abnormally high in MND which causes build-up of toxic proteins and may explain why motor neurons are struck down in MND. This suggests that targeting Rabs may be possibly helpful in MND. We are therefore currently testing drugs that affect Rab function in MND mice to determine if they delay disease onset or improve survival as a result of these studies.

Dr Robyn Wallace, Queensland Brain Institute
Identifying genes that are regulated by TDP-43 and FUS using high-throughput sequencing.

Genetic mutations associated with MND have been identified in both TDP-43 and FUS genes. Protein tangles that aggregate in affected nerve cells are a hallmark of MND and studies of MND patient cells have demonstrated that both TDP-43 and FUS proteins are principal components of these nerve cell aggregates. TDP-43 and FUS are both involved in gene regulation. However, the gene targets of these two proteins in the nervous system are currently unknown and their role in MND remains unclear. The aim of this project is to identify genes that are regulated by the TDP-43 and FUS proteins.

To date, we have identified TDP-43 gene targets in normal mice and in mice that carry an MND-causing mutation in TDP-43. These studies show that genes related to nerve-muscle communication may be altered in MND. We have also confirmed that one of these genes is mis-regulated in MND patients. These studies will improve our understanding of what causes MND and provide rational targets for the future development of new therapies.

Dr Anthony White, Dept of Pathology, University of Melbourne
Does TDP-43 aggregation cause translation arrest in motor neurons?

In this project we have begun to investigate how a protein central to neuronal cell degeneration in MND accumulates and causes abnormal cell function. The protein (TDP-43) is normally found in the nucleus of neurons where it has a number of roles in RNA and DNA maintenance. In MND it can accumulate in the cytoplasm of neurons and forms aggregates with other proteins. Little is known about the processes that cause this change or how it leads to neuronal cell death. We, and others, have found that TDP-43 can also accumulate in RNA stress granules in the cytoplasm in response to cell insults. This is a normal response for TDP-43. However, like other stress granule proteins, TDP-43 should only accumulate in these granules transiently and return to the nucleus after removal of cell stress. We have found in this project that after entering stress granules TDP-43 does not always return to the nucleus upon removal of stress, even though other stress granule proteins do so. The TDP-43 continues to aggregate in the cytoplasm. This is the first evidence that endogenous TDP-43 can form protein aggregates after accumulation in stress granules. We are now investigating how this causes damage to neurons. An important function of TDP-43 is to stabilise the mRNA for various important proteins. If TDP-43 remains in aggregates, it is unable to perform this function and the mRNA is degraded. This will result in a loss of protein expression. We have found evidence that some key proteins involved in survival of neurons have reduced expression when TDP-43 becomes aggregated. We are examining if this is because TDP-43 cannot stabilise the mRNA for these proteins. In addition, we are investigating means of inhibiting the early stages of TDP-43 aggregation. We have reported recently that the accumulation of TDP-43 in stress granules is controlled by cell kinases (signalling proteins) and that by inhibiting one or more of these, we can block TDP-43 from accumulating. We have now found that a small copper-based compound is also able to prevent this accumulation by modulating cell kinase activity. These findings demonstrate a growing understanding of the early events in TDP-43 accumulation and aggregation and potential means of blocking this process. This could lead to development of treatments aimed at blocking abnormal changes to TDP-43 and slowing motor neuron cell death. We are continuing to obtain a better understanding of what cellular factors control TDP-43 aggregation, how this leads to cell death and the best targets for intervening in this process.

MND Research Tissue Bank of Victoria (*mndRTBv)*

Professor Catriona McLean
Mental Health Research Institute, Victoria

The *mndRTBv* collects, processes and stores post-mortem brains and spinal cords and other related samples donated by people with MND, which can be accessed by Australian and international researchers to further investigate MND a brain disease that only affects humans. As well as facilitating scientific research into MND, the *mndRTBv* provides a vital diagnostic service to confirm neuropathology diagnosis of MND. Over the past 12 months the *mndRTBv* has collected, processed and stored 5 new MND brain and spinal cord donations including cerebrospinal fluid (CSF), matched with clinical data. The *mndRTBv* now has a total of 51 MND cases which makes up 61% of the MND cases that are available for research within Australia. Tissues have been provided to 2 new or continuing research projects. Since the inception of the *mndRTBv* in 2003, tissues have been provided to 19 new or continuing Australian research projects which equates to 587 diseased and control tissue samples. Tissues have been distributed to research groups at The University of Melbourne, Florey Neuroscience Institute, Latrobe University, University of Wollongong and The University of Sydney. This work to date has lead to 16 Australian and International publications and conference presentations. The *mndRTBv* hopes that by providing researchers with access to high quality, well-characterised (of an international standard) brain and spinal cord tissue and related sample, we will continue to facilitate research opportunities into MND. It is hoped that this research has the potential to maximise important discoveries, which may lead to improvements in diagnosis, development of early diagnostic tests, therapeutic interventions and/or development of preventative strategies.

MND Research Institute of Australia Office Bearers and Members 2012

The MND Research Institute of Australia is the research arm of MND Australia.
MND Australia is the principal member of the MND Research Institute of Australia.
The operations of both organisations are the responsibility of MND Australia.

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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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New members for Research Committee

Dr Ian Blair and Dr Steve Vucic are welcomed as new members of the Research Committee. Their expertise will contribute to decisions about allocation of funds for 2013 research grants at the next grants allocation meeting to be held on 12 November 2012.

Dr Ian Blair is a principal research scientist at the ANZAC Research Institute (NSW Health and the University of Sydney) where he heads a research group investigating the molecular basis of MND. 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 focussed 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 the Garvan Institute of Medical Research and the University of Washington School of Medicine.

Dr Steve Vucic is an Associate Professor of Neurology at the University of Sydney and Senior Staff specialist in the Department of 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.

Donations

Research funded by the MND Research Institute of Australia is dependent on donations.
To contribute to this vital work, please send your gift to:

MND Research Institute of Australia
PO Box 990, Gladesville NSW 1675

Donations can be made by cheque (payable to MND Research Institute of Australia) or credit card (Visa or MasterCard) or online at www.mndresearch.asn.au.
All donations of $2 and over are tax deductible.

Bequests

Your Will can provide an important way of making a gift that can have lasting influence on MND research and give hope for the future.

If you would like to consider the MND Research Institute of Australia in your Will by providing a Bequest from your Estate, please contact your solicitor.

For more details,
phone Janet Nash, MNDRIA Executive Officer on
02 8877 0990 or email research@mndaust.asn.au.

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