

December 2009

Motor Neurone Disease Research Institute of Australia

The Motor Neurone Disease Research Institute of Australia (initially the ALS Research Foundation) was established as a national organisation 25 years ago in 1984 by Dr Dawn Thew, President of the ALS Society of Australia (later the MND Association of NSW). Dawn was the inaugural Chairperson of the Foundation and in the 1991 ALS-MND News, she wrote:

I was urged to raise a million dollars as soon as possible, as other diseases were more attractive for research since funds seemed to be more forthcoming when a disease was well known in the community.

... We haven't had the first million yet but maybe there is someone out there who can help notch it up for us. Here's hoping it will be soon!

Just before Dawn's death in September this year, she learned that this vision had at last been achieved. Continued growth of funds in 2009 through individual donations, MND Association contributions and bequests has given MNDRIA the means to reach its goal of offering \$1,000,000 for allocation to research projects at the November 2009 grants allocation meeting.

The first grant-in-aid was funded in 1987. By 1991, it was possible to fund four projects for a total \$86,000. The Institute has come a long way since then with Dawn passing on her role to members of the Research Committee. Subsequently chaired by Professors David Burke, Ed Byrne and Perry Bartlett, MNDRIA was successfully run largely by volunteers until 2005 when a part-time Executive Officer was employed. Voluntary assistance in the early years was provided by Dymna Flanagan, Valda Retallic, Graham Lang, David Lamperd and many others. Funds donated for MND research were allocated annually to MND research projects after careful review of all grant applications by the MNDRIA Research Committee. Many dedicated experts have served on this

committee over the past 25 years – all have been approved by the NHMRC as suitable for assessing research proposals.

Professor Dominic Rowe was elected as Chairman of MNDRIA in November 2004. Professor Rowe and his Executive Committee have led the Institute through a period of growth and increased recognition from the research community. The MNDRIA Executive Committee members will retire from office on completion of the amalgamation of MNDRIA with MND Australia as their role will be taken by the Board of MND Australia, but special thanks must go to all of them for the contribution they have made. Honorary Secretary, Paula Trigg, has been an unflagging supporter whose passion and hard work have helped to drive the Institute forward. David Lamperd, as Honorary Treasurer, has helped to nurture funds and introduce appropriate accounting practices. Professor John Pollard has been Public Officer for many years and his wisdom and research experience are greatly valued. Dr Susan Mathers has introduced clinical researchers and Peter Whitehouse has provided a voice for MND Associations. This has been a fantastic team and they have achieved much – not only in growth of research but also in guiding MNDRIA towards amalgamation with MND Australia.

The role of MNDRIA will not change after the amalgamation has been completed, but central management and administration by MND Australia will allow the resources of MNDRIA to be concentrated on research. The Research Committee, who represent all Australian States and cover diverse fields of research, will continue in their role of assessing grant proposals and selecting grant recipients.

A united voice for MND in Australia is the way of the future and must provide greater strength for the target distribution of \$1,000,000 for MND research every year.

Janet Nash

MNDRIA Annual Research Meeting at Gladesville NSW, 4 November 2009

(L to R): Dr Marina Kennerson (NSW), Dr Julie Atkin (Vic), Dr Ian Blair (NSW), Dr Anna King (Tas), Dr Gilles Guillemin (NSW), Paula Trigg (Hon Secretary), Dr Tracey Dickson (Tas), Dr Justin Yerbury (NSW), Dr Fiona Fisher (Vic), Dr James Burrell (NSW), Prof Dominic Rowe (Chairman), Dr Steve Vucic (NSW) and Janet Nash.



Chairman's report

The end of 2009 sees many changes for the Motor Neurone Disease Research Institute of Australia, and my last as the Chairman. At last year's annual general meeting, a committee was formed with members of Motor Neurone Disease Australia and the Motor Neurone Disease Research Institute of Australia, to work towards amalgamation of these two entities. The resolution passed at last year's annual general meeting was based on discussions that were held over the previous two years. I am very grateful to the members of the amalgamation committee from both MND Australia and MNDRIA. Both constitutions required changing so that the amalgamation would go forward. MNDRIA will be subsumed into the organisational structure of MNDA but remains an entity for various reasons. This amalgamation has several advantages, the most important of which is the provision of a unified federal voice for research, patient care and community awareness of motor neurone disease.

Over the last five years the Motor Neurone Disease Research Institute of Australia has been able to provide substantial funding for Australian research into motor neurone disease. This year the funding available is in excess of \$1 million for

grants in aid, doctoral and post doctoral scholarships.

I would like to thank the executive of the MNDRIA as well as the audit and finance committee and the research committee for their efforts through this year. In particular I would like to highlight the efforts of Janet Nash and Paula Trigg. Their efforts, together with everyone else involved in the Motor Neurone Disease Research Institute of Australia have ensured that we continue to fund original research and researchers working in motor neurone disease in Australia. I would also like to thank the individual Motor Neurone Disease Associations of each state who have supported the MNDRIA. Having a single federal body to administer research saves duplication of effort and also provides a unified front to understand the cause and ultimately provide the cure for motor neurone disease.

At the end of today the Motor Neurone Disease Research Institute as its own entity does not exist. It is now up to Motor Neurone Disease Australia to ensure the continued growth of research in MND in Australia. It is imperative to understand that without research an end to this disease is impossible.

*Dominic B. Rowe
Chairman*

Finance Report

The first nine months of the 2009 financial year mirrored that of the challenging 2008 period for individuals, businesses and not for profit organisations. However a well managed Australian economy (over a number of years) together with the current monetary and fiscal stimulus, a healthy banking industry and the added benefit of strong Asian trading partners has influenced a sound domestic recovery. This is at the same time as the world's biggest economies are only just spluttering back to life.

The Audited Financials to 30th June 2009 reflect the prudent but also proactive management of the MND Research Institute's finances by its Audit and Financial Committee. The trading and surplus funds remained secure within the Commonwealth Bank of Australia under the Government Guarantee and the efforts of Janet Nash to continue a successful fundraising strategy and, importantly, to maintain strong relationships with the Institute's supporters have influenced another strong financial performance. The ongoing support from the State Associations (Vic, NSW, Qld, WA and Tasmania) is very much appreciated as it represents nearly a third of the Institutes income.

The following points and chart will assist to provide a summary of the 2009 financial year.

- Total income of \$808,478 comprised \$45,931 of bequests, donations of \$424,334 and \$261,807 from the State MND Associations. Term deposits with high interest helped to produce interest income of \$76,406.

- Total expenditure of \$597,060 comprised primarily of \$554,274 of medical research grants. The remaining expenditure (administration and fundraising) represent 5.3% of total income.
- The resultant net profit of \$211,418 is a 17% improvement on the 2008 financial year.

The financial support of the Institute for the 2009 financial year together with the continuing hard work of Janet Nash has increased overall cash holdings within the CBA accounts to \$1,889,658 as at 30th June 2009 – a terrific result.

Subsequently, at the Audit and Finance Committee meeting of 23rd September 2009 it was agreed to recommend that up to \$1,000,000 be allocated for the 2009 grant applications – whilst maintaining a corpus of \$500,000 to ensure the ongoing financial viability of this important organisation.

The improving domestic and global economy outlook (which will include interest rate rises), together with the proposed amalgamation with MNDA should assist the Institute to maintain its strong financial position during the 2010 period so as to continue the vital support of Australian research into the cause and cure of motor neurone disease.

*David Lamperd
Treasurer*

Note: If you would like to receive a full copy of the audited Financial Statements, please contact Janet Nash at the MNDRIA.

Executive Report

The year in review

MNDRIA was successful in obtaining listing on the Australian Competitive Grants Register (ACGR) – both for grants-in-aid and post doctoral fellowships. This provides a substantial rebate of costs to University Departments receiving funding through MNDRIA, thereby making MNDRIA grants more valuable to them.

A quarterly International MND Research Report has been introduced by MNDRIA in 2009. This has been funded by MND Victoria and the report has been written by Dr Justin Yerbury from the University of Wollongong. Dr Yerbury is the new Bill Gole Post Doctoral MND Research Fellow in 2009. The report has been sent to all MND Associations for distribution to their members. *Advance*, the bi-annual newsletter of MNDRIA, now has a circulation of 4,750 copies which are distributed nationally and requested by State and National libraries.

Research Grants

\$554,274 was awarded for new grants commencing in 2009. In the calendar year 2009 a total of \$509,018 was provided for eight grants in aid (\$238,890), three concurrent Bill Gole Post Doctoral Fellowships (\$217,500), one PhD Scholarship (\$32,628), the Australian MND Registry (\$10,000) and the MND Research Tissue Bank (\$10,000).

Donations and bequests

Major donors continue their generous support for named grants: The Bill Gole Post Doctoral MND Research Fellowship (anonymous), the Peter Stearne Grant for Familial MND Research (the Stearne family), the Charles & Shirley Graham Grant for MND Research (MND Queensland), the Roth Charitable Foundation Grant and four grants funded by MND Victoria: the MND Victoria Grant, the Zo-eè Grant, the Mick Rodger Benalla Grant and the Mick Rodger Grant.

Contributions from State MND Associations accounted for 32% of all funds received, but MNDRIA could not survive without the many loyal supporters who contribute regularly each year. As the work of MNDRIA is becoming more widely known, unsolicited donations are becoming more frequent, often in memory of a loved one. A growing number of people have held fundraising events to raise funds for research. In 2009, internet fundraising

has been enhanced by some supporters setting up their own webpage through GoFundraise, as well as donations received through the MNDRIA website at www.mndresearch.asn.au.

Bequests are received as an unexpected windfall that provides a welcome boost when assessing the funds available to allocate to the next year's grants. Advice was received early in 2009 that MNDRIA was the major beneficiary of the Estate of the late Enid Bush from Western Australia. Receipt of this bequest will allow more money than ever before to be offered for new grants awarded at the November 2009 grants allocation meeting.

Volunteers

Willing help has been gratefully received from regular volunteers, particularly Maureen Burmeister (accounts), Brett Young (legal advice), Alan Hauserman and Libby Gole.

Meetings

The annual MNDRIA Research Meeting in November 2009 continues to provide the opportunity for researchers funded by MNDRIA to present the outcome of their work to their peers and to MNDRIA members. The Research Meeting was held in Sydney in 2007 and Melbourne in 2008.

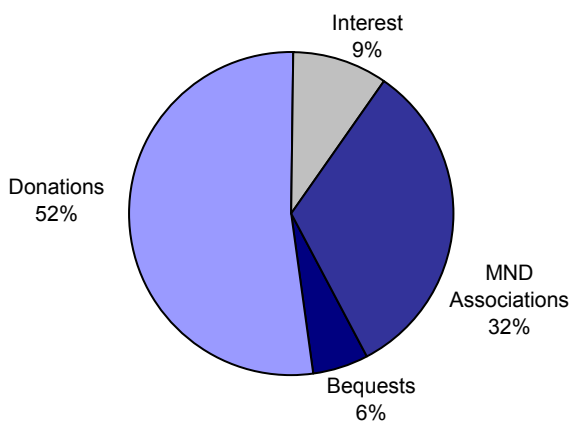
The Executive Committee met in April and September and also by email meetings as required. The Audit & Finance Sub Committee met in September to approve and recommend the accounts and budget for the year. Additional meetings throughout the year have been held by a joint MNDRIA / MND Australia Amalgamation Committee (Dominic Rowe, Paula Trigg, Graham Lang for MNDRIA and Ralph Warren, Bob Howe and David Ali for MND Australia). These committee members worked together to achieve the best possible structure for amalgamation of the two organisations. Legal assistance was provided by Richard Snowden and Cory Hillier from Mallesons Stephen Jaques and we are grateful for much of their time which was provided pro bono.

The final meetings of the Audit & Finance and Executive Committees recommended that up to \$1,000,000 be made available for allocation to grants commencing in 2010.

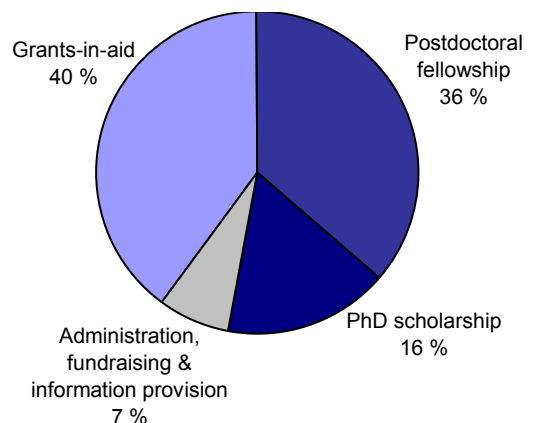
For the first time, this goal has been achieved.

Janet Nash
Executive Officer

Income



Expenditure



MND Research Institute of Australia grants for 2010

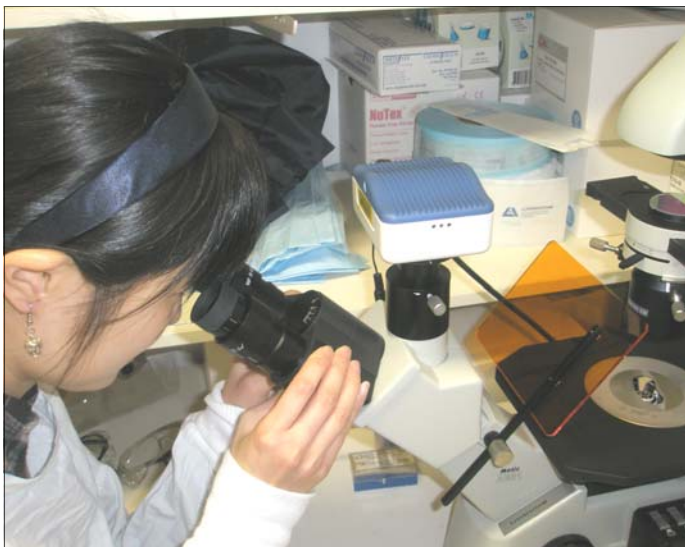
A total of **\$675,000** has been awarded for new grants commencing in 2010. The award of a new three-year postdoctoral fellowship to Dr Shu Yang brings a total of four fellowships to be funded in 2010. A record fourteen grants-in-aid have been awarded to projects around Australia. Together with the ongoing projects from previous years, including three continuing fellowships, one continuing PhD scholarship, and special funding for the MND Research Tissue Bank of Victoria, **\$773,000** will be spent on grants in the 2010 calendar year. The MND Research Institute is now able to make a significant impact on MND research.

MND research fellowships and scholarships

While grants-in-aid support MND *projects*, MND research fellowships and scholarships support the *person* and aim to encourage young scientists to develop a specific interest in MND research.

Bill Gole MND Postdoctoral Fellowship (2010 - 2012)

Dr Shu Yang ANZAC Research Institute, NSW.



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

Proteins that play fundamental roles in MND pathogenesis have recently been identified, providing new hope for understanding the cause of MND and development of therapeutic and diagnostic tools. The 43 kDa TAR DNA binding protein (TDP-43) was recently identified as a signature component of the abnormal protein aggregates found in the brain and spinal cord of most sporadic and familial MND patients. Our group identified several mutant forms of TDP-43 that appear to directly trigger neurodegeneration leading to MND. We hypothesise that identifying the mechanisms through which rare TDP-43 mutations cause MND will be more widely relevant to understanding the cause of familial and sporadic MND. We will establish novel TDP-43-expressing MND cell models and a transgenic mouse model to study the function of mutant TDP-43 protein. The significance of the proposed project includes a greater understanding of how mutant TDP-43 leads to protein aggregation and motor neuron degeneration in MND, as well as knowledge of the functions of other signature proteins in MND, such as FUS, that may provide new diagnostic and therapeutic targets. The establishment of the TDP-43 transgenic mouse model may provide a better model to understand sporadic MND pathogenesis than the existing SOD1 transgenic mouse models. This model may also act as a useful platform for MND therapeutic development.

Continuing Bill Gole MND Postdoctoral Fellowships

Dr Justin Yerbury (2009-2011) University of Wollongong.

Probing molecular mechanisms of microglial and astrocyte activation in ALS.

This project combines unique expertise to perform truly pioneering studies to determine how a genetic defect in a protein, superoxide dismutase, affects immune processes implicated in motor neuron disease. Novel approaches will be used to study relevant molecular interactions, both in the test tube and in animal models. The outcomes will provide a new understanding of these processes and may contribute towards the ultimate development of new therapies.

Dr Anna King (2008-2010) University of Tasmania.

Investigating the causes and consequence of axonal pathology in ALS.

I have recently developed a cell culture model which mimics the degenerative changes in motor nerve cells that underlie the onset of amyotrophic lateral sclerosis, the major cause of human MND. I will use this model to investigate the factors and mechanisms that cause motor neurons to degenerate, an approach which may indicate new therapeutic opportunities for an otherwise incurable condition.

Dr Jennica Winhammar(2008-2010)

Prince of Wales Medical Research Institute, NSW.

Clinical trial to assess the neuroprotective properties of a sodium channel blocking agent in motor neurone disease.

This project will provide clinical trial information related to the potential neuroprotective properties of a sodium channel blocking agent in patients with motor neurone disease. Specifically, it will establish whether the sodium channel blocking agent can slow disease progression.

MNDRIA / NHMRC PhD Scholarship (2009 - 2011)

Dr James Burrell Prince of Wales Medical Research Institute.

Cognition and behaviour in motor neuron disease.

Motor neuron disease (MND) and fronto-temporal dementia (FTD) are fatal neurodegenerative disorders of unknown cause. There are poorly understood clinical and pathological overlaps between MND and FTD which this research aims to clarify. The impact of cognitive deficits on carer burden will also be investigated. It is hoped that this research may contribute to the development of a pathological model that explains the development of MND and FTD.

Grants-in-aid awarded for MND research in Australia in 2010

Grants-in-aid are intended as start up funding for new projects that can 'grow' to produce data that can attract more significant funding from granting bodies such as the NH & MRC. Fourteen new projects have been awarded grants-in-aid for 2010.



Grant-in-aid

Dr Julie Atkin Brain Injury & Repair Group, Howard Florey Institute, University of Melbourne.

Is Protein Disulphide Isomerase (PDI) a novel biomarker for motor neuron disease?

There is currently no early diagnostic test for MND and usually lengthy and detailed clinical investigations are necessary. The evidence we obtained in earlier studies has led us to believe that a protein called PDI may be a new and effective biomarker of MND. In this study we will examine a large group of MND patients in comparison to unaffected individuals, to determine whether PDI could be used to reliably measure disease outcome and progression, and to predict disease in patients with inherited forms of MND. If PDI can reliably diagnose MND, this would facilitate future studies to establish a diagnostic kit for MND or to design clinical trials of new drugs.



Peter Stearne Grant for Familial MND

Dr Ian Blair

ANZAC Research Institute, NSW.

Characterisation and investigation of a new transgenic mouse model expressing mutant TDP-43.

The only proven causes of MND are mutations in genes that lead to death of motor neurons. Using these mutations, mice have previously been developed that mimic features of MND. These mouse models of MND have been a principal tool for testing proposed disease treatments. Unfortunately the promise of treatments shown in existing mouse models have largely proven unsuccessful in human trials. We recently described mutations in a new MND gene, TDP-43. We have developed a new mouse that carries one of these TDP-43 mutations. We now aim to monitor and test this mouse to establish whether it develops similar symptoms to MND. If so, this new mouse model will be available for investigating the biology of the disease and for evaluating treatments.



Mick Rodger MND Research Grant

A/Prof Meng Inn Chuah

University of Tasmania.

Effect of metallothionein and exercise on progression of MND.

Amyotrophic lateral sclerosis (ALS) is the major cause of motor neurone diseases (MND), which are progressive and ultimately fatal diseases caused by the degeneration of motor neurons in

the brain and spinal cord of patients. Unfortunately there are no effective clinical treatments available that can protect motor neurones from such death, with the only drug currently available,

riluzole (rilutek) conferring only a very modest alleviation in symptoms, and is only effective over a short period of several months. Metallothionein (MT) proteins are known to be powerfully neuroprotective in several experimental models of neuronal injury and disease including ALS. We now have preliminary data suggesting that administration of MT might be effective in prolonging survival in an animal model of ALS. This project will explore further this therapeutic potential by assessing the possible benefits of combining MT with an exercise regimen to improve the functional and survival outcome of a mouse model of ALS.

Grant-in-aid

Dr Peter Crouch

Department of Pathology, University of Melbourne.

Investigating cellular hypoxia as a causative factor in MND and as a potential therapeutic target.

The fundamental biological causes of decreased motor neurone function in MND remain unknown. Genetic clues are evident in familial forms of the disease, but familial MND only accounts for a small minority of all cases and these genetic clues therefore cannot explain the majority of cases. Identifying the causes of decreased motor neurone function is an essential step in developing new and more effective therapeutics to treat MND. This project focuses on demonstrating the mechanism of action for a novel therapeutic compound shown to be effective in MND model mice. This work presents a unique opportunity to simultaneously progress the development of this compound towards clinical trials, and to identify what may be an important biological contributor to all forms of MND.

Our work to date has shown that the copper-based compound Cull(at5m) significantly delays the onset of MND-like symptoms in a mouse model of the disease. Most importantly, Cull(at5m) delays the onset of paralysis in these mice. Parallel work has started to reveal important information on how Cull(at5m) may mediate its therapeutic effects. Essentially, we have shown that Cull(at5m) is a relatively inert compound, but when exposed to cells grown with inadequate oxygen supply, the Cull(at5m) becomes activated. When activated, Cull(at5m) induces cellular responses that have the potential to improve neuronal function. This work is highly significant when considered in the context of current MND research, as emerging evidence indicates that impaired cellular responses to inadequate oxygen supply can induce development of MND.

The research described in this application will provide information on the cellular conditions that induce activation of Cull(at5m) and therefore generate its therapeutic activity in MND model mice. In addition, it will provide new information on cellular responses to oxygen supply as a potential biological cause of MND.





Zo-è MND Research Grant

Dr Fiona Fisher

Calvary Health Care Bethlehem, VIC.
Emotion recognition and social communication in MND: impact on behaviour and carer burden.

In recent years, there has been a surge of research into the non-motor symptoms of MND, with the impact of MND on thinking skills, behaviour and

emotional functioning being more widely accepted. Research, while limited at this stage, has shown that MND can damage parts of the brain that are essential for normal understanding of emotions, and in particular in understanding the non-verbal aspects of communication that indicate the emotional states of others. What this means is that some people with MND may have trouble with the finer, more subtle details of social communication, social cognition and the ability behave appropriately in their social interactions with other people. These emotional processing changes have the potential to impact upon the relationship between persons with MND and their carers.

The proposed research project aims to investigate previously identified social-emotional changes and investigate the relationship of such changes with alterations in behaviour. In addition, the relationship between social-emotions difficulties and carer burden will be explored. This will provide new information about the frequency and impact of emotional processing difficulties in people with MND. It will also increase understanding of the relationship of such difficulties to social communication, behavioural changes and carer burden.



Grant-in-aid

Dr Robert Henderson

Department of Neurology,
Royal Brisbane & Women's Hospital.
Novel markers of motor neurone disease- quantitative upper and lower motor neurone markers.

MND is a relentlessly progressive disorder of upper and lower motor neurones. Since the first description of MND in the 19th century, only one

drug (riluzole) with modest disease-modifying potency has been developed. The diagnosis of this disorder is clinical and there is a significant delay between the symptom onset and diagnosis, possibly beyond the therapeutic window. Clinical signs and functional scales are inadequate for detection or quantification of the loss of upper and lower motor neurones. That is the reason why patient survival has been the measure of therapeutic response in many trials. However, the heterogeneity in the rate of progression and survival in MND patients is challenging the outcome of clinical trials.

Our research project focuses on novel markers that are sensitive to the progression of disease, which might enhance the diagnostic algorithm and might be useful to monitor the effectiveness of new therapies. We perform neuroimaging and neurophysiology studies to identify objective upper and lower neurone markers. In combination, these quantitative markers

might be sensitive to early therapeutic effects and might also resolve complexities of phenotypic heterogeneity in clinical trials. Hence, we evaluate longitudinally patients with different clinical phenotypes of MND (e.g. UMN or LMN predominant, pure LMN type) to quantify the rate of progression and to understand if the degeneration of the upper and lower segments is simultaneous, or if independent that neither is the cause or the consequence of the other.

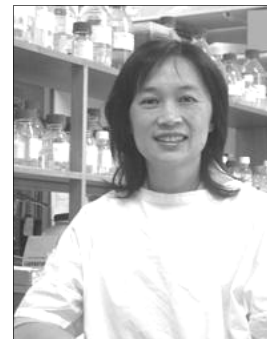
Grant-in-aid

Dr Qiao-Xin Li Dept of Pathology,
University of Melbourne.

Investigating the in vivo targets affected by a novel therapeutic agent for motor neuron disease.

Motor Neuron Disease (MND) affects the motor system required to maintain muscle control. Inevitably the disease progresses to paralysis and premature death, within 3-5 years

after diagnosis. There are limited therapeutic options available for treating the disease. Our current work has identified a compound, known as Cull(atSm), that substantially delays the development of disease symptoms in a mouse model of MND. This proposal is to investigate the optimal treatment scheme for the Cull(atSm) before advancing to preclinical trials, as well as the identification of in vivo targets of Cull(atSm). Ultimately this study will help expedite the development of effective MND therapeutic strategies.



Grant-in-aid

Dr Hakan Muyderman

Medical Biochemistry & Human Physiology, Flinders University, SA.
The role of TDP-43 in astrocytes in motor neuron disease.

The presence of cellular inclusion bodies links a large spectrum of neurological diseases together, including MND. Recently, the TAR-DNA-binding protein TDP-43 was identified as a primary component of these inclusions and mutations in the gene encoding for this protein have been causally linked to familiar forms of MND. However TDP-43 positive inclusions are not only present in motor neurons but also in surrounding glial cells, predominately in astrocytes. Although there is no loss of these cells in MND, affected astrocytes have pronounced changes in expression of genes regulating essential cellular functions. In addition, in some models of MND, sick astrocytes kill healthy motor neurons when the two cell types are grown in culture. Based on these and similar data it has been suggested that motor neuron cell death could partly result from deficiencies in the interaction between motor neurons and astrocytes. However the role of TDP-43 in the interplay between these two cell types is not known. In this context, results recently obtained in our laboratory demonstrate that astrocytes expressing TDP-43 mutations also suffer from changes in normal cell function. Moreover, several of these changes have the potential to severely affect function and survival of motor neurons. Based on



these results, we hypothesise that astrocytes expressing human TDP-43 mutations will impair normal motor neuron function and survival. We believe that a successful identification of astrocytic TDP-43 protein as a component in the pathology of motor neuron disease will present new targets for therapeutic interventions where none exists and will aid in understanding a range of related neurodegenerative diseases.



Grant-in-aid
A/Prof Roger Pamphlett
 Stacey MND Laboratory,
 University of Sydney.
Looking for abnormal gene expression in ALS spinal cords using next-generation sequencing.
 Most researchers now believe that genetic abnormalities underlie sporadic ALS (SALS). Increasing evidence suggests RNA metabolism

may be abnormal in ALS. A powerful way to uncover genetic abnormalities underlying a disease is to extract RNA from the tissue most affected by the disease, and see if this differs from normal tissue. RNA can be abnormal in being (1) under-expressed, (2) over-expressed, or (3) of an abnormal type (e.g., a product with a "misspelling" or an unusual composition of exons). Until now, technological limitations have restricted the use of measuring RNA gene expression to a relatively small number of genes. The latest next-generation sequencing methods can now examine all the RNA transcripts from the entire human genome. We will use Illumina next-generation high-throughput sequencing to examine the complete RNA expression within SALS spinal cords. This study will give us the most complete picture to date of gene behaviour in SALS. These findings will have a direct bearing on any future gene therapy in SALS.



MND Victoria Research Grant
Dr Veena Raykar Rehabilitation,
 St Joseph's Hospital, NSW.
The value of mild-moderate intensity resistance training and aerobic exercise program in patients with early stage MND.
 Current practice in most MND Clinics in NSW is to advise that mild-moderate intensity exercises may be beneficial in the early stages of MND but strenuous exercises to the point of

exhaustion should be avoided. This study is a randomized controlled trial of a defined enhanced exercise program. Sixty consecutive participants recently diagnosed with MND, meeting the inclusion criteria, will be randomized to a standard domiciliary stretching exercise program or an enhanced program of mild-moderate intensity resistance training and aerobic exercise, for six months. Baseline physical and quality of life measures will be recorded and patients will be assessed again at three months and six months from entry to the trial. Outcomes of the trial will be analysed and reported descriptively and in terms of contributory factors for the outcomes.

Grant-in-aid
Dr Mary-Louise Rogers and Prof Robert Rush

Dept of Human Physiology,
 Flinders University SA.
A bio-marker for motor neurone disease.



Diagnosis of motor neurone disease is usually a long, drawn out process that creates anxiety for patients and their families. We are working to find a bio-molecule in urine that can be used to easily diagnose motor neurone disease. This 'biomarker' of the disease will be valuable as a way of objectively measuring progression of the disease and also for determining whether new drugs have value in the treatment of this devastating illness.

Grant-in-aid
Dr Bradley Turner

Florey Neuroscience Institutes,
 University of Melbourne.
A role for survival motor neuron protein in MND?

Understanding the earliest and central pathological events in MND is essential to developing effective treatments. We recently showed that survival motor neuron (SMN) protein levels are lower in laboratory models of MND. SMN deficiency occurs very early before motor neuron loss and symptoms in MND model mice, suggesting that it may be an important mechanism for disease. We now wish to determine whether MND patients are deficient in SMN and whether this correlates with age of diagnosis and disease severity. These studies will indicate whether SMN replacement may be considered useful for MND therapy.



Charles & Shirley Graham MND Research Grant
Dr Robyn Wallace

Queensland Brain Institute.
Identifying genes that are affected by MND causing TDP-43 mutations.
 Protein tangles that aggregate in affected nerve cells are a pathological hallmark of MND. Recent studies have demonstrated that TAR DNA-binding protein (TDP-43) is a principal component of these nerve cell aggregates. This was a major breakthrough in the understanding of MND. However, the function of TDP-43 in the nervous system is currently unknown and its role in the pathogenesis of MND remains unclear. Genetic mutations associated with both familial and sporadic MND have recently been identified in TDP-43. These mutations offer a unique opportunity to determine how abnormal TDP-43 leads to loss of motor neurons in MND patients. The aim of this project is to investigate how these mutations affect the normal function of TDP-43.



Specifically, we will identify genes that are regulated by TDP-43 and determine whether these genes are altered in MND patients with TDP-43 mutations. These studies will improve our understanding of what causes MND and provide rational targets for new therapies.



Mick Rodger Benalla
MND Research Grant

Dr Anthony White Dept of Pathology,
University of Melbourne.

*Investigating the role of biometals in
abnormal metabolism of TDP-43.*

Despite extensive research into the underlying causes of motor neuron cell death, the processes are still poorly understood. Recent discoveries have identified a protein thought to have a key role in the pathways leading to motor neuron degeneration. This protein, TDP-43, had been shown to undergo fragmentation into smaller pieces (called C-terminal fragments, CTFs), followed by aggregation into clumps and are also modified by phosphorylation and ubiquitination. This process is believed to be associated with motor neuron degeneration. However, little is known of the key early processes that lead to TDP-43 fragmentation and aggregation or how this results in motor neuron cell death. We have developed a cell culture model based on use of a motor neuron cell line to investigate factors that influence disease-associated changes to TDP-43. We have so far found that zinc (an important biometal in the brain and neurodegeneration) can induce specific TDP-43 aggregation. We are now further investigating this novel finding and using a unique protein array-based approach to map molecular pathways of TDP-43-mediated motor neuron cell death. The outcomes of this project will provide a significant advance in our understanding of TDP-43 in motor neuron disease and may lead to development of novel treatment approaches for patients with the disease.

MNDRIA Research Meeting at Gladesville NSW on 4 November 2009

Researchers who had received funding from MNDRIA during 2009 were invited to present the findings of their research.

This meeting provides an excellent opportunity for interaction amongst researchers from other laboratories.

Presentations were given by Dr Ian Blair (NSW), Dr Marina Kennerson (NSW), Dr Tracey Dickson (Tas), Dr Julie Atkin (Vic), Dr Fiona Fisher (Vic), Dr James Burrell (NSW) and Dr Steve Vucic (NSW).

Donations

Research funded by the MND Research Institute of Australia is dependent on donations. If you would like 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).

All donations of \$2 and over are tax deductible.

Office Bearers and Members of the MND Research Institute of Australia in 2009

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