

June 2011

The Motor Neurone Disease Research Institute of Australia (MNDRIA) is working to advance research that will contribute to an understanding of the causes and lead to effective treatments and a cure for MND.

The urgency to find the answers for MND has not diminished as more people die each year, usually after only 2 to 3 years from the time they are diagnosed with this incurable disease.

Research is the only way to make a difference. MNDRIA is now making a significant contribution to research in Australia. This is reflected by the quality of grant applications received and the projects that are funded.

Continuing support is provided for established researchers while encouragement for young researchers is generating a new generation of dedicated people who are determined to change the future.

MNDRIA is spending over \$1,000,000 in 2011. This level of funding is the threshold for listing on the Australian Competitive Grants Register so MNDRIA grants continue to attract additional funds for participating universities. The seed funding provided by MNDRIA gives researchers the start they need to get the data required for applications for larger project grants from other sources.

Results of projects funded by MNDRIA in 2010 are reported in this newsletter. Reports from those attending the International ALS/MND Symposium in the USA last December reflect the enormous value of meeting with other researchers. There is much to read as more projects than ever before were funded last year.

The reports contain a common theme of optimism as each research team strives for the breakthrough we all hope for.



Dr Justin Yerbury and members of his growing team at the University of Wollongong

The Snowball Effect

Every dollar donated to MNDRIA is spent on research - but this is just the beginning. The seed funding is sown and can rapidly expand to produce a wealth of investment from other sources.

Dr Justin Yerbury [1] is determined to make a difference in MND research. Justin missed out on his first application for a Bill Gole Postdoctoral Fellowship for MND Research in 2007 but a travel grant to attend the 2008 International ALS/MND Symposium in the UK was provided by MNDRIA to nurture his aim to succeed in MND research.

He obtained an Australian Research Council fellowship for 2008 which allowed him to investigate molecular chaperones and protein aggregates associated with neurodegenerative disease at Cambridge. Justin's next application for a Bill Gole MND Fellowship was successful. The fellowship provides salary for 3 years (2009-2011) for his project

Probing molecular mechanisms of microglial and astrocyte activation in ALS. This is augmented by laboratory space and consumables for his project which are provided by the Illawarra Health and Medical Research Institute (IHMRI) at the University of Wollongong (UoW), as well as additional seed funding of \$12,000 from UoW in 2010.

Working with other researchers, Justin has attracted funds from the Illawarra Retirement Trust Research Foundation (\$60,000, 2010-11: *Molecular chaperones as agents for the ageing process using MND as a model*) and the IHMRI Dementia Grant (\$12,000 in 2011: *Pathological mechanisms of TDP-43 in FTD and MND*).

The big reward came with a National Health and Medical Research Council project grant of \$390,812 for Justin and Dr Leila Luheshi (*Investigating the Propagation of Protein Aggregation in ALS*) commencing this year.

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International Symposium on ALS/MND

The International Symposium on ALS/MND is an annual event which brings together leading international researchers and Health and Social Care Professionals to present and debate key innovations in their respective fields.

The Symposium is organised by the MND Association UK in co-operation with the International Alliance of ALS/MND Associations. MND Australia in partnership with MND NSW will be the hosts for the 22nd International ALS/MND Symposium and associated meetings in Sydney in 2011.

Associated meetings to be held in conjunction with the Symposium are :

- **The 19th International ALS/MND Alliance meeting** for member organisations:
Sunday 27 November - Monday 28 November
- **Ask the Experts** session for people living with MND, their family and friends:
Monday 28 November
- **Allied Professionals Forum:**
Tuesday 29 November

The venue for all meetings will be the Hilton Hotel, Sydney.

The 22nd International ALS/MND Symposium

Wednesday 30 November to Friday 2 December

Sydney will be a meeting place for researchers and health professionals from all around the world. The Australian MND community can take the opportunity to participate and be part of this international team as they discuss the latest research and care developments for people with MND.

The call for papers for the Symposium has now closed and the program will be available soon.

Symposium themes are:

- Respiratory and nutritional management
- Multidisciplinary care and quality of life
- Cognitive and psychological assessment and support
- Imaging, electrophysiology and markers of disease progression

- Therapeutic strategies
- In vitro experimental models
- In vivo experimental models
- Genetics
- Epidemiology
- Human cell biology and pathology

Ask the Experts

Monday 28 November 2pm to 4.30pm

This session at the Hilton Hotel provides an opportunity for people living with MND, their family and friends to ask

questions and hear about the latest findings from international and Australian research experts.

For people who are unable to attend this event in person, there are plans, still to be confirmed, to live stream the event via a dedicated website. This will take place in real time so there be an option to ask questions on line.

Confirmation details will be posted at www.mndaust.asn.au as soon as they are available.

Allied Professionals Forum

Tuesday 29 November

Key themes:

- Support for staff
- E-solutions to improve outcomes for people living with MND
- Advance care planning and decision making
- Integration of palliative care
- Changing Practice
- Long term carer support
- Tailored support for families

This is only the second time these meetings have been held in Australia - the first time was in Melbourne in 2002. This is an invaluable opportunity for people to learn, share ideas, form collaborations and be inspired to continue in the global race to work towards a world without MND.

For more information, go to www.mndaust.asn.au or the symposium page at www.mndassociation.org.



(Continued from page 1)

The Snowball Effect continues with the attraction of students from the UoW School of Biological Sciences to work on MND projects co-supervised by Justin.

The Rotary Health Foundation is funding three-year PhD Scholarships for Rebecca Brown [2], (*TDP-43 aggregation in MND*) and Kate Roberts [3], (*Protein aggregates and neuroinflammation*). Masters student, Jay Pundavela [4], (*Infectious protein aggregates in MND*), five honours students and two research assistants complete the team of which Justin is the leader. Honours projects are being undertaken by Dane Gower [5], (*Small heat shock proteins*

in MND); Luke McAlary [6], (*Biochemical properties of SOD1 that induce aggregation*); Rachael Bartlett [7], (*P2X7 receptor in MND neuroinflammation*); Rafea Zeineddine [8], (*Uptake and degradation of SOD1 in motor neurones and glia*); Kathryn Perkiss [9], (*TDP-43 aggregation and molecular chaperones*) and Steven Gray [10], (*SOD1 activation of astrocytes*). Research assistants Jodi Lee and Lisa Corcoran are not pictured.

It is no surprise that Justin has been awarded the University of Wollongong Vice-Chancellor's Research Excellence Award for Emerging Researcher in 2011.

Reports on attendance at the 21st International Symposium on ALS/MND in Orlando, USA in 2010

from researchers whose grants included funding to attend the symposium.

Funding for most of these grants was provided by MND Victoria.

MNDRIA Travel Grant (Mick Roger Benalla)

Dr Bradley Turner

Last December, the international MND research and care community converged at the theme park capital of the world to share, discuss and debate scientific and clinical strides in the field over the past year. While difficult to resist the temptation of Mickey Mouse and friends, there were plenty of thrills and surprises in the scientific program and daredevil researchers pioneering new technologies to spur development and pursuit of effective treatments for MND.

One of the dominant scientific themes of the conference was RNA biology, lending itself to the increasing belief that RNA defects may partly or even solely cause MND. RNA is the genetic blueprint or message used to build and maintain all cells. Like any message, RNA must be correctly proof-read, handled and posted to often remote locations in cells. Surprisingly, defects in RNA processing steps appear to selectively strike out motor neurones, suggesting that these nerve cells are unusually vulnerable to RNA defects. Here is an account of these sessions and other scientific highlights from the conference.

Shoot the messenger

Day one of the Symposium was largely devoted to TDP-43; the disease signature molecule for MND. TDP-43 forms junk piles in the brain that may kill nerve cells in MND, however the precise action of TDP-43 in disease may be more subtle. Understanding the normal function of TDP-43 may therefore help unravel its rogue function in MND. Clotilde Lagier-Tourenne from UCSD and Janice Robertson from Toronto University shed some light on TDP-43 function in normal brain using a technique to capture its possible partners in crime, namely RNA. Although TDP-43 is highly promiscuous, they showed that it naturally seeks out and binds RNA that promotes motor neuron survival. In contrast, these RNA targets of TDP-43 are abnormal in MND patients, providing the first disease link between TDP-43 and RNA defects in MND. These findings may provide early clues for treatment in MND since RNA defects are likely to be early, if not causative, in the disease process and are highly amenable to gene therapies.

Programmed motor neurones

In an exciting development, Tom Maniatis from Columbia University and iPierian independently reported on preliminary analysis of induced pluripotent stem (IPS) cell-derived motor neurones from MND patients. IPS cell technology allows researchers to isolate skin cells from patients and "reprogram" them into any desired cells which are genetically matched to their donors. This technology was successfully applied to MND in 2008. In this instalment, motor neurones grown from MND patients with TDP-43 or FUS gene defects were maintained long-term and subject to next-generation "deep sequencing" which can identify RNA defects. An abnormal RNA profile was indeed demonstrated in these cells, suggesting that RNA defects in motor neurones may be central to MND. More importantly, IPS cell technology offers the research community a robust supply of patient-derived motor neurones that model the gene complexity of MND, particularly sporadic MND, for applications such as drug discovery.

Greasy cells important for MND?

In a session dedicated to SOD1, the most common genetic defect in MND, Don Cleveland from UCSD reminded the audience that MND caused by SOD1 is likely the sum of damage arising in motor neurones and neighbouring cells. Thus, treatments should be targeted at both motor neurones and glial cells. He outlined two such clinical trials: the first involving direct brain infusion of molecules to block SOD1 commenced 2010, and the second involving spinal transplantation of astrocyte precursor cells commencing 2014. Jeff Rothstein from Hopkins continued the theme of glial cells, implicating a potential new player in MND caused by SOD1. He showed compelling data, although very preliminary, that SOD1 damage with oligodendrocytes, the fatty cells that enwrap motor neurones, strongly influences disease initiation in MND mice. If correct, then these glial cells offer an innovative potential treatment target for MND, in addition to affected motor neurones.

News from Oz

In the poster session, I was confronted with the usual dilemma: patrol my poster or indulge in other posters! Finding a compromise, I presented recent data from our lab funded by MNDRIA showing that SMN, the determining factor of the childhood disorder SMA, is abnormal in MND patients. These findings may be relevant to the field since SMN closely resembles TDP-43, predicting that RNA defects will also arise from SMN abnormality in MND. I was enthused by the feedback of experts in the field who shared my prediction and offered collaboration. Julie Atkin from La Trobe University continued to wave the Aussie banner in her session presenting fresh evidence that proximal cell transport is disrupted early in MND models. These studies highlight a novel pathway for drug intervention in MND which is currently under intense investigation.

Third culprit in three years

To cap off 2010 on a high note, Bryan Traynor from NIH announced exciting news about a new MND gene called VCP, previously implicated in a hereditary muscle wasting dementia syndrome. Using powerful next-generation "exome sequencing" technology capable of unprecedented rapid screening of every known gene within a person, they identified that gene defects in VCP were linked to forms of MND with family history. VCP is a logical candidate for MND because it was previously established that defective VCP leads to TDP-43 junk piles in nerve cells. Together with TDP-43 and FUS, VCP is the third major MND gene to be reported in the last 3 years, adding to a growing list of culprits that help guide researchers to the relevant pathways and mechanisms in MND. These findings also illustrate application of a new and improved technique for efficient genetic diagnosis of MND.

In summary, this conference provided key updates on current MND research themes, advances, breakthroughs, directions and importantly flagged upcoming clinical trials and publications, particularly in the fast evolving area of RNA biology in MND. The results presented this year affirm my belief that MND is becoming the flagship neurological disease for application of cutting edge technologies including IPC stem

cells, deep sequencing and exome sequencing platforms. This information should yield better animal models with improved predictive power for clinical trials. The interaction with national and international basic scientists, clinicians, PALS, CALS and support groups at this venue not possible in everyday science was also invaluable, encouraging international recognition and appraisal of our work and productive collaborations aimed at our goal to change the course of MND.

Mick Rodger MND Research Grant A/Prof Meng Inn Chuah

The International Symposium on ALS/MND brought together biomedical researchers, clinicians and health care professionals to share new developments in the understanding, treatment and management of ALS/MND. I gave a poster presentation under "Theme 1 Therapeutic Strategies" at the ALS/MND Symposium. My poster presented preliminary data that metallothionein-IIA appears to increase survival by delaying late-stage disease progression in G93A SOD1 mice. It also showed that as early as 15 minutes after intramuscular and intraperitoneal injection, MT-IIA can be detected in the vascular system and the parenchyma of the kidney. The poster was well received and I gained valuable feedback. The Symposium also gave me the opportunity to discuss ongoing experiments with other attendees, specifically current experiments investigating possible beneficial effects of combined metallothionein injection and exercise in SOD1 mice.

There were many meeting highlights due largely to the unique nature of participants coming from various specialty backgrounds. The symposium has given me a more balanced view of the topical issues relating to ALS, and enlightened me on the multiple strategies that researchers and professionals are applying to understand and develop better treatment for this disease. One of the major highlights is the opportunity to attend talks by world-renowned researchers such as Prof V Lee, Prof A Al-Chalabi and Prof PN Leigh. I have learnt much from the oral presentation and posters, too many to discuss in detail here but a few bear particular relevance to my work:

A poster (P8) presented by E Tokuda and S-I Ono which showed that metallothionein-I injected intraperitoneally led to longer survival and better functional outcomes in SOD1 mice. They also showed that the injected metallothionein could be found in cells of the spinal cord, suggesting that the injected metallothionein crossed the blood-brain barrier and acted directly on the motor neurons. My study involves intramuscular injection of metallothionein at a slightly lower dosage but combined with a treadmill exercise regimen. It would be interesting to compare the results by Tokuda and Ono with ours to establish whether the beneficial effects of metallothionein can be enhanced by exercise.

The use of exercise as an additional therapy for MND patients is being trialled by the Central California Neuroscience Institute. K Volez and J Rosenfeld (CW241) reported that four patients are currently undergoing partial body weight bearing treadmill training. Preliminary results appear to be promising with three of the four patients showing improved timing in performing 25-foot walk and better lower extremity function.

S Rutkove (C60) introduced electrical impedance myography as an innovative method to quantify motor neurone loss. This measurement which provides a physiological measure in addition to structural atrophy that is commonly observed in ALS, could be applied to my project.

In summary, I have benefitted greatly from attendance at this Symposium; it has given me fresh impetus to continue our work on ALS. I would like to thank MNDRIA and the Mick Rodger MND Research Grant which have provided the financial support to allow me to participate in this event.

Mick Rodger Benalla MND Research Grant PhD candidate Nastasia Lim (for Dr Anthony White)

The International Symposium provided a good number of speakers from different countries working on similar projects. This gave an excellent overview of current work relating to MND and how our own work could fit into what is currently known or how to further develop our own hypotheses in relation to the rapid advancement of the field. What was also important was the additional focus on the current care of MND patients. There were exhibits from a number of international companies and presenters showing the current therapies available to ease the suffering of MND patients, which provided a good reminder of what we are aiming for with our studies.

Of particular interest at the symposium were presentations relating to animal models, including exciting data on MND models, as our lab is currently doing research using mouse models of MND (e.g. SOD and TDP-43 models). Mice with a TDP-43 G384C mutation showed a decrease in performance in an accelerating rotorod and Barnes maze (Julien). The G384C mice also showed increased TDP-43 aggregates, inflammation, cytokines and smaller axons compared to the control and A315T (another TDP-43 MND model) mice. Another mouse model presented had a SOD1 D38G mutation, associated with familial MND and producing abnormal dismutase activity (Joyce). The D38G mouse showed decreases in weight, rotorod performance, grip strength, startle response and produced tremors, as well as a ~20% loss in motor neurons and increased astrogliosis. These models reflect the MND human pathology and could be useful for our own studies in future, particularly with development of our metallo-complex-based therapeutics and attempts to understand how altered TDP-43 processing induces MND.

Proteins of direct interest to our work were also discussed during the symposium. *Drosophila* overexpressing TDP-43 showed an increase in Notch targeted genes (Tibbetts). UG-rich sequences for TDP-43 binding were further identified as a target (Lagier-Tourenne). Chronic excitotoxicity was reported to increase the phosphorylation of TDP-43 and increase ubiquitin immunoreactivity in spinal cord cultures (Ayala). The phosphorylated TDP-43 was then found aggregated into ubiquitin positive SH-SY5Y cells. ERK inactivation was also found in this study to cause TDP-43 fragmentation, phosphorylation and aggregation, thus ERK inhibition could be protective (Ayala). The HFE H63D protein was shown to be associated to increasing the sensitivity of cells to ER stress (Liu). This is similar to our work showing that JNK controls TDP-43 aggregation during stress. Increased

Reports: International Symposium on ALS/MND in Orlando, USA 2010

caspase-3 activity is seen in cell cultures with reduced H63D expression and in a HFE mouse model (Liu). Trafficking pathways were also shown to be altered in mutant SOD1 cell models (Atkin). Decreased BDNF secretion blocked ER and Golgi trafficking in mutant SOD1 cells. Dyenin and COPII, both involved with transport, were also shown to interact with mutant SOD1 (Atkin). These proteins could be of interest to our own work and will be further investigated in our studies.

My poster presentation related to work with TDP-43 in cell culture models, trying to understand how TDP-43 accumulates in cytoplasmic stress granules during oxidative stress. Our findings showed that with SY5Y cells treated with paraquat (to induce oxidative stress), TDP-43 accumulation in stress granules is dependent on JNK activation, increased caspase activity and C-terminal cleavage. Low amounts of the cell permeable bis(thiosemicarbazone) copper complex Cull(atm), which has been shown to be neuroprotective in vivo, inhibited the formation of stress granules and TDP-43 accumulation, thus protecting neurons from paraquat toxicity. Our studies are the first to demonstrate a pathway for TDP-43 accumulation in stress granules and inhibition by a copper complex. It was well received at the symposium during the poster presentations.

Zo-è MND Research Grant

Dr Fiona Fisher

From the grant funding received, two poster presentations were able to be presented at this year's 2010 International Symposium on MND/ALS:

- Fisher, F., Howe, J., Reardon, K. & McPhee M. (2010). *The clinical utility of routine primitive reflex examination in MND.*
- Fisher, F., Pavlis, A., Howe, J., Reardon, K. & Mathers, S. (2010). *The challenges of care-giving: contributions of cognitive, behaviour, and social cognition difficulties in MND.*

In addition, I attended a range of presentations and shared ideas with a number of researchers during the poster sessions.

During my attendance at the symposium, I was exposed to international interdisciplinary clinical management and research practices. The exposure provided insights and interesting comparisons into how services around the world provide high quality support for both patients and carers.

Throughout the symposium I attended talks by neurologists and neuropsychologists from around the world. Discussion included the utility of examinations of frontal and temporal dysfunction to assess cognitive and language disruptions, as well as the clinical and pathological implications of assessing cognition. Each year there is increasing recognition of the importance of early detection and recognition of cognitive changes in MND. The importance of examining the impact of cognitive and behavioural changes on both patients and carers was also highlighted by a number of prominent keynote speakers. The international recognition of the importance of continued research and public education in this area was definitely the highlight of the symposium for me.

Discussion with other researchers highlighted our study as being of similar calibre to those conducted abroad, while enabling the fertilisation of ideas between like-minded professionals. Potential future collaborations with Kings College in London and Penn State in the USA are now being considered in order to draw international comparisons of the results we obtained here.

Networking with international researchers enabled the fertilisation of ideas between like-minded professionals. Discussions of the challenges of conducting clinical research with other researchers facilitated the sharing of ideas to address common hurdles.

This year's symposium again provided an opportunity for researchers to come together to expand their knowledge and share their experiences and insights. In addition to the invaluable networking opportunity the conference afforded, attendance at the symposium furthered my knowledge into the diverse approaches to assessing cognitive, behaviour and social communication changes in MND. The information obtained from this symposium will most certainly inform our team's ongoing research practices and has even provided a number of ideas for future directions.

MNDRIA Grant-in-aid

Dr Qiao-Xin Li

This was my first time attending the annual international symposium on MND/ALS, and it has been a very beneficial experience. I had the opportunity to meet with many researchers and clinicians in this field. I am inspired by their enthusiasm and hard work in trying to help people living with MND/ALS. Through the discussion, I had the chance to learn about the studies that they are doing as well as exchange information and ideas. I also received valuable and constructive feedback on my poster presentation which will be helpful in progressing my research. We have learnt so much about the disease yet we are still struggling to find a cure. I hope it will come in the near future.

This symposium also has many good discussions on the clinical ground that emphasised current drug trials and patient care and support. The conference room for the clinical session was full with attendees. This shows that the communities are trying hard to help those people living with MND/ALS.

I would like to express my thanks for funding this trip to present my research poster at the Symposium. It has been a memorable experience.



Bill Gole Postdoctoral Fellowship for MND Research reports

Bill Gole died from MND in 2003 three years after being diagnosed with the disease. Bill's courageous battle with MND had a lasting impact on many people - his family, his friends, his work colleagues, the health professionals involved with his care, and many others.

Bill Gole's name lives on as young scientists compete for the 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 for MND Research commenced in 2005 and this year the tenth young Australian scientist to gain this prestigious grant has commenced a career in MND research. 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 period of three years.

These brief reports are from the four concurrent Bill Gole Postdoctoral Fellows funded in 2010.

Dr Anna King (2008-2010) University of Tasmania.
Investigating causes & consequence of axonal pathology in ALS.

Nerve cells or neurons are highly specialised and unique cells that have long nerve processes, which are responsible for transmitting signals around the body. Motor neuron disease (MND) is caused by a loss of a specific class of nerve cells, termed motor neurons, which control the muscles. Motor neurons can have very long processes (axons), which can constitute up to 99 percent of the cell. Although we know that motor neurons die in MND, there is evidence that before they die there is a time where the cells are not functioning properly because the nerve signal is not being transferred along the nerve process to the muscle. *We think that protecting the nerve process and restoring function is a potential point of therapeutic intervention for MND, either alone or in combination with therapies that protect the cell body.*

Before therapeutic intervention can be developed we need to find out what is going wrong with the nerve process or axon. The nerve processes of motor neurons extend from the spinal cord to the muscles. When nerve processes in the spinal cord are examined under the microscope they frequently appear to have large swollen structures. The nerve processes in muscle frequently have a type of pathology termed 'dying back' pathology where they appear to no longer connect to the muscle and so cannot stimulate it. *During my Bill Gole Fellowship I have studied these changes in the axons of motor neurons and looked at mechanisms that can cause these types of changes to occur. Furthermore I have determined how these changes affect the normal function of the neuron.* To examine nerve cell axons in detail I have developed techniques to grow motor neurons in a dish so that I can expose them to different conditions that may be present in MND and find out what causes the processes to become swollen and to lose their connections with muscle cells. Using these techniques, I have shown for the first time that the swollen nerve processes, similar to those in MND, may be caused by changes to the cells that normally support the neurons. These supporting cells are known to be important in the development of the disease. I have shown that supporting cells that were old or that had a mutation that causes MND result in more of the nerve processes becoming swollen and this may be why MND develops with age.

To examine more closely what was happening to the nerve processes I investigated the proteins and structures within the cell. I found that within the swollen parts of the axons the proteins that are usually responsible for the cells' scaffolding (cytoskeleton) were highly disrupted and had accumulated. This was similar in the cell culture model and also in a mouse model of MND. Another important aspect of this work was to look at how these swellings affected the function of the nerve cells. I performed live imaging experiments that demonstrated that these swellings did not cause the cells to die rapidly, but rather the movement of components around the cell was slowed. This may result in distal parts of the cell being 'starved' and subsequent loss of connection with the muscle. My previous studies have suggested that loss of connection between the axon and muscle can also be caused by a pathological process called excitotoxicity, where the cell becomes over activated. The Bill Gole Fellowship has enabled me to develop a number of new techniques and models that have contributed to the securing of further funding to expand and continue this project in the future. Our next step is to examine in more detail the changes that are occurring as the nerve process dies back from the muscle and to determine the role of excitotoxicity and support cells in this process. We will do this in both animal and cell culture models. Our studies will also focus on examining the therapeutic potential of protecting the nerve processes in MND and we are currently studying the protective effect of stabilising the cell cytoskeleton.

Despite disappointing therapeutic trials in MND to date, there has been a substantial increase in our understanding of the underlying biology of the disease in recent years. We hope that our approach of looking at the functional structures of the motor neuron, such as the nerve process, will aid in the development of strategies that will protect and repair the damaged cells.

Dr Jennica Winhammar (2008-2010)
Neuroscience Research Australia, University of NSW.
Clinical trial to assess the neuroprotective properties of a sodium channel blocking agent in motor neurone disease.

Nearly 150 years have passed since Charcot defined Amyotrophic Lateral Sclerosis (ALS) and there remains no cure, with riluzole, the only disease-modifying therapy available to slow disease progression. There is evidence of an increase in sodium entering motor neurons in ALS, which may play a key role in their degeneration. Our aim was to undertake a double blind, randomised clinical trial to evaluate whether ALS disease progression may be attenuated with a sodium channel-blocking agent. ALS patients were consecutively recruited and numerous outcomes were measured at each visit such as the respiratory function tests, walking tests, muscle strength and functional scales. In addition, new nerve excitability techniques were undertaken to assess the direct effects of the medication on a neuronal level. The trial has been completed and the data is currently being analysed.

Dr Justin Yerbury (2009-2011) 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

Bill Gole Postdoctoral Fellowship reports

part of the nervous system to other nearby locations. All forms of MND are associated with piles of protein junk called inclusions and also with inflammation of the brain. These protein junk piles can be found in the motor neurones of all MND patients.

I am investigating the possibility that these misshapen proteins found in the junk pile are somehow passed on from one cell to another causing dysfunction of neurones. We have observed this process occurring in neuronal cells in culture dishes. This process mimics an infection in that it can be passed from one cell to the next. We have also shown that these protein aggregates or 'junk piles' are recognized by the brain's immune system and trigger it into action. It is hoped that if we can identify the way that cell death and dysfunction is "passed on" from neurone to neurone, or the mechanism by which the immune system recognizes these molecules we can design a much needed therapeutic.

Dr Shu Yang (2010-2012) ANZAC Research Institute, NSW.
Investigating the role of recently identified mutant genes in MND pathogenesis.

Motor neuron disease is a devastating neurodegenerative disorder caused by death of the nerve cells controlling the voluntary muscles. MND patients experience a series of emerging symptoms including progressive limb muscle weakness, speech and swallowing difficulty and eventually respiratory failure. The disease is often fatal within 2-5 years

of diagnosis. The majority of MND patients are sporadic, but approximately 10% of the patients have a family history. The mechanism underlying MND is unknown. Gene mutations are the only proven causes. In 2006, the TAR DNA binding protein 43 (TDP-43) was identified for the first time as a major component of the protein aggregates found in MND patient brains and spinal cords. Our laboratory found several mutations in MND genes including *TDP-43* and *FUS*, from MND patients. However, it remains unclear how these defective genes cause MND. We found that short-term expression of these genes in nerve cells grown in the laboratory reproduced features seen in MND patient brain and spinal cord cells, e.g. protein aggregation and mislocalisation. We found that mutations in the *TDP-43* gene caused more cell death than the normal *TDP-43* gene in neuronal cells. The mutations in the *TDP-43* gene also led to more TDP-43 mislocalisation, indicating that there may be correlations between protein mislocalisation and development of MND. Our preliminary data also suggested that mitochondria (the cell's energy factory) and key molecules of cell death, e.g. caspases, have been involved in TDP-43 related cell death. We are now investigating the long-term effects of these genes in nerve cells. This will help us to identify specific cell functions that are affected by these defective genes and also allow us to find differences between mutant and normal genes. Further investigations are underway to study how these defective genes cause motor neuron death as a prerequisite to the development of treatments.

Grants-in-aid

MNDRIA grants-in-aid are intended as seed funding for start-up projects so the data can 'grow' to produce sufficient background for an application for more significant funding from the National Health and Medical Research Council.

The number of grants that are awarded each year is dependent on the funds that are available at the time.

Some grants are awarded as named grants and are sponsored by an organisation or individual. This year will see the introduction of the Terry Quinn MND Research Grant after receipt of a generous bequest from the estate of the late Terry Quinn.

Thirteen grants-in-aid were funded by MNDRIA in 2010. Brief reports on these projects are provided here.

Grant-in-aid

Dr Julie Atkin La Trobe University, Melbourne.

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

Neurodegenerative disorders (Alzheimer's, Parkinson's and Motor Neuron Diseases) share common features: abnormal protein clumps within affected cells which are linked to pathology. The lack of effective therapies coupled with the aging population and the incipient projected dramatic increase in the number of persons with neurodegenerative disorders in the coming decades, highlights the need to urgently find effective treatment strategies. Numerous potential therapeutic and/or preventive agents have been tested in clinical trials to these conditions, yet most have failed to show a clear therapeutic benefit. An important aid in drug development and diagnosis is an accurate biomarker of disease severity and progression. A molecule, called PDI, has the potential to meet both these needs.

We have evidence that PDI prevents abnormal clumping in MND and hence has two novel potential applications in these diseases; (1) as a biological marker to track disease progression, (2) as a new treatment to improve disease outcomes. We assess the first possibility in this proposal. The evidence we obtained in our studies has led us to believe that PDI may be a new and effective biomarker of MND.

We also tested PDI in human cerebrospinal fluids from MND patients and unaffected individuals, to determine whether PDI could be used to reliably measure disease outcome and progression. We also hope that PDI could be used 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 animals, called 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 new mice that carry one of these TDP-43 mutations. These mice are currently being bred in our laboratory to establish this mouse colony and

Grants-in-aid

switch-on the defective gene. As a disease with late age of onset, we are now monitoring and testing these mice to establish whether they develop 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.

The degeneration of motor neurones in the spinal cord and brain of patients suffering MND is the primary feature of this debilitating and ultimately fatal disease. Unfortunately there are no clinical treatments that can stop or reverse the progressive course of this disease. Metallothionein (MT) proteins are known to be neuroprotective in several experimental models of neuronal injury and disease. The aim of this project was to investigate whether combining MT with an exercise regimen can result in improvement in the functional and survival outcome of a mouse model of MND.

We are able to show that MT injected into muscle can be detected rapidly in the blood system and some of it appears to be excreted into the urine. We have also developed a method to measure the amount of MT in the spinal cord. Groups of mice have been undertaking exercise and/or MT injection. We have recorded and continue to monitor their weights (twice a week), how well they walk based on their footprints, and their grip strength. On completion of the exercise treatment and when the mice reach their end-point, their spinal cords and muscle tissue are isolated to determine how much MT they contain. We are in the process of graphing and analysing the progress of the mice. So far there do not appear to be significant differences in the functional ability of the different groups although at a few time points, mice which were exercising appeared to have a more normal stride length and possibly a stronger grip. We found large variability in the behavioural characteristics of the mice so it is important that we base our analyses on a sufficiently large sample before drawing firm conclusions. We hope to complete functional analyses of the surviving mice, as well as analyses of MT in the spinal cords in the next few months.

Our work is a first step in determining whether MT in combination with exercise can be of benefit to MND patients. It is likely that before any positive effects of MT and/or exercise can be fully realised, additional experiments will be required. These could include establishing the optimum dosage and length of treatment. Funds permitting, we would also like to understand how motor neurons in the MND spinal cord respond to MT.

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. Some clues are evident in genetic forms of the disease, but these forms of MND only account for a small minority of all cases. Identifying the causes of decreased motor neurone function is an essential step in developing new and more effective therapeutics to treat MND.

Our research focuses on demonstrating the mechanism of

action for a novel therapeutic compound, Cu^{II}(atsm), shown by our team to substantially delay the onset of paralysis in MND model mice. By determining the mechanism of action for Cu^{II}(atsm) in detail our current research activities present a unique opportunity to simultaneously progress the development of Cu^{II}(atsm) towards clinical trials, and to identify what may be an important biological contributor to all forms of MND. Using funds received from the MND Research Institute we have examined Cu^{II}(atsm) activity in a range of cell types grown under conditions that simulate the abnormal conditions that may cause motor neurone degeneration in the spinal cord. We have focused on conditions that decrease the cell's capacity to generate its own energy supply and have found that these conditions induce activation of the therapeutic potential of Cu^{II}(atsm).

Our research is in the pre-clinical development of potential therapeutic compounds. This type of research means that the strong positive outcomes we generate are in reality still many years away from testing our compounds in people with MND. However, the pre-clinical testing that we undertake is essential for new compounds to have any chance to be effective when ultimately given to people with MND.

We will continue our pre-clinical testing of Cu^{II}(atsm) as a potential new therapeutic for the treatment of MND. By determining its mechanism of action in greater detail we will be able to progress Cu^{II}(atsm) further towards clinical trials or develop derivative compounds with improved therapeutic efficacy.

Zo-eè MND Research Grant

Dr Fiona Fisher

Calvary Health Care Bethlehem, VIC.

Emotion recognition and social communication in MND: impact on behaviour and carer burden.

Limited research 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 (i.e. body language) that provide cues to help people determine the emotional states of others. What this means is that some people with MND may have trouble with the finer, more subtle aspects of social communication. This research project compared performances of a group of persons with MND and a group of healthy participants of a similar age and gender.

Results showed persons with MND performed worse overall than healthy participants on measures of social cognition (i.e. interpreting how others are feeling from more subtle gestures and cues), but not on measures of basic emotion recognition (i.e. both groups were well able to recognise common emotions such as happy, sad etc.).

Video-taped conversations between participants and researchers were rated by speech pathologists, specialised in examining subtle aspects of social communication. Overall, the MND group had more difficulties with social communication than healthy participants. This was independent of their level of physical disability.

Difficulties with social communication and accurately perceiving emotional interactions with others can have a negative impact on one's ability to remain emotionally connected to close others. Such difficulties may even affect the appropriateness of a person's behaviour in social situations which may cause embarrassment or lead to social isolation. These changes have the potential to strain relationships between persons with

Grants-in-aid

MND and their carers. Therefore, by continuing to investigate ways these difficulties can be recognised early, appropriate education and strategies can be implemented.

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.

The underlying cause of MND is unknown and there is no effective method of assessing disease progression over time. Such a method would be useful as a measure in clinical trials. MND involves death of upper and lower motor neurons (the nerves that control motor function). This project examines upper and lower motor neurone markers. The lower motor neurone marker uses an electrophysiological measure that can be applied to standard nerve conduction studies (CMAP scan) with a software application using Bayesian statistics. 44 MND subjects have been serially studied using this measure. The data has been presented at international meetings and there is interest in other centres using this method. The upper motor neurone marker diffusion tractography (DT), somewhat similar to having an MRI scan, has been serially applied in 19 subjects and much of the MNDRIA funding has been used to fund these studies. The work has been presented at international meetings. Over the next 6 months the data from the upper and lower motor neurone markers will be combined to help understand the relationship between upper and lower motor neurone degeneration. For MND subjects, this work will assist in understanding the mechanisms of MND and could be applied in treatment trials.

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.

Our previous work has found that orally administrated Cu^{II}(atsm) (an anti-oxidant compound) can substantially delay the development of MND-like symptoms in an MND mouse model SOD1G93A and extend the life by 10% in mice with motor symptoms. Our current work is to test the treatment effects of Cu^{II}(atsm) in combination with Riluzole in the MND mice with motor symptoms, as this reflects the current clinical situation in humans. We found that the MND mice treated with Cu^{II}(atsm) and Riluzole have a life span of 273 days, significantly longer than the mice with single drug treatment by 11%. We have also treated another MND mouse model, SOD1G37R, with Cu^{II}(atsm) to see if the drug is effective in a different model. This treatment started at pre-symptomatic age of 4 weeks. The SOD1G37R mice treated with the drug have also lived longer than the mice without the drug. This confirms that the drug is also effective in another model. Since the drugs were given to the mice after onset of symptoms, the result will be directly relevant to clinical application, and will aid future clinical trials. Although it is still a long way for the use of Cu^{II}(atsm) as a more effective treatment for MND in humans, every outcome from our project is a step closer to this ultimate goal. The fundamental research will lead to a better understanding of the progression of MND and enable us to define whether the Cu^{II}(atsm) work can be progressed to humans.

Grant-in-aid

Dr Hakan Muyderman

Medical Biochemistry & Human Physiology
Flinders University, SA.

The role of TDP-43 in astrocytes in motor neuron disease.

On the microscopic level, MND is characterised by the presence of cellular structures known as inclusion bodies. The major component of these structures is a protein called TDP-43. Changes in the gene coding for this protein (mutations) can cause an inherited form of the disease. Little is known about how changes in the normal function of this protein, or how the mutated forms, cause disease.

Recent results obtained in our laboratory show that these mutations not only cause pronounced effects on normal function of nerve cells, but also alter the function of astrocytes, a specialised supporting cell type in the nervous system that previously have been suggested to play an important role in the development of MND.

In the present study we are investigating the effects of TDP-43 mutations on the normal function of motor neurons and astrocytes and determine if these mutations affect the important interactions that normally takes place between these cell types. These studies are likely to produce novel and important information of the development and progression of MND and provide new approaches for treatment of affected individuals.

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.

The basic genetic pathway is that DNA (in genes) makes RNA, and the RNA then makes proteins. Increasing evidence suggests RNA abnormalities may give clues as to the cause of MND. A powerful way to uncover genetic abnormalities underlying a disease is to extract RNA from the tissue most affected by the disease (the brain or spinal cord in the case of MND), and see if this differs from normal tissue. RNA can be abnormal in being (1) decreased in amount, (2) increased in amount, or (3) of an abnormal type (e.g., with a "misspelling").

Until now, technological limitations have restricted the measuring of RNA to a small number of genes. The latest "next-generation" sequencing methods, however, can examine all the "messenger" RNA (the RNA that makes the proteins) from the entire human genome (all the 25,000 genes). We have therefore set up an international collaboration with The Genome Center at Washington University to look for RNA abnormalities in people with MND who have donated tissues to Australian MND brain banks.

We have so far completed all the complex ethical and legal requirements that are needed for an international collaboration that uses human tissues. We have sent the frozen tissues over to Washington University for analysis. The Washington University team are now assessing which of the spinal cord samples we sent are most likely to give positive results on the RNA testing. The final step will be to undertake the complex statistical analyses on the data obtained to see which RNA is truly abnormal in MND.

By telling us which genetic defects underlie MND, we hope these findings will have a direct bearing on future gene therapy in MND.

Grants-in-aid

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.

An important step in finding effective treatments for MND is to identify biomarkers in animal models of MND that can be used in assessment of potential new treatments. We have preliminary data from the SOD1G93A mouse model of MND that indicates this is achievable. Motor neurons respond to disease by up-regulating various proteins on their nerve terminals; many of these are then shed into body fluids, appearing in both serum and urine. We have evidence that one of these proteins, the neurotrophin receptor p75 (p75NTR) is present in urine of SOD1G93A mice but not age-matched control mice. The aim of this project was therefore to ask if p75NTR is a potential biomarker for MND. Specifically, we tested the hypothesis that the appearance of p75NTR protein in urine provides value as a biomarker for MND.

We have found that the p75NTR protein in urine can be used to diagnose MND in the SOD1G93A mouse model of MND well before any symptoms are present. The appearance of this 'biomarker' of the disease in urine of mice will be valuable as a way to identify the effectiveness of new treatments of this devastating illness. The next stage of our research is the development of a sensitive assay that can detect p75NTR in both serum and urine and can be used to monitor MND treatments in both SOD1G93A mice and humans.

Grant-in-aid

Dr Bradley Turner

Florey Neuroscience Institutes, University of Melbourne.

A role for survival motor neuron protein in MND?

This project examined whether SMN, a molecule important for motor neurons, is abnormal in people with MND. This extends our previous work showing that SMN is extremely low in test tube and mouse models of MND. In this funded project, we have discovered that SMN levels are drastically lower in spinal cords from MND patients compared to normal people. This is an important step because it suggests that low levels of SMN may increase risk for MND. This could also shed some light on what causes MND. Our findings also imply that supplementing SMN may be possibly helpful in MND. We will continue to test whether SMN supplementation in MND mice is beneficial using genetic and drug approaches.

If our proposal is supported, then these results could pave the way for future studies to find, develop and test strategies to supplement SMN in MND.

Charles and 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. TDP-43 is known to regulate other genes in the nervous system but the actual genes it regulates are largely unknown and the role of TDP-43 in MND remains unclear. The aim of this project was to identify genes that are regulated by TDP-43 and to determine whether these

genes are altered in MND patients with TDP-43 mutations.

Using mouse tissue, we have isolated over 2,000 potential gene targets of TDP-43. The targets included 3 genes that have previously been implicated in MND, providing a link between TDP-43 aggregation and familial MND. We have also discovered that many of the TDP-43 target genes are involved in controlling signals between nerve cells and muscles.

We next used the techniques we optimized in the mouse tissue to analyse nerve cells from an MND patient with a mutation in the TDP-43 gene. We discovered that the mutation reduces the ability of TDP-43 to bind to certain target genes, including the 3 MND genes identified in the mouse study. The loss of target gene binding due to the TDP-43 mutation also included several genes that are normally responsible for nerve cell survival, providing key insights into why nerve cells die in MND patients.

These studies are improving our understanding of what causes MND and in the future will provide rational targets for the development of 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.

Little is known about the causes of motor neuron disease. Recent studies have identified a key role for a protein called TDP-43 in MND and in some cases of frontotemporal dementia. While some advances in understanding TDP-43 processing during disease have been made through analysis of genetic mutations, very little is known about the changes that occur to TDP-43 in sporadic MND, which accounts for more than 90% of all cases. Neurodegenerative diseases including MND are known to have important roles for increased chronic oxidative stress and altered metabolism of biometals such as zinc, copper and/or iron. Our studies have been investigating the role of these factors (oxidative stress and biometals) on processing of endogenous (non-mutated) TDP-43 to try and understand the early changes to the protein that may precipitate neuronal dysfunction in MND. Our studies have found that altered zinc levels and more recently, oxidative and nitrogen-based (nitrosative) stresses are associated with robust changes to TDP-43 in neuronal cell cultures. These changes closely re-capitulate the changes to TDP-43 observed in the brains and spinal cord of MND and frontotemporal dementia and include loss of TDP-43 from the nucleus of neurons (where it normally resides), accumulation and aggregation in the cytoplasm of cells, association with stress granule proteins (sites of RNA protection), formation of short C-terminal fragments and ubiquitination of the aggregates (indicating the formation of irreversible protein aggregates). These are all hallmarks of TDP-43 in MND and our studies indicate that induction of chronic nitrosative or oxidative stresses, possibly related to altered metal metabolism can induce these effects in neurons in sporadic disease. We are currently investigating how this process occurs and our studies indicate a role for altered cell signaling processes controlling aggregation of TDP-43. We have also found that a potentially therapeutic compound (Cull(atm)) can prevent this aggregation process and may offer a therapeutic intervention in MND.

MND PhD Scholarships

The MND Research Institute actively encourages young researchers through scholarship support for PhD candidates working on an MND project. One three-year PhD Scholarship is offered each year in partnership with NHMRC. MND Australia is currently seeking ways to provide additional support for MND PhD projects where scholarships are provided by other organisations such as universities and research institutions.

MNDRIA / NHMRC PhD Scholarship (2009-2011)

Dr James Burrell

Neuroscience Research Australia, University of 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 aims to understand these overlaps and to assess other components of cognitive and motor system performance

in both patient groups. Clinical assessments – including a novel test of tool and gesture usage – combined with neurophysiological investigations aimed at identifying and characterising motor neurone dysfunction, both in the brain and at the level of the spinal cord. These measures are being correlated with results of formal cognitive testing. Eye movements are also being tested using equipment designed specifically for the purpose.

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.

The MND Research Tissue Bank of Victoria

The Motor Neuron Disease Research Tissue Bank of Victoria (*mndRTBv*) established in 2003 is a dedicated repository of central nervous system (CNS) samples such as fluids (blood and cerebrospinal fluid {CSF}) and brains and spinal cords obtained from people diagnosed with MND. From these samples, the neuropathologist is able to confirm diagnosis of the disease. More importantly, these samples are then prepared to facilitate their use in histological, proteomic, genomic and biochemical studies and are made available to Australian and International neuroscience research communities to further investigate MND. Our aim is to enhance MND research and encourage new researcher involvement.

Providing researchers with access to high quality, well-characterised (of an international standard) CNS tissue and related samples has facilitated research opportunities into MND. This 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. Furthermore, having such a vital resource available in Australia eliminates the need to access tissue from overseas at great financial expense and time delay.

Since the inception of the *mndRTBv*, tissue has been provided to 18 new or continuing projects which equates to 259 tissue samples. Research projects have been conducted by research groups at The University of Melbourne, Florey Neuroscience Institute, Latrobe University and The University of Sydney. This work so far has led to 15 Australian and International publications and presentations.

As a not for profit research facility the funds received from the MND Research Institute go some way to supporting the day to day operations of the *mndRTBv* and to assist with associated tissue collection and processing costs.

The *mndRTBv* would like to acknowledge the generosity shown by the donor and donor families in donating tissue to

the *mndRTBv*. It is an act of great foresight and kindness to give at a time of loss, so that others may be helped in the future.

The operations of the *mndRTBv* have the generous financial benefit of using the existing infrastructure and facilities already in place within the Victorian Brain Bank Network (VBBN) which leads to substantial cost savings. The benefits include the salary support of the VBBN administration, clinical and scientific staff and infrastructure costs related to building space occupied, property services, IT support, communication systems, administration support, insurance, financial and accounting support, stationary, printing, postage etc and laboratory services; tissue processing, tissue distribution, equipment use and consumables.

The VBBN and *mndRTBv* are part of the Australian Brain Bank Network, an internationally acknowledged Brain Banking Network.

The total number of MND cases available through the *mndRTBv* and the ABBN is now 114. The following websites provide Australian and International researchers with details of diagnostic categories, number of cases available and a central point of contact to access tissue -:

- MND Research Tissue Bank of Victoria:
<http://www.mndtissuebank.asn.au/>
- Victorian Brain Bank Network:
<http://www.mhri.edu.au/VBBN.htm>
- Australian Brain Bank Network:
<http://www.nnf.com.au/abbn/>

We continue to work towards increasing the number of blood, cerebrospinal fluid, brain and spinal cord donations through dissemination of information. Avenues for raising awareness are through announcements in the MND Association of Victoria newsletter, clinicians, word-of-mouth, and a brochure that has been devised for potential donors.

Professor Catriona McLean
Mental Health Research Institute, Victoria

MND Research Institute of Australia

Office Bearers and Members 2010

MND Australia is the principal member of the MND Research Institute of Australia. The operations of both organisations are the responsibility of MND Australia. All research grants are administered through the MND Research Institute of Australia.

DIRECTORS

The board of the MND Research Institute is the same as the board of MND Australia, consisting of an independent elected President and a nominated representative from each member MND Association board, the chair of the MNDRIA research committee and up to three co-opted special tenure directors.

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RESEARCH COMMITTEE

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

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Professor James Vickers, TAS

Grants for MND research for 2012

Closing date for applications is Friday 26 August 2011

Applications are invited for funding for grants-in-aid, a three-year postdoctoral fellowship and a PhD scholarship* in areas of research relevant to motor neurone disease for projects commencing in 2012.

Additional government support is provided to universities with MND grant recipients as MNDRIA has retained listing on the Australian Competitive Grants Register this year.

Go to www.mndresearch.asn.au for application details and grants available. The Research Committee will review all applications and funding decisions will be made at a grants allocation meeting to be held on 29 November 2011.

*Note: Closing date for PhD application through NHMRC is 29 July 2011

Annual allocation of funds for research

An invitation to apply for grants is advertised nationally from May/June each year. The closing date for grant applications is the last Friday in August.

All research proposals received by the closing date are forwarded to the members of the MNDRIA Research Committee for review. Funds available for allocation are determined by the Board of MND Australia prior to the grants allocation meeting which is usually held in October or November. At this meeting, the Research Committee members discuss the relative merit of all grant applications and decide how the available funds will be distributed. Successful applicants are notified after the meeting and funding for their projects commences in January of the following year.

A scientific meeting is held at the end of each year to allow grant recipients to meet with one another and to present the results of their research.

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) or go to 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, Executive Officer Research on 02 8877 0990 or email info@mndresearch.asn.au.