

The Motor Neurone Disease Research Institute of Australia Inc

was established in 1986 with the following objectives:

- To promote medical and scientific research into motor neurone disease
- To determine the relative merits of research proposals for the study of motor neurone disease for the receipt of research grants
- To administer research grants for the study of motor neurone disease
- To facilitate the exchange of information about motor neurone disease
- To affiliate with other bodies, either national or international, as will advance the cause of research into motor neurone disease
- To be an Approved Research Institute by meeting the conditions of the Income Tax Assessment Act Section 73A (including assessment of applications by suitably qualified members of a medical/scientific Research Committee).

New Office Bearers were elected at the Annual General Meeting following the Grants Allocation Meeting held in December 2004. Dr Dominic Rowe (MND Clinic, Royal North Shore Hospital, Sydney) replaces Professor Perry Bartlett as Chairman. Mr David Lamperd remains in his role as Treasurer and Mrs Paula Trigg takes over as Secretary.

The Scientific Panel comprises MND experts from all States of Australia who are leaders in their fields in medical and scientific research.



Researchers funded by MNDRIA at MNDA NSW on 30 March 2005

Left to right

Dr Julie Atkin	MNDRIA Research Fellow 2005-2006
Dr Steve Vucic	MND NSW Clinical Research Scholar 2005-2006
Dr Roger Chung	Bill Gole MND Research Fellow 2005
Dr Valerie Hansen	Bill Gole MND Research Fellow 2005-2006
Dr Elizabeth Coulson	MND Sealey Research Fellow 2001-2003

MND Research - Hope for a future - a scientific meeting that showcased researchers supported by the Motor Neurone Disease Research Institute of Australia, and others working in the field of MND research. The meeting at the new premises of the MND Association of NSW in March engendered a spirit of cooperation and urgency to further research into MND. All present hoped that this meeting will be just the first of a regular series of annual or biannual meetings where Australian MND researchers can share their ideas.

Office Bearers of the MND Research Institute in 2005

Chairman

Dr Dominic Rowe
Royal North Shore Hospital
St Leonards NSW

Treasurer

Mr David Lamperd
Victoria

Public Officer

Professor John Pollard
University of Sydney
Sydney NSW

Secretary

Mrs Paula Trigg
New South Wales

Scientific Panel

Professor Perry Bartlett
Queensland Brain Institute
University of Queensland, Qld

Professor Peter Gage
John Curtin School of Medical
Research, Canberra ACT

Professor Trevor Kilpatrick
Howard Florey Institute
University of Melbourne Vic

Professor Frank Mastaglia
Centre for Neurological and
Neuromuscular Disorders
University of WA

Dr Pamela McCombe
University of Queensland
Royal Brisbane Hospital
Herston Qld

Professor John Pollard
University of Sydney
Sydney NSW

Dr Dominic Rowe
Department of Neurology
Royal North Shore Hospital
St Leonards NSW

Professor Robert Rush
Flinders Medical Centre
Bedford Park SA

Professor Norman Saunders
University of Tasmania
Hobart Tasmania

Support provided by the MND Research Institute in Australia in 2005

BILL GOLE MND RESEARCH FELLOW 2005

Dr Roger Chung

University of Tasmania.

Excitotoxicity and cytoskeletal alterations in the pathogenesis of Motor Neurone Disease

Glutamate is the key chemical involved in transmitting signals between nerve cells within the brain. Changes caused by injury or disease lead to abnormal cell functions and ultimately to death of neurones. The sustained exposure to glutamate which leads to death of neurones is termed *excitotoxicity*. *Excitotoxicity* is thought to be involved in the development of MND, but it is not clear if over-activation of glutamate receptors leads to the specific patterns of nerve cell changes that are seen in MND, and in particular the changes involving neuronal *cytoskeletal proteins* (proteins responsible for maintaining the structure and shape of neurones). Furthermore, it is not entirely clear why motor neurones are particularly susceptible to excitotoxicity.

This project will determine whether excitotoxicity can directly or indirectly cause the changes in cytoskeletal proteins that are seen in MND, and whether the specific cytoskeletal composition of motor neurones contributes to their selective vulnerability.

Finally, we will explore whether a protein that we have developed that promotes brain healing may also have a neuroprotective role in MND.

This project will be undertaken primarily by Dr Roger Chung, under the supervision of Professor James Vickers, who has world-renowned expertise in the study of neurodegenerative disease.

BILL GOLE MND RESEARCH FELLOW 2005-2006

Dr Valerie Hansen

University of Sydney.

Susceptibility to enteroviral infection: a cause of motor neuron disease?

In 90% of cases MND affects one family member only. This sporadic form of MND is very similar clinically and pathologically to the hereditary form. There is a therefore a strong suspicion that genetic defects also underlie the sporadic form of MND.

Sporadic MND may arise in people who are exposed to an environmental agent that is usually harmless. We aim to show that people with sporadic MND have a

genetic difference that allows a group of viruses to kill their motor neurons. In this project Valerie Hansen, a recently graduated PhD researcher from the UK, will examine genes that if abnormal could predispose to motor neuron viral infection. She will use DNA samples from the Australia-wide MND DNA Bank.

Any gene differences found would enable identification of people at risk of MND and set in train preventative strategies, for example vaccination against the responsible viruses. For people who already have the disease, the agents could be directly targeted with antiviral therapy. Furthermore, with these findings research in gene therapy for MND could be planned.

The Bill Gole MND Research Fellowship will be offered again for 2006-2007.

The Fellowship is directed towards postdoctoral scientists with a track record in areas of neuroscience related to motor neurone disease. Closing date for applications is Friday 26 August 2005.

For more details go to the MND Research Institute's website at www.mndresearch.asn.au.

MND NSW CLINICAL RESEARCH SCHOLAR 2005-2006

Dr Steve Vucic

Prince of Wales Medical Research Institute, NSW

Site of origin and patterns of neuronal degeneration in motor neurone disease.

Motor neurone disease is characterised by progressive degeneration of the corticospinal tract, which runs from the brain to the spinal cord, to specific cells called anterior horn cells that control all voluntary movements. The site of onset of this process of nerve degeneration has not been established.

The present project will investigate where MND begins and document how the loss of nerves within the brain, spinal cord and peripheral nerves evolve over time. In addition to providing information about disease progression and thereby prognosis, new quantifiable measures will be developed which may subsequently be used in conjunction with other markers of disease progression to objectively monitor MND patients in future treatment and prevention trials.

GRANTS-IN-AID 2005

Dr Roger Chung, Associate Professor Adrian West and Professor James Vickers

University of Tasmania

Metallothionein-based neuroprotection in a transgenic mouse model of MND

We have recently identified that metallothionein proteins are powerfully neuroprotective in several experimental models of neuronal injury, suggesting that they might be effective in protecting motor neurones in MND.

This project will test metallothionein's neuroprotective ability in an animal model of MND.

Peter G. Noakes

University of Queensland

The effectiveness of C5a receptor antagonists in the treatment of MND

Motor neuron disease is characterised by inflammation within the central nervous system. It is now thought that long term activation of inflammatory process (i.e. complement) within the spinal cord may promote the progression and severity of motor neuron disease.

C5a is one of the most potent molecules activated during the inflammatory response, and via its receptor **C5aR**, induces the widest range of inflammatory effects. These include activation of macrophages, microglia, neutrophils, and astrocytes. These cells can produce toxic compounds and factors that can compromise the function of neurons (motoneurons), as well as inducing other molecules that can breakdown the blood brain barrier. This breakdown may allow for circulating antibodies to enter the spinal cord and target motoneurons for death. These responses have been observed during the progression of motoneuron disease, suggesting that molecules like C5a may have a role in the progression of this disease. Indeed recent studies have shown that long term stimulation of inflammation within the CNS, results in an exacerbation of motor neuron disease in animal models.

These findings suggest that blocking the actions of C5a may act to moderate the onset and severity of motor neuron disease. Our aim is to investigate the therapeutic effectiveness of a new class of C5a receptor antagonists developed by ourselves through Promics Pty. Ltd., in the treatment of motoneuron

disease in a rat model system, the human mutant SOD-1 transgenic rat.

Our findings will have direct implications for the use of C5aR antagonists in the treatment of motor neuron disease in humans.

Dr Roger Pamphlett and

Associate Professor Emma Whitelaw

University of Sydney

Is SOD1 epigenetically silenced in sporadic ALS?

The cause of sporadic amyotrophic lateral sclerosis (SALS) remains unknown. Because the sporadic and familial forms of the disease look so similar clinically and pathologically it is suspected that the sporadic form of ALS also has a genetic basis. However, numerous attempts to find gene mutations in SALS have failed.

We think an *epigenetic* change could underlie SALS. "Epigenetics" are changes in gene expression that are not coded in the DNA sequence itself and so will be missed on the usual mutation analyses. The epigenetic hypothesis explains how an altered gene can be responsible for a condition (like SALS) in which neither parents nor offspring are affected.

The major epigenetic mechanism is methylation of DNA which can either silence a gene or lead to inappropriate expression.

This project will examine a novel hypothesis for the cause of SALS. We will examine the superoxide dismutase 1 (SOD1) gene, the gene in which mutations may be found in familial ALS. We will look to see if abnormal DNA methylation of the SOD1 gene could lead to reduced or inappropriate expression of the SOD1 protein in SALS.

We are fortunate in having an international leader in epigenetic disorders, Prof Emma Whitelaw, to collaborate on this project.

Closing date for applications for grants-in-aid for 2006 is Friday 26 August 2005.

For details go to the MND Research Institute's website at www.mndresearch.asn.au.

Reports from projects funded by the MND Research Institute in 2004 will be provided in the next issue of the MNDRIA newsletter - Advance.

Funding for MND research in Australia

The funding now offered to support research in MND in Australia has grown substantially over the last five years. The MND Research Institute has committed more than \$350,000 to research in 2005.

All funds available through the MNDRIA come through donations from individual supporters and contributions from the State MND Associations of Australia. Traditionally, funding through MNDRIA has been provided primarily for grants-in-aid of other investigations or as seed funding to get projects started to a point whereby they can attract more substantial funding through bodies such as the National Health & Medical Research Council of Australia (NH&MRC). The number of grants-in-aid allocated each year has been determined by the quality of the applications for funding and the amount of funds available for distribution each year.

The Sealey MND Research Fellowship awarded to Dr Elizabeth Coulson in 2001 was made possible through a very generous bequest to MND research. This bequest marked a turning point for research funding through the MND Research Institute of Australia.

The Sealey Fellowship was awarded to cover the full salary of a postdoctoral research Fellow working on a project directly related to MND. With one person dedicated solely to MND research for a 2-3 year period, there is the potential that this will lead to a lifetime involvement in seeking the answers for MND.

The ability to continue funding of MND fellowships has been extended by the generosity of an anonymous donor who in 2005 is funding two new fellowships in memory of Bill Gole who died from MND in 2003. Additionally, the Sealey Fellowship has been reoffered as the MND Research Institute Fellowship so in 2005 the Institute is funding three post doctoral researchers working full-time on MND research.

To add to this focus of targeting specific people to the world of MND research, the NSW MND Clinical Research Scholar has been funded by the MND Association of NSW in 2005-2006. It is vital that excellent research and the best possible clinical care go hand in hand in combating MND. It is only by understanding the mechanisms involved in the disease, that the ability to stop and slow the dreadful effects of MND will come about.

This new approach to funding MND research in Australia can only continue as long as funds are available through donations, but the corner has been turned and it is hoped that greater awareness of MND will increase the support that is already in place. The Australian MND community can be credited with supporting a significant component of the international research into MND.

Dominic B. Rowe
Chairman

Australian mortality rates for motor neurone disease (ICD10 G122)

Data from the Australian Institute of Health and Welfare (AIHW) 2005. GRIM (General Record of Incidence of Mortality) Books. AIHW: Canberra.

Year	Sex	Mortality underlying cause of death*	Age-standardised death rate per 100,000	Percent all causes of death	Mortality multiple causes of death**
1997	Male	175	2.23	0.26	256
	Female	192	2.00	0.31	237
	All	367	2.09	0.28	493
1998	Male	231	2.95	0.34	296
	Female	200	2.02	0.33	248
	All	431	2.42	0.34	544
1999	Male	251	3.04	0.37	310
	Female	184	1.83	0.30	227
	All	435	2.35	0.34	537
2000	Male	253	3.06	0.38	313
	Female	204	1.95	0.33	246
	All	457	2.43	0.36	559
2001	Male	280	3.26	0.42	358
	Female	191	1.80	0.31	234
	All	471	2.43	0.37	592
2002	Male	294	3.25	0.43	353
	Female	207	1.92	0.32	256
	All	501	2.51	0.37	609
2003	Male	275	2.92	0.40	349
	Female	255	2.30	0.40	296
	All	530	2.60	0.40	645

*All Australian registered deaths where MND was the underlying cause of death

**All Australian registered deaths where MND was an associated or underlying cause of death (also called multiple cause of death)

Mortality rates for motor neurone disease are increasing. A possible explanation is increased longevity in the Australian population, but it is only through research that answers for causes, treatments and cures for MND will be found.

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