

zo-ee MND Research Grant 2007**\$25,000****Professor James Vickers**

Menzies Research Institute, University of Tasmania

Unravelling the cellular pathology underlying neuronal degeneration in MND

Amyotrophic lateral sclerosis (ALS) is the major cause of motor neuron disease. There have been significant advances in the understanding of the underlying pathology of this progressive and degenerative condition, and yet the important links between potential causative factors have not been clearly established. One of the critical changes in motor neurons involves the abnormal accumulation of filamentous proteins in axons. This may be related to the blockage of flow of proteins down the axon, leading to impaired function of motor neurons and subsequent degeneration. We have recently derived preliminary data using cultured spinal motor neurons that links the overactivity of excitatory receptors with a pattern of axonal pathology that mimics ALS. This application explores this interrelationship further and also examines the potential role of known genetic causative factors. In addition, potential therapeutic approaches based on stabilizing axonal filamentous proteins will be investigated.

Report:

This study utilises spinal nerve cells grown in culture to determine how these neurons degenerate in amyotrophic lateral sclerosis, the most common cause of motor neuron disease. Changes that mimic the specific pattern of motor neuron degeneration can be induced by overexciting nerve cells or by exposing them to an environment mimicking the ageing of the nervous system.

The cause of the loss of function of nerve cells in ALS is unknown, however there is substantial evidence that the clinical symptoms are due to degenerative changes within the axons of the nerves prior to cell death. One of the key pathological features of the disease is the accumulation of filamentous proteins in axons of spinal motor neurons, which may be related to the blockage of flow of proteins, leading to impaired function. However, important links between this pathology and potential causative factors have not been clearly established. We have demonstrated that the over-stimulation of excitatory receptors, termed excitotoxicity, can result in accumulations of proteins in the distal portion of the axon. Moreover this pattern of axonal pathology is specific for spinal motor neurons and thus mimics the pathology of ALS. In recent studies we have linked defective interactions between neurons and surrounding non-neuronal cells with more proximal ALS-like axonal accumulations. Interestingly, unlike distal axon accumulation, this proximal axonopathy was not linked to rapid cell death. The contribution of proximal and distal axonal pathology to the loss of function of motor neurons in ALS will be the subject of future investigations. This project aims to identify important new points for therapeutic intervention involving motor neuron protection in ALS.

zo-ee MND Research Grant 2008**\$25,000****Dr Qiao-Xin Li**Department of Pathology, Centre for Neuroscience and Bio21 Institute, University of Melbourne. *The use of CuATSM treatment to identify cellular mechanisms of motor neuron degeneration in ALS.*

The most significant obstacle faced with respect to developing therapeutic strategies to treat ALS is that the biochemical mechanisms that cause motor neuron degeneration are not well understood. We have identified a compound, known as CuATSM, that substantially delays the development of ALS-like symptoms in a mouse model for ALS. ALS mice develop physical symptoms synonymous with ALS in humans, including paralysis and premature death. However, when treated with CuATSM the development of these symptoms is substantially

delayed. Most strikingly, CuATSM increases the survival of ALS mice by significantly delaying the onset of paralysis. The significance of our finding lies not in the potential use of CuATSM as a therapeutic for ALS in humans, but in using this compound to identify significant biochemical events that contribute to development of the disease. Our rationale is that since CuATSM delays the onset of ALS symptoms, a comparison of CuATSM treated and placebo treated ALS mice will help identify important CuATSM mediated biochemical differences. The identification and characterisation of such differences will help expedite the development of effective ALS therapeutic strategies.

Report:

Our research team has identified that a compound known as CuATSM substantially delays the development of MND symptoms in a mouse model for MND. Most strikingly, CuATSM increases the survival of MND mice by significantly delaying the onset of paralysis. Our preliminary biochemical analyses suggest that the positive therapeutic effects of CuATSM in the MND mice are due to its capacity to prevent the death of motor neurons in the spinal cord. The focus of our team now is to establish how CuATSM is working on a molecular level. This is the basis of our project.

Frustratingly, the MND community is all too aware that there are very few therapeutics available to treat the disease, and that the benefits of the therapeutics that are available are relatively small. We believe the most significant obstacle in the development of more effective therapeutics for MND is a fundamental lack of knowledge in understanding what causes the disease and how currently available therapeutics work. We are dedicated to this project because we have a potential therapeutic for MND that is working in mouse studies, and the expertise of our research team is in developing therapeutics and defining how they work. Success in our endeavours will establish the validity of our therapeutic for potential use in humans and will provide valuable knowledge about the causes of the disease.

By achieving our aims, this study will help us understand how spinal cord motor neurons die in MND. It will also help expedite the development of effective MND therapeutics and/or confirm the potential use of our compound CuATSM for use in humans.

We cannot promise that our work will lead directly to the use of CuATSM as a more effective treatment for MND in humans. But we can promise that every outcome from our project is a step closer to this ultimate goal, and we desperately want this to give some hope to people living with MND. Our research team is internationally recognised as leading the world in the development of therapeutics for neurodegenerative diseases such as MND. We want the MND community to know we are committed to this project, and we hope this brings them some assurance at times of immense personal hardship.

Although we have some very promising results already, this is just a first step towards defining the potential for CuATSM in treating patients with MND. Defining optimal dose and treatment regimes in the mouse model is our first priority. By achieving this we will have the basis on which to best identify exactly how CuATSM prevents the physical symptoms of MND. This fundamental research will lead to a better understanding of the pathological progression of MND and enable us to define whether our CuATSM work can progress to humans, or whether chemists within our team will be able to refine CuATSM to generate compounds with even better therapeutic outcomes.

zo-ee MND Research Grant 2009

\$30,000

Dr Louisa Ng Rehabilitation Physician, Royal Melbourne Hospital, VIC

Disability in motor neurone disease.

This study aims to paint a holistic profile and health care needs for persons with MND in an Australian sample, and in doing so identify gaps in knowledge and in service provision to enable recommendations for future development of health care services to best meet the needs of the identified priorities. The study aims (1) to determine the experience of disability in people with MND in Victoria; (2) to provide an understanding of the current use of services and the perceived needs of people with MND from the perspective of these people and their carers, hence identifying gaps in service provision and (3) to describe the experience and the impact of disability, handicap and environmental factors in people with MND using the International Classification of Functioning, disability and health (ICF).

Report:

This research project describes the disability experience and needs of MND from the perspective of the people with MND themselves and from their caregivers. This enables health professionals managing MND to be better informed with the aim of providing improved treatment/management.

44 persons with MND (pwMND) and 37 caregivers were recruited through a large tertiary multidisciplinary centre and interviewed. A similar interview was used for all participants (pwMND and caregivers). An open-ended questionnaire with the single question, "what are the main problems you face in your everyday life" was asked, followed by a series of questionnaires on self-reported perceived needs for services and actual services received, anxiety, depression and stress, quality of life and coping strategies. In addition, caregivers were asked to rate their burden of care on a 0-100 scale.

Data from the questionnaires is still being analysed but preliminary findings include:

- Doctors may underestimate the issues of pain and spasticity/cramps/spasms.
- Psychosocial support may be an area of need that should be further explored.
- Many of the disabilities reported are amenable to rehabilitation treatment. This reinforces the recommendation by the European Federation of Neurological Societies that pwMND be able to access multidisciplinary rehabilitation services.
- Many issues with hobbies/leisure activities and socialising are amenable to technological advances currently available. More consideration of the use of such technology could facilitate these activities
- It was noted that in general, most participants were very satisfied with their current level of services. This is likely attributed to the multidisciplinary care that they receive and also to the close links between their health care provider and MND Association of Victoria which provided many of their equipment and advocacy needs.
- Interventions such as determining service needs from the caregivers perspective are necessary to reduce poor outcomes among both caregivers and care recipients with MND.

In using the International Classification of Functioning, disability and health (ICF) to describe the problems and the impact of the problems that the MND population faces, it will be possible to compare the experiences of the MND population in Australia to the international perspective.

zo-ee MND Research Grant 2010

\$35,000

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.