

► **New Research and Clinical Grants for the Study of ALS**2

► **Damaged Motor Neurons in ALS Contribute to their Own Death**3

► **ALS Hard on Family Caregivers**4



Research News

JUNE 2007 - VOLUME 14

Welcome to Research News. This newsletter is sent to those who have signed up for ALS Society of Canada bulletins, the members of the ALS Society of Canada board of directors, provincial society staff, ALS researchers, ALS unit board members, ALS clinics, ALS society volunteers, and international ALS/MND organizations. If you wish others to receive this newsletter, please forward e-mail addresses to Bobbi Greenberg – bg@als.ca – requesting inclusion in the UPDATE e-list.

In this newsletter we are bringing together and reporting on current research. ALS Canada does not assume responsibility for the information contained in this newsletter.

ALS Society of Canada
265 Yorkland Boulevard, Suite 300
Toronto, Ontario M2J 1S5
Tel. 416-497-2267/ 1-800-267-4257
Fax 416-497-1256 • www.als.ca



DOCTORAL RESEARCH AWARDS ANNOUNCED

The ALS Society of Canada and CIHR INHMA (Institute of Neurosciences, Mental Health and Addiction) are pleased to announce the two recipients of this award. David Gosselin at Université Laval whose project is entitled *Increasing microglial expression of CCR2 and IGF-1 through*

genetic engineering of hematopoietic stem cells for the treatment of ALS and Xiao Yang Shan at Simon Fraser University who will be studying *The role of O-glycosylation in a mouse model of ALS*. The recipients will receive a stipend of \$21,000 per annum plus a \$1,000 research allowance for up to three years.

FIRST ANTIBODY THAT DETECTS ONLY KNOWN CAUSE OF ALS

Researchers at the University of Toronto's Faculty of Medicine have developed the first antibody that detects the only known cause of ALS.

The latest findings, published in the online edition of *Nature Medicine* on May 7, are significant as they provide the world's first tool for recognizing misfolded conformations of the enzyme SOD1. Mutations in the gene encoding SOD1 cause approximately one to two per cent of all ALS cases. "This antibody will enable researchers

to investigate whether misfolded SOD1 is involved in other forms of ALS," says Janice Robertson, PhD, Canada Research Chair in the molecular mechanics of ALS at the Centre for Research in Neurodegenerative Diseases and one of the lead authors of the study. "This is important to determining if SOD1 is relevant in ALS cases that are not caused by mutations in SOD1. If this is the case, then the antibody could potentially be used in biomarker studies to facilitate earlier diagnosis of the disease."

Continued on page 2



TDP-43 IMMUNOREACTIVITY IN NEURONAL INCLUSIONS IN FAMILIAL ALS WITH OR WITHOUT SOD1 GENE MUTATION

Japanese researchers published this paper in the May edition of *Acta Neuropathologica*. Their findings indicate that the histological and molecular pathology of sporadic ALS can occur as a phenotype of familial ALS without SOD1 mutation. For more information [click here](#).

TRYPTOPHAN 32 POTENTIATES AGGREGATION AND CYTOTOXICITY OF AN SOD1 MUTANT ASSOCIATED WITH FAMILIAL ALS

The research team of Jeffrey Agar, PhD, at Brandeis University in Waltham, MA., (Agar was formerly with the Durham lab in Montreal) and Durham lab colleagues published this paper in the March 27th issue of *Journal of Biological Chemistry*. This study provides in-vivo evidence that normally occurring oxidative modification to SOD1 promotes aggregation and toxicity of mutant proteins. For more information [click here](#).

MOTOR NEURONS MAY HAVE UNIQUE STRESS RESPONSE

The Durham Lab at the Montreal Neurological Institute, McGill University, identified a new pathway for turning on heat shock protein production in neurons, one that didn't trigger this response in non-neuronal cells. The researchers say that if that problem could be remedied, it might become a therapeutic avenue in ALS. The paper, published in the January issue of *Molecular and Cellular Neuroscience*, can be downloaded by [clicking here](#).

NEUROFILAMENT mRNA STABILIZATION BY TDP-43

Researchers led by Dr. Michael Strong at Robarts Research Institute and The University of Western Ontario found that a protein newly implicated in ALS alters the message that directs construction of the scaffold inside motor neurons. This gives a new focus to the effort to find effective treatment for the disease. The scientists found that the protein - TDP-43 - interacts directly with the messenger that carries genetic instructions that allow the motor neuron to carry out internal tasks. The investigators propose that TDP-43 preserves the messenger

RNA directing construction of the neurofilaments. These scaffold proteins in turn allow transport of key cell materials from the nerve cell body in the spinal cord to its distant endings on muscle.

This emerging area in the search for ALS therapeutics will require additional validation to see in what precise way the findings relate to the disease process. The project is jointly funded by The ALS Association and the ALS Society of Canada. The study was published in the March 20 online issue of *Molecular and Cellular Neuroscience*. For more information [click here](#).

NEW RESEARCH AND CLINICAL GRANTS FOR THE STUDY OF ALS

The Les Turner ALS Foundation, a local independent ALS agency, located in Skokie, Illinois, is offering research and clinical study grants of up to \$50,000 per year. The grants will be awarded for one or two years. Grantees will be selected on the scientific merit of

the application and its relevance to ALS. A letter with a one-page summary of the proposed research or clinical study and its relevance to ALS must be submitted to the foundation for preliminary review by July 15, 2007. For more information please visit: www.lesturnerals.org

FIRST ANTIBODY THAT DETECTS ONLY KNOWN CAUSE OF ALS

Continued from page 1
The antibody - SOD1-exposed-dimer-interface antibody (SEDI-antibody) - also opens up the possibility of developing immunization strategies for the treatment of ALS caused by SOD1 mutations, according to Avi Chakrabarty, PhD, of the Ontario Cancer Institute at the University Health Network, senior author of the study. "The SEDI antibody also

has utility in drug discovery efforts for identifying chemical chaperones that prevent or reduce misfolding of SOD1 in ALS," he explains. More than 130 mutations have been identified and it is not yet known how so many different mutations result in the same disease, while the normal enzymatic function of SOD1 is not affected. For more information [click here](#).

DAMAGED MOTOR NEURONS IN ALS CONTRIBUTE TO THEIR OWN DEATH

Researchers from The Ludwig Institute and the University of California, San Diego School of Medicine have discovered that when motor neurons damaged by ALS inappropriately send the wrong signal, immune cells react by killing the messenger. This study combined isolation of the specific cell type (mouse or rat spinal motor neurons) with micro array analysis of gene expression at several time points with respect to onset of clinical symptoms in the SOD1 transgenic animals - genes which were dysregulated in all three mutant lines of SOD1 mice were compiled. The authors

concluded "The unexpected induction of mRNAs of the classic complement pathway long before appearance of obvious clinical symptoms and before major neuroinflammation suggests that mutant SOD1-induced up-regulation of motor neuron derived complement components is a likely aspect of a toxicity developed within motor neurons that contributes to neurodegeneration." Their surprising finding provides new direction for therapies to treat ALS.

The study was published in the online April 27 issue of the *Proceedings of the National Academy of Sciences*.

SCIENTISTS PRODUCE NEURONS FROM HUMAN SKIN

Scientists from Université Laval's Faculty of Medicine have succeeded in producing neurons in vitro using stem cells extracted from adult human skin. According to lead researcher Professor François Berthod this is the first time such an advanced state of nerve cell differentiation has been achieved from human skin. This breakthrough could eventually lead to revolutionary advances in the

treatment of neuromuscular disease. The paper was published in the February issue of the *Journal of Cellular Physiology*.

"Producing neurons from skin cells could solve the problem of human neural cell availability for research," explains Berthod. "Since neurons do not multiply, researchers now have to rely on laboratory animal neurons to perform their experiments".

NEURAL STEM CELLS

Italian investigators published a paper entitled "Neural stem cells LewisX+ CXCR4+ modify disease progression in an ALS model" in the April 17 issue of *Brain Advance Access*. The authors state that, "Basic advances in understanding stem cells suggest their use as a possible therapeutic strategy, but many

biological hurdles (such as the definition) of the better cell type and methods of transplantation in humans) need to be overcome in order to prove that stem cells can be a realistic therapeutic strategy in neurodegenerative diseases." For more information [click here](#).

DIFFERENTIATION BETWEEN PLS AND ALS

Dr. Michael Strong and colleagues published this paper in the February issue of *Archives of Neurology*. Six hundred and sixty-one patients with ALS and 43 patients with PLS were included in the study to determine which clinical features at onset and during follow-up could help differentiate between PLS and ALS. The authors stated that their findings suggest that a patient presenting with spasticity who does not develop wasting within three years most likely has PLS. For more information [click here](#).

THREE FAMILIES WITH ALS AND FTD WITH EVIDENCE OF LINKAGE TO CHROMOSOME 9p

A team led by Dr. Guy Rouleau at the CHUM Research Institute, Notre Dame Hospital in Montreal and colleagues published this paper in the February 15 issue of *Archives of Neurology*. The objective of the study was to determine whether additional families have ALS and FTD (frontotemporal dementia) linked to chromosome 9p. The authors note that, "Other genes in the newly defined 9p locus will be further prioritized for mutation screening by sequencing in our three new families with ALS, FTD, or both, particularly those genes expressed in the brain. Finding the mutation and the responsible gene would have a substantial effect on understanding the etiology of these two diseases."



DALHOUSIE NEUROSURGEON DISCOVERS SPINAL CORD SYSTEM

Dr. Robert Brownstone at the Faculty of Medicine, together with his co-authors have revealed a neuromodulatory system within the human spinal cord that provides valuable new knowledge for researchers looking to solve some of spinal research's biggest challenges. The scientists identified a discrete group of spinal interneurons which serve to amplify the excitatory input to the alpha motor neurons in the anterior horn. The discovery of this system has significant implications for how doctors and researchers understand and treat diseases such as ALS or injuries to the human spinal cord. The study published in the February 7 online issue of *Proceedings of the National Academy of Sciences of the United States of America* can be found by [clicking here](#).

CONTINUUM OF FRONTAL LOBE IMPAIRMENT IN ALS

The objective of this study was to identify the nature and prevalence of cognitive and behavioral abnormalities in ALS patients. The University of California, San Francisco researchers concluded that in their sample (30 new patients with ALS were recruited), a sizable proportion of patients with ALS possess a range of behavioral and cognitive changes that lie on a spectrum of frontotemporal impairment. Right hemisphere atrophy may be a biomarker for cognitive impairment in patients with ALS. The study was published in the April 2007 of *Archives of Neurology*.

NEW STEM CELL RESEARCH PUBLISHED

A team of Harvard researchers has used embryonic stem cells derived from mice carrying a human gene known to cause a form of ALS, to create an in-vitro model of the disease. Harvard researchers Kevin Eggan, PhD, and Tom Maniatis, PhD, are the senior authors of the study. They also confirm that glial cells bearing the same mutation have a direct and non-cell autonomous effect on motor neuron survival. This study (published in the April 15 issue of *Nature Neuroscience*) has major implications for the field of embryonic stem cell research because, Eggan explains, if you have embryonic stem cells that carry the genes for the disease - in this case ALS - "you can

make limitless quantities of the cells affected by the disease, study the disease process, and have an in-vitro model for studying possible treatments."

In the same issue of *Nature Neuroscience*, a group of Columbia University Medical Center researchers, led by Dr. Serge Przedborski, report that specific glial cells, called astrocytes, produce a soluble toxic factor that leads to motor neuron death, but not to death of other classes of spinal neurons. Przedborski says that this means that astrocytes are intimately involved in the disease process. If so, this discovery could provide a new route to developing treatments.

ALS HARD ON FAMILY CAREGIVERS

Italian researchers report that family caregivers of ALS patients are at higher risk for depression than patients they care for. These findings were published in the March 20 issue of *Neurology*. The study

involved 31 male and female ALS patients along with their main caregiver, who usually was a family member, and was not a paid medical professional. For more information [click here](#).

NUTRITIONAL ADVICE AND TREATMENT - BY DIETITIANS TO PATIENTS WITH ALS/MOTOR NEURONE DISEASE

Elaine Cawadias, dietician at The Ottawa Rehabilitation Centre The Ottawa Hospital was one of the authors on this paper. The aim of this study was to survey the knowledge, practice and guideline use of dietitians working in ALS/MND centres/clinics across England, Wales, Northern Ireland and Canada. The authors concluded that "Nutritional assessment techniques and dietary advice should be

standardized. Dietetic collaboration at national and international level is recommended to reduce professional isolation. Training and support in ALS/MND nutrition should be made available as part of post-dietetic registration. Further dietetic research is required to stimulate nutritional care." The paper was published in the *Journal of Human Nutrition and Dietics* (2007).

CLINICOPATHOLOGIC FEATURES OF FTD WITH PROGRANULIN SEQUENCE VARIATION

An international team of researchers led by Jordan Grafman, PhD, National Institutes of Health in Bethesda, Maryland, published this paper in the January 31 edition of *Neurology*. The objective of the study was to describe clinical, pathologic, and genetic features of three FTD patients having either a family history of FTD or of ALS. The

scientists stated that they found two progranulin (PGRN) mutations associated with FTD, in affected individuals who are members of families with possible autosomal dominant FTD. A third PGRN sequence variation (R433W) was found in an FTD patient with family history of ALS. Progranulin is a type of protein known as a growth factor. For more information [click here](#).

A STRUCTURAL MODEL THAT HELPS SOLVE A SCIENTIFIC MYSTERY

University of North Carolina at Chapel Hill researchers have developed a new structural model that helps solve a scientific mystery - how the protein dynein fuels itself to perform cellular functions vital to life. These functions include mitosis (cell division into identical cells). While the research offers no immediate application to human disease, the authors noted that mutations of

dynein have been implicated in some neurodegenerative and kidney disorders. The disruption of dynein's interaction with a particular regulator protein causes defects in nerve cell transmissions and mimics the symptoms of people with ALS. The paper was published in the December 5, 2006, issue of the *Proceedings of the National Academy of Sciences*. For more information [click here](#).

ALS INCIDENCE IN NOVA SCOTIA OVER A 20-YEAR PERIOD: A PROSPECTIVE STUDY

Dalhousie University researchers conducted this study to determine the current incidence of ALS in Nova Scotia and to compare this to data collected in 1984 and 1995. Previous studies have suggested that the incidence of ALS in Nova Scotia is relatively high and increasing over time. The authors concluded that, "The age-adjusted incidence of ALS

in Nova Scotia has remained stable over the period 1984-2003. The incidence is similar to that reported in several other parts of the world." The study was supported by a grant from the Nova Scotia ALS Society. The study was published in the February issue of the *Canadian Journal of Neurological Science* (2007). For more information [click here](#).

ETHNIC VARIATION IN THE INCIDENCE OF ALS - A SYSTEMATIC REVIEW

It is now widely accepted that the incidence (number of new patients who develop disease each year divided by the number of people in the group being studied) is uniform across Caucasian populations, but whether racial variation across other ethnicities exists remains unknown. The Irish and American investigators studying this issue concluded that, "The incidence of ALS may be lower among African, Asian, and Hispanic ethnicities than among whites. We conclude with proposals for a prospective epidemiologic study concentrating on non-Caucasian populations." This article was published in the March 27 issue of *Neurology*. For more information please [click here](#).

HOW COMMON ARE THE "COMMON" NEUROLOGIC DISORDERS

A team led by Dr. Deborah Hirtz at the National Institutes of Neurological Disorders and Stroke/National Institutes of Health, analyzed approximately 500 studies published from 1990 to 2005 to track 12 neurological disorders. They concluded that, "Using the best available data, our survey of a limited number of disorders shows that the burden of neurological illness affects many millions of people in the United States." The paper was published in the January 30th issue of *Neurology*. For more information [click here](#).