Research News

FEBRUARY 2007 - VOLUME 13

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

ALS SLA

VACCINE FOR FAMILIAL ALS TESTED IN MICE

A study led by Jean-Pierre Julien, PhD., and colleagues at Laval University in Quebec City has developed a vaccine for familial ALS. The vaccine delayed the onset of the disease and also prolonged the life of the sick mice by approximately one month. The paper entitled "Therapeutic effects of immunization with mutant superoxide dismutase in mice models of ALS" was recently published in the online issue of *The Proceedings of the National Academy of Sciences*.

"Our previous finding that extracellular mutant SOD1 can provoke motor neuron death (Urushitani et al (2006) *Nature Neuroscience*. 9, 108-118) led us to test immunization against mutant SOD1 in mice models of ALS. In this PNAS paper, we report that vaccination with mutant SOD1 was effective in alleviating disease symptoms and delaying mortality in two ALS mouse models. From these results, we propose that immunization against mutant SOD1, and especially passive immunization approaches, should be explored as a potential therapeutic approach for human ALS cases linked to SOD1 mutations," explains Julien. For more information **click here**.

CALL FOR PARTICIPATION IN ALS RESEARCH

For more than two decades, Dr. Guy Rouleau and his lab at the University of Montreal have put a continuous effort into the identification of genes causing ALS. The success of this research is dependent on voluntary blood sample collection from families with affected individuals. Sample collection is instrumental in discovering new genes responsible for ALS.

Individuals that have ALS with or without a family history of the disease are invited to contribute to the study. It is a confidential process and packages with instructions will be sent to interested participants. For more information contact sample co-ordinator Isabelle Thibault, 514-890-8000 x 24857, e-mail isabelle.thibault@crchum.qu.ca.

NOVEL ENVIRONMENTAL TOXINS: STERYL GLYCOSIDES AS A POTENTIAL ETIOLOGICAL FACTOR FOR AGE-RELATED NEURODEGENERATIVE DISEASES

Another paper written by Chris Shaw and colleagues at the University of British Columbia was published in the December online issue of *Journal of Neuroscience Research*. The study provided evidence that compounds in cycad and bacteria are toxic in nerve cells growing in the lab and in mice. For more information **click here**.

COLLABORATION FUNDS HISTORIC $36 MILLION ALS DRUG SEARCH

Last month the largest ALS drug discovery project in history was launched as a joint venture by the Muscular Dystrophy Association, (MDA) through its Augie's Quest initiative, and the ALS Therapy Development Institute. The three-year, $36 million project, will attempt to identify biochemical targets and find drugs that work on them in ALS.

OKLAHOMA RESEARCHER RECEIVES MUSCULAR DYSTROPHY GRANT

Kenneth Hensley, PhD, an Oklahoma medical research foundation scientist has received a $158,000 grant from the MDA to study whether acetaminophen, the active ingredient in Tylenol, protects motor neurons against ALS. Hensley will use acetaminophen to treat mice bred to exhibit a condition similar to ALS. If successful, the research could expand to human trials.

ALUMINUM ADJUVANT LINKED TO GULF WAR ILLNESS INDUCES MOTOR NEURON DEATH IN MICE

University of British Columbia researcher Chris Shaw, PhD, and colleagues have published this study in the February issue of *NeuroMolecular Medicine*.

Associated with some cases of Gulf War Illness (GWI) are increased incidences of ALS and other neurological disorders. Whereas many environmental factors have been linked to GWI, the role of the anthrax vaccine has come under increasing scrutiny. Among the vaccine's potentially toxic compounds are the adjuvants aluminum hydroxide and squalene. The authors examined whether these compounds might contribute to neuronal deficits associated with GWI and developed an animal model for examining the potential neurological impact of aluminum hydroxide, squalene, or aluminum hydroxide combined with squalene. The experiments described in the paper were designed to provide an accurate multilevel analysis of the potential impact of aluminum hydroxide and squalene on the nervous system over extended time periods on an outbred strain of young male mice. Aluminum hydroxide is a substance routinely added to many common vaccines to spur production of antibodies, although scientists are not sure how it does that. Squalene, a cholesterol-building compound occurs naturally in the body in small quantities. The findings of this study suggest a possible role for the aluminum adjuvant in some neurological features associated with GWI and possibly an additional role for the combination of adjuvants. For more information **click here**.

INDUCTION OF MULTIPLE HEAT SHOCK PROTEINS AND NEUROPROTECTION IN A PRIMARY CULTURE MODEL OF FAMILIAL ALS

Heather Durham, PhD, and colleagues at the Montreal Neurological Institute, McGill University, published this paper in the November 2006 issue of *Neurobiology of Disease*. High threshold for stress-induced activation of the heat shock transcription factor (Hsf1) may contribute to vulnerability of motor neurons to disease and limit efficacy of agents promoting expression of neuroprotection heat shock proteins through this transcription factor. Heat shock proteins protect against mutant SOD1 in cells growing in lab dishes. The authors state that, "Because not all drugs that induce the heat shock response are effective in neurons, primary spinal cord-DRG cultures represent an excellent model for secondary screening of compounds before testing in animal models or patients with neurodegenerative disease." For more information **click here**.

LOSS OF NITRIC OXIDE-MEDIATED DOWN-REGULATION OF NMDA RECEPTORS IN NEUROFILAMENT AGGREGATE-BEARING MOTOR NEURONS IN VITRO: IMPLICATIONS FOR MOTOR NEURON DISEASE

A substantial literature supports the concept that motor neuron death is mediated via calcium influx, primarily through non-NMDA class of glutamate receptors. In this study, the Strong lab (at the Robarts Research Institute in London, Ontario) builds on previous work which demonstrated that calcium influx through motor neuron NMDA (N-methyl-D-aspartic acid) receptors is a mediator of programmed cell death pathways. Now, using an in-vitro model of motor neuron pathology - human neurofilament light chain overexpressing (hNFL+/+) spinal motor neurons-these investigators have established that the increased calcium influx is not a simple result of increased expression of the NMDA receptors. Rather, the diseased motor neurons display altered regulation of nitric oxide (NO) production. NO modulates the NMDA-receptor calcium influx, and thus the diseased motor neurons can be protected by addition of exogenous NO. Whether the in-vivo source of such NO acts intracellularly or extracellularly remains to be determined. These studies suggest an additional approach to motor neuron maintenance/therapy based on subtle but critical regulation of NO. This study was published in the January issue of *Free Radical Biology & Medicine*. For more information **click here**.

RESEARCHERS DISCOVER GENE CONTRIBUTING TO ALZHEIMER'S

U of T Centre for Research in Neurodegenerative Diseases researcher Ekaterina Rogaeva, PhD, and a group of international colleagues are one step closer to understanding one of the causes of Alzheimer's disease and identifying people who run a larger risk of getting the disease. The group has discovered a gene that when defective results in the buildup of a toxic protein byproduct in the brain and contributes to the onset of Alzheimer's at approximately age 70. The paper was published in the January 14 online issue of *Nature Genetics*.

ANALYSIS OF IFT74 AS A CANDIDATE GENE FOR CHROMOSOME 9P-LINKED ALS-FTD

Is the title of a paper that was published in the December 13, 2006 online issue of *BMC Neurology*. The paper describes sequence analysis of the candidate gene intraflagellar transport 74 (IFT74) in two chr 9p21-linked ALS-FTD, kindreds and in unrelated cases of ALS-FTD (n =20); FTD (n = 195); ALS (n=210) and more than 1,000 control subjects. Sequence variants in the gene were identified; however results provide suggestive but not definitive evidence for the role of this gene in ALS or FTD. The study was carried out by a large international group, including Ekaterina Rogaeva at the University of Toronto, Centre for Research in Neurodegenative Disease. For more information **click here**.

ALS – AN UPDATE FOR FAMILY PHYSICIANS

London, Ontario doctors Christen Shoesmith (neuromuscular fellow at the London Health Sciences Centre), and Michael Strong wrote this article in the December issue of Family Physician. The authors concluded that because ALS is a complex disease, care of ALS patients is best provided at multidisciplinary clinics that specialize in managing patients with ALS. To read a copy of the article **click here**.

MARK YOUR CALENDARS

FRONTOTEMPORAL DEMENTIA IN ALS

The second international research conference will be held from June 10 - 13 at the Best Western Lamplighter Inn in London, Ontario. The event is sponsored by the ALS Society of Canada; The ALS Association; ALS Society of (Windsor) Essex County, and The Michael Halls' Endowment. For more information contact Rita Casciano, conference co-ordinator at 519-663-3874 or e-mail rita.casciano@lhsc.on.ca

NEW DIAGNOSTIC TEST

Australian researchers from the University of New South Wales (UNSW), the Prince of Wales Medical Research Institute (POWMRI) and the Prince of Wales Hospital have found a quicker and more effective way to diagnose motor neuron disease.

The diagnostic test, which was carried out at POWMRI, involves transcranial magnetic stimulation (TMS), a painless technique that involves a magnetic coil being held to the patient's head. The coil stimulates the underlying motor cortex, resulting in involuntary movement of the hand or leg. The research was published in the September 2006 *Journal Brain*. For more information **click here**.

ABSENCE OF TUMOR NECROSIS FACTOR α DOES NOT AFFECT MOTOR NEURON DISEASE CAUSED BY SOD1 MUTATIONS

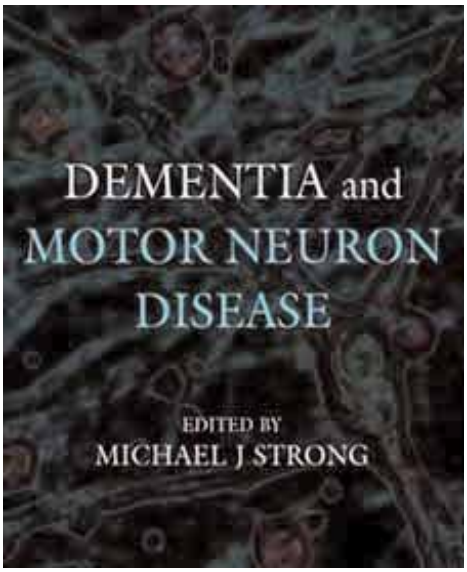
Jean-Pierre Julien, PhD, and colleagues at Laval University published this paper in the November issue of *Neurobiology of Disease*. An increase in the expression of the proinflammatory cytokine tumor necrosis factor (TNFα) has been observed in patients with ALS and in the mice models of the disease. Under certain conditions TNFα can induce or exacerbate neuronal cell death. The authors stated that their " results provide compelling evidence indicating that TNFα - does not directly contribute to motor neuron degeneration caused by SOD1 mutations." For more information **click here**.

DEMENTIA AND MOTOR NEURON DISEASE

This 256-page reference textbook, edited by Dr. Michael Strong features the following:

- Comprehensive work ideal for clinical and research groups focusing on dementia or ALS, as well as those working in the fields of neuroimaging and neuropsychology ;
- frontotemporal dementia, including history, anatomy, and impairment; clinical phenomenology and treatment; cognitive dysfunction; neuroimaging; molecular and cellular neuropathology; genetics; and neurochemistry
- contributions from international opinion leaders in dementia and motor neuron disease

For more information about the book, **click here**.



MANIPULATION OF PROTEIN KINASES REVEALS DIFFERENT MECHANISMS FOR UPREGULATION OF HEAT SHOCK PROTEINS IN MOTOR NEURONS AND NON-NEURONAL CELLS

Heather Durham, PhD, and colleagues at the Montreal Neurological Institute published this paper in the January issue of *Molecular and Cellular Neuroscience*. Motor neurons have a high threshold for induction of heat shock proteins in response to stress, a property associated with impaired ability to activate heat shock transcription factor 1. Heat shock proteins are a group of proteins whose expression is increased when the cells are exposed to elevated temperatures. This study demonstrated that the impaired heat shock response in motor neurons is not due to altered phosphorylation of Hsf1 by kinases previously shown to affect activation of Hsf1 in other cells (PKC, GSK3beta, ERK1, CaMKIIalpha). The largest group of kinases are protein kinases, which act on and modify the activity of specific proteins. These are used extensively to transmit signals and control complex processes in cells. The results of the study point to novel mechanisms of activation of heat shock genes in motor neurons that have relevance to exploitation of endogenous stress responses therapeutically. For more information **click here**.