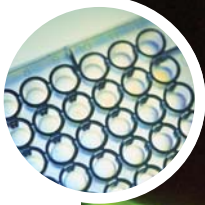


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# Research News

## SEPTEMBER 2008 - VOLUME 18

### ALS CANADA SUPPORTS LITHIUM TRIAL

The ALS Society of Canada is supporting two parallel and extremely important missions to help people with ALS.

The first is supporting the funding of a national clinical trial to confirm data from an Italian clinical study that demonstrated significant positive effect in slowing the progression of ALS in patients in the early stages of the disease, through the use of lithium. Secondly, the lithium clinical trial is the first joint effort by Canadian ALS clinicians who have formed a consortium - CALS - the Canadian ALS Clinical Trials and Research Network. CALS will represent ALS Centres across the country and provide clinical trial participation opportunities for many more patients. The formation of CALS is being supported by ALS Canada. Historically, few clinical trials have taken place in

Canada. This model will remain in place for future trials, giving all persons living with ALS across Canada and not just those living in large metropolitan areas the increased opportunity to participate in clinical trials. CALS will be joined in the clinical trial by NEALS - the Northeastern ALS Consortium, which includes internationally renowned ALS expert neurologists from Harvard, Columbia, Johns Hopkins, Emory, and a number of other prestigious university-based ALS Centres.

In the Italian clinical study, published in the February, 2008 issue of *Proceedings of the National Academy of Sciences*, Italian researchers stated that all subjects treated with lithium, in combination with riluzole, were alive at the end of the follow up (15 months), and their quality of life was not modified. By contrast, 29 per cent of the

patients receiving riluzole alone died during the study. The Italian study used a small sample of patients.

The combination of both lithium and riluzole in ALS patients appeared to keep patients alive longer and slow loss of breathing capacity and other clinical measures of disease progression.

Lithium is a salt that has numerous actions in the nervous system. As a mood-altering drug, it is best known for its use in treating bipolar disorder. It is a potentially toxic drug and must be taken under a doctor's supervision with frequent monitoring of blood levels. Lithium protects neurons in the brain in animal models of neurodegenerative diseases, including Alzheimer's and Parkinson's diseases, and has recently shown to do the same in a mouse model of ALS. "Health Canada has approved

this cutting-edge clinical trial protocol designed by lead investigator Dr. Lorne Zinman, medical director of the ALS Clinic at the Sunnybrook Health Sciences Centre in Toronto. Drugs for the Canadian component of the trial have been donated by the manufacturers. Since there is no cure for ALS yet, research into treatments gives hope to ALS patients and their families," explains David Cameron, President & CEO of ALS Canada.

The one-year joint Canadian-U.S. clinical trial is planned to commence this fall. The ALS Canada-supported trial will be a double-blind, placebo-controlled trial. Up to 250 patients (125 of whom will be in Canada) will be randomized and take lithium or placebo, so neither the patients nor doctors will know who is receiving the lithium treatment or placebo.

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## MANAGEMENT OF ALS

French researchers Philippe Corcia and Vincent Meininger, published a study in *Drugs* 2008;68(8):1037 earlier this year entitled *Management of Amyotrophic Lateral Sclerosis*. Even though ALS remains fatal, several advances have been made during the last decade in improving the consequences of motor dysfunction, quality of life and survival time of patients. Treatment of ALS cannot be restricted to riluzole, the only drug that has been proved to modify the evolution of the disease. Symptomatic treatments have an important role in controlling the major consequences of the disease, such as pain, sleep disorders, spasticity, sialorrhoea (drooling), emotional lability, depression and digestive disorders (constipation and reflux). All these symptoms need to be recognized and possible treatments identified to provide the most appropriate management of patients with ALS.

The authors state, "Important findings have been made in understanding the nature of the degenerative process that affects the motor neurons. Despite the negative results obtained until now, we hope to demonstrate very soon a greater improvement in therapy."

The authors conclude, "Besides somatic management, which remains important, we have to improve the quality of life of the patients but also of the caregivers, whose involvement is significant."

For more information [click here](#).

## PROTEIN STABILITY AND AGGREGATION PROPENSITY PLAY A ROLE IN ALS PATIENT SURVIVAL

Mutation in the SOD1 gene account for 10-20 per cent of inherited ALS cases.

Now, a group of researchers at Brandeis University in Waltham, Massachusetts and Brigham and Women's Hospital in Boston, Massachusetts, attribute longevity in familial ALS patients to a couple of properties of the SOD1 protein. The study was published in the July 29, 2008 issue of *PLoS ONE*. Researchers reported that both the stickiness of SOD1 and its decreased stability account for 69 per cent of survival from familial ALS. This provides

### LESSONS LEARNED IN ALS RESEARCH

A number of therapies have shown promise in pre-clinical models of motor neuron disease. Many of these treatment approaches, however, failed in human studies. American researchers Veena Lanka and Merit Cudkowicz published a study in *Amyotrophic Lateral Sclerosis* in June 2008 entitled "Therapy development for ALS: Lessons learned and path forward."

It is important to identify whether the past trials were unsuccessful due to wrong therapy and biological target or because of flaws in trial design and conduct. One reason for an unsuccessful trial is the wide variety of *in vitro* and *in vivo* models available to study both the biology and screen therapeutic compounds. There is not enough information available to either validate or invalidate these models as useful preclinical screen to accurately predict therapies that will succeed in humans. The models are invaluable as tools to test proof of concept that the

evidence that SOD1 stability and its aggregation propensity is the main toxic causes of ALS.

The current study looked at the difference in disease progression in patients with differing mutations. The team found that those mutations that made SOD1 more likely to unfold from its normal structure, and those that made it more likely that SOD1 would stick to other unfolded SOD1 molecules correlated with reduced survival times post disease onset.

For more information [click here](#).

proposed therapy has desired biological activity.

The authors state, "Better biomarkers of disease and markers of biological activity of the therapies under further development are urgently needed. Obtaining information regarding dosage, pharmacokinetics, short-term safety and biological activity in well designed phase I and II studies is critical to the design of phase III trials that will yield meaningful results."

The authors conclude, "With improved clinical standards of care, availability of rigorously trained clinical trial sites and better understanding of challenges in trial design and conduct in ALS, the chances of success are greatly improved."

For more information [click here](#).

## UMBILICAL CORD BLOOD CELL TRANSPLANTS IN MOUSE MODELS OF ALS

A study at the University of South Florida has shown that transplants of mononuclear human umbilical cord blood (MNChUCB) cells may help patients suffering from ALS. This study was published online in the June 2008 issue of *PloS ONE*. Researchers transplanted human umbilical cord blood (HUCB) cells into mouse models with ALS. Cells were transplanted at three different dose strength levels (low, moderate and high) to determine the degree to which dose levels of transplanted cells might delay disease symptom

progression and increase lifespan. Researchers determined that the moderate-strength dose of HUCB cells was most effective in increasing lifespan and reducing disease progression. According to the research team, modulating immune and inflammatory effectors with HUCB cells could have a protective effect on dying motor neurons. The team had previously shown that HUCB cell transplants reduced inflammation and provided neuroprotection in models of stroke and Alzheimer's disease.

For more information [click here](#).

## ALS AND STEM CELLS

Direct injection of stem cells in ALS is problematic because of the large expanse of the neuraxis that would need to be injected. Researchers at the University of British Columbia, Vancouver General Hospital, and the University of Iowa Hospitals and Clinics, published a study in the March 2008 online issue of *Muscle and Nerve* entitled "Pilot study of granulocyte colony stimulating

factor (G-CSF)-mobilized peripheral blood stem cells in ALS."

Researchers reasoned that transiently increasing the number of circulating hematopoietic stem cells might be a useful therapeutic approach. However, agents stimulating the activation and mobilization of hematopoietic stem cells may have adverse effects such as activation of microglial cells.

For more information [click here](#).



More than 120 researchers and young investigators attended ALS Canada's 4th Annual Research Forum in Toronto last May.

## HIGH QUALITY OF LIFE

A study conducted by Dorothee Lule, Sonja Hacker, Albert Ludolph, Niels Birbaumer and Andrea Kubler reports that patients with ALS experience a high quality of life and are satisfied with their lives. The study was published in the June 2008 issue of *Deutsches Ärzteblatt International*.

The authors showed that the quality of life of ALS patients does not depend on the severity of their physical restrictions. In contrast, it was found that patients who have to be given artificial respiration are more satisfied than patients who do not need it. These studies found no correlation between physical disability in ALS and either depression or the quality of life. The severity of depression was found to be inversely related to educational status. In ALS patients, the quality of life was comparable with healthy controls.

For more information [click here](#).

## ALS CANADA SUPPORTS LITHIUM TRIAL

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Participants will take twice-daily doses of lithium carbonate to reach and maintain the same blood level used in the Italian study. The disease course and safety assessments will be measured at regular intervals over that time.

Denise Figlewicz, PhD, Director of Research at the ALS Society of Canada says, "We welcome this opportunity to support the lithium clinical trial. The promising results from the Italian study data serve as the impetus for new research and treatment strategies. This is very exciting news for the ALS community. We also welcome this opportunity to work together with our American colleagues. This collaborative approach between Canada and the United States and will serve as a model for subsequent clinical trials."

The clinical trial is funded in part by ALS Canada. Other funding partners from the United States include the National Institutes of Health/National Institute of Neurological Disorders and Stroke and The ALS Association.

Information about the upcoming clinical trials will be posted on ALS Canada's web site as it becomes available.



## FINDING CLUES FOR NERVE CELL REPAIR

A new study at the Montreal Neurological Institute at McGill University identifies a key mechanism for the normal development of motor neurons. The study was published in June 2008 in the *Proceedings of the National Academy of Sciences*.

"We have identified a key factor, called Runx1, which controls the correct development of motor neurons in the upper part of the spinal cord. Runx1 helps motor neurons to maintain their status by regulating the expression of a set of specific genes. In doing so, it might also help motor neurons find their target muscles," explains Dr. Stefano Stifani, neuroscientist at the Montreal Neurological Institute and lead investigator in the study.

For more information [click here](#).

## UC RESEARCH SHOWS RISK OF ALS EXPOSURE IN GULF WAR VETERANS IS TIME LIMITED

Researchers at the University of Cincinnati (UC), said that cases of ALS among soldiers who served in the first Persian Gulf War were caused by certain events during their deployment to the war zone and that exposure and illness is not as widespread as previously thought. The study was published in the July issue of *Neuroepidemiology*.

Lead researcher, Ronnie Horner, said, "The outbreak was time-limited. We actually saw a declining risk after 1996; therefore, the risk is not continual. The pattern of disease onset suggests that whatever exposure occurred among these soldiers most likely happened sometime between August 1990 and July 1991, the period of the first Gulf War."

Now, researchers at Duke, Durham Veterans Affairs Medical Center and UC are taking it one step further and are conducting studies to find possible exposures these veterans had while deployed to the Persian Gulf area that may be the cause of the outbreak.

For more information [click here](#).

## HUMAN ALS-ASSOCIATED MUTATION IN VAP33A

ALS8 is caused by a dominant mutation in an evolutionarily conserved protein, VAPB (vesicle-associated membrane protein (VAMP)-associated membrane protein B)/ALS8). Researchers have established a fly model of ALS8 using the corresponding mutation in *Drosophila* VAPB (dVAP33A) and examined the effects of this mutation on VAP function using genetic and morphological analyses. Researchers from the University of California, Anuradha Ratnaparkhi, George Lawless, Felix Schweizer, Peyman Golshani, and George Jackson, published the study in June 2008

in *PLoS ONE* online. In another study published by researchers from the Baylor College of Medicine in Houston, Texas in the June 2008 issue of *Cell Press* online revealed that specifically [a point mutation - P56S - in the major sperm protein - MSP- domain of the human VAPB is associated with ALS]. MSP domains of VAP proteins are cleaved and secreted ligands for Eph receptors. The P58S in *Drosophila* VAP33 leads to a failure to secrete the MSP domain as well as ubiquitination, accumulation of inclusions in the endoplasmic reticulum, and an unfolded protein response.

For more information [click here](#).

## NEW MOTOR SYSTEM IMPAIRMENT DIAGNOSING TOOL DEVELOPED

The DIMETER system is a new tool that will assist doctors and other health professionals to objectively evaluate the tremors exhibited in the hands and fingers of patients affected by some disorders that impair their motor skills, such as ALS. Researchers Antonio Barrientos and Roberto Gonzalez from The Universidad Politecnica de Madrid, published this study in the January online issue of *Medical News Today*.

To make such measurements, DIMETER uses an electromechanical apparatus that is controlled by the hand or finger of the affected patient

and registers the movement and the forces that are generated. Using this device and a computer monitor, doctors execute a series of virtual static and motion tests. In any of these tests a weight can be added to the patient to evaluate the effect on the tremor while the system constantly monitors and records each movement.

The computer gathers the data and processes it to provide the doctor with the information needed for the patient's evaluation in a numerical or graphical format to the level of detail required.

For more information [click here](#).