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.

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2008 ALS SOCIETY OF CANADA RESEARCH FORUM

More than 100 ALS researchers and young investigators attended the fourth annual ALS Research Forum, held in Toronto May 3-5.

PERIPHERIN AND ALS DISEASE PATHOLOGY

Canadian and U.S. researchers have published a paper entitled "An aggregate-inducing peripherin isoform generated through intron retention is upregulated in ALS and associated with disease pathology," in the February issue of Journal of Neuroscience.

In this study, evidence presented suggests that a novel splice form of peripherin, a lesser studied component of ALS inclusions, is upregulated in ALS and is linked with disease pathology. Previous studies of peripherin, a neuronal intermediate filament protein and component of ubiquitinated inclusions and axonal spheroids in ALS, have shown that overexpression of the protein is associated with motor neuron degeneration in transgenic mice.

These are the first findings to prove that peripherin splicing defects are present in ALS cases and may be involved in the generation of disease pathology.

For more information click here.
Researchers at the ALS Therapy Development Institute (TDI) in Cambridge, Massachusetts, recently released the results of a five-year study suggesting that no significantly positive outcomes were seen in any of the drugs previously believed to extend the survival rate in the commonly used ALS mouse model. The paper, published in the January issue of *Amyotrophic Lateral Sclerosis*, not only highlights the five-year drug screening effort, but also explains why so many compounds previously thought to work in mice don't perform well in clinical trials.

Scientists screened the drugs in 18,000 genetically engineered mice across 221 independent studies only to find no significantly positive outcomes for any of the compounds previously believed to extend the lifespan of the ALS mouse model.

"Researchers have been puzzled as to why animal results have failed to replicate in the clinic. It appears this animal model is subject to greater variability than many investigators realized. The exciting part of this study is that one can now identify and substantially eliminate the biological variability to fully exploit the value of this animal model for identifying effective treatments," says Sean Scott, the principal investigator and president of the Cambridge-based ALS TDI.

For more information click here.

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ELEVATION OF LIPIDS: A PROTECTIVE FACTOR IN ALS

In an effort to identify the high prevalence of malnutrition and weight loss affecting ALS patients, scientists in France have focused their attention on lipids - a major source of energy for muscles - to see its impact on disease progression and survival.

Hyperlipidemia, the elevation of lipids in the bloodstream, was twofold higher in patients with ALS than in the control group. Likewise, steatosis, the build up of fat, was more prevalent in the patients with ALS. Studies correlating the data have shown that the abnormally high levels of lipids in the blood significantly increased survival by more than 12 months. This not only highlights the importance of nutrition on disease progression, but also draws attention to treating these patients with lipid-lowering drugs, which are frequently prescribed.

The study was published in the February issue of *Neurology*.

For more information click here.

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DECIPHERING THE STANDARD MURINE MODEL OF ALS

From compounds such as minocycline, creatine, ritonavir, celecoxib, sodium phenylbutyrate, ceftriaxone, thalidomide, and riluzole - the only drug approved for ALS treatment - no extended survival benefits were identified.

"Researchers have been puzzled as to why animal results have failed to replicate in the clinic. It appears this animal model is subject to greater variability than many investigators realized. The exciting part of this study is that one can now identify and substantially eliminate the biological variability to fully exploit the value of this animal model for identifying effective treatments," says Sean Scott, the principal investigator and president of the Cambridge-based ALS TDI.

For more information click here.

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ASTROCYTES IN FAMILIAL ALS

Astrocytes are large non-neuronal cells found in the central nervous system that provide structural support for the neurons, forming an integral part of the blood-brain barrier and are involved in repairing nerve tissues. To determine whether mutant SOD1 damage to astrocytes contributes to disease progression in ALS, researchers at the Ludwig Institute for Cancer Research in the U.S. and the RIKEN Brain Science Institute in Japan, genetically removed the mutant SOD1 gene, but only in astrocytes.

Unfortunately, disease onset and early disease was not slowed down, however late stages of the disease were extended, nearly doubling the normal life expectancy in the mouse models. This evidence suggests that astrocytes are likely to be a viable target to slow the rate of disease progression and extend survival rates in patients with ALS.

"Silencing the mutant gene in the astrocytes not only helps protect the motor neuron, but delays activation of mutant microglia that act to accelerate the progression of ALS," says Don Cleveland, PhD, University of California, San Diego, professor of medicine, neurosciences and cellular and molecular medicine and member of the Ludwig Institute for Cancer Research. The study was published in the March issue of *Nature Neuroscience*.

For more information click here.
GENE-TARGETED THERAPIES

In a recent neurological review published in the February issue of Archives of Neurology, Timothy Miller, MD, PhD, assistant professor of neurology at the Washington University School of Medicine and colleagues investigated the mechanisms of antisense oligonucleotides and RNAi in decreasing protein levels that may contribute to various diseases, such as ALS, where abnormal protein aggregation has been linked to pathogenesis.

Both antisense oligonucleotides and RNAi provoke the destruction of the messenger RNA, resulting in less protein production. Simple modifications, such as this, where the amount of offending protein present is reduced, may prove to be an effective therapy.

Evidence to date suggests that nucleic acid-based therapies, such as those dealing with oligonucleotides and RNAi, show promise in treating a number of neurodegenerative diseases where abundant protein production is an issue. As more specific genes are linked to these diseases, the potential of applying gene-targeted therapies draws nearer.

The authors conclude that "the identification of the genes and proteins involved in many neurodegenerative diseases offers the exciting possibility of modifying those disease-linked proteins to develop novel, targeted therapies for diseases such as ALS. The challenges are clear, but once we navigate the details of delivery and safety, gene-targeted therapies are likely to become an important treatment option for currently untreatable neurodegenerative diseases."

NEW INSIGHTS INTO ALS PREVENTION

Keiichi Kadoyama and colleagues at the Osaka University in Japan report on a possible therapeutic agent that may delay disease progression in ALS patients in the October 2007 issue of Neuroscience Research.

The authors state that "although prevention of motoneuronal degeneration has been postulated as the primary target for a cure, accumulating evidence suggests that microglial accumulation contributes to disease progression."

Using double transgenic mice overexpressing mutant SOD1 (Cu/Zn superoxide dismutase) and HGF (hepatocyte growth factor), researchers found a marked decrease in the number of microglia present. Loss of motor neurons in facial and hypoglossal nuclei was also reduced. "These findings suggest that in addition to direct neurotrophic activity on motor neurons, HGF-suppression of gliosis may retard disease progression, making HGF a potential therapeutic agent for the treatment of ALS patients."

For more information click here.

MR IMAGE ANALYSIS OF ALSD

A study published in the September 2007 issue of the American Journal of Neuroradiology suggests that ALS is not an isolated motor neuron disorder but a multisystem disorder with differing symptoms, leading some patients to develop dementia.

The study, conducted by researchers in Japan, randomized patients into two groups: ALSD (ALS and dementia) and classic ALS. Neuropathologic examinations, specifically MR imaging, of the ALSD group revealed that the medial cortex of the anterior temporal lobe was consistently involved - a characteristic of ALSD and a useful clue for the differential diagnosis of ALSD. This data suggests that MR imaging may be a valuable tool in identifying and characterizing ALSD perhaps at an earlier stage, as the involvement of additional brain structures along with the motor neuron system were observed in this study.

DISULFIDE BOND IN FAMILIAL ALS

Scientists in Japan have recently uncovered evidence suggesting that upon mild oxidative stress in vitro, Cu/Zn-superoxide dismutase (SOD1) readily forms an incorrect disulfide bond between the cysteines at positions six and 111 of the mutant SOD1 - resulting in high molecular weight aggregates, ubiquitylation, and neurotoxicity, which leads to neuronal cell death in familial ALS.

Replacement of the cysteines significantly reduced these effects. However, further studies will need to be carried out in mutant SOD1 transgenic mice in vivo to clarify the roles of each cysteine residue in the pathogenesis of ALS. The study was published in the September 2007 issue of The Journal of Biological Chemistry.

For more information click here.
EALSC UNVEILS GOOD PRACTICE POINTS FOR THE MANAGEMENT OF ALS

In a review of the techniques used in the diagnosis and clinical management of ALS, international researchers at the European ALS Consortium (EALSC) working group have outlined guidelines supporting the prompt diagnosis and optimal symptom management needed to improve the survival rate and quality of life for ALS patients.

With data from 2003 to December 2006, this review addresses 10 central issues in the current optimal clinical approach to ALS:

• Diagnosing ALS/MND
• Breaking the news: communicating the diagnosis
• Multi-disciplinary care in management of ALS
• Neuroprotective treatment
• Symptomatic treatment (Sialorrhoea, Bronchial secretions, Cramps, etc.)
• Genetic testing and counselling
• Non-invasive and invasive ventilation in ALS patients
• Enteral nutrition in ALS patients
• Communication in ALS patients
• Palliative and end-of-life care

The authors state that "during the course of the disease, every effort should be made to maintain patient autonomy. Advance directives for palliative end-of-life care are important and should be discussed early with the patient and relatives if they so wish."

The study was published in the August 2007 issue of Amyotrophic Lateral Sclerosis.

For a complete list of guidelines and practice points [click here].

NEUROMUSCULAR DYSFUNCTION IN THE MUTANT-SOD1 MOUSE MODEL OF ALS

A study on the number of motor neurons and the uptake and transport of fluorogold - a fluorescent dye used to outline neurons - in mutant-SOD1 mice was recently conducted by ALS researcher Charles Krieger and colleagues in British Columbia in hopes of better understanding the interaction between motor neuron dysfunction and denervation in ALS.

Researchers found that in these severely affected mice, motor neuron loss was moderate, while retrograde uptake and transport were extremely impaired. This not only corresponds with progressive muscle denervation but also suggests that the debility experienced in ALS may partially be the result of weakened retrograde uptake and transport. The study was published in the January issue of Amyotrophic Lateral Sclerosis. For more information [click here].

NDEL1 AND VIMENTIN DYNAMICS

Researchers at Hotchkiss Brain Institute, Picower Institute for Learning and Memory, and Harvard Medical School have recently narrowed their focus on Ndel1, a gene they believe is responsible for diseases featuring transport/trafficking defects and impaired regeneration, such as ALS.

Ndel1 is essential for mitotic cell division and neuronal migration, particularly through the regulation of cytoplasmic Dynein function. Neurons need Ndel1 to power up the Dynein motors that drive cell migration in brain development. If Ndel1, Dynine, or Lis1 - lissencephaly protein, involved in several developmental processes mediated by the Dynein/dynactin pathway - are not present, the connection between the centrosome and the nucleus is lost and the process of cell migration comes to a halt.

To prove this theory, researchers isolated an Ndel1 complex composed of the intermediate filament (IF) Vimentin, the molecular motor of Dynine, Lis1, and alpha-coat protein (COP), a vesicular protein. The presence of Ndel1 promoted the interaction between Lis1, COP, and the Vimentin-Dynein complex, activating the Dynein-mediated transport of Vimentin. As expected, the loss of Ndel1 interrupted Vimentin transport causing these filaments to accumulate and alter the process of neurite formation. Neurite formation is also essential to the process of regeneration. Neurite formation is also essential to the process of regeneration. Thus, Ndel1 may be a potential target for neurological diseases, such as ALS, that feature transport and trafficking defects.

The results were published February 26 in The Journal of Biological Chemistry online issue.

For more information [click here].

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Montreal researchers have recently uncovered evidence suggesting that oxidation of wild-type SOD1 leads to its misfolding, consequently having many of the same toxic properties associated with mutant SOD1.

In vitro studies of oxidized/misfolded SOD1 and in vivo studies of misfolded SOD1 have shown selective toxicity towards motor neurons, suggesting that the presence of these protein species may lead to ALS, even in individuals not carrying the SOD1 mutation.

In the December issue of *Annals of Neurology*, investigators propose that oxidized/ misfolded SOD1 is the cause of most forms of classic ALS and should be a primary target for the design of therapeutic treatments for the disease.

For more information click here.

**OXIDIZED/MISFOLDED SOD1: THE CAUSE OF ALS?**

Montreal researchers have recently uncovered evidence suggesting that oxidation of wild-type SOD1 leads to its misfolding, consequently having many of the same toxic properties associated with mutant SOD1.

**GSK3BETA: A POTENTIAL THERAPEUTIC TARGET IN ALS**

The deposition of highly phosphorylated microtubule-associated tau protein has been observed in ALS patients with cognitive impairment (ALSci).

In an effort to understand this accumulation, scientists at the Robarts Research Institute at the University of Western Ontario in London, Ontario, have examined whether the expression of two protein kinases responsible for mediating tau hyperphosphorylation, glycogen synthase kinase 3-beta (GSK3beta) or cyclin-dependent kinase 5 (CDK5), are also altered.

To assess GSK-3beta activity, the team examined GSK3beta, phospho-GSK3beta and phospho-beta-catenin expression, and found an increased level of expression of all three in both ALS and ALSci, when compared to the control. However, no significant difference was observed between the control, ALS or ALSci in the expression of CDK5 or p25/p35.

In the study, published in the February issue of *Brain Research*, the authors conclude that "GSK3beta expression is upregulated in ALS and ALSci and that GSK3beta activation is associated with the intraneuronal deposition of hyperphosphorylated tau protein. This supports the potential role for GSK3beta as a therapeutic target in ALS."

For more information click here.

**UNPRECEDENTED METHOD TO PREDICT ALS**

Using a genomic pathway approach for studying Parkinson's disease, researchers in Miami are currently developing a model that is highly predictive in identifying people who are more susceptible to ALS.

By studying common variations within the genes for the axon guidance pathway - which wires the brain during fetal development and maintains and repairs brain wiring throughout life - several gene variations that collectively predicted those at high risk of developing ALS were identified. This genomic pathway approach suggests that even for disorders that appear sporadic, genetic factors may still play a major role. Statistically, the probability that these findings were by chance is extremely small, less than one in one trillion.

"The mission of our research is to predict, prevent and halt brain aging disorders," says Demetrius Maraganore, MD, Mayo Clinic neurologist and principal investigator. "I envision a day when we will be able to do a simple blood test and predict whether a person is at high risk to develop brain aging disorders such as ALS, Parkinson's disease and even Alzheimer’s disease by studying common gene variations in disease pathways. In persons at high risk, we may be able to prevent the diseases, slow or halt their progression by developing drugs that target the same disease pathways. For ALS and Parkinson's disease, our study is a major step in these directions."

The study was published in the January issue of *Plos One*. For more information click here.
In a study published in the February issue of The Journal of Clinical Investigation, scientists at the University of Iowa Carver College of Medicine and The University of Kansas have found an interaction between two proteins, which when treated can slow the progression of ALS in mice, nearly doubling the survival rate.

Investigators discovered that when SOD1, a protein that is mutated in familial ALS, and Rac1, a protein that regulates the production of reactive oxygen species (ROS) by way of the Nox2 protein complex, bind together, ROS are produced. Although ROS are required for normal cell functions, too much can cause oxidative stress. And an abnormal rate of ROS production likely contributes to the pathogenesis of ALS and other neurodegenerative diseases.

When the Nox2 protein was removed, the lifespan of the mice with familial ALS almost doubled. Blocking Nox2 by apocynin has also been shown to slow the progression of the disease and increase the lifespan of mice with ALS. These results suggest that the dysfunctional interaction between SOD1 and Rac1 may be the underlying cause for the overproduction of ROS in familial ALS, a finding that could lead to a treatment for some forms of the disease.

This discovery confirmed a previous report published in the October 2007 issue of The Journal of Clinical Investigation by John Engelhardt, PhD, and colleagues at the University of Iowa, who had found a reduced rate of progression and increased survival in mutant SOD1 mice that lacked expression of either Nox1 or Nox2, although the effects were more dramatic in the absence of Nox2. As the Nox proteins are carried on the X chromosome, female mice lacking one copy of either gene showed delayed disease onset, suggesting that even a 50 per cent decrease in the expression of these proteins offered some protection.

Additional studies conducted by Don Cleveland and Séverine Boillée at the Ludwig Institute for Cancer Research in La Jolla, California, and also published in February issue of The Journal of Clinical Investigation, have further confirmed the harmful role of the Nox2 protein in ROS production and the beneficial effects of apocynin in prolonging survival and delaying onset. However, they found that apocynin only affected the production of ROS by a glial cell line, not a neuronal cell line, supporting the notion that apocynin effectiveness may be mediated via glial cells, most likely microglia. Recognizing the wide range of neurotoxic and neurotrophic compounds that microglia - the inflammatory cells of the CNS - release, they represent another candidate for the non-cell autonomous killing of neurons. Mutant SOD1 ALS transgenic mice produce elevated levels of Nox2 and superoxide in spinal cord microglia, both of which can lead to neuronal toxicity. For more information please click on the following articles:

• click here
• click here
• click here
GENE MUTATION RESPONSIBLE FOR ALS

Working independently, Dutch and Irish researchers have uncovered an important clue to the mystery behind ALS. In two genome-wide association studies, researchers aimed to identify genetic variations that increase the risk of developing ALS. Both groups found that a single gene, dipeptidyl-peptidase 6 (DPP6), may raise the risk of contracting the non-hereditary form of ALS, sporadic ALS. A single nucleotide polymorphism (SNP) in DPP6, a gene on chromosome seven which codes for an enzyme that is an integral part of neuronal A-type potassium channels, is currently the strongest genetic link to sporadic ALS and may provide researchers a new lead in understanding the causes of ALS.

Combining their data with U.S. data, Dutch researchers identified 15 SNPs that were further analyzed on independent populations across Europe. After combing through the genetic material of 1,700 ALS patients and comparing it to 1,900 control participants, an extensive analysis revealed that a single DNA mutation in DPP6 increased the risk of getting the disease by approximately 37 per cent.

In a study to validate the U.S. and Dutch data, Irish researchers also carried out a genome-wide association study of 222 Irish patients with sporadic ALS and 217 control participants. They found 35 SNPs associated with ALS; however, none reached the Bonferroni statistical threshold of significance. Subsequently, a combined analysis revealed the DPP variation as the top-ranking SNP associated in ALS in all three data sets, Irish, Dutch and U.S. The study was published in the March issue of Human Molecular Genetics. The correlation between DPP6 and ALS is of particular interest since impaired potassium channel function has been associated with ALS. As such, DPP6 could be a new link in ALS pathology.

In the January issue of Nature Genetics, Dutch authors concluded that "the identification of a common variant within DPP6 is an exciting first step in the genetic study of sporadic ALS, and it opens up new avenues for studying the molecular basis of this devastating disease."

For more information please click on the following articles:
- click here
- click here

PROTEIN CHARGE A FACTOR IN THE INITIATION OF ALS ASSOCIATED WITH SOD1 MUTATIONS

Familial ALS has been associated with more than 100 Cu/Zn-superoxide dismutase (SOD1) missense mutations, leading to protein misfolding and aggregation. Neural damage is believed to result from the accumulation of these SOD1 deposits. However, in studying transgenic mice, it was noted that neuronal changes appear long before SOD1 inclusions are detected.

The results of a study conducted by Swedish researchers - published in the July 2007 issue of The Journal of Biological Chemistry - have suggested that overall, the mutations have a tendency to decrease the net negative charge of the proteins, diminishing their macromolecular solubility in vivo. This reduction in the repulsive charge was particularly noticed in mutant SOD1-associated ALS, suggesting that protein aggregation may be a primary event in the mechanism behind ALS. For more information click here.

TROPHOS IDENTIFIES A NOVEL DRUG CANDIDATE FOR ALS

Trophos SA has published details of their compound, TRO19622. Authors Christopher Henderson, PhD, Rebecca Pruss, PhD, and colleagues published the study in the May issue of the Journal of Pharmacology and Experimental Therapeutics. They have identified two protein targets of TRO19622 that are present in the outer mitochondrial membrane - suggesting that the drug has therapeutic potential in illnesses with mitochondrial dysfunction. Pre-clinical trials have shown TRO19622 to be well-tolerated in both healthy volunteers and ALS patients. This data suggests that with further clinical evaluation TRO19622 may prove to be a potential treatment for ALS. For more information click here.
A new study published in the December 2007 issue of the Journal of Neuropathology and Experimental Neurology has researchers at the University of Toronto Centre for Research in Neurodegenerative Diseases saying that in contrast to current thinking, TDP43 (TAR DNA-binding protein) may not be the major ubiquitinated target within skein-like and round inclusions involved in ALS.

ALS has been characterized by the presence of various types of ubiquitinated inclusions in the cytoplasm of motor neurons; as such it is believed that by uncovering these targets we may be able to identify new gene candidates and clues to better understand the mechanism of disease. Following the recent discovery of the TDP43 protein as a component of ubiquitinated inclusions, Teresa Sanelli and colleagues were hoping that TDP43 might be the key ubiquitinated target and major disease protein in ALS. However, using 3-D deconvolution imaging they found this was not the case.

The researchers concluded, "these findings raise the possibility that TDP-43 may not necessarily be the key disease protein in ALS and indicate that the major targets of ubiquitination remain to be identified."

For more information please click on the following articles:
• click here
• click here

TDP43: PERHAPS NOT A MAJOR UBIQUITINATED TARGET OF ALS
TEVA’S COPAXONE: AN INEFFECTIVE TREATMENT FOR ALS

Teva Pharmaceutical Industries Ltd. announced that its multiple sclerosis drug Copaxone failed to improve symptoms of ALS during a year-long trial.

In a phase II trial involving 366 patients, Copaxone was deemed to be safe and well-tolerated, however the endpoint of increased survival was not met. Nevertheless, Teva is not giving up on ALS treatments and will "continue developing innovative treatment options such as talampanel for such a devastating disease," says Vincent Meininger, principal investigator of the study.

MANUFACTURING AGREEMENT SIGNED BETWEEN ALS TDI AND MICROBIX FOR HIGH QUALITY ADENOVIRAL STOCKS

The ALS Therapy Development Institute (ALS TDI), located in Cambridge, Massachusetts, has announced that they have signed a deal with Microbix Biosystems Inc., a Toronto-based company, to manufacture adenoviral stocks to be tested in the mouse model of ALS. Under the one-year contract, Microbix will use its technology to produce, purify, and characterize numerous adenoviruses - non-pathogenic viruses that can deliver select genes to key sites in the body or cultured cells for therapeutic purposes - to move therapies to sites of ALS pathology.

"The relationship with Microbix will allow the R&D team at the ALS TDI to test dozens of adenoviral constructs to knock down the expression of genes or over-express genes that may impact disease progression in the mouse model of ALS," says Steve Perrin, chief scientific officer at ALS TDI.

ALS DRUG TRIAL HALTED

In February, CytRx Corp announced that it would be halting its phase IIb trial with arimoclomol for the treatment of ALS at the request of the U.S. Food and Drug Administration (FDA) due to a lack of data.

Although use of arimoclomol generated no harmful safety data during previous clinical trials involving humans, the FDA wants further analysis of the previously completed animal toxicology studies in rats.

On March 24, CytRx announced that it had filed a response with the FDA in its decision to place a clinical hold on the phase IIb trial. "We will continue working with the FDA to determine as expeditiously as possible the need, if any, to conduct additional toxicology or other studies before or concurrently with the resumption of our Phase IIb clinical trial, or to modify the protocol for this trial," says CytRx's president and CEO Steven Kriegsman.

PROTEIN DELETION DELAYS MOTOR NEURON LOSS IN ALS MICE

Researchers at the Royal College of Surgeons in Ireland, the Innsbruck Medical University in Austria, and the Walter and Eliza Hall Institute of Medical Research in Australia, have identified a protein that may contribute to defects in protein quality control, leading to the onset of fatal neurodegenerative diseases such as ALS.

Previous studies revealed that the activation of the BH3-only protein Puma (p53-upregulated modulator of apoptosis) was responsible for endoplasmic reticulum (ER) stress. Both the SOD1 mouse model and human post-mortem samples of ALS have provided evidence that ER stress levels increase and defects in protein degradation in motor neurons continue during disease progression.

Prior to the onset of these symptoms, a significant up-regulation of Puma in the motor neurons of the SOD1 mouse model was noted. While the genetic deletion of Puma significantly improved motor neuron survival and delayed disease onset in the mice models, there was no substantial increase in overall survival rates. These findings demonstrate that in vivo, Puma plays an important role during the early stages of chronic neurodegeneration. The study was published in the December 18 issue of the Proceedings of the National Academy of Sciences.

For more information [click here](http://www.als.ca/researchers).