THE ALS FORUM

Discovering a Common Goal, Discovering a Cure

ALS Forum e-Newsletter Volume 116 **November 14, 2014**

Visit the ALS Forum website to read the complete stories featured in this e-newsletter. Please forward this e-newsletter to friends and colleagues who may be interested in learning more about ALS.

Resources:

The ALSGene tool: www.ALSGene.org

The PRO-ACT Database: www.ALSDatabase.org

NEALS Biofluid Repository Available to Researchers

NINDS Fibroblast Repository

VABBB Tissue Request Information Site

Funding Opportunities:

ALS ACT, ALSA, NEALS and the ALS Finding a Cure Foundation RFP: Phase II Clinical Development of Novel, High-Potential Treatments for People with ALS.
Letter of Intent due January 9, 2015.

Webinar:

NEALS Webinar: Mexiletine Study - Results Overview.Nov 21, 2015, 3-4pm EST.

Upcoming Meetings:

November 2014

November 15-19, 2014: Washington, DC: The

Conference News

Collaborations Abound at the International Conference on Frontotemporal Dementias

Frontotemporal lobar degeneration (FTLD) is an umbrella terms for neurodegenerative diseases characterized by brain atrophy in the frontal or temporal lobe. As with ALS, FTLD is highly heterogeneous with respect to clinical manifestations, pathways affected, and underlying genetic causes, and is viewed by researchers as spectrum of diseases, which extends from parkinsonian symptoms on one end and ALS on the other. The groundbreaking discovery 8 years ago of progranulin as a major genetic cause of FTLD launched the field forward, followed soon thereafter by key discoveries of TDP-43, C9ORF72 hexanucleotide repeats and tau-PET tracers. Now in its 9th year, the International Conference on Frontotemporal Dementias (ICFTD), which convened on Oct 23-25 in Vancouver, British Columbia, has grown into an international conference with researchers from 30 countries who gathered to share scientific findings and discuss avenues for advancing therapy development for FTLD. Click here to read more about the latest findings on FTLD proteins, clinical studies, and physiological markers!

Research News

Inhibitor of Astrocyte Sodium/Potassium ATPase May be Beneficial in ALS

Unhealthy astrocytes accelerate motor neuron death in some forms of ALS (see Apr 2007 news story, Feb 2014 news story), but the precise mechanisms of this non cell-autonomous degeneration are not well understood. A new study by Azad Bonni and colleagues from the Washington University in St. Louis, which was published Oct 26 in *Nature Neuroscience,* suggests that the sodium/potassium pump (Na+/K+ ATPase), may be partially to blame. The scientists report that the alpha2-Na+/K+ ATPase, a crucial enzyme for maintaining cellular resting potential, is expressed at higher levels in both mouse models of ALS and spinal cord tissue from ALS patients. An approved inhibitor of the ATPase called digoxin, which is normally used for treating cardiac failure, is beneficial for motor neuron survival. How does the alpha2-Na+/K+ ATPase induce toxicity? Click here to find out more.

Annual Society for Neuroscience Meeting

November 16-18, 2014: New York, NY: Partnering for Cures

December 2014

December 3-5, 2014: San Antonio, TX: World Stem Cell Summit

December 3-6, 2014: Cold Spring Harbor, NY:Neurodegenerative Diseases: Biology & Therapeutics

December 5-7, 2014: Brussels, Belgium:International Conference on ALS/MND

December 17-20, 2014: Hotel Vila Galé Coimbra, Portugal: Mitochondria, Metabolism and Disease

January 2015

January 13-17, 2015: Hokkaido, Japan: Society for Neuromuscular Sciences 8th Annual Scientific Meeting

January 25-30, 2015: Taos, New Mexico:Neuroinflammation in Diseases of the Nervous System

February 2015

February 1-3, 2015: Cambridge, UK: Biomarkers for Brain Disorders: Challenges and Opportunities

Feb 17-19, 2015: Boston, MA: World CNS Summit 2015

Feb 23-24, 2015: Manchester, UK: 10th Annual Biomarkers Congress

Young Astrocytes Ameliorate ALS Motor Neuron Survival

A new report led by Clive Svendsen of the Cedars-Sinai Medical Center in Los Angeles, California reinforces the critical importance of trophic support from astrocytes for motor neuron survival in ALS. The study in press at *Neurobiology of Aging* suggests the although aging astrocytes derived from mutant SOD1 mice are toxic to motor neurons (see Apr 2007 news story), this is not the case for astrocytes from young pups. What distinguishes the young and old astrocytes? Older astrocytes expressing mutant SOD1 exhibit increased DNA damage and expression of senescence markers, such as P21, at an accelerated pace. Svensen and colleagues show that astrocytes can be 'rejuvenated' by priming with GDNF. Is GDNF mediating this effect through the Na+/K+ ATPase (see earlier story, this issue)? Click here to find out more.

EphA4 Proteases Regulate Spinal Motor Axon Guidance

Key proteins and molecular pathways during nervous system development often emerge in adulthood as important mediators of neurodegenerative disease. One such example is the ephrin receptor EphA4, which is important for providing guidance signals for developing axons and was recently identified as a modifier gene in ALS (see Aug 2012 news story). New findings published Oct 20 in *Current Biology* shed light on regulation of Eph signaling during development via proteolysis, and reveal potential new avenues for modifying ALS progression. Researchers from the Max Planck Institute of Neurobiology in Martinsried and the Institut de Recherches Cliniques de Montréal demonstrate that proteolytic cleavage of Eph receptors is necessary to 'unmask' ephrins (the Eph receptor ligands) on the cellular targets, and thereby expose the necessary navigational signals for axons to reach their correct, final target. Where do developing motor axons go when EphA4 proteolytic cleavage is blocked? Click here to find out.

Twin-derived iPSCs Shed Light on Parkinson's Disease

Monozygotic twins discordant for a neurodegenerative disease provide a rare opportunity to delve into the genetic and non-genetic contributors to disease pathophysiology (See Sept 2014 news for a recent story on insights from twins discordant for C9ORF72 ALS). Using induced pluripotent stem cell (iPSC)-derived dopaminergic neurons from monozygotic twins discordant for Parkinson's disease (PD), a team of researchers from the New York Stem Cell Foundation Research Institute have created a unique model of Parkinson's disease (PD) in a dish. The study, published in the November 6 *Cell Reports*, revealed both genetic abnormalities common to both twins, such as the glucocerebrosidase (GBA) mutation, and unique characteristics of only the affected twins' neurons, such as elevated levels of monoamine oxidase B (MAO-B) activity. The researchers were able to restore normal function of these cells by reducing MAO-B activity and increasing expression of GBA. Click here to read more about these discoveries and their therapeutic implications.

Drug News

Crowdsourcing Project Predicts ALS Disease Progression

Feb 25-26, 2015: La Jolla, CA: Biocom Global Life Sciences Partnering Conference

March 2015

March 1-3, 2015: San Diego, CA: 9th Annual Drug Discovery for Neurodegeneration Conference

April 2015

April 7-11, 2015: Soelden, Austria: The 17th International Neuroscience Winter Conference

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Although the majority of ALS patients survive only 2-5 years after diagnosis, the rate of disease progression varies significantly. This heterogeneity poses a major challenge for clinical trial design, since large cohorts of ALS patients are required to detect significant treatment effects. In the Nov 2 Nature Biotechnology, a team of researchers led by Prize4Life and the Dialogue for Reverse Engineering Assessments and Methods (DREAM) published results of a crowdsourcing project, which leveraged the PRO-ACT ALS clinical trials database to identify algorithms capable of predicting an individual's ALS disease progression based on their short-term clinical data (see Nov 2012 news story). The algorithms outperformed predictions by ALS clinicians, and are estimated to enable a 20% reduction in the number of patients required for future ALS clinical trials. Click here to read more about the winners of this challenge, and the next one coming up in 2015.

Neuralstem Stem Cells Survive Long Term Following Spinal Cord Transplantation in ALS Patients

Concurrent with the U.S.-based Phase II clinical trial of Neuralstem's NSI-566 human spinal-cord derived neural stem cells (HSSC) as a treatment for ALS (see June 2014 Conference news, Aug 2014 news story), the company has just published long-term cell survival data from the Phase I trial. In work published Oct 22 in Annals in Clinical and Translational Neurology online, a team of researchers led by Jonathan Glass of Emory University in Atlanta, Georgia report that NSI-566 HSSC survived for up to 2.5 years following spinal cord transplantation in six of the Phase I patients. The transplanted stem cells survived even in the absence of ongoing immunosuppression, and some stem cells differentiated into neurons. These promising results support the use of transplanted stem cells to provide long-term neurotrophic support to degenerating spinal motor neurons in ALS. Click here to read more.

Hypertension Drug May Reduce Risk of ALS

A new study suggests that angiotensin-converting enzyme inhibitors (ACEIs), widely prescribed medications for treating high blood pressure and coronary artery disease, may also dramatically reduce the risk of ALS. The study, published on Nov 10 in *JAMA Neurology* online by a team led by Charles Tzu-Chi Lee of the Kaohsiung Medical University, Kaohsiung, Taiwan, was based on data from the whole Taiwanese population seen in medical practice, including 729 ALS patients and almost 15 thousand unaffected individuals. ALS Patients who had received ACEIs at a dose greater than 449.5 cumulative defined daily dose in four years had a 57% lower risk of ALS. These findings provide a promising lead, which will need to be further validated in additional animal and clinical studies. Click here to read more.

AB Science Publishes Preclinical Data on Masitinib in Stroke

New data is emerging about the neuroprotective properties of masitinib, an inhibitor of the c-kit tyrosine kinase, which is currently in Phase III clinical trials for ALS (see Nov 2013 news story). The drug targets mast cells and macrophages and exhibits anti-inflammatory properties. AB Science, the Paris, France-based pharmaceutical company that developed the drug, recently announced the publication of preclinical results on the effects of masitinib treatment in ischemic stroke. The findings, published in the Oct 26 edition of *Naunyn-Schmiedeberg's Archives of Pharmacology*, demonstrate that masitinib reduces brain

ischemia induced by experimental stroke, likely by reducing permeability of the blood brain barrier. Click here to read more about these new results.

The ALS Forum was developed by Prize4Life, Inc.

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