ALS Forum e-Newsletter Volume 132 **July 24, 2015**

The ALS Ice Bucket Challenge is coming back this August! To learn more visit www.alsicebucketchallenge.org. To support the ALS Forum click here. Your contributions will help enrich this resource!

Visit the ALS Forum website to read the complete stories featured in this e-newsletter. Please let your friends and colleagues know about the ALS Forum. It is easy to sign up for the newsletter here.

Resources:

ALS Drugs in Development Database

The ALSGene tool: www.ALSGene.org

The PRO-ACT Database: www.ALSDatabase.org

NEALS Biofluid Repository Available to Researchers

VABBB ALS CNS Tissue Request Information Site

Funding Opportunities:

ALS Therapy Alliance (ATA) RFP. Applications due Oct 15, 2015.

California Stem Cell Agency (CIRM) 2.0 Awards. Due last business day of each month.

Webinars:

ALSA/NEALS PALS Webinar: A "Cool" New Duke ALS Research Program Focused on ALS Reversals. Aug 6, 2015:11:00AM-12:00PM PST.

Research News

Ramping Up Autophagy May Help Alleviate Neurotoxicity in ALS

Stimulating the catabolic process of autophagy could provide key means to battling ALS. As reported in the Jun 17 Journal of Neuroscience, scientists led by Robert Kalb of Children's Hospital of Philadelphia,were able to increase the degradation of misfolded superoxide dismutase 1 (SOD) by promoting autophagy. Whereas mutant SOD1 is a major cause of familial ALS, some studies suggest that misfolding of the wild-type protein may also contribute to sporadic ALS (see Oct 2010 news). The researchers used several models to inhibit cytohesins, intracellular controllers of membrane trafficking and protein sorting. Blocking cytohesins with a small molecule called SecinH3 increased lysosomal degradation of the aberrant SOD1 and ameliorated motor neuron survival. Cytohesins are now a potential target of interest in the treatment of ALS.

Study Finds Single Brain Injury Insufficient to Precipitate ALS

Several studies have suggested a link between traumatic brain injury (TBI) and neurodegenerative disease, including a correlation between a single TBI and Alzheimer's disease. Evidence also exists for an increased predisposition to ALS among athletes who have suffered repeated blows to the head (see Sept 2012 news; Nov 2012 news; Oct 2014 news). In the June 22 *eNeuro* online, Clive Svendsen and colleagues from Cedar Sinai Medical Center in Los Angeles, California report that a single TBI was not sufficient the hasten the onset or progression of ALS in a transgenic rat model of the ALS. In light of these findings, understanding the difference between an acute versus

Upcoming Meetings:

Call for Papers - deadline Sept 24, 2015! See AMIA 2016 Joint Summits on Translational Science and listing below.

September 2015

Sept 3-6, 2015: Prague, Czech Republic: 2nd World Congress on Neurotherapeutics

Sept 9-11, 2015: Philadephia, PA: CNS Diseases World Summit

Sept 19-20, 2015: Montreal, Canada: 10th Annual Symposium of the Fondation Andre-Delambre

Sept 27-29, 2015: Chicago, IL: American Neurological Association Annual Meeting

Sept 24-25, 2015: Ottawa, Canada: Ottawa International Conference on Neuromuscular Biology, Disease and Therapy

Sept 27-29, 2015: Chicago, IL: American Neurological Association Annual Meeting

Sept 30 - Oct 4, 2015: Brighton, UK: 20th International World Muscle Society Congress

October 2015

Oct 15-16, 2015: Chicago, Illinois: 10th Brain Research Conference RNA Metabolism in Health and Disease.

Oct 17-21, 2015: Chicago, Illinois: The Society for Neuroscience Annual Meeting.

repeated head trauma may help understand if and how TBI can contribute to the development of ALS.

Novel Antibodies Reveal Functions of C9ORF72 Gene Products

Mutations in the C9ORF72 gene are the most common genetic cause ALS and frontotemporal dementia. The gene itself codes for two protein isoforms, a long form (C9-L) and a short form (C9-S), whose functions remain elusive. Janice Robertson and her team at the University of Toronto in Ontario, Canada created antibodies to detect and distinguish the two isoforms, enabling them to examine their differential characteristics. In the July 14*Annals of Neurology* online, the researchers report that the C9-S is localized to the nuclear membrane in healthy motor neurons, but to the plasma members in ALS motor neurons. Furthermore, the C9 isoforms interact with the nuclear pore complex, which shuttles proteins, including TDP-43, across the nuclear membrane. This study provides a link between a pathological hallmark of ALS - the mislocalization of TDP-43 from the nucleus to the cytoplasm - and ALS-causing mutations in C9ORF72.

Meta-Analysis Examines Link Between Formaldehyde Exposure and ALS

Neurotoxicity is amongst the many pernicious effects that have been attributed to formaldehyde exposure. The fixative, which works by cross-linking proteins, has been shown to cause protein aggregation in neurons. Nevertheless, the link between formaldehyde and an increased risk of ALS remains elusive, as studies have yielded mixed results. In the July 13 *Journal of Neurology Neurosurgery & Psychiatry*, researchers led by Marc Weisskopf from the Harvard School of Public Health in Boston, Massachusetts describe results of a meta-analysis of ALS mortality and degree of occupational exposure to formaldehyde. The researchers used records from the National Longitudinal Mortality Study (NLMS), an NIH-sponsored study, which includes close to 1.5 million records from the U.S.. Men with high probability and intensity of formaldehyde exposure, who were all funeral directors, had approximately three times the risk of dying of ALS than those who had not been exposed. However, the study was limited by several factors, including the small number of ALS deaths in the cohort, suggesting that follow up studies are merited before strong conclusions can be made.

Drug News

Cytokinetics Begins Phase III Trial of Tirasemtiv in ALS

California based biopharmaceutical company Cytokinetics has announced the initiation of a Phase III clinical trial of *tirasemtiv* in ALS. The drug, a small molecule troponin activator, works in part by augmenting calcium sensitivity and thereby increasing skeletal

Oct 31-Nov 5, 2015: Santiago, Chile. World Congress of Neurology

November 2015

Nov 14-18, 2015: San Francisco, CA: American Medical Informatics Association (AMIA) Annual Symposium

December 2015

Dec 11-13, 2015: Orlando, FL: International Symposium on ALS/MND.

2016

January 2016

Jan 24-27, 2016: Santa Fe, New Mexico: Keystone Symposium on Molecular and Cellular Biology: Axons: From Cell Biology to Pathology.

March 2016

March 21-22, 2016: San Francisco, CA: AMIA Joint Summits on Translational Science

April 2016

Apr 2-6, 2016: Solden, Austria: 18th International Neuroscience Winter Conference.

April 16-23, 2016: Vancouver, Canada:American Academy of Neurology (AAN) Annual Meeting.

July 2016

July 2-6, 2016: Copenhagen, Denmark:10th FENS Forum of Neuroscience

muscle force even with diminishing neural input (see Feb 2012 news). In the Phase II clinical trials, which concluded last year, the company reported no significant changes in the primary endpoint, ALS-FRS. However, the drug exerted a statistically significant and potentially clinically beneficial effect on respiratory function in ALS patients, as assessed by slow vital capacity (SVC), an indicator of muscle strength for those that control breathing (see April 2014 news; Oct 2014 news). The company aims to confirm and extend these promising findings with a year-long Phase III clinical trial, entitled VITALITY-ALS (Ventilatory Investigation of Tirasemtiv and Assessment of Longitudinal Indices after Treatment for a Year in ALS). The trial will enroll close to 500 participants with ALS throughout North America and Europe.

Aquinnah Pharmaceuticals to Advance Development of TDP-43-Targeting Compounds

Aquinnah Pharmaceuticals is a new startup company in the neurodegenerative disease space, which was launched last year on the foundation of research from the laboratory of Benjamin Wolozin at Boston University. The company is focused on developing drugs that target TDP-43, a protein found aggregated and misfolded in the majority of cases of ALS and frontotemporal dementia, and pathological stress granules (which have been implicated in the pathology of ALS as well as other neurodegenerative diseases (see June 2013 news). The company has recently received $0.5M in grants from the ALS Association to advance their lead compounds toward clinical development.

Denali Appoints Carole Ho as Chief Medical Officer

South San Francisco-based Denali Therapeutics has appointed physician-scientist and industry leader Carole Ho as Chief Medical Offer and Head of Development. The company was launched earlier this year with $217M in venture capital funding and a leadership team of top researchers at Genentech with the aim to develop breakthrough therapies for neurodegenerative diseases, including ALS, Parkinson's and Alzheimer's diseases (see May 2015 news). Dr. Ho, a neurologist who has served in leadership positions in Genentech and Johnson & Johnson, will lead translational and clinical development programs at the company.

ALSA Awards $11.6 Million in Grants for Research, Biomarkers, Drug Development and Clinical Trials

The ALS Association has announced 58 new research grants totaling $11.6M to fund research into genetics of ALS, new disease models, biomarkers, drug development and clinical trials. The list of grants provides an overview of exciting and cutting edge research ongoing in the ALS field. In addition to academic groups, the grants will help support several biotechnology start-up companies, including Origent Data Sciences, a spin-off of

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Sentrana, one of the winners of the ALS Prediction Prize (see June 2012 news), Voyager Therapeutics (see Feb 2014 news) and Aquinnah Pharmaceuticals (see this newsletter) in the U.S., as well as Treeway (see Jan 2015 news) and Neurimmune (see April 2013 news) in Europe. Click here to read the full list.

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