THE ALS FORUM
PRIZE4LIFE
Discovering a Common Goal, Discovering a Cure

ALS Forum e-Newsletter Volume 142 **December 18, 2015**

Visit the ALS Forum website to read the complete stories featured in this e-newsletter. It is easy to sign up for the newsletter here.

We want to thank you for your readership and feedback in 2015, and we wish you and your families Happy Holidays and a wonderful New Year! We will be returning with more dedicated ALS research and drug development news after the New Year.

Resources:

ALS Drugs in Development Database

ALSGene

The PRO-ACT Database

NEALS Biofluid Repository Available to Researchers

VABBB ALS CNS Tissue Request Information Site

TargetALS Cores

Funding Opportunities:

MND Association, Chief Scientist of Scotland, Marie Curie. Palliative Care Research RFP. Applications due Jan 14, 2016

California Stem Cell Agency (CIRM) 2.0 Inception Awards. Applications dueJanuary 15, 2016.

Upcoming Meetings:

Research News

Pathological Hallmarks of ALS Without Degeneration in Two New Mouse Models of C9ORF72 ALS and FTD

Two new mouse models of C9ORF72 mutations exhibit characteristic pathological features of ALS and frontotemporal dementia (FTD) but no motor or cognitive deficits, nor a shortened lifespan, as reported in back-to-back articles in the December 2*Neuron*. Two teams, led by Robert Baloh from the Cedars-Sinai Medical Center in Los Angeles and Robert Brown of the University of Massachusetts Medical School in Worcester, have generated bacterial artificial chromosome (BAC)-transgenic mice that express the C9ORF72 gene with varying numbers of hexanucleotide repeats, ranging from 100-1000 copies, depending on the model. The mice expressed dipeptide repeat proteins (DPRs) and RNA foci, but exhibited no motor or cognitive behaviors typical of ALS or FTD. Despite the limits of these models, researchers are optimistic that they may have potential as research tools to identify the environmental factors that drive disease and to identify therapeutic candidates that target DPRs and RNA Foci.

Eye Movements May Provide Window Into Brain Function in ALS

Studies published the November 11 *PLoS One* suggest that deficits in eye movements may shed light on loss of brain function in ALS patients. Researchers from the University of Ulm, Germany, tracked the performance of ALS patients on eye gaze

2016

January 2016

Jan 12-16, 2016: Hokkaido, Japan: The Society of Neuromuscular Sciences Inc., 10th Annual Scientific Meeting.

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

February 2016

Feb 25-26, 2016: Manchester, UK: 11th Annual Biomarkers Congress.

March 2016

March 6-8, 2015: Miami, FL:Annual Drug Discovery for Neurodegeneration Conference.

April 2016

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

April 5-7, 2016: Boston, MA:BioIT World Conference & Expo.

April 6-7, 2016: Boston, MA:11th Neurotech Investing and Partnering Conference.

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

April 20-22, 2016: Washington, DC: World Orphan Drug Congress

April 25-27, 2016: Boston, MA: Stem Cell Summit.

tasks, and detected ocular deficits in approximately half of ALS patients as compared to controls. The impairments appeared in two stages: the first was associated with disrupted ocular movements associated with loss of executive function, while the later stage was characterized by erratic ocular movements that are typically linked to brainstem or precerebellar networks. Interestingly, these stages correlate with different stages of ALS disease progression, according to a staging model based on TDP-43 proteinopathy. The researchers posit that tracking eye gaze may eventually evolve into an important marker for assessing disease progression, which could be used as a secondary end point in ALS clinical trials.

Protein Aggregates Clog Nucleocytoplasmic Transport in Multiple Diseases

New findings from the Max Planck Institute of Biochemistry in Martinsried, Germany, suggest that impaired nucleocytoplasmic transport caused by protein aggregates is a common feature of many neurodegenerative diseases, including Alzheimer's, Huntington's, and ALS. By tagging both artificial and natural proteins, such as TDP-43 and huntingtin, with nuclear export and import signals, the researchers were able to parse how subcellular localization impacts toxicity of protein aggregates. In the December 3 *Science* online, the team reports that primarily cytoplasmic rather than nuclear aggregates of proteins impaired nucleo-cytoplasmic transport of proteins and RNA. Recently, other reports have found that the mutations of ALS and FTD-linked gene, C9ORF72, also resulted in deficiencies in transport across the nuclear envelope (see Aug 2015 news). Further research is needed to determine whether impaired nuclear transport is the primary toxicity driving neuronal death or whether other contributing factors are also critical.

Amyloid Deposits May Cause Cognitive Impairments By Restricting Brain Blood Flow

Researchers from Virginia Tech Carilion Research Institute and the University of Alabama at Birmingham School of Medicine have found that toxic proteins associated with Alzheimer's disease may not only cause neuronal death directly, but also may exert detrimental effects by restricting cerebral blood flow. By integrating complementary *ex vivo* and *in vivo* imaging techniques, the researchers found that the rigid amyloid plaques surrounding blood vessels, which are a hallmark of the disease, disrupted regulation of blood flow by astrocytes and limited the flexibility of blood vessels. Removal of these deposits could potentially improve cognitive function in people with AD by restoring blood flow to the brain. These findings, reported in the November 23 *Brain* online, follow another study in spinal muscular atrophy (SMA) that also highlighted the role of impaired vasculature in neurodegeneration (see Nov 2015 news).

May 2016

May 19-21, 2016: Milan, Italy: Annual ENCALS Meeting.

May 26-28, 2016: Edinburgh, Scotland:European Conference on Rare Diseases and Orphan Products.

June 2016

June 5-9, 2016: Whistler, British Columbia, Canada:Keystone Symposia, Autophagy: Molecular and Physiological Mechanisms.

June 12-16, 2016: Keystone, Colorado;Keystone Symposia, Common Mechanisms of Neurodegeneration.

June 12-16, 2016: Keystone, Colorado:Keystone Symposia, Microglia in the Brain.

July 2016

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

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New Wearable Microscope Tracks Motor Unit Activity in Live Humans

A new wearable microscope enables *in vivo* monitoring of individual muscle fiber contractions in live humans, a feat that has not been possible despite our longstanding physiological understanding of how muscles contract. According to the report in the December 16 *Neuron* online, researchers led by senior authors Scott Delp and Mark Schnitzer at Stanford University in Palo Alto, California, have developed a microscope by connecting an infrared light source to a fine needle containing miniaturized optics that is inserted into the muscle. The device can distinguish fast and slow twitch muscles, stimulate muscle contractions, and track changes in properties of the individual contractile units of skeletal muscles, or sarcomeres, that occur due to injury or disease. This compact, portable device could fit on a bedside pushcart, and the researchers hope to ultimately develop it into a clinically useful device for diagnosing neuromuscular diseases and monitoring their progression in human patients.

Drug News

Treeway's TW001 Shows Promising Results in Two Clinical Trials in ALS

Dutch biotechnology company, Treeway, has successfully completed two Phase I clinical trials of TW001 for ALS (see March 2015 news). TW001 is an oral formulation of edaravone, a free radical scavenger and antioxidant drug originally approved in Japan for treating stroke. Earlier this year, Mistubishi Tanabe Pharma obtained Japanese Pharmaceutical and Medical Device Agency (PMDA) approval to market edaravone for ALS in Japan under the name Radicut (see June 2015 news), and Mitsubishipresented results of the phase III trials at the International Symposium on ALS/MND in Orlando, Florida. Unlike edavarone, which requires intravenous administration, TW001 can be taken orally, allowing for more convenient and frequent drug administration. The Phase I trials included both single and dose escalation studies, and demonstrated that TW001 is safe and well-tolerated. Treeway is aiming to begin a pivotal phase II/III trial of TW001 in 2016.

Biogen and Isis Pharma to Launch Clinical Trial of Antisense Drug for SOD1-ALS

Biogen and Isis Pharmaceuticals have announced the initiation of a phase I/II clinical trial of ISIS-SOD1$_{Rx}$ (BIIB067), an antisense oligonucleotide (ASO) therapy targeting superoxide dismutase (SOD1). ASOs recognize and target specific RNAs for destruction (see Jan 2013 news, Oct 2013 news), ultimately reducing expression of their protein products. ISIS-SOD1$_{Rx}$ is

specifically designed to inhibit production of mutant SOD1, which underlies approximately 20% of familial ALS cases and confers toxicity through a gain-of-function mechanism. The ASOs to be tested in this trial are a second generation, more potent version of ASOs previously tested and shown to be safe in phase I trials (see May 2013 news). The current trial will test not only safety, but also treatment effect on SOD1 protein levels in the cerebrospinal fluid, as a measure of drug activity. The study, entitled "Single and Multiple Dose Study of BIIB067 (Isis-SOD1Rx) in Adults With Amyotrophic Lateral Sclerosis (ALS)" will be conducted in two phases, the first of which will enroll both SOD1-ALS patients and patients without SOD1 mutations. Read more here and here.

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