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

ALS Forum e-Newsletter Volume 141 **December 4, 2015**

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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:

NCATS Pre-clinical Research Based on Existing Repurposing Tools (R21). Letter of intent due December 13, 2015.

MDA Research Grants.Letter of Intent due Dec 15, 2015.

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

California Stem Cell Agency (CIRM) 2.0

Conference News

Inducible TDP-43 Mouse Models Show Promise for Recovery from motor neuron Neurodegeneration

Two new mouse models of TDP43 proteinopathy may lead to new insight into approaches to reverse the damage caused by neurodegeneration. As reported at the RNA Metabolism in Neurological Disease meeting, a satellite of the Society for Neuroscience annual meeting held in October, scientists from the laboratory of Virginia Lee at the University of Pennsylvania have created mice that express a repressible transgene of human TDP-43, a hallmark of ALS and frontotemporal dementia, which lacks a nuclear localization signal. When the mutant transgene was expressed, cytoplasmic TDP-43 inclusions accumulated in the spinal cord and mice developed motor neuron degeneration. When transgene expression was shut down, the mice improved in health, regained motor function, and established new neuromuscular connections. A second group of scientists, at the University of New South Wales in Sydney, Australia, also recently reported similar results using a different, inducible mutant TDP-43 mouse line, (iTDP-43^{A315T}).

RAN Translation Surfaces in Huntington's Disease

Researchers led by Laura Ranum at the University of Florida in Gainesville have discovered that repeat-associated no-ATG (RAN) translation of repeats in a coding region play a role in pathology of Huntington's disease (HD). This form of peptide translation from repeat-rich transcripts is a known contributor to toxicity of ALS-causing expansions in the C9ORF72 gene (seeFeb 2013 news), but has not yet been described in HD. At the RNA Metabolism in Neurological Disease conference, Ranum

Inception Awards. Applications dueJanuary 15, 2016.

Upcoming Meetings:

December 2015

Dec 10-12, 2015: Atlanta, GA: World Stem Cell Summit.

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

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

presented data on four newly-identified repeat polypeptides translated from CAG coding repeats in the huntingtin gene. These peptides accumulate in vulnerable regions of the brain in HD in a distinctive pattern from the characteristic polyglutamine of the mutant huntingtin protein. Interestingly, expression of the polypeptides differed in tissue from adult-onset HD and juvenile forms of the disease. Click here to read more about these intriguing findings.

Research News

"Non-Disease" Protein Aggregates Precipitate Neurodegeneration Via Multiple Mechanisms

The role of protein aggregates in the pathogenesis of neurodegenerative disease may be as much about their mere presence as their specific identity. Recent studies conducted at Trinity College Dublin in Ireland investigated whether different aggregate forms of a non-disease protein could be toxic. The scientists developed a specialized assay using Hen Egg White Lysozyme (HEWL) protein that was manipulated to take on oligomeric or amyloid fibril forms. According to the report in theNovember 20 *Journal of Biological Chemistry*, prefibrillar oligomers and mature fibril forms were all cytotoxic *in vitro,*however, when tested *in vivo*, only the oligomers inhibited hippocampal long term potentiation (LTP). The results suggest that protein aggregates at different stages of amyloid formation all contribute to degeneration through distinct mechanisms. Understanding these nuances could aid in development of therapies that target diverse protein aggregates, including some forms associated with ALS, such as TDP-43 (see June 2011 news, Sept 2014 news).

New Drosophila Model Reveals Mechanisms of Astrocyte-mediated Neurodegeneration

Astrocyte dysfunction contributes to neuronal death in ALS and other neurodegenerative diseases, but the precise mechanisms of toxicity are not well understood (see Oct 2011 news). Mel Feany and colleagues at the Brigham and Women's Hospital in Boston, MA, have taken a step toward identifying pathways mediating glia-induced neuronal death by developing a fruit fly model of Alexander disease, a neurodegenerative disease with a glial dysfunction etiology. As reported in the Nov 26 *Nature Communications*, by screening for suppressors and enhancers of glial toxicity, the team honed in on nitric oxide (NO) signaling. The researchers confirmed their findings in a mouse model of the disease, as well as in brain tissue from patients. These findings point to a central mechanism contributing to glial-induced neuronal death in Alexander disease, and could shed light on other degenerative diseases linked to astrocyte dysfunction.

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.

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

Drug and Device News

Aquinnah Pharma Receives NINDS Grant for ALS Drug Development

Cambridge, MA-based Aquinnah Pharmaceuticals has been awarded $680,000 from the National Institute of Neurological Disorders and Stroke (NINDS) for the research and development of ALS drugs. Founded in 2014 and building in work from the laboratory of co-founder Benjamin Wolozin at Boston University, the company focuses on creating drugs aimed to disrupt TDP-43 aggregation and stress granule formation. This announcement follows on the footsteps of another grant received from the ALS Association, to further advance their drug discovery program for ALS (see July 2015 news).

Japan Approves Robotic Exoskeleton That Help ALS Patients Move Limbs

Japan's health ministry has approved the manufacture and sale of a wearable walk-assist robot as a therapeutic medical device for orphan diseases. It is the first wearable medical robot to be approved in Japan. Just one of several such technologies from the Japanese company, Cyberdyne, the Hybrid Assistive Limb for Medical Use, lower limb type (HAL-ll) acts as a robotic exoskeleton that can translate week nerve impulses into robotic motion, helping the patient's limbs move in the desired direction. Evidence from trials suggest that regular training sessions with HAL-ll may help increase non-assisted movement and muscle function, potentially delaying disease progression. The system is already approved in Europe, and is primarily used by people with spinal cord injuries. In Japan, the product is targeted for use in people with ALS, as well as those suffering from other motor neuron disorders, and the company is seeking insurance coverage for ALS in Europe as well.

BrainStorm's NurOwn Clinical Trial Passes Safety Review

Brainstorm Cell Therapeutics has announced that the Data and Safety Monitoring Board, an independent group of experts responsible for assessing safety of ongoing clinical trials, has given the green light for the company to continue its phase II clinical trial of NurOwn for ALS. The safety review was based on data from 47 of the 48 patients enrolled in the U.S.-based randomized, double-blind, placebo-controlled phase II clinical trial (see Apr 2014 news). Both the intrathecal and intramuscular injections of the autologous, neurotrophic factor-secreting mesenchymal stem cells were deemed safe and well-tolerated. This milestone is one of several recent advances for the company: it has also recently been awarded a major grant from Israel's Office of the Chief Scientist to advance the NurOwn

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program, and has secured a partnership to improve and scale up manufacturing of NurOwn.

Spark Reports Promising Preclinical Results for Neurodegenerative Disease Gene Therapy

Gene therapy company Spark Therapeutics has achieved promising results in preclinical experiments for treating Batten disease, a fatal, juvenile neurodegenerative disorder. Spark's therapy called SPK-TPP1 is recombinant adeno-associated viral (AAV) vector that expresses the deficient protein in forms of the disease caused by mutations in a lysosomal protease called tripeptidyl peptidase I (TPP1). In collaboration with Beverly Davidson and colleagues from the Children's Hospital of Philadelphia, intraventricular delivery of a single dose of SPK-TPP1 in a canine model of the disease increased TPP1 expression through the CNS, delayed disease onset and progression, prolonged lifespan, and decreased cognitive deficits. The results were published in the Nov 11 *Science Translational Medicine* and represent another preclinical proof-of-concept for an effective gene therapy for neurodegenerative diseases. Gene therapy approaches targeting SOD1 and C9ORF72 are also under development for ALS (see Nov 2015 news).

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