ALS Forum e-Newsletter Volume 143 **January 15, 2016**

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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:

California Institute of Regenerative Medicine (CIRM) 2.0 Quest Awards.Applications due March 15, 2016.

CIRM Partnering Opportunity for Discovery Stage Research Projects. Challenge

Conference News

News from the International Symposium on ALS/MND

At the International Symposium on ALS/MND in Orlando, Florida, scientists, neurologists, and people with ALS were excited to hear about clinical progress to treat motor-neuron disease. Attendees pondered the preliminary, but positive, results of gene therapy trials in spinal muscular atrophy-results that may open the door for similar gene therapy in ALS. They heard news of completed and ongoing trials of edaravone, a drug that may slow ALS in certain people, and about therapeutics that relieve distressing problems with speech and swallowing. Basic science also made a showing. A better understanding of how pathogenic proteins travel from cell to cell emerged, and researchers debuted new genetic variants to explain some inherited ALS risk.

Click here to read 3 exciting reports on the meeting:

Part I: Gene and Stem Cell Therapies Make Strong Showing at ALS/MND Meeting

Part II: Help for Speech, Swallowing, and Salivation Problems in ALS

Part III: Does Free Radical Scavenger Edavarone Slow ALS?

Research News

Award.Applications due March 30, 2016.

CIRM Partnering Opportunity for Translational Research Projects. Applications due July, 2016.

NIH Therapeutics for Rare and Neglected Diseases (TRND) Program and NIH Bridging Interventional Development Gaps (BrIDGs). Now accepting rolling applications.

Upcoming Meetings:

February 2016

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

March 2016

March 6-8, 2016: Miami, FL:Annual Drug Discovery for Neurodegeneration Conference.

March 20-23, 2016: Arlington, VA: MDA Clinical Conference.

April 2016

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

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

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

SOD1 Trimers are Toxic to Motor Neurons

Mutations in superoxide dismutase (SOD1) underlie approximately 20% of cases of inherited ALS, but how the mutated protein causes motor neuron death, and the precise forms of protein aggregates that contribute to disease pathophysiology are not known. Researchers from the University of North Carolina in Chapel Hill have that SOD1 oligomers can form trimers that are highly neurotoxic. As reported in the December 30 *Proceedings of the National Academy of Sciences*online, the researchers combined high-speed atomic force microscopy (HS-AFM) and structural molecular simulations to elucidate the SOD1 aggregate structure. They next conducted toxicity assays in motor neuron-like cell cultures to test proteins designed to promote or destabilize SOD1 trimers, and found structures that promoter trimer stabilization are the most neurotoxic. These findings could provide the basis for designing drug candidates that disassemble these toxic species.

MicroRNA-218 is Essential for Motor Neuron Survival

Researchers from the laboratory of Samuel Pfaff from the Salk Institute in La Jolla, California, have identified a motor neuron-enriched microRNA that prevents motor neuron degeneration. By selectively labeling, purifying and sequencing RNAs enriched in motor neurons, first author Neil Amin and colleagues identified one particularly abundant microRNA. According to a report in the December 18 *Science*, microRNA-218 (miR-218) is expressed in developing and mature motor neurons and suppresses over 300 genes. The team generated mice lacking miR-218 using CRISPR-Cas9 technology, and found that these mice exhibited neuromuscular junction defects, and motor neuron hyper-excitability and degeneration reminiscent of ALS (see Sep 2015 news). Although a direct link between miR-218 and motor neuron diseases has not yet been demonstrated, this work demonstrates the role of microRNAs extends beyond nervous system development into the realm of neurodegeneration.

Drugs News

Brainstorm's Stem Cell Therapy Safe in Humans

According to a report in the Jan 11 *JAMA Neurology*

online, autologous mesenchymal stem cells (MSC) engineered to produce neurotrophic factors (MSC-NTF) are safe and well tolerated in ALS patients. These stem cells, which are being developed by Brainstorm Cell Therapeutics under the name NurOwn, are MSCs extracted from each participant's bone marrow that are treated with growth factors, driving them to

April 15-21, 2016: Vancouver, Canada:American Academy of Neurology 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 28-31, 2016: Copenhagen, Denmark: Congress of the European Academy of Neurology.

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,

secrete neurotrophic factors that promote motor neuron survival. In this open-label phase I/II trial, led by Dimitrios Karussis of the Hebrew University-Hadassah Medical Center in Jerusalem, the cells were administered either intramuscularly, intrathecally, or both. The results also hinted that the therapy slows disease progression, but larger studies are needed to determine this conclusively. A Phase II trial of 48 patients is currently underway in the US, and results should be available later this year (see Oct 2015 news).

Cytokinetics Launches Phase II Trial of New Skeletal Muscle Activator in SMA

South San Francisco, CA-based Cytokinetics has opened enrollment for its phase II clinical trial of CK-2127107 in patients with Type II, Type III, or Type IV spinal muscular atrophy (SMA). CK-212707 is a next-generation fast skeletal muscle activator that regulates the troponin complex and increases skeletal muscle contractility. This drugs belongs to a class of skeletal muscle activators being developed by Cytokinetics, which also includes tirasemtiv, the company's drug candidate for ALS, currently in phase III clinical testing (see July 2015 news). The primary objective of this trial is to evaluate the pharmacodynamics effects of a new formulation of the drug, while secondary objectives are to determine the safety, tolerability and pharmacokinetics of the drug. Development of CK-2127107 is part of a broader collaboration between Astellas Pharma and Cytokinetics to develop skeletal muscle activators to treat muscular diseases.

Scholar Rock Secures Funding to Advance its Myostatin Inhibitor into Human Trials

Myostatin, a member of the transforming growth factor beta (TGFβ) protein superfamily, is primarily expressed in skeletal muscle and is a negative regulator of muscle growth. Inhibition of myostatin attenuates muscle atrophy in ALS mouse models, and could potentially have beneficial functional effects in humans (seeHolzbauer et. al., 2006, May 2012 news). This is a good reason to keep your finger on the pulse of startup company Scholar Rock,which is developing new approaches to regulate myostatin and other growth factors, with a goal to begin its first clinical trial in primary myopathies in early 2017. The company's monoclonal antibody myostatin inhibitor, called SRK-015, targets the latent form of myostatin, thereby preventing non-specific effects across TGFβ superfamily members. The company has recently closed a round of funding that will take it through clinical trials of SRK-015.

Takeda Expanding ALS Investments with Aquinnah Partnership

Denmark:10th FENS Forum of Neuroscience

October 2016

Oct 16-18, 2016: Baltimore, MD: American Neurological Association Annual Meeting.

November 2016

Nov 12-16, 2016: San Diego, California: Society for Neuroscience Annual Meeting.

December 2016

Dec 7-9, 2016: Dublin, Ireland: International Symposium on ALS/MND.

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Takeda Pharmaceuticals, the largest pharmaceutical company in Japan, is expanding its presence in the ALS space with two new partnerships: a new $5M investment in Aquinnah Pharmaceuticals, a Cambridge, MA-based startup company that is developing small molecule therapeutics that prevent TDP-43 protein aggregation and stress granule formation (see Nov 2015 news), as well as a 3-year research collaboration with the University College London, to identify genes and signaling pathways that regulate neuronal health and survival in ALS, Huntington's disease and Parkinson's disease.

Neurona Therapeutics to Pursue Stem Cell Transplantations to Treat Neurological Diseases

A new preclinical stage biotechnology company called Neurona Therapeutics was recently launched based on the pioneering work of researchers from the University of California, San Francisco, including Arturo Alvarez-Buylla, Arnold Kriegstein, John Rubinstein and Cory Nicholas. The company's therapeutic approach is founded on discoveries from founders' laboratories on cortical development and the ability of specialized cell transplantation into the adult central nervous system to rebalance and repair neuronal circuitry. The company has not declared its primary therapeutic focus, but these approaches could potentially apply to diverse conditions, such as epilepsy, spinal cord injury, and neurodegenerative diseases.

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