ALS Forum e-Newsletter Volume 139 **November 6, 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:

TargetALS Target Validation Core. Proposals due Nov 13, 2015.

ALSA, ALS ACT, ALS Finding a Cure, NEALS Phase II Clinical Development RFP. Letter of Intent due Nov 30, 2015.

MDA Venture Philanthropy.Letter of intent due Dec 1, 2015.

MND Association, Chief Scientist of Scotland, Marie Curie. Palliative Care Research

Conference News

Highlights from the "RNA Metabolism in Neurological Disease Conference"

The RNA Metabolism in Neurological Disease conference, co-organized by Paul Taylor of St. Jude Children's Research Hospital in Memphis, Tennessee, and Fen-Biao Gao of the University of Massachusetts Medical School in Worcester, was recently held in Chicago just prior to the annual Society for Neuroscience Annual Meeting. Alzforum writer Amber Dance brings us these highlights:

Mouse Models Suggest C9ORF72 Gain-Of-Function Is to Blame

One exciting conference session focused on new mouse models of C9ORF72 ALS and frontotemporal dementia (FTD). Despite differences in the phenotypes of the different modes, several common elements emerged. Loss-of-function models exhibited a deleterious, hyper-immune response, but did not always exhibit signs of neurodegeneration. In contrast, gain-of-function transgenic mouse models had notable cognitive and/or motor deficits reminiscent of these neurodegenerative diseases, suggesting that gain-of-function mechanisms play the primary role in disease pathophysiology. Read more here.

C9ORF72 Mutant RNAs May Form Liquid Droplets and Precipitate Protein Aggregation

Two recent publications revealed that the ALS-linked, RNA-binding proteins hnRNPA1 and FUS can assemble into a liquid droplets inside the cytosol, and promote formation of cellular granules (see Oct 2015 news, and Oct 2015 webinar). Presenter Marta Fay and fellow researchers from the Brigham and Women's

RFP. Applications due Jan 14, 2016

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

Upcoming Meetings:

November 2015

Nov 13, 2015: Boston, MA:ALS TDI Leadership Summit.

Nov 18-20, 2015: Gold Coast, Australia:International Conference on Neurology and Epidemiology.

Nov 29-Dec 4, 2015: Cambridge, UK: Molecular Neurodegeneration.

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.

Hospital in Boston, Massachusetts, showed preliminary data suggesting that the RNA transcribed from the mutant C9ORF72 gene may also aid in the assembly of these liquid droplets. Using the expanded repeats of the mutant gene, the scientists found that precipitation of the cellular granules was specific to the GGGGCC repeats, and not the antisense CCCCGG RNA. Further experiments showed that the number of granules was roughly proportional to the length of the repeat RNA, which could further explain why longer repeats cause disease whereas short repeat do not. Read more here.

RNA-Binding Protein Shunned from Nucleus by C9ORF72 RNA

Recent discoveries have identified a critical role for the C9ORF72 gene in regulating nucleo-cytoplasmic transport (see Aug 2015 news), and now researchers have identified the first RNA-binding protein to be blocked from performing its role in the nucleus due to these transport defects. Christian Haass' and colleagues at the German Center for Neurodegenerative Disease in Munich presented data suggesting that heterogeneous nuclear ribonucleoprotein A3 (HnRNP A3) represses expression of C9ORF72 repeats, and when ousted from the nucleus, the C9ORF72 RNA wreaks havoc on the cells in the form of RNA foci and di-peptide repeat proteins. Read more here.

Research News

Researchers Use Light to Restore Function to Denervated Muscles

Neural prostheses can restore movement to paralyzed limbs by stimulating motor axons, but do not improve function when the muscles are denervated, such as in ALS. Victor Rafuse and his team at Dalhousie University in Halifax, Nova Scotia, Canada, have engineered a novel way to overcome this barrier by directly stimulating muscle in a controllable manner. Reported in the Oct 13 *Nature Communications*, the scientists expressed the light-activated channelrhodopsin-2 in the denervated skeletal muscles of transgenic mice. 10 daily doses of transcutaneous light was sufficient to decrease muscle atrophy and improve muscle contractile strength. The team hopes to find avenues to employ a similar approach in humans to improve function of muscles denervated due to injury or disease.

Scientists Treat Parkinson's in Mouse Model by Bypassing the Blood-Brain Barrier

By repurposing an old medical procedure called nasal mucosal grafting, researchers are creating new ways to deliver drugs to the brain, without the hindrance of the blood-brain barrier. As published in the Sep 8 *Neurosurgery*, scientists at Massachusetts Eye and Ear Infirmary/Harvard Medical School and Boston University used this approach to administer glial-derived

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.

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

neurotrophic factor (GDNF) through a mucosal graft in the skull of Parkinson's disease mouse models. First author Benjamin Bleier and colleagues found that this mode of administration was equivalent to direct drug administration into the brain and progression of PD was attenuated in the treated mice, and. Such a technique could provide a means to administer therapies for a multitude of neurological and psychiatric conditions.

Drug News

ALS Stratification Challenge Winners Developed Algorithms to Identify ALS Patient Subgroups

Prize4life, DREAM and Sage Bionetworks have announced the winning teams of the DREAM ALS Stratification Prize4Life Challenge, an open science challenge to computationally identify ALS patient subgroups in order to ultimately help improve ALS clinical care and clinical trial design. Participants analyzed clinical trial data from the PRO-ACT database, as well as national ALS registry data from Ireland and Italy, and developed algorithms to identify features of ALS patient subgroups and predict either disease progression or survival for the subgroup. The three winning teams of the four sub-challenges hail from academic groups in the US and Taiwan, and will share cash prizes that were raised through a crowdfunding campaign on Indiegogo. IBM, Biogen and Eli Lilly were supporting industry partners.

Isis Pharmaceuticals Applies Antisense Technology to Combat Two Neurodegenerative Disorders

Isis Pharmaceuticals, a biotech company that company that specializes in RNA-targeting therapies, has recently had two major breakthroughs in neurological diseases (for their work in ALS see Jan 2013 news, Oct 2013 news). The company, in a partnership with Roche, has created an antisense oligonucleotide (ASO)-based therapy against Huntington's disease (HD), called ISIS-HTTRx. Injected directly into spinal fluid, the drug will hopefully prevent or delay the progression of HD by inhibiting production of the aberrant HTT protein. Phase 1 of testing ISIS-HTTRx in humans is now underway at the University College London Hospital in the UK, and will continue in patients across Europe and Canada. Isis Pharma has also collaborated with scientists from The Jackson Laboratory to develop a novel mouse model of spinal muscular atrophy (SMA), a pediatric motor neuron disease that leads to impaired mobility and muscle atrophy. The researchers were able to increase the lifespan and neuromuscular health of the mice with ASOs designed to increase levels of the survival motor neuron 1 (SMN1) protein. The results were published last month in PNAS.

Verge Genomics Applied Network Algorithms to Identify Drugs for ALS, AD

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Verge Genomics, a new startup company out of the YCombinator accelerator program, has received $4 million in seed funding to develop its computational drug discovery platform for applications in the neurodegenerative disease space. Founded by scientists from University of California, Los Angeles, Verge uses computational network analysis to map disease-causing genes and then identify FDA-approved drugs that target those same pathways and can be repurposed. This "genomic network" approach has already yielded several candidate drugs for Alzheimer's disease and ALS, and is at the stage of advancing these drug from early *in vitro* testing to preclinical testing in animal models. Stay tuned!

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Prize4Life, Inc. | PO Box 5755 | Berkeley | CA | 94705