ALS Research Forum e-Newsletter Vol. 158 **August 19, 2016**

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ALS researchers are invited to submit comments on the draft ALS Clinical Trial Guidelines. The open comment period ends August 31, 2016. For copies of the handouts, slides, and presentations from the ALS Clinical Trial Guidelines Workshop, click here.

Research News

UBQLN2 Helps the Proteasome Tackle Aggregated Proteins

Mutations in Ubiquilin-2 (UBQLN2) are associated with ALS and ALS/FTD, but the functional implications of the mutations have not been well understood. In the August 11 *Cell* online, researchers show that UBQLN2 binds the chaperone protein HSP70 and functions as a shuttle to mobilize aggregated proteins to the proteasome for degradation. In cellular models, reducing UBQLN2 expression impaired clearance of protein aggregates, while mutant forms of UBQLN2 were unable to effectively recruit protein substrates for disposal. The results identify a new mechanism by which the cell can eliminate protein aggregates via proteasomal degradation independent of autophagy, and further implicate defects in misfolded protein clearance in ALS pathogenesis. They also suggest that mutations in UBQLN2 cause ALS by a loss of function, though other mechanisms may also be at play.

U.S. National ALS Registry Reports Updated ALS Prevalence Estimates

The U.S. National ALS Registry has released an updated report of prevalence estimates for ALS in the U.S. for the years 2012-2013. The estimated prevalence rate was 4.7 per 100,000 in 2012 and 5.0 per 100,000 in 2013. The authors suggest that the slight increase compared to the first report (see Oct 2014 news) was likely due to better detection methods and increased awareness of the registry. ALS was reported to be most common among white males and people between the ages of 60 and 69. The full report was published in the *Morbidity and Mortality Weekly Report* on Aug 5, 2016.

Targeting Spt4 Suppresses Pathological Features of C9ORF72 Mutations

Hexanucleotide repeat expansions in the *C9ORF72* gene are the most common genetic cause of ALS and FTD. The repeats drive expression of expanded sense and antisense transcripts, as well as dipeptide repeat (DPR) proteins, all of which exhibit neurotoxic properties (see Aug 2014 news; Oct 2015 news). In the Aug 12 Science, researchers identify a transcription elongation factor, called Spt4 (and its human ortholog SUPT4H1), which selectively regulates expression of the expanded *C9ORF72* allele. In both *C.elegans* and *Drosophila* models expressing C9ORF72 expansions, knocking down Spt4 expression improved the phenotype and extended lifespan. In ALS patient-derived iPSCs, knockdown SUPT4H1 reduced accumulation of both types of RNA foci and of DPR proteins, suggesting that targeting SUPT4H1 could suppress all three toxic products of the expanded repeats, making it an attractive target for C9 ALS/FTD therapies.

New Neuroimaging Technique Tracks Epigenetic Changes in the Living Human Brain
A modified positron emission tomography (PET) imaging method enables real-time monitoring of epigenetic regulation of gene expression in the living human brain. The method uses a radioactively labeled, blood brain barrier-penetrant, small molecule called "Martinostat", which binds histone deacetylases (HDACs), enzymes that regulate gene expression by modifying the chromatin acetylation state. According to the paper in the August 10 *Science Translational Medicine*, proof-of principle experiments in healthy individuals revealed a stereotypic pattern of HDAC expression according to brain region. In order to investigate whether deviations from this pattern may occur in disease states, the investigators are now examining people with schizophrenia and Huntington's disease. This approach could yield insights on epigenetic mechanisms in ALS and potential new therapeutic strategies, notwithstanding disappointments to date with HDAC inhibitors as ALS therapies (Piepers et al., 2009).

Drug News

Cytokinetics Completes Enrollment in Phase III Trial of Tirasemtiv in ALS
The biotechnology company Cytokinetics has announced completion of patient enrollment in its Phase III randomized, double-blind, placebo-controlled clinical trial of *tiramsemtiv* in ALS, called VITALITY-ALS (Ventilatory Investigation of Tirasemtiv and Assessment of Longitudinal Indices after Treatment for a Year in ALS). Over 700 patients from 81 research centers in 11 countries have enrolled in the trial, aimed at testing the effect of the skeletal muscle activator *tirasemtiv* on slow viral capacity (SVC), a measure of respiratory function, as well as on other measures of muscles strength (see July 2015 news; March 2016 news). Results of the study are expected in the second half of 2017.

NeuroBANK Program to be Expanded With Large Grant
The NeuroBANK™ program at the Neurological Clinical Research Institute (NCRI) has received $3.6M in funding from The ALS Association, Massachusetts General Hospital (MGH), and ALS Finding A Cure to support its expansion over the next 3 years. NeuroBANK is a patient-centric clinical research platform that facilitates integration of information across research projects, and provides core services for clinical research

studies. It incorporates ALS Common Data Elements and standardized operating procedures in combination with a Global Unique Identifier (GUID) system to uniquely identify ALS patients while protecting their identity. The program is geared to help accelerate workflow in clinical research studies and to facilitate data integration across multiple studies, locations and biorepositories, which has become particularly important with the emergence of large scale precision medicine studies in ALS (see March 2016 news).

AxoSim Explores Nerve-On-A-Chip Technology for ALS, MS

AxoSim Technologies, a start-up company founded by researchers from Tulane University in New Orleans, has been awarded close to $0.5M in federal funding to develop its "Nerve-On-A-Chip" technology for applications in drug screening and space research. The technology is a 3D cell-based model designed to accurately mimic the structure and function of living neural tissue, and provide a more physiologically realistic platform for preclinical testing of drug candidates (Curley et al., 2011; Huval et al., 2015). The chip consists of neural cultures within a hydrogel scaffold that provides structure and supports cell survival, axon outgrowth and myelination. The company is partially being funded to investigate applications of this platform for drug testing in neurodegenerative disease, including ALS and multiple sclerosis.

Invitae Expands Its Diagnostic Tests for Neuromuscular and Neurodegenerative Diseases

The genetics diagnostics company Invitae Corporation has expanded its available tests to include new panels for neurodegenerative and neuromuscular conditions. The diagnostic panels are updated as research reveals new genes of interest for various diseases, and the company has significantly expanded its neurology testing to include 17 genes associated with Parkinson's disease, 78 genes covering neuropathies such as Charcot-Marie-Tooth (CMT) disease, and additional panels for hereditary spastic paraplegia and other motor neuropathies. To date, known ALS-associated genes, including SOD1, C9ORF72, and TDP-43 are not included.

Funding Opportunities:

August 2016

Target ALS Foundation Industry-Led Consortia. LOI due Aug 31, 2016.

Target ALS Foundation Young Investigator-Led Collaborative Projects. LOI due Aug 31, 2016.

September 2016

MDA Venture Philanthropy. LOI due Sep 1, 2016. Next cycle LOI due Dec 1, 2016.

Frick Foundation for ALS Research Grants. Application due Sept 30, 2016.

October 2016

CIRM Accelerating Therapies: Public-Private Partnership Program (ATP3). Application due Oct 31, 2016.

December 2016

NEW! MDA Investigator-Initiated Research Grants. LOI due Dec 15, 2016.

NEW! MDA Young Investigator Development Grants. LOI due Dec 15, 2016.

Full List of Funding Opportunities >>

Job Opportunities:

Director, Neuroscience Research & Drug Discovery, Verge Genomics, San Francisco, CA.

Scientist I - Electrophysiology, Research, Biogen, Cambridge, MA.

Director, Neurodegenerative Disease Research Center, Arizona State University, Tempe, AZ.

Clinical Research Assistant Project Manager, Northeast ALS Consortium (NEALS), Boston, MA.

NEW! Postdoctoral Positions, Institute of Genomic Medicine, Columbia University, New York, NY.

Full List of Job Opportunities >>

Upcoming Meetings:

September 2016

Sept 7-9, 2015: Baltimore, MD: Neurological Disorders Summit.

Sept 25-28, 2016: Bar Harbor, ME: Molecular Mechanisms of Axon Degeneration.

October 2016

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

Oct 19-21, 2016: London, UK: The Lancet Neurology Conference: Preclinical Neurodegenerative Disease.

November 2016

Nov 10-11, 2016: San Diego, CA: RNA Metabolism in Neurological Disease.

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

December 2016

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

Full List of Upcoming Meetings>>

Resources:

ALS Drugs in Development Database

ALSGene

Alzforum ALS Mouse Model Database

The PRO-ACT Database

NEALS Biofluid Repository Available to Researchers

VABBB ALS CNS Tissue Request Information Site

Target ALS Core Facilities