ALS Research Forum e-Newsletter Vol. 157 **August 5, 2016**

We hope you are having a wonderful summer!
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ALS Clinical Trial Guidelines - open comment period ends Aug 31, 2016.
ALS researchers are invited to submit comments on the draft ALS Clinical Trial Guidelines. The open comment period ends Aug 31, 2016. For copies of the handouts, slides, and presentations from the ALS Clinical Trial Guidelines Workshop, click here.

Conference News

Do SOD1 Aggregates Contribute to Parkinson's Disease?
Mutations in cooper-zinc superoxide dismutase (SOD1) underlie 20% of familial ALS cases, and are thought to cause ALS through an acquired toxic function of mutant SOD1, which misfolds and aggregates in the cell. At the annual International Congress of Parkinson's Disease and Movement Disorders, held June 17-23 in Berlin, Germany, researchers presented data suggesting that toxic SOD1 aggregates may contribute to Parkinson's disease (PD). The researchers detected pathological copper depletion in neurons of the substantia nigra vulnerable to degeneration in PD, which prompted them to examine SOD1 expression, a protein whose structure and function are impacted by copper levels. Strikingly, a five-fold increase in abundance of SOD1 aggregates was observed in the substantia nigra compared to control brain regions. These findings revisit the question of whether SOD1 aggregation is a driver of neuronal death or rather a consequence of the degenerative process.

Research News

International Collaboration Identifies Four New ALS Genes
Two papers published in the July 25 Nature Genetics online reveal discoveries of four new ALS genes. One study describes the identification of mutations in *NEK1,* which account for approximately 3% of ALS cases in European and European-American populations. The gene was identified through multiple lines of investigation that

combined data analysis of whole exome sequencing from familial ALS cases from the U.S., whole genome sequencing (WGS) of ALS patients from an isolated community in the Netherlands, and WGS from thousands of sporadic ALS patients and controls sequenced as part of the Project MinE initiative. *NEK1*, which encodes the serine/threonine kinase NIMA (never in mitosis gene-A)-related kinase, functions in neuronal transport and cytoskeletal integrity. A second gene, called *C21ORF2*, increased the risk of developing ALS by 65%. The precise function of the encoded leucine-rich-repeat protein is not well understood, but it is required for formation of primary cilia, it resides in mitochondria of immune cells, and interacts with NEK1. These genetic analyses suggest that in ALS, one or two rare genetic variants can substantially increase disease risk, as compared to other conditions in which a large number of low risk variants combine to trigger disease.

C9ORF72 Regulates Initiation of Autophagy

Hexanucleotide repeat expansions in the *C9ORF72* gene are the most common genetic cause of ALS and frontotemporal dementia (FTD), but the function of encoded protein is not well understood. A study published June 22 online in the EMBO Journal suggests that C9ORF72 regulates autophagy initiation. The C9ORF72 protein interacts with proteins of the Unc-51-like kinase 1 (ULK1) autophagy initiation complex, as well as with regulator of autophagy, Rab1a. In addition, silencing of *C9ORF72* expression using RNA interference impairs initiation of autophagy in cell lines and in primary neurons. The findings suggest that C9 mutations may contribute to disease through loss-of-function mechanisms that impair initiation of autophagy, in addition to previously described gain-of-function toxicity caused by RNA foci and dipeptide repeat proteins (see Oct 2015 news).

Analysis of Brain Atrophy Patterns Reveals Subtypes of bvFTD

Behavioral variant frontotemporal dementia (bvFTD) is characterized by a broad spectrum of symptoms, such as memory impairments, executive dysfunction, lack of inhibition, and difficulty interpreting social cues. The underlying causes are also varied, with both sporadic cases, and cases linked to mutations in *C9ORF72*, tau or other genes. In the July 18 JAMA Neurology, researchers attempt to classify cases of bvFTD based on the brain regions and networks affected by the disease in patients. In a retrospective observational study of 90 patients with bvFTD, the researchers analyzed the anatomical patterns of degeneration in MRI images, and identified clusters of patients with shared atrophy patterns. Interestingly, one group exhibited only subcortical degeneration and mostly exhibited TDP-43 pathology, while other subtypes with shared regions of brain atrophy were highly varied with respect to pathology and mutations.

New Method: Neuromuscular Junctions on a Chip

In the August 3 Science Advances, researchers led by Roger Kamm from the Massachusetts Institute of Technology (MIT) in Cambridge, MA, describe a new microfluidic device that models the neuromuscular junction (NMJ), and can serve as a platform to study NMJ degeneration in diseases such as ALS. The microfluidic device provides a more realistic *in vitro* model for NMJs than the typical petri-dish-based

models by incorporating two important physiological features of the NMJ: a three-dimensional structure, which is created using a 3D hydrogel, and compartmentalization of the motor neurons and muscles to mimic the physical separation in the body. The system, which uses mouse embryonic stem cell-derived motor neurons and myoblast-derived muscle cells, enables tracking of muscle force, as well as control over motor neuron activity through optical excitation.

Drug News

Antisense Therapy Improves Motor Function in Infants with SMA, Based on Interim Phase II Trial Analysis
Biogen and IONIS Pharmaceuticals have announced that the antisense oligonucleotide therapy nusinersen has met the primary endpoint following interim analysis of the Phase III double-blind, randomized clinical trial to treat infant onset spinal muscular atrophy (SMA): the drug significantly improved achievement of motor milestones in treated as compared to untreated infants. Nusinersen, previously called IONIS-SMN Rx, increases levels of the survival of motor neuron (SMN) protein by modulating splicing of *SMN2*, a gene closely related to the *SMN1* gene mutated in SMA. Biogen has exercised its option to license and commercialize the technology from IONIS (see Dec 2014 news), and is planning to apply for regulatory approval in the US this year. If approved, this would be the first FDA-approved drug to treat SMA.

ProMIS Neurosciences to Develop TDP-43-Targeting Antibody Therapies
The Toronto-based biotech company ProMIS Neurosciences (formerly Amorfix Life Sciences) announced initiation of a program to identify and develop therapeutic antibodies that target disease-associated variants of TDP-43. TDP-43 is an RNA-binding protein that normally localized to the nucleus, but in ALS and FTD, it accumulates in pathological cytosolic aggregates that interfere with normal cellular functions (see Feb 2014 news). The company plans to use its specialized computational platforms to predict novel epitopes on toxic variants of TDP-43, and design antibodies to selectively target these forms, while retaining crucial functions of the native protein (see March 2014 news).

Funding Opportunities:

August 2016

The Judith and Jean Pape Adams Foundation ALS Research Grants. Application due Aug 12, 2016.

Accelerating Drug Discovery for Frontotemporal Degeneration. LOI due Aug 12, 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

NEW! MDA Venture Philanthropy. LOI due Sep 1, 2016.

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

October 2016

NEW! CIRM Accelerating Therapies: Public-Private Parntership Program (ATP3). Application due Oct 31, 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.

NEW! Assistant Project Manager, Northeast ALS Consortium (NEALS), Boston, MA.

NEW! Principal Research Associate, Genzyme, Framingham, MA.

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

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

NEW! 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