ALS Forum e-Newsletter Volume 136 **Sept 25, 2015**

Visit the ALS Forum website to read the complete stories featured in this e-newsletter. Please let your friends and colleagues know about the ALS Forum. It is easy to sign up for the newsletter here.

Resources:

ALS Drugs in Development Database

The ALSGene tool: www.ALSGene.org

The PRO-ACT Database: www.ALSDatabase.org

NEALS Biofluid Repository Available to Researchers

VABBB ALS CNS Tissue Request Information Site

Funding Opportunities:

ALS Therapy Alliance (ATA) RFP. Applications due Oct 15, 2015.

California Stem Cell Agency (CIRM) 2.0 Awards. Due last business day of each month.

Upcoming Meetings:

September 2015

Sept 27-29, 2015: Chicago, IL: American Neurological Association Annual Meeting

Research News

Magnetic Stimulation Reveals Excitable ALS Brains

Cortical hyperexcitability has been reported as a feature of sporadic ALS, but whether this phenomenon also occurs in familial ALS cases due to C9ORF72 expansions was previously unknown. Steve Vucic and colleagues from the University of Sydney, Australia, examined this question using transcranial magnetic stimulation (TMS), a noninvasive approach to stimulate neurons in the brain and track movement in the periphery. According to their report in the Sep 8 *JAMA Neurology* online, cortical motor neurons of symptomatic patients carrying C9ORF72 mutations are hyperexcitable relative to controls, as in sporadic ALS patients, while asymptomatic expansion carriers do not exhibit abnormal activity. These findings suggest that cortical hyperexcitability is an intrinsic feature of the pathophysiology of ALS, and TMS measurements could be useful for assessing drug effects in clinical trials. This approach has already been incorporated as a primary outcome measure in the upcoming clinical trial of retigabine (see Apr 2015 news).

ALS-Associated Kinase Assists in Mitophagy

Deficits in autophagy, the mechanism by which cells destroy damaged organelles and proteins, contribute to motor neuron demise in ALS. Researchers from laboratory of Wade Harper at Harvard Medical School in Boston, Massachusetts, have now characterized how the ALS-associated protein, TBK1, which acts downstream of the familial Parkinson's disease proteins PINK1 and Parkin, promotes ubiquitin-mediated destruction of faulty

Sept 24-25, 2015: Ottawa, Canada: Ottawa International Conference on Neuromuscular Biology, Disease and Therapy

Sept 27-29, 2015: Chicago, IL: American Neurological Association Annual Meeting

Sept 30 - Oct 4, 2015: Brighton, UK: 20th International World Muscle Society Congress

October 2015

Oct 15-16, 2015: Chicago, Illinois: 10th Brain Research Conference RNA Metabolism in Health and Disease.

Oct 17-21, 2015: Chicago, Illinois: The Society for Neuroscience Annual Meeting.

Oct 31-Nov 5, 2015: Santiago, Chile. World Congress of Neurology

November 2015

Nov 4-6, 2015: Clearwater, FL: Annual NEALS Meeting.

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

Nov 14-18, 2015: San Francisco, CA: American Medical Informatics Association (AMIA) Annual Symposium

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

December 2015

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

mitochondria, or mitophagy (see Sep 2015 news). According to a report in the Sep 10 *Molecular Cell*, TBK1 initially binds Optineurin in the cytoplasm, which loosely binds ubiquitin molecules attached to damaged mitochondria. Subsequent activation of TBK1 strengthens the Optineurin-ubiquitin bonds and triggers recruitment of the autophagy machinery. The authors also report that TBK1 interacts with a second autophagy receptor called NDP52. Click here to read more.

Neurofilaments May Enable Differential Diagnoses of MNDs

Neurofilament proteins, which provide crucial cytoskeletal support to neurons, have been shown to be elevated in the blood and cerebrospinal fluid (CSF) of patients with ALS (see June 2015 news). However, it is unclear whether neurofilaments can serve as a biomarker to distinguish motor neurons diseases from their disease mimics. Researchers led by Markus Otto from the University of Ulm, Germany, assayed the CSF of 455 patients with ALS, primary lateral sclerosis (PLS), motor neuron disease (MND) mimics, and neurological controls. According to the findings published in the Aug 21 *Journal of Neurology, Neurosurgery, and Psychology*, both neurofilament light chain (NfL) and phosphorylated neurofilament heavy chain (pNfH) were significantly elevated in CSF from patients with either ALS or PLS (classified here jointly as MND), but not in the MND mimics, thereby providing a marker to distinguish the two categories. Other proteins, such as Tau and phospho-tau, did not differ amongst the groups.

Prohibitins Promote Proper Myelination

Impaired signaling between axons and Schwann cells leads to deficits in myelination and to axonal degradation, but investigating the signaling pathways at the axo-glial interface has proven to be technically challenging. Laura Feltri from the University of Buffalo in New York and colleagues have established a new model to study these juxtracrine, or contact-mediated, interactions. As reported in the Sep 18 *Nature Communications*, the researchers created a co-culture system with chambers containing axons and glia separated by a membrane, which enabled them to selectively isolate glial projections responding to axonal signaling. By conducting proteomic analysis of the glial leading edge, the researchers successfully identified a novel protein family required for myelination, called Prohibitins. Transgenic mice lacking Prohibitin-2 in glial cells exhibited impaired myelination and motor deficits. This technique could be applied to study other degenerative diseases, including ALS, where impaired communication between neurons and glia contributes to disease pathology.

TGF-β Isoforms are Potential ALS Muscle Biomarkers

2016

January 2016

Jan 24-27, 2016: Santa Fe, New Mexico: Keystone Symposium on Molecular and Cellular Biology: Axons: From Cell Biology to Pathology.

March 2016

March 6-8, 2015: Miami, FL:Annual Drug Discovery for Neurodegeneration Conference.

March 21-22, 2016: San Francisco, CA: AMIA Joint Summits on Translational Science

April 2016

Apr 2-6, 2016: Solden, Austria: 18th International Neuroscience Winter Conference.

April 16-23, 2016: Vancouver, Canada:American Academy of Neurology (AAN) Annual Meeting.

July 2016

July 2-6, 2016: Copenhagen, Denmark:10th FENS Forum of Neuroscience

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In the brain and spinal cord, transforming growth factor-β1 (TGF-β1) mediates the detrimental effects of astrocytes on motor neuron survival in ALS (see April 2015 news). Now, the TGFβ superfamily of cytokines is resurfacing in ALS muscle. As reportedin the Sep 16 *PLoS One*, researchers from the University of Alabama at Birmingham suggest that proteins from the TGF-β superfamily of cytokines are potential muscle biomarkers for ALS. Peter King and colleagues detected elevated levels of the TGF-β1, 2, and 3 isoforms in muscle biopsies from ALS patients, as well as in muscle samples from both presymptomatic and symptomatic G93A-SOD1 ALS mice. In the mice, expression of the TGF-β downstream signaling mediators Smad2 and Smad3 also exhibited progressive increase in expression as disease symptoms progressed. Follow-up studies to characterize the temporal profile of TGF-β isoform expression in human muscle could provide additional support for these proteins as muscle biomarkers of ALS disease progression.

Drug News

UK Public-Private Partnership Focuses on TDP-43-Targeting Drugs

The Dementia Consortium, a public-private partnership based in the UK, is now dedicating close to $500 thousand dollars to a project for the discovery and development of drugs for ALS and frontotemporal lobar degeneration (FTLD). The consortium is a collaboration between Alzheimer's Research UK, Medical Research Council (MRC) Technology, and the private companies Eisai and Lilly. The project, which will be carried out in part by researchers at the Italian non-profit organization International Centre for Genetic Engineering and Biotechnology (ICGEB), is aiming to identify drugs that clear the aberrant, cytosolic aggregations of TDP-43, a pathologic feature of both ALS and FTD. Several promising compounds have been identified that increase clearance of TDP-43 aggregates, and these compounds are undergoing further validation at the MRC to establish the mechanism of action and effect in animal models.

Community Effort Underway to Develop ALS Drug Development Guidance

A collaborative effort of patients, healthcare professionals, scientists, and industry experts is underway to develop an ALS drug development guidance document to help accelerate therapy development for the disease. The goal of the document is to provide the biopharmaceutical industry with guidelines for the regulatory process in ALS drug development, as well as to provide community input to the FDA on how to approach the regulatory pathway for ALS therapies. The initiative was inspired by the groundbreaking efforts of the Parent Project Muscular

Dystrophy, who developed an FDA guidance document for Duchenne muscular dystrophy (see Oct 2014 news), and is being shaped at all stages by input from patients and their families. The guidance document will be made available to the public for feedback in early 2016, and subsequently submitted to the US FDA for approval. Representatives from Prize4Life are also excited to be participating in the initiative.

Medicinova Expands Phase II Ibudilast Study to Include Advanced ALS Patients

Pharmaceutical company MediciNova has started enrolling ALS patients in advanced stages of the disease into its Phase II clinical trial of MN-166, or ibudilast (see Aug 2014 news). The FDA recently approved the company's amendment to expand the ongoing study in patients not using NIV to include 60 advanced ALS patients on NIV support. MN-166 is a small molecule phosphodiesterase 4 and 10 inhibitor and a macrophage migration inhibitory factor inhibitor that suppresses pro-inflammatory cytokines and stimulates expression of neurotrophic factors. The current study is investigating the safety and tolerability of MN-166 when given as an adjunct to riluzole in people in early and late stage ALS.