ALS Forum e-Newsletter Volume 135 **Sept 14, 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:

Clinical and Translational Science Award (CTSA U54). Applications due Sept 25, 2015.

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

Research News

C9ORF72 Repeats Disrupt Nuclear-Cytoplasmic Transport

The most common genetic cause of familial ALS and frontotemporal dementia is an expansion of GGGGCC repeats in the C9ORF72 gene (C9 ALS-FTD), but it is unclear how exactly this mutation drives ALS pathology. Three recent studies, two of which were published 26 Aug in *Nature* and the third in *Nature Neuroscience*, reveal a novel mechanism by which the expanded C9ORF72 gene does its damage: impaired nuclear-cytoplasmic transport. Aaron Gitler at Stanford University and fellow scientists used a genetic screen in yeast to find modifiers of GGGGCC repeat-related neurotoxicity. They identified RanGAP1, an enzyme that helps regulate protein trafficking into the nucleus. At Johns Hopkins University, Jeffrey Rothstein and colleagues discovered that RanGAP1 binds with the hexanucleotide repeat RNA and becomes mislocalized. Small-molecule inhibition of nuclear export in flies expressing the repeats rescues the impaired transport. Fen-Biao Gao and Paul Taylor of St. Jude Children's Research Hospital in Memphis, Tennessee, and colleagues conducted a genetic screen in mutant flies, which also revealed several proteins involved in the nuclear pore complex and nuclear transport. When examining iPSC-derived neurons from C9 ALS-FTD patients, they found excessive RNA accumulation in the nucleus as compared to controls, providing further support for the transport defects. The debate continues on whether aberrant RNAs or proteins produced from the mutant C9ORF72 are responsible for these defects. Read more here.

Although Parkin Helps, PINK1 is Sufficient for Mitophagy

Sept 19-20, 2015: Montreal, Canada: 10th Annual Symposium of the Fondation Andre-Delambre

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

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

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

December 2015

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

Impaired mitophagy, the process by which the cell rids itself of old or damaged mitochondria, contributes to pathology of both ALS and Parkinson's disease (see Jul 2015 news). Mitophagy is triggered by accumulation of the ubiquitin kinase PINK1 on damaged mitochondria. In what was previously considered a linear cascade, PINK1 phosphorylates the ubiquitin ligase, parkin, which in turn, ubiquitinates proteins on the mitochondrial outer membrane, leading to engulfment of the mitochondria into an organelle called the autophagosome (see Oct 2014 news). Parkin, whose mutation causes a familial form of Parkinson's disease, was thought to be essential for mitophagy, but a study reported in the 20 August *Nature* suggests otherwise. Michael Lazarou and colleagues of the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland, have found that the even in the absence of Parkin, the ubiquitin kinase PINK1 can trigger mitophagy at a low rate, by directly phosphorylating ubiquitin. Parkin, however, still greatly enhances mitophagy, allowing the cell to turn over damaged organelles and aberrant proteins before they become toxic.

Phase Transitions of FUS Protein Cause Detrimental Aggregation

Mutations in the gene Fused in Sarcoma (FUS) cause ALS, and cytosolic aggregates of the prion-like protein are found in most forms of ALS and in a subset of frontotemporal dementia cases. A new report in the Aug 27 *Cell* found that protein aggregation may be the detrimental effect of a functionally-important process by which prion-like proteins form transient liquid compartments in the cell, such as stress granules (see Dec 2013 news). Researchers form the laboratories of Tony Hyman and Simon Alberti of the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden, Germany examined the dynamics of FUS liquid droplet formation *in vitro* using photobleaching and 3-dimensional imaging, and found that the FUS protein forms liquid droplets, which convert over time to a 'frozen', aggregated state, a process that is accelerated by mutations in the FUS protein. Click here to read more about these elegant experiments.

iPSC-Derived Neuromuscular Junctions Generated *in Vitro*

In the September *Stem Cell Research*, scientists at Ulm University and Eberhard Karls University in Germany describe a novel *in vitro* co-culture system to study neuromuscular junctions (NMJs) derived from differentiated human iPSCs. Tobias Boeckers and colleagues developed a novel protocol (see related Aug 2015 news) to generate mature muscle fibers by selection of CD34+ myoblasts. Directed differentiation of these precursors yielded multinucleated, striated myotubes that generated action potentials in response to acetylcholine (ACh). When these muscle fibers were co-cultured with motor neurons that had been derived from the same iPSC line, they first displayed aggregation of ACh receptors in clusters along the

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 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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muscle fibers, and after 3 weeks, exhibited a characteristic end-plate morphology with expression of pre- and post-synaptic markers in apposition. If further experiments reveal that these NMJs form electrophysiologically active synapses, this could provide a valuable platform for research and drug testing for ALS. Read more here.

Drug News

Second Clinical Trial of Diaphragm Pacing Terminated After Troubling Results

A second European clinical trial to test efficacy of NeuRx Diaphragm Pacing System (DPS) in ALS has been been terminated early, due to evidence of detrimental effects of the device. RespistimALS, co-led by Jésus Gonzalez-Bermejo and Thomas Similowski at the Assistance Publique - Hôpitaux de Paris in France, aimed to examine whether implanting the DPS early in the disease course, prior to the onset of hypoventilation, could attenuate respiratory decline in ALS patients. All the study participants were implanted with the device, but it was only activated in the treatment cohort. In response to recent termination the DiPALS study due to an increase in mortality of ALS patients with DPS, an intermediary review of the French data was conducted, which revealed similar findings. These data have stirred a conundrum surrounding the benefits of DPS, since in the US, the device has been implanted in ALS patients since 2011 under a humanitarian device exemption granted by the FDA. Clickhere and here to read more.

Answer ALS Secures $20M for Multi-Institute ALS Personalized Medicine Initiative

The Johns Hopkins University in Baltimore, Massachusetts General Hospital in Boston and Cedars-Sinai Medical Center in Los Angeles have announced the launch of the largest, collaborative, ALS personalized medicine program as part of Answer ALS. The program was initiated in response to the 2013 Team Gleason Summit (see July 2013 news), and has now secured $20M in funding. The research programs under the current initiative will include collection of longitudinal data from over 1000 ALS patients, collection of clinical data real time, generation of iPSCs from the patients with comprehensive 'omics and clinical data, a national collaborative consortium, and finally, developing analytic tools for analysis of the large data sets. All the data will be made open access to the research community. How this program will be coordinated with similar ongoing efforts (see July 2015 news) is still undetermined.

Karyopharm Therapeutics Testing its Nuclear Transport Compounds for ALS

Karyopharm Therapeutics is a clinical stage pharmaceutical company best known for its lead compound selinexor, currently in clinical testing for hematological malignancies and solid tumors. With new findings on the central role of C9ORF72 in nuclear-cytoplasmic transport (see Aug 2015 news), the company has announced their entry into the ALS arena with their small molecule modulators of this critical pathway. Specifically, the plan to test their inhibitor of the nuclear export protein XPO1, KPT-350, as a candidate therapy for ALS. A second compound developed by the company that also targets XPO1, called KPT-276, was used by Rothstein and colleagues to rescue the nuclear transport detects in C9ORF72 mutant flies (see Jan 2015 conference news). The company is already collaborating with several academic researchers to test the therapeutic efficacy of this compound in patient-derived iPSCs and in rodent models of ALS.

Biohaven Acquires Glutamate-Modulating Prodrugs from ALS Biopharma

Canadian biotechnology company, Portage Biotech, has announced that its subsidiary, Biohaven Pharmaceuticals, has obtained the worldwide intellectual property rights to 300 prodrugs from ALS Biopharma, an early stage biotechnology company that specializes in discovery and development of therapies for ALS. The prodrugs, which were designed by scientists from the Fox Chase Chemical Diversity Center, are new molecular entities that function as modulators of glutamate signaling. In light of the known role of glutamate excitotoxicity in the pathophysiology of ALS, these compounds are of potential interest as candidate therapies for the disease.

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