ALS Research Forum e-Newsletter Vol. 162 **October 28, 2016**

Visit the ALS Research Forum to read the complete stories featured in this e-newsletter. Friends and colleagues can sign up for the newsletter here. Follow us on Facebook and Twitter for the latest updates.

Your opinion matters!

As we explore ways to improve the ALS Research Forum, we would like to hear your input on the resources you would find most useful. Our brief, 5-question survey should take less than 5 minutes to complete: https://www.surveymonkey.com/r/2016_ALSRF The survey has been extended until **October 31**! Thank you for your time and input!

Research News

G Quadruplexes Sequester a Splicing Factor in the C9ORF72 Brain

Stable three-dimensional structures called RNA-based G quadruplexes (G-Qs) have been proposed to form in C9ORF72 ALS by folding of expanded hexanucleotide repeat RNA (see Nov 2013 news), but whether they form in C9 ALS patients, and how they affect cellular function, is unknown. A study in the September 13 eLife shows for the first time that RNA G-Qs form in patient-derived cells and tissue from C9ORF72 ALS patients. There they trap the splicing factor hnRNP H, leading to missplicing of its targets in patient brain. The study strongly implicates hnRNP H sequestration as a pathogenic event in C9ORF72 ALS, but further work is needed to characterize the functional implications of these splicing changes and their impact on ALS pathophysiology.

C9ORF72 Emerges as Regulator of Actin Dynamics

Do intronic expansions in C9ORF72 lead to ALS and FTD through loss- or gain-of-function mechanisms? A study published October 10 in Nature Neuroscience points to loss of the C9ORF72 protein function as a major contributing factor. When C9ORF72 expression was reduced in primary motor neurons, axons were shorter with smaller growth cones, whereas overexpression enhanced axonal growth. Follow on mass spectrometry-based proteomic analysis revealed interactions between C9ORF72 and cofilin, an important regulator of actin dynamics. Further studies revealed that the

C9ORF72 protein directly binds Arf6 and Rac1 GTPases, which enhance cofilin function and promote actin polymerization and axonal growth. C9ORF72-depleted motor neurons, patient-derived iPSCs and post-mortem ALS brain samples were all found to have decreased cofilin activity and impaired actin dynamics.

Mitochondrial Dysfunction Takes Center Stage in C9ORF72 ALS/FTD
ALS-associated mutations in SOD1 and TDP-43 yield mutant proteins that bind mitochondria and impair their function (see Dec 2010 news, July 2016 news). A new study reveals that C9ORF72 does this too. According to a paper in the October 16 Neuron, dipeptide repeat (DPR) proteins translated from ALS- and FTD-linked C9ORF72 repeat expansions interfere with mitochondrial function. Motor neurons (MNs) derived from C9ORF72 ALS patients iPSCs exhibited increased DNA damage and oxidative stress, an effect that was also caused by overexpression of poly glycine-arginine (GR) DPR proteins in control iPSC-derived neurons. Analysis of the binding partners of poly GR proteins revealed interactions with mitochondrial ribosomal proteins that interfere with mitochondrial function, leading to oxidative stress and increased DNA damage.

Liquid Droplets Link FUS, TDP-43 and C9ORF72
Two papers published October 20 in Cell online reveal a shared downstream mechanism that mediates toxicity of several ALS and FTD-linked mutations - disruption of membrane-less organelles. Low complexity domain (LCD) proteins, such as FUS, had been previously shown to condense into liquid droplets that form a membrane-less organelle structure (see Oct 2015 news). In the current studies, the researchers analyzed binding partners of dipeptide repeat (DPR) proteins translated from C9ORF72 repeat RNA, focusing on arginine-rich DPRs, and found that the majority of proteins that bind them are LCDs, including TDP-43, FUS, hnRNPA1 and hnRNPA2B1. The interactions between arginine-rich DPRs and a variety of LCDs promote formation of abnormally viscous liquid organelles, which severely limit protein movement, and disrupt essential cellular functions.

Drug News

FDA Gives the Go-Ahead for Phase I Trial of ALS Stem Cell Therapy
Researchers at Cedars-Sinai Regenerative Medicine Institute in Los Angeles, CA, have obtained FDA approval to initiate a Phase I clinical trial testing a new candidate stem cell therapy for ALS. The stem cell therapy is based on transplantation of human neural progenitor cells (hNPCs) that are genetically engineered to secrete glial cell line-derived neurotrophic factor (GDNF), a protein with known neuroprotective effects. In ALS rat models, transplanted hNPCs expressing GDNF integrated into the spinal cord and improved motor neuron survival (Klein et al., 2005, Suzuki et al., 2007). The planned safety trial will entail unilateral injection of stem cells into the spinal cord, allowing for direct comparison within each patient of the treated and untreated side. The trial is predicted to begin recruiting patients before the year's end.

Lunasin Trial Introduces New Paradigm for ALS Clinical Trials

Researchers led by Richard Bedlack from Duke University's ALS Clinic in Durham, North Carolina, and the patient network PatientsLikeMe (PLM) have launched an innovative clinical trial to test efficacy of the peptide supplement Lunasin in ALS. The trial was motivated by the surprising case of an ALS patient who reported reversal of his symptoms while taking the supplement (see ALSUntangled report). The partners at Duke and PLM set out to systematically test its effect in a way that would be both inexpensive and attractive for patient recruitment. To this end, they designed a unique Phase II clinical trial that relies on patient reported outcomes and data from historical controls for the placebo arm. In addition, they publicized the protocol to enable patients outside the trial to report their outcomes.

Funding Opportunities:

November 2016

NEW! Ford Foundation Fellowship Programs. Application due Nov 10, 2016

December 2016

MDA Investigator-Initiated Research Grants. Letter of Intent due Dec 15, 2016.

MDA Young Investigator Development Grants. Letter of Intent due Dec 15, 2016.

January 2016

NEW! CIRM Funding Opportunity: DISC1: The Inception Awards. Application due by Jan 20, 2017.

Full List of Funding Opportunities >>

Job Opportunities:

NEW! Scientists I, Neuro Discovery Research. Biogen, Cambridge, MA.

NEW! Postdoctoral Position. RIC Sensory Motor Performance Program, RIC, Chicago, IL.

NEW! Postdoctoral Position - Fenghua Hu Lab. Cornell University, Ithaca, NY.

Research Scientist. AC Immune, Lausanne, Switzerland.

Biostatistician, Research Fellow, University of Dublin, Ireland.

Director of Neurodegeneration Disease Models, Allector, San Francisco, CA.

Full List of Job Opportunities >>

Upcoming Meetings:

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.

March 2017

Mar 29-Apr 2, 2017: Vienna, Austria:International Conference on Alzheimer's and Parkinson's Diseases.

April 2017

Apr 22-28, 2017: Boston, MA. American Academy of Neurology Annual Meeting. **Abstracts due October 24, 2016.**

July 2017

July 23-28, 2017: Stowe, VT: Gordon Research Conference on ALS and Related Motor Neuron Diseases. Applications due June 25, 2017.

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
