ALS Research Forum e-Newsletter Vol. 161 **October 14, 2016**

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Your opinion matters!

As we explore ways to improve the ALS Research Forum, we would like to hear your input on **content of interest to you**. Please let us know by answering 5 brief questions here: https://www.surveymonkey.com/r/2016_ALSRF
Thank you for your input!

Conference News

ICFTD 2016 Conference Coverage
At the International Conference on Frontotemporal Dementias (ICFTD), held August 31 to September 2 in Munich, Germany, researchers and clinicians convened to share advances in research and therapy development for frontotemporal lobar degeneration. Read further coverage of the conference covering topics of new FTD outcome measures, FTD genes, and research models.

Tests of Social Cognition Hold Potential as FTD Outcome Measures
Many of the standard measures used to evaluate symptoms of frontotemporal dementia (FTD) were originally designed to assess executive and cognitive changes in Alzheimer's disease. As discussed at ICFTD, these tests are inadequate for assessing the unique behavioral and cognitive symptoms of FTD, which include personality changes and loss of social skills. A variety of new, promising tests of social cognition are being evaluated as outcome measures for FTD. Some assess behavior in a variety of social situations, while others examine more unusual symptoms associated with specific brain circuits, such as smell aversion or music processing. More work is needed to validate these measures and identify the most useful ones for use in clinical trials.

FTD Gene Hunt Turns UP CYLD and Modifying Factors
Mutations in tau, progranulin and C9ORF72 are linked to FTD, but these genes account

for only a small proportion of FTD genetic risk factors. At ICFTD, researchers reported on several newly-identified, rare genetic mutations associated with the disorder. One culprit was a gene called CYLD, which encodes a deubiquitinase that slows autophagy. The identified variant enhances the deubiquitinase function, and may cause toxic buildup of aggregated proteins. A second study honed in on rare variants of dipeptidyl peptidase 6 (DPP6). The DPP6 protein regulates expression of potassium channels, and loss of function may cause neuronal hyperexcitability in FTD. Other studies unearthed genetic modulators of disease progression and age of onset, each of which provide additional insights into pathological pathways and targets for therapy.

New Data Reinforces Concept of Protein Propagation

At ICFTD, several talks featured new animal models that shed light on the pathophysiology of FTD. Speakers presented a new mouse model of TDP-43 proteinopathy was generated with an inducible, neuron-specific TDP-43 transgene (see Nov 2015 news). The mice exhibited cytoplasmic TDP-43 inclusions, selective motor neuron loss, and shortened lifespan. Remarkably, if the transgene was shut off 6-8 weeks after induction, the mice regained motor function and lifespan. Recovery was not as successful when TDP-43 expression was induced in mice older than one year of age. Also presented were mice modeling TREM2 mutations implicated in ALS, FTD and AD (see Feb 2014 news). Other speakers shared findings on pathological protein propagation between neurons in FTD, with evidence from both from mouse models and human tissue (see Jan 2016 news).

Research News

PFN1 Mutant Mice Exhibit Features of ALS, but Lack TDP-43 Pathology

Profilin 1 (PFN1), a protein that regulates actin polymerization, is mutated in approximately 1-2 percent of inherited ALS (see July 2012 news). A new mouse model, which expresses the ALS-associated C71G mutation in PFN1 was reported in the September 28 PNAS. The model exhibits several clinical hallmarks of ALS, including adult-onset motor neuron degeneration, muscle weakness, paralysis, and premature death. Surprisingly, PFN protein aggregates accumulated in motor neurons only after symptom onset, suggesting that protein aggregation may not be the primary trigger for neurodegeneration. Although the mutant PFN1 mice exhibit features of human ALS, such as cytoskeletal defects and accumulation of ubiquitin/p62 aggregates, they lack the characteristic TDP-43 pathology found in the majority of human ALS cases.

Does Smoking Lead to Worse Outcomes in People with ALS?

People who are smokers at the time of their ALS diagnosis are unlikely to survive as long as people who have already quit smoking or never started, according to a report in the September 21 Journal of Neurology, Neurosurgery, and Psychiatry. The correlation between smoking and disease prognosis is largely independent of COPD status at diagnosis, although additional health risks associated with smoking may also shorten life expectancy. How does smoking affect ALS outcomes? Several hypotheses have been raised, including effect on oxidative stress and induction of epigenetic modifications, but further research is needed to characterize the mechanisms

underlying this effect.

Largest Human Imaging Study Reports on First 5000 Volunteers
In the September 19 *Nature Neuroscience*, researchers report the first results from the largest human imaging study ever, which aims to image 100,000 healthy participants within 5 years. As a subset of participants gradually develop neurological diseases, the imaging data may shed light on presymptomatic features and lifestyle habits linked to disease, including ALS. This imaging study, part of the U.K. Biobank epidemiological study, entails collecting structural, functional, and diffusion MRI images of the brain to garner information on brain structure, integrity of axonal tracts, and neural activity, respectively. Even in this initial dataset, researchers identified intriguing correlations between the MRI phenotypes and a variety of lifestyle factors assessed though questionnaires, blood samples, genetic testing, and medical records. Read more about the potential impact of this project for neurodegenerative disease research here.

Drug News

MeiraGTx Targeting TDP-43 Toxicity in Gene Therapy Program
Gene therapy startup company MeiraGTx has announced expansion of its gene therapy program targeting ALS in collaboration with researchers from Weill Cornell Medical College in New York and LSU Health Sciences Center in Shreveport. The company is targeting the upframeshift protein 1 (UPF1), a master regulator of the nonsense-mediated mRNA decay (NMD) pathway, which disposes of mRNAs with premature termination codons. In animal models expressing TDP-43, overexpression of UPF1 preserved motor function as compared to untreated controls (see June 2015 news; Jackson et al., 2015). Interestingly, UPF1 has also been shown to suppress FUS toxicity in cellular models (Barmada et al., 2015), offering an additional application for this candidate therapy. The partners have entered into a research collaboration for pre-clinical testing of this therapy in animal models.

AveXis Reports Promising Interim Phase I Results of AVXS-101 in SMA
Shortly after of the announcement by Biogen and IONIS Pharmaceuticals of positive interim results from the Phase III clinical trial of nusinersen in spinal muscular atrophy (SMA, see Sep 2016 news), gene therapy company AveXis reported promising interim Phase I trial results of their candidate SMA therapy, called AVXS-101. While nusinersen increases expression of the SMN2 gene to compensate for lack of SMN protein, AVXS-101 is designed to deliver a functional copy of the mutated SMN1 gene (see Dec 2015 news). At a conference this month, the study principal investigator reported that as of September this year, 11 of 12 patients in the high dose cohort achieved head control and could sit unsupported. Remarkably, two patients have learned to walk independently. Detailed results were reported in the press release.

Funding Opportunities:

October 2016

MNDA Biomedical Research Project Grants. Summary Application due by Oct 28, 2016.

CReATe Clinical Research Scholars Program. Application due by Oct 31, 2016.

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

Full List of Funding Opportunities >>

Job Opportunities:

NEW! Research Scientist. AC Immune, Lausanne, Switzerland.

Biostatistician, Research Fellow, University of Dublin, Ireland.

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

Postdoctoral Position, Roger Sher Lab, Stony Brook University, Stony Brook, NY.

Postdoctoral Position, Joe Lewcock Lab, Denali Therapeutics, South San Francisco, CA.

Full List of Job Opportunities >>

Upcoming Meetings:

Please note the abstract submission deadline for AAN is Oct 24, 2016.

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

NEW! 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
