ALS Forum e-Newsletter Volume 125 **April 17, 2015**

Visit the ALS Forum website to read the complete stories featured in this e-newsletter. Please forward this e-newsletter to friends and colleagues who may be interested in learning more about ALS.

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:

Department of Defense ALS Research Program: Therapeutic Idea Award.Pre-application deadline: May 11, 2015, 5:00pm EST.

Department of Defense ALS Research Program: Therapeutic Development Award. Pre-application deadline: May 11, 2015, 5:00pm EST.

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:

April 2015

April 18-25, 2015: Washington, DC: The American Academy of

Research News

A New Study Reveals Three Distinct Strains of SOD1

Aggregates of misfolded proteins are a hallmark of many neurodegenerative diseases, including Alzheimer's, Parkinson's and ALS (see May 2014 news story; Dec 2012 news story). However, not all mutated proteins are created alike - different protein conformations, or "strains", have different functions and toxic properties. In a publication in the March 23 *Proceedings of the National Academy of Sciences*, researchers led by Stefan Marklund at Umea University in Sweden applied a novel technique to analyze distinct strains of aggregated superoxide dismutase (SOD1), a protein mutated in up to 20% of familial ALS cases. The approach, called binary epitope mapping, uses antibodies to detect distinct regions of the protein that are exposed in non-native proteins conformations, creating an antibody 'signature' for different mutated SOD1 strains. Interestingly, the least structurally stable SOD1 strain was associated with the most aggressive form of ALS in mouse models, suggesting that the strain of SOD1 may dictate the course disease progression (See Oct 2014 news story). The researchers next plan to expand their antibody panel and examine the SOD1 strain signatures in human samples. Click here to read more about this original approach and new insights on SOD1 toxicity.

Second Study Salutes TANK-Binding Kinase 1 as ALS Gene

In February of this year, scientists reported that TANK-binding kinase 1 (TBK1) was a potential amyotrophic lateral sclerosis gene (see Feb 2015 news). Now, another research group provides additional support for these findings and extends the association to frontotemporal dementia (FTD). The research team, led by Jochen Weishaupt of Ulm University in Germany, identified TBK1 mutations in 4% of the 252 familial ALS cases examined based on analysis of exome sequencing data. Examination of the kindreds in 7 families revealed 33 cases of ALS and 7 with no symptoms, suggestive of a high penetrance for TBK1 mutations. Surprisingly, over 50% of the mutation carriers exhibited cognitive impairment, some with clear signs of FTD. How do mutations in TBK1 cause ALS and/or FTD? Click here to read more about the study, and hypotheses for how TBK1 exerts its effects.

Neurology (AAN) Annual Meeting.

April 21-23, 2015: Boston, MA: BioIT World Conference & Expo.

April 27-29, 2015: Boston, MA: Stem Cell Summit '15.

May 2015

May 5-7, 2015: Philadelphia, PA: Biomarker & Diagnostics World Congress 2015

May 21-23, 2015: Verbania, Italy: European Network for the Cure for ALS (ENCALS) Annual Meeting.

May 31 - June 4, 2015: Jerusalem, Israel: EMBO Workshop, Macromolecular Assemblies at the crossroads of cell stress and function.

June 2015

June 14-17, 2015: Heidelberg, Germany:EMBO Symposium on Mechanisms of Neurodegeneration.

June 14-18, 2015: San Diego, CA: 19th International Congress of Parkinson's Disease and Movement Disorders.

June 19 - 24, 2015: Breckenridge, Colorado:Keystone Symposia: Autophagy

June 20-23, 2015: Berlin, Germany: 1st Congress of the European Academy of Neurology.

June 24-27, 2015: Stockholm, Sweden:International Society for Stem Cell Research Meeting.

New Study Suggests Protective role for Methylation in C9ORF72 Mutations

Four years after the description of the link between hexanucleotide nucleotide repeat expansions in the C9ORF72 gene and ALS and frontotemporal dementia (FTD), researchers are still baffled by how these mutations cause disease. One proposed hypothesis supports a gain-of-function mechanism involving production of abnormal RNA and dipeptide species (seeAug 2014 news story; Oct 2013 news story), while the loss-of-function hypothesis supports toxicity due to haploinsufficiency. A new study published in the March 20 *Neurology* online by senior author Edward Lee and first author Corey McMillan at the University of Pennsylvania, provides further support for the gain-of-function hypothesis. The researchers assessed methylation of C9ORF72 gene promoter, which shuts down transcription of the gene, in DNA from blood samples of a small cohort of mutation carriers with either FTD, ALS-FTD or ALS with mild cognitive impairment. Methylation of the C9ORF72 gene promoter was positively correlated with slower atrophy in select brain regions and reduced cognitive decline, suggesting that silencing gene expression is protective against toxicity of C9ORF72 mutations. Click here to read more detail about these intriguing findings and next steps for validating these results.

Plasma Profiling Reveals Three Potential ALS Biomarker Proteins

Researchers at the Sweden's KTH Royal Institute of Technology in Stockholm, Sweden and the Medical University of Warsaw, Poland have identified three proteins that are potential ALS biomarkers. In one of the most extensive plasma profiling studies in ALS conducted to date, samples from 367 Polish ALS patients and 101 controls were analyzed with antibodies targeting 278 proteins. Three proteins were expressed at higher levels in samples from ALS patients: neurofilament medium polypeptide (NEFM), solute carrier family 25 (SLC25A20), and regulator of G-protein signaling 18 (RGS18). Jointly, these proteins could provide an integrated snapshot of disease pathophysiology, with markers of neuronal structure, mitochondrial function/integrity, and cell signaling, respectively. The findings from this study werepublished in the Aug 1 *Annals of Clinical and Translational Neurology* last year, and the researchers are now expanding the data set to includes samples from Sweden, Poland and Germany as well as cerebrospinal fluid samples from ALS patients. If validated in further studies, these candidate biomarkers could help advance ALS diagnosis as well as drug development. Click hereto read more.

Drug News

July 2015

July 15-18, 2015: Bilbao, Spain: XII European Meeting on Glial Cells in Health and Disease

July 27-29, 2015: Rome, Italy: 4th International Conference and Exhibition on Neurology and Therapeutics.

September 2015

Sept 3-6, 2015: Prague, Czech Republic: 2nd World Congress on Neurotherapeutics.

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

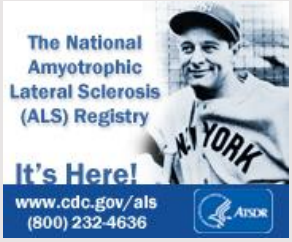
October 2015

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.

December 2015

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



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Heated Debate Over Access to GM604 Continues

On March 25, 2015, ALS patients and their families held a rally on Capitol Hill demanding accelerated approval of GM604, a drug developed by California biotechnology company Genervon. The drug is a short peptide derived from motoneuronotrophic factor (MNTF), a protein involved in embryonic development, and it modulates over 80 ALS-related genes. Last fall, Genervon announced via press release results of a 12 patient Phase II study, as well as a single compassionate use patient (see Jan 2015 news story). In February this year, the company filed a formal request for an Accelerated Approval Program from the FDA, which would grant drug approval based on a surrogate endpoint, without the need to conduct lengthy, expensive clinical trials. As the ALS community awaits the decision by the FDA about GM604, the debate around access to this drug continues. Leaders in the clinical and research community have voiced concern that the due to the small scale of the Phase II trial, further confirmation of the results in a larger study of longer duration is necessary, while from the perspective of ALS patients, the promise of benefits from the experimental drug far outweigh the risks of side effects or lack of efficacy. Click here to read the recent Washington Post article on the debate.

Keyboard Typing Patterns May Contribute to Parkinson's Diagnosis

An individual's style of keyboard typing is so distinctive that it can be used as a biometric signature for security purposes. A new study out of Massachusetts Institute of Technology (MIT) suggests that this signature can also be translated into a potential diagnostic tool for detecting motor impairments. The researchers have developed an algorithm that analyzes keystroke patterns and detects changes in that pattern that are suggestive of motor impairments. In a preliminary study in 21 patients with Parkinson's disease (PD) and 15 controls, the researchers were able to distinguish the PD patients from controls based on greater variability of their keystroke patterns. If these findings are confirmed in a larger study, this may present a new avenue for earlier diagnosis of PD, and possibly of other motor disorders such as ALS. Click here to read more.

Catabasis Pharmaceuticals Advancing Multi-Target Approach for DMD, ALS

Cambridge, MA-based Catabasis Pharmaceuticals has developed a unique platform for engineering multi-target drug candidates that simultaneously modulate multiple disease-relevant pathways. The company is now in the process of raising a $20.4M round of financing to continue to advance their specific therapeutic programs. In addition to their company's NF-kB inhibitor, CAT-1004, which is projected to enter Phase I/II clinical trials for Duchenne Muscular Dystrophy (DMD) in 2015, the company is

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developing CAT-4001, a dual Nrf2/NF-kB inhibitor for ALS, which targets both oxidative stress and inflammatory pathways (seeMarch 2014 news story). CAT-4001 is currently in preclinical testing, and if positive results are obtained, the drug is projected to enter clinical trials in 2016. Click here to read more.

New Test Detects Mutant Huntingtin in CSF

Huntington's disease-causing mutations in the huntingtin (mHTT) gene were first identified in 1993, but until now the mutant protein was undetectable in living patients due to its low concentration in the cerebrospinal fluid (CSF). According to the publication in the April 6 *Journal of Clinical Investigation*, a new immunoassay is able to detect mHTT for the first time in the CSF of HD patients. The assay, developed by an international team of researchers from the University College London, UK, IRBM Promidis in Pomezia, Italy, University of British Columbia, Canada and the CHDI Foundation, enables measurement of mHTT levels in the CSF with high sensitivity and specificity, and importantly, is able to detect changes in mHTT protein concentration as the disease progresses. As this approach is further refined and tested, it could potentially be adapted into a biomarker for drug effect on mHTT concentration, but in human trials and in preclinical studies. Clickhere to read more.

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