ALS Forum e-Newsletter Volume 124 **March 27, 2015**

Just a few days left - the survey closes on March 30th! Please take a few moments to provide feedback on the ALS Forum and eNewsletter by responding to our survey: https://www.surveymonkey.com/s/ALSForum. Thank you!

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.

Please provide your feedback on the ALS Forum 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

Webinars:

ALSA Research Update: The Neurocollaborative: Therapy Development for ALS. April 7, 2015: 4:00pm EST.

Funding Opportunities:

CDC Grant: Analyze and Evaluate Potential Risk Factors for ALS. Applications due Apr 6, 2015.

Biomarkers Across Neurodegenerative Disease (BAND) RFA. Letter of Intent due April 9, 2015, 6:00pm EST.

Department of Defense ALS Research Program:

Research News

Chaperone Deficiency May Cause Selective Motor Neuron Degeneration in ALS

ALS is characterized by selective degeneration of motor neurons in the cerebral cortex, brainstem and spinal cord, but the molecular mechanisms underlying this selective vulnerability are not well understood. A new study published in the March 19th *Neuron* online from the laboratory of Don Cleveland at University of California, San Diego suggests that the molecular chaperone macrophage migration inhibitory factor (MIF) may be partially the blame. Mutations in SOD1, which account for approximately 20% of familial ALS cases, cause misfolding of the protein and abnormal binding to mitochondria and the endoplasmic reticulum in motor neurons (see July 2011 news story). The researchers discovered that MIF is expressed at high levels in other cell types, and inhibits mSOD1 binding to organelles in those cells. Expressing MIF in motor neurons derived from induced pluripotent stem cells from mSOD1 mice increased neuron survival in culture three fold. This exciting discovery of MIF's function raises additional questions about the magnitude of MIF's role in motor neuron vulnerability, and the applications of these findings to ALS not due to SOD1 mutations. Click here to read more.

C9ORF72 Repeats Are Methylated in ALS and FTD

Hexanucleotide repeat expansions in the C9ORF72 gene underlie approximately 40% of familial ALS and 25% of familial frontotemporal dementia cases. However, the mechanisms by which these repeats lead to neuron degeneration are still unclear (see Nov 2014 news story). In a recent publication in the February 26 *Acta Neuropathologica* online, Ekaterina Rogaeva and colleagues from the University of Toronto demonstrate that these repeats become methylated once they reach 90 copies. Using an elegant approach, adapted from studies in Fragile-X syndrome, the researchers modified unmethylated cytosines into pyrimidines to distinguish them from the methylated residues in a subsequent PCR reaction. A clear pattern emerged in which repeat DNA from

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 7-11, 2015: Soelden, Austria: The 17th International Neuroscience Winter Conference.

April 7-8, 2015: San Francisco, CA: The 10th Annual Neurotech Investing and Partnering Conference.

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

ALS and FTD patients was methylated, whereas samples from individuals with fewer than 70 repeats were not. Although methylation normally silences gene expression, further work is necessary to decipher how methylation of the repeats is impacting C9ORF72 gene expression and toxicity. Click here to read more.

40 New Candidate ALS Genes Identified in Large Trio Study

A publication in the March 16 *Scientific Reports* by researchers from the University of Sydney, Australia and Washington University School of Medicine, St. Louis has identified 40 new candidate ALS genes through a trio analysis of 44 ALS patients and their unaffected parents. The researchers performed exome sequencing on all 44 trios and identified the recessive and *de novo* mutations in the children, focusing on rare variants and variants predicted to affect protein function. Of the 40 candidate risk gene identified, one gene called CHRM1 was identified in a prior trio analysis (see May 2013 news story) and a second gene, ITPR2, was previously described in the literature as linked to ALS. Although the mutations identified modify cellular functions relevant to ALS, such as translational regulation and dynein-domains, further corroboration in larger ALS cohorts is necessary to confirm the association between these variants and ALS. Click here to read more.

RNA-Binding Protein Controls Ataxin-1 Expression

A common link between ALS and spinocerebellar ataxia (SCA) was found with the discovery that mutations in ataxin-2 can cause both diseases, depending on the length of a specific polyglutamine repeat (see Aug 2010 news story). A new study by Huda Zoghbi and colleagues from the Baylor College of Medicine in Houston, Texas unravels a regulatory mechanism of a related gene, ataxin-1, that causes SCA and may also be linked to ALS (Conforti et al., 2012). In a publication in the March 12 *Cell,* the researchers demonstrate that the RNA-binding protein, Pumilio1, binds to the ataxin-1 3' untranslated region (UTR) and destabilizes its mRNA. Pumilio1 knockout mice exhibit a movement disorder and neurodegeneration similar to SCA1 null mice. Pumilio binding represents a mechanism for regulating translation of a protein, which at high levels can be neurotoxic even in its wild-type form. Such a mechanism for limiting protein translation may also apply to other proteins that are toxic at high levels even in their wild-type form, and points to the importance of examining the 3'UTR for variants that modulate expression of disease-linked proteins. Click here to read more.

Drug News

Treeway's ALS Drug Candidate TW001 Granted Orphan Drug Designation

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: Berlin, Germany: 1st Congress of the European Academy of Neurology.

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

December 2015

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

The Dutch biotechnology company Treeway, which was founded by the ALS patients and entrepreneurs Bernard Muller and Robbert Jan Stuit (see Jan 2015 news story) has announced that the US Food and Drug Administration (FDA) has granted orphan drug designation to its ALS candidate therapy TW001. TW001 is a reformulated therapeutic drug that acts as a radical scavenger and has demonstrated efficacy in previous clinical trials (for an undisclosed indication). The orphan drug designation will help promote a US clinical program in ALS, and will grant financial incentives for the company. The decision by the FDA follows that of the European Medicines Agency, which granted the drug orphan status in November 2014. Click here to read more.

AB Science Obtains Orphan Drug Designation for Masitinib

AB Science has announced that masitinib, its drug candidate currently in Phase III clinical trials for ALS, has been granted orphan drug designation by the FDA. Masitinib, an inhibitor of c-kit receptor tyrosine kinases, inhibits release of cytotoxic substances from mast cells and exerts anti-inflammatory effects. Masitinib has also demonstrated neuroprotective properties in preclinical models of stroke (see Nov 2014 news story) and is approved for treatment of certain cancers in dogs. The orphan drug designation will grant AB Science financial incentives for developing masitinib, such as seven years of marketing exclusivity upon drug approval. Click here to read more.

$100 Million Public-Private Venture Fund to Focus on Dementia Research

The difficult funding climate of NIH budget cuts and pharmaceutical companies withdrawing from early stage research and development in the neurosciences creates a need for creative funding solutions to continue to fuel the drug development pipeline for CNS diseases. Disease-specific venture funds are beginning to appear as a welcome newcomer to the rare disease landscape. Last year, the Qurit Alliance investment fund was launched with the goal of raising €100 million for investments in ALS drug discovery and development (see April 2014 news story).On March 17th, the UK Secretary of State for Health announced the first venture fund focused specifically on dementia research - the Dementia Discovery Fund. The fund has raised $100 million with backing from the U.K. government, Alzheimer's Research UK, and five large pharmaceutical companies, including Johnson and Johnson and GlaxoSmithKline. Investments from the fund will support preclinical drug development with existing solid proof-of-concept data, and companies will be allowed to bid for further development of projects if they are successful. To read more about this exciting new initiative to advance dementia research and drug development, click here.

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Cal State Team Developing Affordable Brain-Computer Interface Communication Device for ALS Patients

A team of researchers from California State University, Fullerton, has received funding from the Disability Communications Fund to develop a low-cost, brain-computer interface-based communication device for ALS patients within a year. The team, lead by Kiran George, is developing a device based on a wireless headset with 4-5 sensors to track patient biosignals, such as electroencephalogram (EEG) for brain activity and electromyography (EMG) for facial expressions, which are translated into computer commands to use email, text or video. The communication system is being designed from low-cost, off-the-shelf components to create an affordable option for patients with minimal design time. The project first prototype could be tested on patients as early as May 2015. Click here to read more about this exciting new project.

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