ALS Forum e-Newsletter Volume 126 **May 1, 2015**

Visit the ALS Forum website to read the complete stories featured in this e-newsletter.

May is ALS Awareness Month! Please use this opportunity to let your friends and colleagues who may be interested in learning more about ALS 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:

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.

Webinars:

ALSA/NEALS PALS Webinar: Why do people get ALS? Epidemiological studies to find answers.May 4, 2015: 12-1 pm PST

Conference News

Highlights of the 2015 Neuro Investing and Partnering Conference
The Annual Neurotech Investing & Partnering Conference celebrated its tenth anniversary this year in San Francisco on April 7-8, 2015. Hosted by the Neurotechnology Industry Organization (NIO) and NeuroInsights, the meeting provides a unique opportunity for leaders from the pharmaceutical, medical devices, software and diagnostics industries to discuss partnership and investments opportunities to advance development of new therapies for diseases of the brain nervous system. While the meeting spanned a range of thought-provoking topics, two sessions were of particular relevance to those interested in ALS, presenting new treatments for multiple sclerosis and cutting-edge approaches to drug delivery across the blood brain barrier. Click here to read Prize4Life's full report:
Part I: New Strategies in Multiple Sclerosis
Part II: Crossing the Blood Brain Barrier

Research News

Could Gluten Play a Role in Neurological Dysfunction in ALS?
Though gluten sensitivities are often thought to be associated with celiac disease, some studies suggest they may also cause neurological symptoms that mimic ALS. Recently, Vivian Drory and colleagues at the Tel Aviv Sourasky Medical Center in Israel assayed for specific biomarkers of gluten sensitivity in patients with ALS. As reported in the April 13 *JAMA Neurology*, the authors find that, compared to healthy controls, a higher percentage of ALS patients produce antibodies against transglutaminase 6 (TG6), a brain-enriched, gluten-processing enzyme. People with autoimmunity against TG6 could represent a unique subset of patient with ALS-like symptoms. For such patients, could a gluten-free diet be sufficient to alleviate motor symptoms and thwart neurological damage? Find out more here.

Revamped Phosphatase Inhibitor Shows Promise in ALS Mouse Model
The accumulation of misfolded proteins triggers a cellular stress response called the unfolded protein response (UPR), which temporarily halts protein translation. In 2011 senior author Anne

Upcoming Meetings:

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 7-10, 2015: London, Ontario, Canada.International Research Workshop on Frontotemporal Dementia in ALS.

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.

Bertolotti of the Medical Research Council Laboratory of Molecular Biology in Cambridge, England first reported that the α2-receptor agonist, guanabenz, could protect cells from the damaging accumulation of misfolded proteins by attenuating translation and prolonging activation of the UPR (Tsaytler et al., 2011). Guanabenz acts by selectively inhibiting the 15A regulatory subunit of protein phosphatase 1 (PPP1R15A), whichdephosphorylates the α subunit of translation initiation factor 2 (eIF2α) and allows protein synthesis to resume. But this anti-hypertensive drug also caused undesirable side effects, such as lethargy and somnolence. In a report in the April 10 *Science*, Bertolotti and colleagues characterize the guanabenz derivative Sephin1, a selective PPP1R15A inhibitor that does not bind theα2-adrenergic receptor, and therefore does not cause the side effects observed with guanabenz. In a mutant superoxide dismutase 1 (SOD1) mouse model of ALS, Sephin1 dramatically reduced protein aggregation and motor neuron atrophy. In contrast to this work, other studies point to potential detrimental effects of prolonged UPR activation (see Oct 2013 news story). Click here for more details.

A Link Between Viral Infection and Early-Onset ALS?

Dominant mutations in the senataxin gene are known to cause a rare form of juvenile ALS, but the exact mechanism by which this occurs is unknown. Senataxin (SETX) is a nucleic acid helicase which separates strands of DNA-RNA hybrids, but the specific functions of the wild-type protein have remained rather elusive. In a recent report in the March 30 *Nature Immunology* online scientists at the Icahn School of Medicine at Mount Sinai, New York have identified an antiviral function for SETX. Senior authors, Harm van Bakel and Ivan Marazzi and colleagues shows that the protein helps control inflammation and suppresses the replication of various viruses. Accordingly, when senataxin knockout mice were infected with Sendai virus, an RNA respirovirus, expression of antiviral genes increased dramatically in their lungs. The author believes their findings "indicate a potentially causal link among inborn errors in SETX, susceptibility to infection and the development of neurologic disorders". Clickhere to read more.

Study Identifies Role for MicroRNAs in Noise Control

MicroRNAs (miRNAs) are small non-coding RNAs that modulate gene expression, either by inhibiting protein translation or promoting RNA degradation. According to a new study published in the April 3 *Science,* miRNAs may also be critical for regulating noise, or random fluctuations, in protein production. Researchers led by senior authors Alexander van Oudenaarden of the University Medical Center Utrecht, Netherlands, Debora Marks of Harvard Medical School in Boston and Nils Blöthgen of Humboldt Universität in Berlin, have used a combination of experimental

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.

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.

December 2015

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

and computational methods to reveal how miRNAs might regulate noise in gene expression. The researchers used a single-cell synthetic reporter assay to monitor how miR-20 regulates expression of an mCherry gene with varying copies of miR-20 binding sites in its 3'UTR. Interestingly, the miRNA reduced noise specifically at low gene expression levels. The authors estimated that the vast majority of mouse genes are expressed weakly enough that miRNAs could reduce variability in gene expression levels. What impact could these findings have on neurodegenerative diseases, where miRNAs are known to play an important role (see Nov 2013 news story; Nov 2014 news story)? Find out by reading more here.

Drug News

ALSA, MGH and HSCI Collaborate with GSK to Test Retigabine in ALS

Data from both human studies and preclinical models points to an increase in neuronal firing, or hyperexcitability, in ALS neurons (see Jan 2015 news story; Bae et. al., 2014). Last year, work from the groups of Kevin Eggan at the Harvard Stem Cell Institute (HSCI) in Cambridge, MA and Clifford Woolf at the Boston Children's Hospital demonstrated that the anti-epileptic drug retigabine is effective in reducing hyperexcitability in stem cells derived from ALS patients (Wainger et. al., 2014; April 2014 news story). The first author on that study, Brian Wainger, is now the principal investigator of a clinical trial testing the ability of retigabine to reduce neuronal hyperexcitability in ALS patients. In parallel, samples will be collected to derive stem cells from participating patients to examine whether predictive measures of drug efficacy can be identified. The study will be conducted at 12 sites in the Northeast ALS Consortium (NEALS), with drug provided by GlaxoSmithKline (GSK) and funding from the HSCI, the ALS Association, GSK and the MGH Neurological Clinical Research Institute (MGH NCRI). This trial is remarkable as it is the first to be initiated based solely on preclinical evidence from patient-derived stem cells without companion mouse studies. As Lucie Bruijn, Chief Scientist for the ALS Association, said: "It is our hope that this novel approach demonstrates promising results and leads to better clinical trials for ALS patients in the future". Click here to read more.

Resource: Library of ALS Patients-Derived Stem Cells Now Open to Researchers

Although rodent models of ALS have been a valuable tool for unraveling disease mechanisms, positive results in these models have thus far not translated into effective therapeutics in humans. Recently developed methods for deriving stem cells from ALS patients are providing a promising new avenue to understand molecular pathways in ALS and to screen for drugs effective at

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modulating those pathways (see this issue). Now, researchers led by Jeffrey Rothstein from the Johns Hopkins University in Baltimore have created the largest public repository of induced pluripotent stem cells (iPSC) from familial ALS (fALS) patients, described in detail in the March 11 *PLOS ONE* (Yi, L., et. al., 2015). The library includes cell lines derived from 22 fALS patients carrying mutations in the most common fALS linked genes, including SOD1, C9ORF72, and FUS. These iPSCs can be differentiated into astroglia, which have been implicated as central players in non-cell autonomous mechanisms mediating ALS disease progression (See Feb 2014 news story). This valuable resource for research and drug screening is available through theCoriell Institute to researchers from both academia and commercial entities. Click here to read more.

Transcranial Magnetic Stimulation May Distinguish ALS from Non-ALS Mimic Disorders

The long interval between first symptoms and a confirmed ALS diagnosis, which can be as long as 18 months, limits many patients from participating in clinical trials early in the course of disease when interventions may have a greater therapeutic effect. A new neurophysiological tool called threshold-tracking transcranial magnetic stimulation (TMS) can distinguish ALS from non-ALS 'mimic' neuromuscular disorders in early stages of the disease, according to work presented at the 2015 American Academy of Neurology Annual Meeting. Nimeshan Geevasinga and colleagues from the University of Sydney, Australia, report that in a study of 333 patients with definite, probable, or possible ALS, or affected by other neuromuscular disorders, the TMS method distinguished ALS from non-ALS mimics with a sensitivity of 73% and specificity of 82%. With further validation, this approach could be used not only for diagnostic purposes, but also to assess drug efficacy. In fact, TMS is being incorporated as an assessment tool in the clinical trial of retigabine, discussed above. Click here to read more about these results.

Medicinova: Positive Interim Safety Data of MN-166 in ALS

Medicinova has announced positive interim safety data from its Phase II trial randomized, double-blind, placebo-controlled of MN-166 in ALS (see Aug 2014 news story). MN-166 (ibudilast) is a first in-class, orally bioavailable small molecule phosphodiesterase-4 and -10 inhibitor, as well as and a macrophage migration inhibitor factor inhibitor, which exerts both anti-inflammatory and neuroprotective effects. The interim review of data from the first 21 subjects enrolled in the clinical trial found no increase in adverse events in treated subjects as compared to placebo-treated patients. Based on these data, the trial will continue to complete full enrollment and trial rollout. Interestingly, the trial leveraged the CDC National ALS Registry, and all

registered patients who met the inclusion criteria were notified of the trial. Click here to read more.

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