THE ALS FORUM

Discovering a Common Goal, Discovering a Cure

ALS Forum e-Newsletter Volume 109 **August 8, 2014**

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:

The ALSGene tool: www.ALSGene.org

The PRO-ACT Database: www.ALSDatabase.org

NEALS Biofluid Repository Available to Researchers

NINDS Fibroblast Repository

VABBB Tissue Request Information Site

Funding Opportunities:

Blueprint Neurotherapeutics Network (BPN): SBIR Small Molecule Drug Discovery and Development for Disorders of the Nervous System (U44)

Webinars:

August 8, 2014, 1:00-2:00PM EST: ALSA/NEALS PALS Webinar - ALS Clinical Trial Pipeline Series - Summer 2014

Upcoming Meetings:

August 2014

August 10-15, 2014:

Research News

Survival Factor Protects Neurons from Mitochondrial Damage

An elegant study published in the July 15 *Science Signaling* out of the laboratory of Mohanish Deshmukh at the University of North Carolina, Chapel Hill, sheds light on how neurons avoid apoptosis in the face of mitochondrial damage. Under conditions of stress, damaged mitochondria release cytochochrome c (Cyt c) into the cytoplasm, which triggers apoptosis. Neurons, however, can recover from this insult and restore normal cellular function by expressing an E3 Ligase called parkin-like cytoplasmic protein (PARC) (for a role for parkin in ALS see Jan 2013 News), which targets Cyt C for degradation and thereby prevents apoptosis. Interestingly, PARC is also highly expressed in cancer cells and promotes their resistance to cell death. Does PARC dysfunction play a role in ALS? Possible associations between PARC mutations and ALS are noted in ALSGene, and mitochondrial dysfunction is a known contributor to ALS (see Nov 2011 News). Further work is needed to uncover whether this pathway plays a role in ALS and whether it has potential as a novel therapeutic target. Click here to read more.

Study Claims a 21% Genetic Risk for Sporadic ALS

To what extent is ALS genetically inherited? A new study from the groups of Bryan Traynor and Michael Nalls at the National Institute of Aging in Bethesda, Maryland published in the July 14 *JAMA Neurology*online concludes that genetic risk factors account for at least 21 percent of the risk for sporadic ALS. Since only 0.5% of the genetic risk arises from known ALS mutations, there remains an abundance of risk genes yet to be discovered. The investigators applied a new approach to analyze the patient genetic data called genome-wide complex trait analysis (GCTA), which estimates the risk due to all combined single-nucleotide polymorphisms (SNPs) in either a chromosome or genome, rather than for each individual SNP (see for example, May 2013 News). The findings from this GCTA analysis can now focus investigators' attention on specific regions of the genome that are most likely to contain ALS risk genes. To read more about the heritability of ALS, click here.

Newport, RI: Gordon Research Conference: Neural Development, From Stem Cells to Circuits

September 2014

September 8-10, 2014: Philadelphia, PA: 3rd International Conference and Exhibition on Neurology & Therapeutics

September 17-20, 2014: Minneapolis, MN: 1st ALS Research Group Meeting

October 2014

October 12-14, 2014: Baltimore, MD: American Neurological Association's 2014 Annual Meeting

October 23-25, 2014: Vancouver, Canada: The 9th International Conference on Frontotemporal Dementias

November 2014

November 13-14, 2014: Arlington, VA: 24th Neuropharmacology Conference

November 13-14, 2014: Arlington, VA: 9th Brain Research Conference Neuroprotection: Basic mechanisms and translational potential

November 15-19, 2014: Washington, DC: The Annual Society for Neuroscience Annual Meeting

December 2014

December 3-5, 2014: San Antonio, TX: World Stem Cell Summit

December 3-6, 2014: Cold Spring Harbor, NY:Neurodegenerative Diseases: Biology &

C9ORF72 Dipeptides Block RNA Synthesis in the Nucleolus

A new study from Steven McKnight's laboratory at the University of Texas Southwestern Medical Center in Dallas, Texas, adds another piece to the puzzle of how C9ORF72 mutations cause ALS. In the July 31 *Science* online, the researchers report that protein di-peptides translated from the C9ORF72 intronic expansion flood the nucleolus and inhibit normal RNA processing. The abnormal di-peptides (see Feb 2013 News) inhibit ribosomal RNA synthesis and mRNA splicing and are eventually toxic to cells. The link between C9ORF72 mutations and nucleolar dysfunction has already been described, though by a different mechanism whereby truncated RNA products sequester crucial RNA-binding proteins (see Mar 2014 News). Together these studies paint a picture of both RNA and peptide-based toxic mechanisms associated with C9ORF72 expansions. It will now be intriguing to see whether these cell culture results can be replicated in human ALS tissue. Click here to read more.

TREM2 Mutations Impair Phagocytic Activity in Frontotemporal Dementia

Triggering receptor expressed on myeloid cells 2 (TREM2) is a cell surface protein that mediates phagocytosis and is highly expressed by microglia. TREM2 variants are associated with several neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, frontotemporal dementia (FTD) and ALS (see Oct 2012 News,Nov 2012 News, Feb 2014 News). However, how the mutations affect TREM2 function is not well understood. A new study published July 2 online in *Science Translational Medicine* from the laboratories of Christian Haass at the Ludwig Maximilian University of Munich and Marco Colonna of Washington University, St. Louis, reports that mutant TREM2 does not undergo processing at the cell surface, and therefore cannot activate phagocytic pathways. The researchers report that soluble TREM2, the cleavage product of TREM2, was absent from the cerebrospinal fluid (CSF) of a homozygous carrier of the TREM2 mutation. Surprisingly, AD or FTD patients who did not carry TREM2 mutations also had reduced levels of soluble TREM2 in the CSF, suggesting that TREM2 processing defects may contribute more broadly to these diseases. Is this also the case in ALS? TREM2 levels are elevated in the spinal cord of ALS patients (see Feb 2014 News), but its precise function in the disease remains to be elucidated. Click here to read more.

Drug News

Phillips and Accenture Partner to Read ALS Patients' Minds

Royal Phillips and Accenture are jointly developing software that can increase the independence of ALS patients and improve quality of life. The application works with an electroencephalography (EEG) headset developed by Emotiv, which can record the patient's EEG brain activity and translate it into the desired commands for Phillips devices, such as turning on lights or television. The application can also respond to eye or voice commands, providing a technology that can support patients at several stages of the disease. Although the software is currently only at the proof-of-concept stage, it is already being tested in patients. The companies are now looking for partnerships that can help develop the

Therapeutics

December 5-6, 2014: Brussels, Belgium:International Conference on ALS/MND

December 17-20, 2014: Hotel Vila Galé Coimbra, Portugal: Mitochondria, Metabolism and Disease

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application into a viable product. Click here to read more

Kadimastem and Merck Enter Neurodegenerative Disease Partnership

Kadimastem, an Israeli biotechnology company focused on stem-cell therapies for diabetes and neurodegenerative diseases, has entered into a drug screening collaboration agreement with Merck Serono. The initial therapeutic focus is on multiple sclerosis (MS), leveraging Kadimastem's drug screening platform of stem cell-derived oligendendrocytes and Merck's compound libraries. With Kadimastem's interest in other diseases, such as ALS (see July 2014 News), the collaboration may expand into drug screening for other neurodegenerative diseases using Kadimastem's platform for stem cell-derived astrocytes. This collaboration builds on a prior agreement between the two companies from 2012 surrounding drug screening for MS. Merck will pay Kadimastem an up-front fee as well as undisclosed milestone payments. Click here to read more.

First Ever Parkinson's Disease Vaccine Shows Promise

The first ever clinical trial of a Parkinson's disease (PD) vaccine is achieving promising results. AFFiRiS AG, a Vienna-based biotechnology company developing peptide-based vaccines, reported results of a phase I clinical trial in PD patients of their proprietary anti-alpha-synuclein therapy, called PD01A. Alpha-synuclein protein aggregates are a hallmark of PD pathology, and researchers have hypothesized the reducing protein accumulation would be an effective therapeutic strategy for PD. In this trial, funded by the Michael J. Fox Foundation, two doses of the therapeutic vaccine were shown to be safe and well-tolerated, meeting the primary endpoint of the trial. In addition, the vaccine-treated patients showed a trend toward functional stabilization. The next step is a follow-up study to assess clinical and immunological effects of a booster vaccine, which is expected to begin recruiting in September 2014. Click here to read more.

Proteostasis Meet Preclinical Milestone for Neurodegenerative Disease Drugs

Proteostasis Therapeutics, a biotechnology company focused on therapeutics that target protein chaperones and the proteasomal degradation pathways, announced achievement of a major preclinical milestone in drug development for neurodegenerative diseases. In collaboration with Biogen Idec, the company is developing compounds that enhance proteasomal activity by inhibiting Usp14, a deubiquitinating enzyme that targets several key proteins implicated in neurodegenerative diseases. The company successfully completed its preclinical milestone by demonstrating that these Usp14 inhibitors successfully clear aggregation-prone proteins in a neurodegenerative disease animal model. These drugs may have therapeutic potential for ALS too, since Usp14 stabilizes TDP-43 (Lee *et. al.,* 2010) and Usp14 inhibitors may be effective at clearing pathological TDP-43 aggregates characteristic of the disease. Click here to read more.

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