THE ALS FORUM

Discovering a Common Goal, Discovering a Cure

ALS Forum e-Newsletter Volume 95 **October 25, 2013**

Be sure to check out our newly redesigned ALS Forum website. We hope you like what you see and we would love to know what you think. Please email jgoodman@prize4life.org with any feedback you may have.

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:

Visit the PRO-ACT Database at www.ALSDatabase.org

NEALS Biofluid Repository Available to Researchers

NINDS Fibroblast Repository

VABBB Tissue Request Information Site

Funding News:

MNDA Calls for Project Grant Applications. The summary application deadline is November 1, 2013.

Upcoming Webinar:

The ALS Association's Research Update Webinar Series continues with Dr. Ammar Al-Chalabi ofKing's College, London, U.K. who will be discussing Clinical Staging as a Tool for ALS Care and Research. The webinar will be held onMonday, October 28, 2013 at 4pm EST.

Research News

RNA Deposits Confer Toxicity in C9ORF72 ALS

It's been nearly two years since the discovery of the ALS-linked gene C9ORF72 and researchers are working hard to understand how the hexanucleotide repeat expansion in C9ORF72 influences the development of ALS and frontotemporal dementia (FTD). Earlier this year, two studies showed that the hexanucleotide repeat expansion in C9ORF72 is translated into dipeptide repeat (DPR) proteins (if you missed these stories, you can check out Dr. Amber Dance's summaries of the *Science* and *Neuron* papers). Now new research published online in *Neuron* on October 16, and led by Dr. Jeffrey Rothstein from Johns Hopkins University, shows that RNA transcribed from the hexanucleotide repeat in C9ORF72 might sequester a number of important RNA-binding proteins into RNA foci, thereby preventing the RNA-binding proteins from executing their normal cellular functions. In order to assess the effects of blocking sequestration of these proteins into RNA foci, the researchers identified antisense oligonucleotides (ASOs) against C9ORF72 that significantly decreased the RNA foci levels but didn't influence the level of C9ORF72 RNA. These ASOs were protective in cell death paradigms and restored normal gene expression in neurons generated from the skins cells of patients with the C9ORF72 hexanucleotide repeat expansion. Dr. Rothstein is working with Isis Pharmaceuticals to develop these ASOs into potential therapies, following on the footsteps of the recent Phase I clinical trial of ASOs against SOD1. You can't miss this jam-packed story - click here to read it now.

PERKing Up Protein Synthesis May Prevent Neurodegeneration

A recent *Science Translational Medicine* paper published online on October 9 made a big splash in the neurodegenerative disease field by providing evidence that inhibiting the unfolded protein response (UPR) could be neuroprotective. The study, led by Dr. Giovanna Mallucci from the University of Leicester, UK, found that an inhibitor of PERK (PKR-like endoplasmic reticulum kinase) protects neurons from cell death in a mouse model of prion disease. The PERK inhibitor (originally developed

Click here to register.

Upcoming Meetings:

October 29-30, 2013: Boston, MA: SciBX Summit on Innovation in Drug Discovery and Development 2013

November 3-5, 2013: New York, NY: FasterCures: Partnering For Cures

November 7-8, 2013: San Diego, CA: 8th Annual Brain Research Conference: RNA Metabolism in Neurological Disease

November 7-8, 2013: San Diego, CA: Workshop, Introduction to Stereology for Neuroscientists

November 8, 2013: San Diego, CA: NINDS Workshop, Mechanisms of Misfolded Protein Propagation in Neurodegenerative Diseases

November 9-13, 2013: San Diego, CA: Society for Neuroscience Annual Meeting: Neuroscience 2013

December 4-5, 2013: Milan, Italy: 21st Annual Meeting of the International Alliance of ALS/MND Associations

December 6-8, 2013: Milan, Italy: 24th International Symposium on ALS/MND

February 2-4, 2014: Miami, FL: ADDF's 8th Annual Drug Discovery for Neurodegeneration Conference

by GlaxoSmithKline for another indication) was even neuroprotective when administered nine weeks after disease onset in these mice. Unfortunately, the treatment caused massive weight loss in the mice, which forced the group to prematurely terminate their study. What do these findings mean for other neurodegenerative diseases such as ALS? PERK's role in the UPR is to phosphorylate the eukaryotic initiation factor 2alpha (eIF2alpha), and then phosphorylated eIF2alpha turns off protein synthesis. Inhibiting PERK and turning back "on" protein synthesis is neuroprotective. So is it worth trying the GSK PERK inhibitor in SOD1 G93A mice? Probably not, as the dramatic weight loss induced by the PERK inhibitor would most likely exacerbate the disease in these mice. However, this research is definitely intriguing and provides insight about relevant pathways to target. Click here to read the complete story and find out what these findings mean for ongoing therapy development for neurodegenerative disease.

Study Links Motor Neuron Disease to New Receptor Tyrosine Kinase

A group of researchers led by first author Yuji Takahashi, now at the National Center of Neurology and Psychiatry in Tokyo, Japan, and by senior author Shoji Tsuji of the University of Tokyo, Japan identified a new potentially ALS-linked gene, erythroblastic leukemia viral oncogene homolog 4 (ErbB4), the findings of which were published online on October 10 in the *American Journal of Human Genetics*. The researchers identified a family of eight children, three of whom were diagnosed with familial ALS (evidence suggested the father had the disease as well, but he was not diagnosed before his death). The authors tried to identify novel mutations in the children that were not present in the mother. Through a complicated linkage analysis (due to the fact that the group was so small and it was unknown if some of the children might develop the disease later on in life) the researchers identified seven genetic regions that might be associated with the disease. Whole-genome sequencing of these regions led to the identification of ErbB4 with a R927Q mutation, which was not present in over 470 control samples. To gather more evidence the researchers sequenced over 360 familial cases and over 810 sporadic cases of ALS. They identified the ErbB4 R927Q variant in a familial ALS case as well as one sporadic ALS case with an ErbB4 R1275W mutation. So is ErbB4 the next C9ORF72? Probably not. Although the findings are intriguing, they definitely require further investigation. Click here to find out what others are saying about this finding and its relevance to ALS.

Surprise Save: Excitability Protects Neurons from Lou Gehrig's

Many researchers believe one of the ways in which motor neurons die in ALS is through an excitotoxicity mechanism mediated by excess glutamate. The only FDA approved drug for ALS, riluzole, works by indirectly blocking excitation resulting from glutamate receptor activation. However, new research out of Dr. Pico Caroni's laboratory at the Friedrich Miescher Institute in Basel, Switzerland and published in *Neuron* on October 2 challenges assumptions about this excitotoxicity mechanism. Dr. Caroni, along with first authors Smita Saxena and Francesco Roselli, showed that the most susceptible neurons to motor neuron death are those that are "least electrically excitable." They then tried to link this surprising observation with the notorious ALS culprit, SOD1. Through a series of experiments the authors showed that increasing excitability in motor neurons decreased levels of misfolded

April 23-24, 2014: Boston, MA: The Neurotech Investing & Partnering Conference
2014 Advances in Drugs, Devices and Diagnostics for the Brain and Nervous System

April 23-25, 2014: Boston, MA: Stem Cell Summit 2014

April 26 - May 3, 2014: Philadelphia, PA: American Academy of Neurology 2014 Annual Meeting

June 14-15, 2014: New London, NH: Gordon Research Seminar: Barriers of the CNS, The Neurovascular Unit: Partners for Life

June 15-20, 2014: New London, NH: Gordon Research Conference:Barriers of the CNS. Expanding the Understanding of CNS Barriers in Health and Disease

June 22-27, 2014: Waterville Valley, NH: Cell Biology of the Neuron: Mechanistic Insight into Neuronal Development, Plasticity, Disease and Regeneration

SOD1, while decreasing excitability led to increased levels of misfolded SOD1. Click here to read Dr. Amber Dance's coverage of this "exciting" (bet you didn't see that coming) and evolving story.

Drug News

NeuroVigil Joins with NASA to Develop Assistive Technologies for ALS
While NASA may be best known for rockets and rovers, NASA is broadly interested in innovative technologies that make seemingly impossible things, like space flight, possible. Now NASA is announcing a new collaboration with NeuroVigil, which is the brainchild of NeuroVigil Chairman and CEO Dr. Philip Low. Using findings from his Ph.D. thesis work Dr. Low created the iBrain, which uses electroencephalography (EEG) to monitor brain activity in order to identify potential disease-relevant biomarkers. A fateful meeting with Dr. Stephen Hawking convinced Dr. Low to use his technology to assist ALS patients. Now, NeuroVigil is hoping to use the iBrain for "mind-based communication", translating the EEG reading of patients into words, which would enable ALS patients to communicate using only their thoughts. The goal of NeuroVigil's collaboration with NASA is to improve the technology and develop other ways to assist patients with ALS and other disorders of the central nervous system. Click here for more on the collaboration and NeuroVigil's technology, and here for information about the upcoming clinical trial.

Amgen and KineMed Join Forces to Track Down Pathogenic Proteins
The "Disease Pathway Experts" at KineMed Inc. have teamed up with the drug development experts at Amgen in order to learn more about the stability and regulation of different proteins in neurodegenerative diseases like ALS. Using KineMed's specialized mass spectrometry technology called the Dynamic Proteomics Platform, the two groups are teaming up to track the synthesis and breakdown rates of proteins that can become misfolded and accumulate in the brains of people with neurodegenerative diseases. As part of the $1M ALS Biomarker Prize competition, KineMed was awarded a 'thought' prize for their Dynamic Proteomics Platform technology by Prize4Life in 2007. The 'thought' prize was awarded to five groups with promising biomarker concepts. By understanding the dynamics of misfolded proteins through this collaboration, KineMed and Amgen hope to develop diagnostic tests and drugs to potentially slow the spread of these diseases (let's hope they are interested in looking at ALS-linked proteins TDP-43 and SOD1). For more on the partnership and research plans, click here.

Xonovo Tests Novel Drug in Alzheimer's, Potentially Also ALS?
Xonovo Inc. recently licensed the intellectual property rights for the small molecule XN-001 from the Oklahoma Medical Research Foundation (OMRF). XN-001 is a synthetic derivative of Lanthionine Ketimine (LK) which increases the activity of CRMP2. XN-001 has been shown to "improve both axonal transport and autophagy" and has shown benefit in several neurodegenerative disease mouse models, including SOD1 mice. Xonovo initially plans to move XN-001 forward in Alzheimer's disease, with the goal of completing their preclinical studies and moving into patients within two years. With promising preclinical findings in SOD1 mice, hopefully Xonovo will also consider advancing XN-001 for

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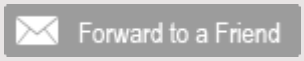

ALS. Stay tuned to the ALS Forum e-Newsletter to find out.

FDA Grants $1M to Test Memantine in ALS

The US Food and Drug Administration (FDA) just awarded $14 million in funding to support efforts to develop therapeutics for 15 rare diseases. One of the awardees was Dr. Todd Levine from the PNA Center for Neurological Research in Phoenix, Arizona. Dr. Levine was awarded $990,000 distributed over the course of three years to support his Phase IIb clinical trial of memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist with the potential to block glutamate mediated excitotoxicity (currently on the market for Alzheimer's Disease), for the treatment of ALS. Memantine has had a long history of being tested in ALS. In 2005 a group from The Burnham Institute in La Jolla, California reported a 7% increase in survivalin memantine treated SOD1 mice. In 2010, a group at the Institute of Molecular Medicine at the University of Lisbon in Lisbon, Portugal reported their results of a Phase II/III study of memantine. The study foundmemantine to be safe and well-tolerated in people living with ALS. Unfortunately, the researchers were unable to comment about the effect of memantine on survival. Another Phase II study sponsored by the University of Alberta in Canada examined the effect of memantine on functional outcomes (no outcome reported). Finally, a third Phase II study (run by Dr. Levine himself) tested both the tolerability and safety of memantine in ALS. The study also looked to see if drug treatment could be correlated to changes in a CSF biomarker. Unfortunately, because the study was open label, no conclusion could be made regarding the efficacy of the drug. Although many clinical studies have been conducted, we still don't have a clear answer about the efficacy of memantine in ALS. Let's hope Dr. Levine's next study will be appropriately powered (and blinded) so that we can finally have an answer to this unsolved question.

The ALS Forum was developed by Prize4Life, Inc.
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Identified content provided through a partnership with the Alzheimer Research Forum.