THE ALS FORUM

Discovering a Common Goal, Discovering a Cure

ALS Forum e-Newsletter Volume 98 **March 4, 2014**

February 28th was International Rare Disease Day, which was established to raise public awareness of rare diseases like ALS. This is the perfect opportunity to resume our coverage of cutting-edge ALS research and drug development news. We didn't want you to miss any of the recent groundbreaking news, so we have also included links to interesting stories from December and January. As always, you can find all of these news on the ALS Forum.

Since Prize4Life will be exclusively focusing on the $1M ALS Treatment Prize going forward, the ALS Forum will be supported by our sister organization, Prize4Life-Israel. Thanks to these changes, we can ensure that the ALS Forum and the ALS bi-weekly newsletter will continue to be developed as valuable resources for the research community, and you will be kept abreast of the most cutting edge stories happening in ALS.

Resources:

Visit the new ALSGene tool at www.ALSGene.org

Visit the PRO-ACT Database atwww.ALSDatabase.org

NEALS Biofluid Repository Available to Researchers

NINDS Fibroblast Repository

VABBB Tissue Request Information Site

Upcoming Meetings:

Research News

Escort Service: A cytoplasmic role for TDP-43

TDP-43 (TAR DNA-binding protein 43), a nuclear regulator of mRNA metabolism, is known to form cytoplasmic aggregates in ALS, FTLD, and other neurodegenerative disorders. However, it has been widely debated whether TDP-43 serves a physiological function outside the nucleus. A new study published online on February 5th in Neuron by Paul Taylor and colleagues at St. Jude Children's Research Hospital in Memphis, Tennessee, reveals a novel, cytoplasmic function for this RNA-binding protein. The new work suggests that TDP-43 plays an important role in shuttling mRNA-containing granules along axons to nerve terminals to enable rapid, local translation in response to neuronal activity. The researchers examined wild type human TDP-43 in motor neurons from flies and primary cortical neurons from mice and compared them to two ALS-causing mutant forms of the protein. While the wild-type form could be found along the extent of the axon, the mutant

March 16-19, 2014: Chicago, IL: Muscular Dystrophy Association (MDA) Clinical Conference

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

April 29 - May 1, 2014: Boston, MA: BioIT World Conference and Expo

April 29-30, 2014: Boston, MA: Translational CNS summit

May 7-8, 2014: San Francisco, CA:Neurogaming Conference

May 8-10, 2014: Berlin, Germany: The 7th European Conference on Rare Diseases & Orphan Products (ECRD)

May 22-24, 2014: Leuven, Belgium: European Network for Cure of ALS (ENCALS) 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

form built up in the cell body and was rarely visible in the axon. In an elegant series of experiments, the researchers used an mRNA beacon, a fluorescent reporter for the neurofilament-light chain (NF-L) transcript that is known to bind TDP-43, to track the motion of the protein in live cells. The native form moved anterogradely along the axon, while the mutant form moved retrogradely toward the cell body. Impaired anterograde transport was also apparent in pluripotent stem cells from ALS patients carrying mutations in TDP-43. These findings suggest that impairments in axonal trafficking, in addition to loss of nuclear function and protein aggregation, contribute to disease in mtTDP-43 mediated ALS and FTLD. Click here to read the full story.

Death in a Dish: Astrocytes from ALS Patients Flick Necroptosis Switch in Motor Neurons

Studies in transgenic mouse models of familial ALS have identified a critical role for non-neuronal cells in motor neuron degeneration. Astrocytes that express mutant SOD1 can trigger motor neuron death in mice, primary neurons, and embryonic stem cell-derived motor neurons (see stories in October 2003, April 2007 and December 2008). However, the toxic factor(s) that trigger(s) motor neuron death is/are unknown and the precise mechanism of motor neuron death is not well understood. Moreover, it is unclear how the findings from the mutant SOD1 models translate to the human sporadic ALS disease.

A new study, published online on February 6th in Neuron and led by Diane Re and Virginia Le Verche in Serge Przedborski's laboratory at Columbia University in New York, reveals that astrocytes derived from sporadic ALS (sALS) patients are capable of triggering a form of programmed cells death called necroptosis in motor neurons, even after such astrocytes are cultured alone for a month. In this study, astrocytes from postmortem motor cortex and spinal cord tissue of six sALS patients and 15 controls were isolated and grown in culture for a month and were subsequently combined with motor neurons derived from human embryonic stem cells. While motor neurons co-cultured with astrocytes from non-sALS controls thrived, motor neurons began to rapidly perish after just four days in culture with sALS astrocytes. Other types of neurons were resistant to the death signals delivered by sALS astrocytes, and fibroblasts from sALS patients did not harm motor neurons. By treating the cultures with inhibitors to RIP1 and MLKL, two proteins involved in necroptosis, but not with inhibitors of TDP-43 or SOD1, the investigators were able to reverse this toxic effect. These findings provide a new model for drug screening for ALS, as well as for investigating the factors that trigger necrotopsis in motor neurons. Click here to read more.

Transcription Factor Nourishes Neuron-Muscle Pair in ALS

Disease

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

June 28-29, 2014: Hong Kong, China: Gordon Research Seminar: Molecular & Cellular Neurobiology, Exploring the Frontiers of Foundational and Translational Neuroscience

June 29 - July 4, 2014: Hong Kong, China: Gordon Research Conference: Molecular & Cellular Neurobiology, Mechanisms of Neural Development, Circuit Assembly, Synaptic Plasticity and Neuropsychiatric Disorders

July 5-6, 2014: Easton, MA: Gordon Research Seminar: Intrinsically Disordered Proteins, Fundamental Characteristics and Approaches to Understand the Biological Functions of IDPs

July 5-10, 2014: Nice, France: The 13th International Congress on Neuromuscular Diseases - ICNMD 2014

July 6-11, 2014: Easton, MA:Gordon Research Conference: Intrinsically Disordered Proteins, Understanding Intrinsically Disordered Regions (IDRs) at Different Scales: From Single Molecules to Complex Systems

July 12-17, 2014: Copenhagen, Denmark: Alzheimer's Association International Conference

Model

The causal relationship between muscle atrophy and motor neuron death in ALS has long been debated. Previous work from Don Cleveland's lab and others has suggested that muscle pathology does not trigger neuronal degeneration in ALS (see May 2012 news story), and improving muscle function does not prevent denervation. In line with those findings, a new study published on January 13th in the Proceedings of the National Academy of Sciences online by Rhona Seijffers and colleagues at Children's Hospital in Boston, examined whether activating transcription factor 3 (ATF3), a factor known to promote neurite regeneration after injury, can be beneficial in a mouse model of ALS. In collaboration with Robert Brown's group at the University of Massachusetts Medical School in Worcester, the researchers examined motor neuron survival, axonal damage, and muscle innervation in mice co-expressing ATF3 and the human mutant superoxide dismutase 1 (mSOD1) gene. The mice co-expressing ATF3 and mSOD1 exhibited increases in motor neuron survival and delayed muscle denervation. These mice also retained muscle mass for significantly longer than mSOD1 mice. However, despite preservation of muscle mass and motor neuron axons, extension of lifespan was modest, and the rate of disease progression was similar to that of the mSOD1 mice. Therapies targeted to the pro-survival and regeneration genes that are activated by ATF3 could be promising for treating ALS, however, it is unlikely that activating ATF3 targets would be sufficient on its own. To read more about these interesting findings, click here.

Exome-Network Combination Uncovers New Disease Genes

One of the emerging challenges in discovering new disease-associated genes is combining them into a full picture of interaction networks, and understanding the biological pathways that are affected by the disease. A new study published on January 31st in the journal Science and led by Joseph Gleeson from the University of California, San Diego, successfully combined exome (expressed regions of the genome) sequencing and gene interaction network analysis to identify 18 new genes that cause a group of rare movement disorders called hereditary spastic paraplegias (HSPs). The researchers analyzed the exomes of 55 families with high rates of disease showing an autosomal recessive inheritance pattern. By examining homozygous regions for rare gene variants they identified 15 new gene candidates in addition to known HSP genes. Five of these gene candidates were confirmed to be present in HSP patients. Others were shown to cause movement disorders when knocked-down in a zebrafish model. The complete interaction network of nearly 600 proteins, or the "HSPome", provides clues toward which biological pathways may be harmed in HSP, such as protein trafficking, endosome sorting, protein degradation, lipid metabolism, axon and

July 13-15, 2014: Prince Edward Island, Canada: Biotechnology & Human Health Symposium

July 26-27, 2014: Girona - Costa Brava, Spain: Gordon Research Seminar: Neurobiology of Brain Disorders, Neurodegeneration and Aging-related Disorders of the Nervous System

July 27 - August 1, 2014: Girona - Costa Brava, Spain: Gordon Research Conference: Neurobiology of Brain Disorders, Neurodegradation and Aging-related Disorders of the Nervous System

August 2-3, 2014: Andover, NH: Gordon Research Seminar: Musculoskeletal Biology & Bioengineering, Bridging the Disciplines

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synapse development, and purine nucleotide metabolism. Interestingly, the HSPome overlapped with known genes for Alzheimer's Disease, Parkinson's Disease, and ALS. These findings reveal commonalities among the neurodegenerative diseases and provide further support for classifying them based on affected pathways rather than as separate diseases. To read more about these findings in HSP and how they can inform research on ALS, click here.

Research News Updates from December and January:

Check out the full stories on the ALS Forum by clicking the links below!

National Institutes of Health Tackles Irreproducibility Problem

TDP-43 Routes Mapped in Alzheimer's, Frontotemporal Dementia

Familial ALS More Common Than Thought - Do We Need a New Definition?

Biomarker Panel Predicts Slow or Fast ALS

Stress Relief: Anti-Stress Granule Therapy Saves ALS Models

Drug News

Looking Back at Advances in ALS for 2013
The ALSTDI has created an engaging and interactive timeline of last year's key milestones in ALS research and development. The summary covers notable therapies in clinical development and new treatment strategies, including antibodies targeting misfolded SOD1, small molecules to reduce neuroinflammation in motor nerves, and adult stem cells derived from patients' bone marrow to secrete neuroprotective substances. Technologies and devices that may aid diagnosis and prediction are also on list. For example, electromyography (EMG) to improve diagnosis by checking for subclinical signs of ALS, a whole-brain magnetic resonance technique as a quantifiable neuroimaging marker for ALS, and an ALS cognitive test. To take a look at the full 2013 timeline, click here.

Glaxo Compound Slows Lou Gehrig's Disease in Animal Models
Stress granules are dense aggregates that contain RNA and

protein and appear in the cytosol under conditions of stress. A recent study, published online on December 15 in Nature Genetics by Nancy Bonini from the University of Pennsylvania and colleagues, may have found a key to reducing neuronal toxicity in ALS by modulating stress granules. In ALS patients carrying a mutated TAR DNA-binding protein 43 (TDP-43) gene TDP-43 accumulates in the cytoplasm rather than being localized to the nucleus and has a toxic effect on neurons. Previous work has demonstrated that genes that modulate stress granules also affect TDP-43 toxicity. In an attempt to reverse TDP-43 toxicity, the researchers targeted eIF2α, a translation initiation factor that is found in its phosphorylated form in stress granules. They used a small-molecule inhibitor of eIF2α phosphorylation developed by GlaxoSmithKline to try to inhibit stress granule accumulation in fruit fly and mammalian neurons. TDP-43-expressing flies treated with the inhibitor showed greater physical strength and better climbing ability than the untreated controls. The inhibitor also reduced the risk of cell death in these models. The findings could provide the groundwork for new ALS therapies that target stress granule accumulation. To read the full story, click here.

Neuralstem Raises $19.6M in a Stock Offering to Support ALS Therapy Through Phase II

Neuralstem's Phase II trial in ALS will likely get a boost in funding through their recent $19.6M stock offering. Neuralstem, which received financial support from the National Institutes of Health and from the ALS Association for the Phase II study, is testing their spinal cord-derived neural stem cells (called NSI-566) in ALS patients. The cells are injected at various segments of the spinal cord to integrate into the motor neuronal circuitry. Interim results from the Phase I study led by Dr. Eva Feldman can be found here. The Phase II study is aimed at identifying the maximal-safe tolerated dose of the treatment, and the trial is expected to be completed in late 2014. Click here to read more.

Neurophage Pharmaceuticals Awarded Second Grant for Parkinson's Disease Program

Cambridge, MA-based Neurophage Pharmaceuticals has been awarded a second grant from the Michael J. Fox Foundation for Parkinson's Research (MJFF) for further development of its second generation drug candidate, NPT088. The drug is based on Neurophage's general amyloid interaction motif (GAIM) technology, which can simultaneously target multiple misfolded proteins and reduce levels of pathogenic protein aggregates. In preclinical studies, treatment with GAIM-based candidates led to reduced levels of protein plaques and to cognitive behavioral improvements in animal models. The GAIM-based therapies holds promise for a broad range of neurodegenerative diseases associated with misfolded

proteins, including ALS. We have previously reported on exciting developments in Neurophage's pipeline in the June 3, 2013 Conference News Story. Neurophage will leverage the funding from MJFF to conduct preclinical studies on the effect of NPT088 on alpha-synuclein accumulation in the brain. In parallel, Neurophage has an active program in Alzheimer's Disease, and is on track to begin clinical trials in 2015 for testing whether its drug candidate can successfully break down aggregates of amyloid beta or tau protein in humans. Click here and hereto read more about Neurophage's unique multi-target drug candidate.

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