THE ALS FORUM

Discovering a Common Goal, Discovering a Cure

ALS Forum e-Newsletter Volume 99 **March 14, 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:

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:

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

Research News

What's the FUS About? New ALS Model Thickens the Plot

Mouse models of ALS that recapitulate different aspects of the human disease are essential tools for understanding ALS disease pathology and developing effective therapies. A recent report published in the February 10 *Journal of Clinical Investigation* from the laboratory of Eric Huang at the University of California, San Francisco describes a new mouse model carrying a single point mutation in the fused in sarcoma (FUS) gene, a mutation commonly found in familial ALS patients (see initial results reported in the February 2013 story). In the mice, this mutation leads to serious motor defects and accelerated death. The motor neurons that survive exhibit defects in DNA repair and gene splicing. Unlike some prior mouse model of FUS mutations, this mouse model expresses mutant FUS protein at levels similar to the endogenous protein. However, unlike ALS in humans, these mice exhibit incomplete loss of motor neurons and nuclear localization of FUS protein, which typically redistributes to the cytoplasm in human ALS where it forms RNA-protein aggregates. To read more about this new mouse model and its valuable applications for ALS research, click here.

TREM2 Variant Doubles the Risk of ALS

The Triggering Receptor Expressed on Myeloid cells 2 (TREM2) protein is an innate immune receptor expressed on microglia, as well as other cell types. Over the past few years, mutant forms of the protein have been implicated as genetic risk factors for several neurodegenerative diseases including Alzheimer's disease (November 2012 news story), frontotemporal dementia (October 2012 news story) and Parkinson's disease (October 2013 Alzforum story). ALS is now joining the crowd: a recent report from Matthew Harm's lab at Washington University in St. Louis, published in the February 17 *JAMA Neurology*, found that humans carrying TREM2 mutations have more than double the risk of developing the disease. In addition, wild-type TREM2 gene

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 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

expression is elevated almost threefold in the postmortem spinal cord of ALS patients and in SOD1-G93A transgenic mice. It remains unclear how TREM2 mutations relate to ALS pathology, but it is likely that microglia are involved. Next steps are to investigate what aspects of the microglial response are mediated by TREM2, and determine how these protein variants contribute to disease severity and progression. Click here to read more.

RNA-DNA Pairs: At the Root of C9ORF72 Repeat Damage?

A hexanucleotide repeat expansion (HRE) in the C9ORF72 gene is the most common genetic cause of amyotrophic lateral sclerosis and frontotemporal dementia. A recent report in published on March 6 in*Nature* led by first author Aaron Haeusler and colleagues at Johns Hopkins University in Baltimore, MD, describes a new structural mechanism for the C9ORF72 gene's involvement in ALS. The investigators found that the gene can fold back upon itself during transcription to form a single-stranded, guanine- rich, DNA structure called a G-quadruplex. The second DNA strand can form RNA-DNA duplexes that disrupt transcription, causing accumulation of truncated, toxic RNA fragments. The researchers propose a compelling model in which the unfinished mRNA products aggregate and sequester crucial RNA-binding proteins, leading to cell stress. These findings are not without controversy however, being largely based on in vitro observations, and suggesting that the HRE in C9ORF72 has seemingly both loss of function effects, due to incomplete transcription of the C9ORF72, and toxic gain-of-function properties that contribute to ALS, whereas many in the field are skeptical of the loss-of-function hypothesis. Read more about related findings here, and about these recent findings here.

TDP43: A Protein that Lingers on

One of the hallmarks of neurodegenerative diseases is the abnormal accumulation of protein aggregates due to decreased stability of these disease-associated proteins. This is most likely the case for mutant superoxide dismutase (SOD1) found in familial ALS patients (see January 2011 story). A new study published on February 6 in the *Proceedings of the National Academy of Sciences* from Samar Hasnain's group at the University of Liverpool, UK, shows that the opposite may be true for TAR DNA binding protein-43 (TDP-43). High cytoplasmic levels of TDP-43 protein are found in the vast majority of sporadic ALS patients, and mutations in the protein are associated with a subset of familial ALS cases. The researchers show that two forms of mutant TDP-43 protein with mutations in the nucleic acid binding domain exhibit increased half-life and thermal stability, as well as resistance to unfolding, rendering them more resistant to degradation and prone to accumulation in the cell. Interestingly, these mutations have little impact on

Research Conference: Molecular & Cellular Neurobiology, Mechanisms of Neural Development, Circuit Assembly, Synaptic Plasticity and Neuropsychiatric Disorders

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TDP-43 protein secondary, tertiary, or quaternary structure. These new findings reveal a potential new target for drugs that aim to destabilize TDP-43. Click here to read more.

Drug News

Third Rock's Voyager Hunts for CNS Disorders with Gene Therapy

Cambridge, MA-based Voyager Therapeutics has completed a $45M Series A round of equity financing for development of gene therapy and microRNA therapeutics for the treatment of central nervous system diseases. The company has its eyes set on ALS, Friedreich's Ataxia and Parkinson's disease. Voyager's therapeutic strategy uses adeno-associated viral (AAV) vectors to introduce either a normal copy of a mutated gene or a microRNA to shut down a detrimental gene. AAV vectors are promising as vectors for gene therapy in humans, due to their relatively weak immunogenicity and their ability to generate widespread expression of the target gene in the brain. To treat ALS, Voyager plans to express micro RNAs that suppress mutant superoxide dismutase 1 (SOD1) expression. AAV-based therapies are already being developed by Dimension Therapeutics for rare diseases (see November 2013 drug news) and by AveXis for treating spinal muscular atrophy (see AveXis press release) and of course Isis Pharmaceuticals (see below) has a major anti-sense program directed at knocking down SOD1 as well. Voyager plans to build a rich AAV library to ultimately treat a variety of rare diseases. As for ALS - they hope to enter clinical trials in a couple of years. Click here to read more.

Isis Pharmaceuticals Shows Promising Spinal Disorder Treatment Data

Spinal muscular atrophy (SMA) is a rare genetic motor neuron disorder, caused by recessive mutations in the survival motor neuron 1 (SMN1) gene. A nearly identical gene, SMN2, also codes for survival motor neuron protein but does not produce a significant amount of protein due to a point mutation that results in defective splicing (See research news stories on March 2011 and June 2011). Isis Pharmaceuticals, a Carlsbad, California-based company, has developed an antisense oligonucleotide technology, ISIS-SMNRx, to specifically target and block an intronic splicing silencer sequence in SMN2, in order to enable translation of functional SMN2 protein and thereby replace the missing protein. In a partnership with Biogen Idec, Isis is currently testing the compound in an open-label, multiple dose phase II study. Isis has previously reported promising results in a phase I study with an increase in the muscle function of participating patients detected up to fourteen months following the high-dosage treatment (see news

story). Data from the phase II studies will be shared at the American Academy of Neurology meeting in April 2014. Another promising therapeutic for SMA is under development by Trophos, who just announced results of its pivotal trial of olesoxime in SMA. To read more about the ongoing trials click here and here.

Amorfix Leads the Way for ALS Research

A new study from Amorfix Life Sciences, led by Chief Scientific Officer Dr. Neil Cashman and published in the *Proceedings of the National Academy of Sciences* on February 18 online, sheds light on how ALS spreads throughout the nervous system. The researchers have previously shown that mutant SOD1 can cause wild-type SOD1 to misfold and acquire toxic properties. This new report shows that misfolded SOD1 can also spread from cell to cell, and induce template-directed misfolding of native SOD1 via a prion-like mechanism. Prion-like proteins are not new to ALS - TDP-43 also exhibits prion-like properties (see July 2010 news story). These findings provide additional research support for Amorfix's approach to treating ALS by developing therapeutic antibodies that target misfolded SOD1. To read more, click here.

Experimental Stroke Drug Brings New Hope for ALS

Protecting the blood-spinal cord barrier may delay motor neuron degeneration in ALS mice. A new study published on March 3 in the*Proceedings of National Academy of Sciences* from Berislav Zlokovic's laboratory at University of Southern California, CA, reports that an activated protein C analog being developed to treat stroke patients appears to restore the integrity of the blood-spinal cord barrier, which disintegrates in ALS (read more about this in our November 2009 research story). When the drug was administered to mutant SOD1 mice, the mice retained blood-spinal cord barrier integrity and displayed delayed onset of motor neuron degeneration. The drug, called 3K3A-APC, is being developed by Zlokovic's start-up company, zzBiotech. Although at this time the company's focus is on stroke, these findings suggest that the therapeutic approach may hold promise for ALS patients too. To read more, click here.

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