THE ALS FORUM

Discovering a Common Goal, Discovering a Cure

ALS Forum e-Newsletter Volume 97 **December 16, 2013**

2013 was a great year for the ALS Forum and the ALS Forum e-Newsletter! In the past year The ALS Forum was redesigned and upgraded, making the content on the site easier to find and use. In addition, the number of subscribers to the ALS Forum e-Newsletter increased by 25% and is now approaching 1000. The management team at Prize4Life would like to thank the readers of the ALS Forum e-Newsletter and the users of the ALS Forum website for your continued interest and for all of your efforts to advance ALS research!

In observance of the holiday season, the ALS Forum e-Newsletter will be taking a hiatus and will resume in 2014. To stay updated with the latest coverage of ALS research and industry news, please visit the ALS Forum website at www.ResearchALS.org. Wishing you and your loved ones a wonderful holiday season and a very happy New Year!

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 at www.ALSDatabase.org

NEALS Biofluid Repository Available to Researchers

NINDS Fibroblast Repository

VABBB Tissue Request Information Site

Funding News:

The National Center for Advancing Translational Sciences (NCATS) isaccepting applications for the National Institutes of Health's Bridging Interventional Development Gaps (BrIDGs) program. The application deadline is January 10, 2014.

Conference News

Researchers Revel in C9ORF72 Advances at RNA Symposium
Two days before the annual Society for Neuroscience Meeting, researchers from across the globe convened at the "RNA Metabolism in Neurological Disease" satellite symposium held in San Diego, California November 7-8, 2013. As you may have guessed, C9ORF72 stole the show (for more information, read the *Neuron* and *Science Translational Medicine* stories previously covered in the ALS Forum e-Newsletter). Click here to read Dr. Amber Dance's complete coverage of the latest C9ORF72 research discoveries discussed during the meeting, including 1) that C9ORF72 RNA might form a G-quadruplex structure, 2) that hexanucleotide repeat length does not seem to predict/correlate with phenotype, and 3) the latest updates on the growing list of C9ORF72 animal models, including flies, zebrafish, and even mouse models (yes, they are coming!). If you couldn't make the meeting, now is your chance to read the latest buzz on the rapidly evolving C9ORF72 story.

Profilin-1 Links Cytoskeleton and RNA Aggregation in ALS
Over the past few years a number of RNA binding proteins, including TDP-43, FUS, ataxin-2, and more recently, hnRNPA1 and hnRNPA2B1, have been identified as components of potentially toxic stress granules found in ALS and FTD (although apparently not all stress granules are the same, as highlighted in the "FUS RNA Granules Not So Stressed Out?" story below). At the recent satellite symposium "RNA Metabolism in Neurological Disease" Dr. Aaron Gitler of Stanford University described the identification of another ALS-linked gene that appears to associate with stress granules, profilin-1. Dr. Gitler was surprised to find profilin-1 localizing to stress granules in both yeast and mammalian

Upcoming Meetings:

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

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

cells, as profilin-1 is known to bind actin, not RNA. Dr. Gitler and colleagues are currently trying to understand how localization of profilin-1 to stress granules may relate to mutant profilin's role in ALS. Their working theory is that profilin-1 may have a role in stress granule disassembly. Click here to find out how Dr. Gitler and colleagues used the power of yeast genetics to uncover this exciting and surprising link.

The Four Stages of TDP-43 Proteinopathy

While certainly grabbing a fair share of the limelight, C9ORF72 didn't steal the whole show at the "RNA Metabolism in Neurological Disease" satellite symposium. The RNA-binding protein TDP-43 was also featured at the symposium, but not for its ability to bind RNA. Instead, the focus was on the apparent spreading of pathological protein aggregates of TDP-43 from neuron to neuron. In her fascinating presentation, Dr. Virginia Lee of the University of Pennsylvania (UPenn) described how TDP-43 aggregates spread in a "sequential pattern", which could be classified into four distinct stages in ALS patients. The aggregates first appear in the motor cortex and then spread both forward towards the frontal cortices and down into the spinal cord. These results, published in a tour-de-force paper in the *Annals of Neurology* in July of this year, were identified through a collaboration between senior-authors Drs. Lee and Trojanowski (UPenn), and Dr. Heiko Braak (University of Ulm in Germany), and were led by co-first authors, Drs. Johannes Brettschneider and Kelly Del Tredici (both of the University of Ulm). Click here to read Dr. Amber Dance's coverage of this controversial topic.

Blocking a "micro"RNA Yields a "Big" Survival Benefit in SOD1 Mice

A recent study out of Dr. Timothy Miller's laboratory at Washington University in St. Louis and led by first author Erica Koval suggests that certain microRNAs (miRNAs) might be a new therapeutic target in ALS. The results of this study were presented by Koval at the "RNA Metabolism in Neurological Disease" satellite symposium held November 7-8, 2013 in San Diego, California and were recently published in *Human Molecular Genetics*. Koval and colleagues found that miR-155 is upregulated in the spinal cords of both familial and sporadic ALS patients and miR-155 is known to increase neuroinflammation. The authors then worked with Regulus Therapeutics to develop an anti-miRNA treatment against miR-155. Koval treated the high copy SOD1 G93A mice with the anti-miR-155 therapy and found that the mice receiving the treatment lived on average 10 days longer than control mice. Although some mechanistic and toxicology work remains to be completed, these results suggest that miRNAs could be important therapeutic targets in ALS. Click here to read Dr. Amber Dance's coverage and find out which mRNA targets miR-155 regulates.

Research News

Breaking News: ALSGene is Officially Open for Business; Alzforum Launches New Website

Calling all ALS geneticists, if you haven't yet checked out ALSGene (www.ALSGene.org), be sure to head there now. ALSGene is the first genetic database released on the new XGene platform, developed by the creators of the popular AlzGene, PDGene, and MSGene sites.

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

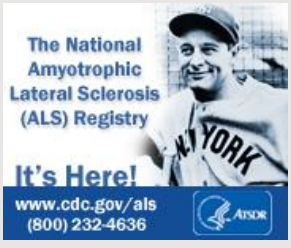
July 6-11, 2014: Easton, MA: Gordon Research Conference: Intrinsically Disordered Proteins, Understanding Intrinsically Disordered Regions (IDRs) at Different Scales: From Single Molecules to Complex Systems

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

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

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



Download your free copy:

Featuring a new website layout with easy to navigate tabs, a top results list, and direct links to the most recently published genome wide association (GWA) studies, ALSGene provides a comprehensive tool for meta-analysis of proposed ALS-related variants. Be sure to check out ALSGene and let usknow what you think. Not coincidentally, our collaborators at Alzforum (www.alzforum.org) have also just launched their newly updated website. The website doesn't just look beautiful -- it also includes expanded content, including valuable new databases and tools that are sure to be a boon to the entire neurodegenerative disease research community.

Opening the Doors to Clinical Trial Data

Most clinical trial data isn't released into the public domain, and for many valid reasons. There are a number of potential problems that could come with the release of clinical trial data, for example the identification of trial participants, the compromising of ongoing trials, and the potential for lawsuits. However, many patient advocacy groups and researchers want clinical trial data to be publicly shared, both to increase transparency and to enable analyses about the data that could give rise to important new insights about disease processes and trial design. Now, a new policy set forth by the European Medicines Agency (EMA) is helping to increase the amount of clinical trial data publicly available. Starting in 2014 the EMA will publish trial data for "all new approved drugs, and provide data from individual patients upon request". This controversial new ruling has both benefits and risks. However, not all data sharing initiatives are this controversial. In the US there are several nonprofit organizations (including Prize4Life) working to generate clinical trial databases to benefit the greater research community. Last December, Prize4Life and the Neurological Clinical Research Institute at Massachusetts General Hospital launched the PRO-ACT database (www.ALSDatabase.org), consisting of over 8,500 deidentified ALS patient records from 17 completed Phase II and Phase III clinical trials conducted by companies including Sanofi, Novartis, Teva, and Regeneron. Researchers have begun using the data in PRO-ACT for a variety of novel research projects, including identifying factors that might either influence or be predictive of disease progression. Prize4Life just presented the results of an initial analysis of the PRO-ACT data at the International ALS/MND Research Symposium in Milan, Italy. Click here to read the entire "Clinical Trial Data" story and decide for yourself if you think the pro's outweigh the con's and if more clinical trial data should be made publicly available.

Paper Alert: TDP-43 Mouse Problematic Model for Testing ALS Therapeutics

The gold standard for preclinical studies in ALS is the SOD1 G93A mouse. However, to date the overwhelming majority of therapeutics showing a positive outcome in this model have failed to translate to clinical benefit (although a highly rigorous study completed in 2008 by ALS TDI suggests that none of these earlier preclinical studies were adequately powered). In addition, only around 2% of the ALS patient population are believed to have a mutation in SOD1, which causes many researchers to question whether the SOD1 G93A model is the best preclinical model for ALS. Researchers have been searching for alternative preclinical models, including TDP-43, FUS, and now C9ORF72-based models. Many researchers had high hopes for the

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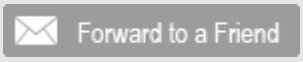

TDP-43 mice, as TDP-43 is mutated in some rare cases of ALS and the majority of people with ALS and FTD have cellular inclusions of TDP-43-containing aggregates. Unfortunately, the TDP-43 mice created to date have largely failed to live up to expectations. An extensive study, recently completed by a joint team at ALS TDI and The Jackson Laboratory, of the first TDP-43 mouse model to be created argues that this mouse model is not a suitable model for preclinical testing. Want to find out why they make this claim? Click hereto read Dr. Amber Dance's coverage of the TDI and JAX study.

FUS RNA Granules Not So Stressed Out?
As it turns out, not all "stress granules" are created alike. New research out of Dr. Stavroula Mili's laboratory at the National Cancer Institute in Bethesda, Maryland and led by first author Dr. Kyota Yasuda showed that wild-type FUS, which is predominantly located in the nucleus, can also localize to cytoplasmic structures known as adenomatous polyposis coli (APC) containing foci. These APC-containing RNA-protein complexes, which include both mRNAs and several other proteins, are found in axon growth cones where there is localized translation of specific mRNAs. Surprisingly, the authors found that FUS is required for the translation of some of these mRNAs. ALS-associated mutations in FUS caused the APC-specific RNA-protein complexes to relocate to the interior of the cell, away from the axonal protrusions. Normally, stress granules are translationally silent; however, the researchers found that the stress granules containing the mutant FUS were translationally active! These findings suggest that not all granules are created alike. Click here to read the full story and find out what some ALS researchers think of this novel finding.

Drug News

Project A.L.S. Teams Up with Eli Lilly to Find Drugs for ALS
Eli Lilly is partnering with Project A.L.S. in order to expand the pipeline of potential drugs for ALS. Under the agreement, Project A.L.S. will screen small molecules that were originally developed by Lilly to target pathways involved in cancer to see if these small molecules have any activity in blocking the toxicity associated with ALS. Prize4Life's Scientific Advisory Board member Dr. Tom Maniatis along with Dr. Thomas Jessell, both professors at Columbia University and Project A.L.S. Research Advisory Board members, have identified that there is overlap between some of the inflammatory signaling pathways activated in cancer and in ALS. Hopefully this partnership will lead to the identification of potential new therapeutics for ALS.

ImStar Announces the Identification of Lead ALS Drug Candidate
ImStar Therapeutics just announced that they have selected IMS-088 as their lead drug candidate for the treatment of ALS. IMS-088 is chemically similar to withaferin A, which is a natural compound isolated from the leaves of the winter cherry plant. The company plans to continue the preclinical development of IMS-088 during 2014, with the goal of taking this drug towards the clinic. ImStar's Chief Scientific Officer Dr.Jean-Pierre Julien said "we hope to establish IMS-088 as a safe and effective new drug candidate for ALS."