THE ALS FORUM

Discovering a Common Goal, Discovering a Cure

ALS Forum e-Newsletter Volume 92 **September 13, 2013**

Welcome back from our end of summer hiatus! This issue of The ALS Forum e-Newsletter is jam-packed with the latest in ALS research and drug news. Be sure to read on to make sure you are up-to-date and in the know!

Notice anything different? Your eyes aren't playing tricks on you! The ALS Forum and The ALS Forum e-Newsletter have a brand new look! Now that you have checked out the redesigned e-Newsletter, be sure to check out the 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

Funding News:

National Institute of Environmental Health Sciences (NIEHS) released a new RFA: Research Linking Environmental Exposure to Neurodegenerative Disease (R21). Letter of Intent due September 30, 2013.

NCATS Therapeutics for Rare and Neglected Diseases seeks collaborative partnerships with academic laboratories, not-for-profit organizations, and for-profit companies

Research News

One Mutation, Two Diseases in Family with Ataxin-2 Expansion

Researchers at Columbia University in New York City were the first to show that an expanded polyglutamine repeat region in ataxin-2 can cause both spinocerebellar ataxia type 2 (SCA2) and amyotrophic lateral sclerosis (ALS) in the same family. The findings were published online on August 16 in *JAMA Neurology*. The researchers identified a family where a woman had SCA2 and her uncle had ALS. After sequencing, they showed that the woman with SCA2 and her uncle, who died from ALS, had 40 and 39 polyglutamine repeats respectively. The normal number of polyglutamine repeats is 22 or 23, repeat numbers between 27 and 33 increase the risk for ALS, and repeats numbering more than 34 cause SCA2 with almost 100% penetrance. The uncle with ALS harbored a number of repeats that would normally be characterized as SCA2; so does this mean he was misdiagnosed or do we need to reevaluate how we define these diseases? Click here to read Dr. Amber Dance's exciting coverage of this thought provoking finding.

Is FUS to Blame for Neurons Vulnerable to FTLD and ALS?

Research out of Nagoya University in Japan, led by Dr. Gen Sobue and Dr. Shinsuke Ishigaki, suggests that selective cortical and motor neuron vulnerability in frontotemporal dementia (FTLD) and amyotrophic lateral sclerosis (ALS) could result from loss of FUS activity. Although the exact role of FUS has yet to be elucidated, it is believed to potentially regulate the splicing and transcription of thousands of RNAs. In FTLD and ALS, the normally nuclear FUS loses its ability to regulate RNAs when it relocates to the cytoplasm. To determine which RNAs might be affected by FUS relocation in FTLD and ALS, the authors examined the FUS transcriptome in several primary cell types (motor neurons, cortical

Letter of Intent due September 16, 2013.

Upcoming Meetings:

September 18-20, 2013: Aspen, CO: Accelerating Translational Neurotechnology: Fourth Annual Aspen Brain Forum

September 21-26, 2013: Vienna, Austria: XXIth World Congress of Neurology: Neurology in the Age of Globalization

October 2-4, 2013: Clearwater Beach, FL:2013 Annual NEALS Meeting

October 3, 2013: Boston, MA: 9th Annual ALS TDI Leadership Summit

October 14-15, 2013: Tel Aviv, Israel: BrainTech Israel 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 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

neurons, cerebellar neurons, and astrocytes) under conditions where FUS was normally expressed and when FUS was silenced. The cortical neurons, motor neurons, and glia each had more than 2,000 genes that were differentially regulated in the absence of FUS. The researchers found that 775 of these genes overlapped between the cortical and motor neurons, whereas only about 40 overlapped with the glia. The authors suggest that the similar FUS transcription profiles in the cortical and motor neurons are the reason for the selective vulnerability of cortical and motor neurons in FTLD and ALS. Click here to read the full story and find out what other researchers are saying about these controversial conclusions.

SOD1-Targeted Therapy Shows Survival Benefit in Two Different SOD1 Mice

Researchers at The Research Institute at Nationwide Children's Hospital and the Ludwig Institute at the University of California, San Diego, led by Dr. Brian Kaspar and Dr. Don Cleveland, were able to show a survival benefit in both SOD1 G93A and SOD1 G37R mice by administering an adeno-associated virus serotype 9 carrying an shRNA construct directed against SOD1 (AAV9-SOD1-shRNA). The research was published online in *Molecular Therapy* on September 6. Female mice that were administered AAV9-SOD1-shRNA at 1 day of age showed a survival benefit of over 51.5 days or 39%. When female mice were treated at day 85, the survival benefit was still fairly impressive, 30 days or 23%. Similar results were observed in the SOD1 G37R mice, these mice showed a survival benefit of 22% when treated after disease onset. However, the team didn't stop there; they also tested the therapy in nonhuman primates, showing that they could decrease wild-type SOD1 protein levels by 87% in the spinal cord. Although more work is still needed, the team is definitely looking to move AAV9-SOD1-shRNA into the clinic as quickly as possible. Click here to read the full story.

Scientists Reveal New VCP Mechanism That May Contribute to ALS

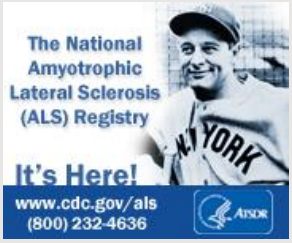
Researchers at St. Jude Children's Research Hospital and the University of Colorado, Boulder may now have a better understanding of how mutations in Valosin Containing Protein (VCP) cause ALS. The findings, which were published in *Cell*, showed that VCP is important for the disassembly and clearance of RNA granules. In the case of VCP mutations, these RNA granules may not be cleared as quickly, leading to the accumulation of granules in neurons and ultimately cell death. Many recent papers have presented further evidence for the role of RNA binding proteins (i.e., TDP-43, FUS, as well as the recently identified hnRNPA1 and hnRNPA2B1) and RNA granules in neuronal cell death. Looks like RNA granules could be the next hot target in ALS.

Drug News

ALS TDI Partners with Anida Pharma to Test Novel Therapy in ALS

The ALS Therapy Development Institute (ALS TDI) and Anida Pharma, Inc. have announced their formal collaboration to test Anida's compound, Neuroprotectin D1 (NPD1), in SOD1 G93A mice to determine if there is "functional benefit." ALS TDI has already tested NPD1 in a small proof-of-concept preclinical study and has shown that they can deliver NPD1 in "pharmacologically active levels" to the central

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



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nervous system of the mice. The encouraging proof-of-concept results supported investigation of NPD1 in an expanded preclinical study. NPD1 is thought to prevent neuronal death by reducing neuroinflammation as well as providing some trophic support. Read more about the collaboration here.

Biogen Puts Up $100M for a Neurological Disease Collaboration with Isis

Isis Pharmaceuticals is the leader in the development of antisense oligonucleotide (ASO) therapies. The ASO approach could provide a new therapeutic avenue for many diseases, and many big pharmaceutical companies are jumping at the chance to partner with Isis on the development of these novel therapies. Biogen Idec has already partnered with Isis on the development of ASO therapies for spinal muscular atrophy and myotonic dystrophy type 1. Now, Biogen and Isis are collaborating again on the development of ASO therapies for neurodegenerative disorders. Biogen CEO George Scangos suggested that the partnership may focus on ALS, where ASO-based therapies have already shown promise. In 2012, Isis completed a Phase I trial of their ASO drug targeted against SOD1. The results of the study were positive - the ASO drug was shown to be well tolerated and safe - which is a good precedent for this new Biogen/Isis collaboration. Click here to read more about the agreement.

Two Phase II Study Results Published for Cytokinetics' Tirasemtiv

Cytokinetics has announced the publication of two manuscripts describing the results of two previously completed Phase II trials of tirasemtiv, a fast skeletal muscle troponin activator, in people with ALS. The papers are published in the journal *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*. Jeremy Shefner, MD, PhD, Professor and Chair at the Department of Neurology at the Upstate Medical University, State University of New York was lead author on both publications. Dr. Shefner commented that these two trials showed that tirasemtiv "appears to be generally well-tolerated and to impact positively tests of strength, endurance and respiratory function that may be relevant to preserving the functional status of patients with ALS." Results from these two initial trials will inform the ongoing Phase IIb clinical trial, BENEFIT-ALS (Blinded Evaluation of Neuromuscular Effects and Functional Improvement with Tirasemtiv in ALS). The trial is currently enrolling 680 patients. More information on these earlier Phase II results and the Phase IIb trial now in progress can be found here.

CIRM Selects ALS Research for $2.3 million in Candidate Drug Development

The California Institute for Regenerative Medicine (CIRM), a California stem cell research funding agency, has awarded over $41 million to researchers at California-based universities and companies developing new therapies for difficult diseases, such as muscular dystrophy and Huntington's Disease. Among the new awardees is Dr. Steven Finkbeiner of the Gladstone Institutes in San Francisco, who was awarded $2.3 million to support his work on a new drug to treat ALS. The drug stimulates the nervous system to protect itself by removing disease-causing proteins. The class of drugs that Finkbeiner is studying is already approved by the Food and Drug Administration for other purposes, making it more likely that a new application to ALS would

allow the drug to proceed quickly to clinical trials. For more on the CIRM awards and Feinkbeiner's work, clickhere.

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