DISCOVERING

THE ALS FORUM

A CURE

ALS Forum e-Newsletter Volume 89 **July 12, 2013**

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:

Request for Proposals:Accelerating Drug Discovery for Frontotemporal Dementias. Letter of Intent due before August 22, 2013.

Upcoming Webinar:

The ALS Association's Research Update Webinar Series continues with Dr. Lucie Bruijn Presenting a Research Overview Webinar on July 23, 2013 at 4pm EST. Click here to register.

Upcoming Workshop:

Harvard NeuroDiscovery Center Digital Image Analysis with

Research News

An Extra Strain on the Brain: α-Synuclein Seeds Tau Aggregation, Implications for ALS

Recent findings from a number of different laboratories including the laboratories of Dr. Virginia Lee and Dr. John Trojanowski, both at the Perelman School of Medicine at the University of Pennsylvania, and Dr. Neil Cashman's laboratory at the University of British Columbia in Vancouver, Canada, have suggested that pathogenic forms of neurodegenerative disease-linked proteins, including α-synuclein, tau, TDP-43, and SOD1, can "spread" disease from one neuron to another. This apparent spreading is reminiscent of the mechanism observed in prion diseases. Now, Dr. Lee's laboratory has found additional evidence to support that pathogenic neurodegenerative disease-linked proteins are potentially acting like prions. Dr. Lee, along with first author Dr. Jing Guo, showed that α-synuclein can assemble into two different aggregated forms, each showing a different conformation and protein-seeding potential (for example, one strain seems to preferentially seed α-synuclein and the other tau). This strain phenomenon is known to be common among prions, and this intriguing new study suggests it may be common to pathogenic neurodegenerative disease-linked proteins, including SOD1 and TDP-43. Potentially, understanding the biology and kinetics of different "strains" of protein aggregates could help us understand disease heterogeneity as well, particularly in ALS. For example, Dr. Jeffrey Agar's lab at Brandeis University showed in 2008 that different SOD1 mutations have different rates of assembly into aggregates; the faster the aggregation kinetics, the faster the disease course in ALS patients. Maybe there are different strains of SOD1 and TDP-43 that also show this property? Click here to read Dr. Amber Dance's full coverage of this exciting article.

Brain Imaging Distinguishes C9ORF72 From Other Types of ALS

ALS is a diverse and heterogeneous disease that presents as multiple phenotypes -- from purely motor defects to ALS with frontotemporal dementia. Researchers and clinicians have had a difficult time segregating ALS into subtypes because of this large phenotypic diversity; however new research out of Trinity College Dublin in Ireland may help solve this problem. The study, published online

ImageJ Workshop 2013, held July 17-July 19, 2013. Click here to register.

Upcoming Meetings:

August 10-16, 2013: Andover, NH: Gordon Research Conference: Cellular & Molecular Mechanisms of Toxicity

September 4-5, 2013: Helsinki, Finland: 2nd Biannual European Neurotech Investing and Partnering Conference

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

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

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

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

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

in *Neurology* on June 14, showed that ALS patients with C9ORF72 hexanucleotide repeat expansions have a distinct pattern of degeneration in the brain that allows them to be differentiated from ALS patients harboring a normal-length C9ORF72 gene using magnetic resonance imaging (MRI). The authors suggest that MRI could one day be used as an ALS biomarker, potentially for diagnosis and prognosis. Click here to read the full story and find out how C9ORF72 ALS is differentiated from typical FTD using MRI.

Clearly Defined "Staging" in ALS May Give New Insights into Disease Progression

Researchers at the Perelman School of Medicine at the University of Pennsylvania and the University of Ulm in Germany have been able to classify four distinct neuropathological "stages" of ALS, the findings of which were recently published in the *Annals of Neurology*. Led by co-investigators Dr. John Trojanowski of the University of Pennsylvania and Dr. Heiko Braak of the University of Ulm, the research team looked for TDP-43 aggregates in the brains and spinal cords of post-mortem ALS patients. By examining where pathological TDP-43 aggregates were located in the brains and spinal cord of ALS patients, they were able to classify four distinct stages of TDP-43 "spreading" in the patients. The researchers first identified TDP-43 in the spinal cord, motor cortex and brainstem, primarily in the neurons that controlled breathing and movement. TDP-43 aggregates then spread to other regions of the brain, such as those involved in balance, as ALS symptoms progressed. Dr. Trojanowski hopes that these newly identified neuropathological stages will help elucidate the role that TDP-43 may play in transmitting ALS either from cell to cell and/or region to region. Click here to read this provocative story.

Brain Imaging Suggests Neurotransmitter Imbalance in ALS

Move over magnetic resonance imaging (MRI), there's a new imaging method in town that one day may serve as a biomarker to "assist in diagnosis, prognosis or stratifying clinical trial participants." What is this "new and improved" imaging method? Magnetic resonance spectroscopy (MRS). MRS is essentially MRI on magnetic field steroids. Using the stronger magnetic field, MRS can produce chemical spectra for each of the different chemical moieties floating inside of a person's body (think back to that organic chemistry you studied long ago!). Dr. Eva Feldman, professor of neurology at the University of Michigan in Ann Arbor, along with first author Dr. Bradley Foerster, showed that they could use MRS to identify levels of neurotransmitters, including GABA and glutamate, in healthy individuals and ALS patients. Interestingly, the ALS patients had lower levels of GABA and higher levels of glutamate as compared to the healthy controls. Click here to read the full story and find out what the authors think about the potential of MRS as an ALS biomarker.

Nature Neuroscience Highlights Modern Lab Tools - Stem Cells for ALS

On June 25, *Nature Neuroscience* published eight different reviews on modern neuroscience techniques in their special feature entitled "Focus on Neurotechniques". Each of the eight comprehensive reviews discusses the advantages, as well as the challenges and limitations, of each technique. Topics covered include stem cells, functional connectivity magnetic resonance imaging, optogenetics, optogenetic

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pharmacology, super-resolution light microscopy, immunogold labeling for electron microscopy, transcriptional magnetic stimulation, and perceptual decision-making studies in rodents. The stem cell article may be of particular interest to the ALS community, as it specifically mentions the relevance of stem cells to ALS (the article was co-authored by Dr. Kevin Eggan of Harvard University). Click here to read more about this informative series.

Conference News

11th Annual ENCALS Meeting: Growth Factor Producing Astrocytes, the Next Clinical Trial in ALS?
At the 11th Annual meeting of The European Network for a Cure of ALS (ENCALS) held May 31, 2013 through June 2, 2013 in Sheffield, England, Dr. Clive Svendsen, Director of the Cedars-Sinai Regenerative Medicine Institute in Los Angeles, California, gave a dynamic presentation about the therapeutic opportunity for stem cells and growth factors in ALS. Dr. Svendsen described his work using stem cell-derived astrocytes that have been genetically modified to produce glial-derived neurotrophic factor (GDNF). Experiments in SOD1 rats showed that these genetically modified astrocytes protected motor neurons in the spinal cord from death. Dr. Svendsen is hoping to use this exciting data to get FDA approval for a Phase I/IIa trial of the GDNF-producing stem cell-derived astrocytes in ALS patients. Read more about Dr. Svendsen's stem cell and growth factor work here.

Cutting a New Path to a Cure: Team Gleason Holds ALS Summit
As part of its efforts to expand awareness and promote research for ALS, former NFL player Steve Gleason's Foundation Team Gleason convened atwo-day ALS summit in New Orleans, Louisiana at the end of June. More than forty medical experts and research scientists, and over 80 advocates, caretakers, organizations (including Prize4Life), and patients were in attendance. The summit was also webcast, with an additional 1,500 people tuning in from around the world. Gleason urged all the attendants to "think like a beginner" and set their preconceptions aside when trying to find new avenues for ALS detection and treatment. NO WHITE FLAGS!

Drug News

Cytokinetics and Astellas Pharma Join Forces to Fight Muscle Disease
Cytokinetics, Inc., the San Francisco-based company currently conducting a Phase II ALS clinical trial of the fast skeletal troponin muscle activator tirasemtiv, has signed a $490 million collaboration with Astellas Pharma, Inc. The two companies will be working together to develop new skeletal muscle activators, with Astellas Pharma focusing on non-neuromuscular indications and Cytokinetics focusing on neuromuscular targets including ALS. Unfortunately, the Phase II tirasemtiv trial had a recent setback due to a computer programming error that resulted in 58 patients receiving placebo instead of the study drug, but Cytokinetics hascorrected the error and the trial is back on track. You can learn more about the collaboration between Cytokinetics

and Astellas Pharma here.

Neuralstem CEO Celebrates Progress and Looks To the Future

Neuralstem's CEO Richard Garr recently reflected on the substantial progress the company has made since embarking on a "journey ... to find a potential treatment for ALS." In his blog post, Garr commented on the presentation that Dr. Eva Feldman, principal investigator on the Neuralstem Phase I trial and the upcoming Phase II trial, gave at theCanadian Neurological Sciences Federation's Annual Congress in June. During her presentation Dr. Feldman chose to focus on the "remarkable surgical feat involved in this therapy," which is often overlooked and "taken for granted." For example there are extreme technical challenges involved with injecting stem cells into the spinal cord, in an area so small it is "the equivalent of hitting the chin on President Roosevelt's face on [a] dime." Also, Dr. Feldman spoke about the exciting expansion of the Phase II trial to include more patients who can be treated with "more cells" at two additional centers. Garr noted that "the FDA is getting comfortable with this ground breaking technology and totally new approach to treating this terrible disease." Clearly great "progress" indeed.

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