THE ALS FORUM

Discovering a Common Goal, Discovering a Cure

ALS Forum e-Newsletter Volume 100 **March 28, 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

Funding Opportunities:

A new grant from ALSA and Robert Packard Center

Upcoming Webinars:

April 7, 2014: ALSA/NEALS: Biomarkers in ALS

Upcoming Meetings:

April 6-11, 2014: Olympic Valley, CA: Keystone Symposia: Stem Cells and Reprogramming

April 23-24, 2014: Boston, MA: The Neurotech

Research News

A New Approach for Generating Muscle Cells from Human Stem Cells

A study published on March 21 in *Stem Cells Translational Medicine*reports on a new method for generating large numbers of skeletal muscle cells and myogenic progenitors from human embryonic stem cells (hESC). Researchers in Masatoshi Suzuki's Laboratory at the University of Wisconsin-Madison School of Veterinary Medicine have developed a new protocol to derive myogenic progenitors and differentiated muscle cells from hESCs using free-floating spherical cultures in the presence of specific growth factors. The major advantage of this method is that it does not require genetic modification of the cells, and yields a higher percentage of partially and fully differentiated muscle cells than other methods. In addition, this method can be used to generate muscle cells from induced pluripotent stems cells originating from ALS patients or patients with other neuromuscular disorders, providing a useful *in vitro*platform for drug research. Click here to read more.

How a Small Worm May Help the Fight against Neurodegenerative Diseases

Toxic aggregates of misfolded proteins are a hallmark of many neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), Alzheimer's (AD), Parkinson's (PD), and Huntington's (HD). A new study, published on March 13 in the journal *Cell*,from Adam Antebi's laboratory at the Max Planck Institute for Biology of Ageing in Cologne, provides new insights into the quality control mechanisms that normally help protect against protein toxicity. N-acetylglucosamine, an N-linked glycan precursor, appears to be critical for preventing protein aggregates from forming and for clearing the aggregates that are already present in the cell. When this compound is added to the growth medium of distinct*C. elegans* models of neurotoxicity, it alleviated protein toxicity, delayed onset of paralysis, and extended lifespan. These findings suggest that activation of the hexosamine pathway by N-acetylglucosamine

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 12-17, 2014: Stockholm, Sweden:Keystone Symposia: Adult Neurogenesis

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

supplementation may be a promising avenue for therapeutic intervention in diseases associated with protein aggregate toxicity. Click here to read more.

Loss of ALS-Related TDP-43 Protein Causes Death in Animal Model

Transactive response DNA binding protein (TDP-43) cytoplasmic aggregates are found in >95% of ALS cases, however, their association with ALS disease mechanisms remain unclear (see discussion in news stories from April 2011, November 2013 and February 2014). A recent study, published online on March 10 in the *Proceedings of the National Academy of Sciences* from Zyoshang Xu's laboratory at University of Massachusetts Medical School in Worcester, hypothesized that accumulation of TDP-43 in RNA-protein aggregates reduces the amount of TDP-43 protein available to perform essential RNA metabolism functions in the nucleus. To test this hypothesis, the group generated transgenic mice with partial loss of TDP-43 expression using transgenic RNAi. These mice developed motor dysfunction, paralysis and death, suggesting that motor neurons are particularly vulnerable to TDP-43 dysfunction. Loss of TDP-43 was also associated with concurrent changes in the splicing of TDP-43 target genes similar to observations from human ALS cases. Click here to read more.

A Blood-Based Diagnostic Biomarker for Alzheimer's Disease?

ALS patients commonly receive a physician's diagnosis only after a long period of inexplicable symptoms. Identification of a biomarker for early diagnosis holds the promise of increasing success of ALS clinical trials by enabling earlier intervention and potentially improving outcomes. A big step in that direction has been made for Alzheimer's disease patients. The blood-plasma levels of 10 lipid metabolites may prove accurate enough to diagnose Alzheimer's disease (AD) before the onset of cognitive symptoms, a study published in the March 9 *Nature Medicine* reports. The 5-year research study, led by Howard Federoff at Georgetown University Medical Center, Washington, D.C, and Mark Mapstone at the University of Rochester School of Medicine, New York, involved annual blood draws and cognitive tests on 525 adults of age 70 and older. Approximately 5% of the participants developed mild cognitive impairments or AD over the course of the study, and these same subjects exhibited low baseline levels of 8 phosphatidylcholines and 2 acylcarnitines. Subsequent blinded sample validation was able to predict future onset of cognitive impairment with 90% accuracy. Further research is necessary to elucidate whether this biomarker is specific to AD or is a general marker of neurodegeneration.
Click here to read more.

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

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Drug News

Final Results of Neuralstem Phase I Stem Cell Trial in ALS Published

The much-anticipated final results from Neuralstem's Phase I safety trial of intraspinal neural stem cell transplantation for treating ALS were published in the March 7 issue of *Annals of Neurology*. The report includes data from the six patients who received cervical spinal cord injections in addition to lumbar injections. The final results show that transplantation of these cells at both cervical and lumbar segments can be done safely in human patients. Interestingly, over 50% of the patients participating in the trial demonstrated improvements in functional outcomes measures following treatment. Phase II trials for Neuralstem's therapy are ongoing (see stories in September 2013 and January 2014). Click here to read more.

Regulatory T Cells Targeted in Upcoming Clinical Trial

ALS patients with high numbers of circulating regulatory T cells appear to live longer and exhibit slower disease progression than most ALS patients. Could boosting the number of regulatory T cells be beneficial for *all* ALS patients? Increasing evidence from Phase I and II studies in patients undergoing stem cell transplantation to prevent graft vs. host disease (GVHD) suggests that treatment with low doses of interleukin-2 (IL-2) boosts regulatory T cell numbers. This will now be tested in ALS patients in a Phase I/II randomized, placebo-controlled clinical trial that will be starting in April 2014 under the direction of Gilbert Bensimon from Assistance Publique - Hôpitaux de Paris. Click here to read more about low-dose IL-2 therapy and this upcoming clinical trial in France.

Anavex to Initiate Pre-Clinical Studies in ALS Models

Mutations in Sigma-1 receptor (S1R), a membrane protein involved in preventing protein aggregation in the endoplasmic reticulum, have been implicated in juvenile forms of ALS (see August 2011 story). An agonist to the receptor, developed by Anavex Life Sciences to treat Alzheimer's disease, has now been shown to protect motor neurons from apoptosis, attenuate ALS progression and extend survival in mutant SOD1-G93A mice. Anavex is now planning to initiate preclinical studies of this S1R agonist in ALS models as a potential therapeutic for ALS. Click here to read more.

PET Scans Distinguish ALS Patients from Healthy Controls

An effective ALS biomarker for assessing disease progression could potentially shorten the duration of clinical trials and significantly cut their cost. One such promising approach, called electrical impedance myography, was developed by Seward Rutkove, who was awardedPrize4Life's $1M ALS Biomarker Prize for his work. A new study, published online on March 10 in *JAMA*

Neurology, describes a different approach based on ^{18}Fluorodeoxyglucose-positron-emission tomography (FDG-PET). FDG-PET is able to distinguish between ALS patients and healthy controls based on differences in glucose metabolism in various areas of the brain. Interestingly, C9orf72-positive ALS patients exhibit metabolic patterns that are distinctive from C9orf72-negative cases. The research team, led by Philip van Damme at the University Hospital Leuven, Belgium, analyzed scans from 81 patients and 20 controls using machine learning methods, and correctly identified 95% of the ALS patients. Future plans include continuing to validate this approach and testing its diagnostic potential in early stage ALS patients. Click here to read more.

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