THE ALS FORUM

Discovering a Common Goal, Discovering a Cure

ALS Forum e-Newsletter Volume 104 **May 23, 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:

CDMRP FY14 Amyotrophic Lateral Sclerosis Research Program (ALSRP)

6th PG Award Applications Open

Upcoming Meetings:

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

Conference News

Highlights from the Translational CNS Summit 2014, April 29-30, Boston, MA

Prize4Life recently took part in the Translational CNS Summit 2014 organized by Hanson Wade on April 30th, 2014 in Boston, MA. The focus of the meeting was on derisking CNS drug development and improving success rates of clinical trials. The Summit offers a unique forum for brainstorming discussions among top executives and leaders in the neurological disease space, on approaches to overcome key challenges to drug development for neurological disease. While many of the session included thought-provoking discussions, we have decided to focus on a few highlights of the 2nd day with potential relevance to ALS. Click here to read the full report.

Brainstorming about ALS Research and Drug Development at ALSA Drug Company Working Group Meeting

Prize4Life was excited to participate in the Drug Company Working GroupMeeting sponsored by the ALS Association at the 2014 American Academy of Neurology Annual Meeting in Philadelphia. The meeting of over 60 attendees from industry, academia and government, was full of stimulating discussions surrounding cutting edge research and drug development findings in ALS. Nicholas Maragakis, M.D., from Johns Hopkins University gave an update on applications of induced pluripotent stem cells (iPSC) in ALS research, and Robert Baloh, M.D., Ph.D., of Cedars-Sinai Medical Center in Los Angeles shared the latest insights on the role of C9orf72, and how the known mutations cause ALS. On the clinical development side, Shafeeq Lahda, M.D., from the Barrow Neurological Institute in Phoenix laid out the pilot clinical trial he is leading of an anti-inflammatory arthritis treatment in ALS. The presentations concluded with much-awaited discussion by Andrew Wolff, M.D., Chief Medical Officer of Cytokinetics, about the mixed results of the Phase II trial of tirasemtiv in ALS. To read the full report from the ALS Association, click here.

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

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Research News

CSF-Tau Emerges as Potential Diagnostic Biomarker for ALS

A major challenge for drug development in ALS is the lack of reliable biomarkers for early diagnosis. Due to the long time lapse between first symptoms and diagnosis, clinical interventions are usually only initiated at advanced stages of the disease. A recent study by John Trojanowski and colleagues at University of Pennsylvania, published April 1 in *JAMA Neurol.*,provides initial evidence that levels of Tau protein in the cerebrospinal fluid (CSF-Tau) can serve as a diagnostic biomarker and distinguish ALS from other diseases with similar early symptoms. In a study performed on 51 ALS patients and 23 patients with four-repeat tauopathies (4R-tau), a low ratio of phospho-tau/total-tau was able to distinguish ALS patients from supranuclear palsy and 4R-tau patients with greater than 90% sensitivity and specificity. Interestingly, other studies have shown that phospho-tau/total tau ratio may be useful for diagnosing other neurodegenerative diseases, such as Alzheimer's, Parkinson's disease and frontotemporal dementia. The next planned steps toward validating the new biomarker are to confirm these results in a larger scale, multi-center study. Click here to read more.

Astrocyte Diversity Sheds Light on Development and Disease

Malfunctioning astrocytes have long been implicated in development and progression ALS. Work from Don Cleveland's laboratory at the University of California, San Diego has shown that expression of mutant superoxide dismutase, one of the known genetic causes of ALS, exclusively in astrocytes leads to development of ALS-like symptoms. Other studies, led by Serge Przeborkski's group at Columbia University, have shown the astrocytes derived from ALS patients trigger death of non-mutant motor neurons (see Feb 2014 news story). Now, investigators from David Rowitch's laboratory at University of California, San Francisco, provide the first demonstration that astrocytes located in spatially distinct regions of the spinal cord exhibit distinct gene expression and function. In the study, published online April 28, 2014 in *Nature*, first author Anna Molovsky and colleagues demonstrate that a subset of astrocytes in the spinal cord secrete Semaphorin 3a, a protein necessary for survival of motor neurons of the sensorimotor circuitry controlling reflexive movements. Loss of astrocyte Semaphorin 3a leads to defects in α-motor neuron axon guidance their selective death. This work raises the long-term possibility of developing therapies targeted at astrocyte that are particularly relevant for motor circuits that degenerate in ALS. Click here to read more about these intriguing findings.

New Findings about Protein Aggregation and Chaperones May Help Limit Neuronal Damage

Two new collaborative studies between Chris Dobson, Tuomas Knowles and Michele Vendruscolo's research groups at the University of Cambridge, UK shed light on how to potentially limit damage to neurons caused by misfolded proteins. In the first study, published May 9 online in*Proceedings of the National Academy of Sciences (PNAS)*, the researchers performed *in vitro* aggregation assays using seed α-synuclein amyloid fibrils and found that the rate of secondary nucleation of these seed fibrils is greatly accelerated under acidic conditions. At pH values below 6, which are found in some intracellular organelles such as

endosomes, the balance is shifted toward nucleation and protein aggregation. These findings shed light on mechanisms of protein aggregation and spread in Parkinson's disease, but also have implications for other protein misfolding diseases such as Alzheimer's disease and ALS. A second study, published May 20 in *PNAS* from Chris Dobson's laboratory, demonstrates an approach for improving effectiveness of molecular chaperones, the enzymes that ensure correct folding of proteins. When a chaperone called αλπηα2-macroglobulin (αλπηα2M) comes into contact with the oxidant hypochlorite, it becomes much more effective at ensuring that amyloid-βετα peptide folds correctly. These finding may ultimately help identify avenue to improve chaperone function and accelerate clearance of neurotoxic misfolded proteins. Click here to read more about these findings.

Genetic Risk Factors for Neurodegenerative Disease Tied to Immune Cell Function

Proinflammatory processes have been implicated in disease progression in ALS, but how genetic risk factors for ALS affect immune system function is largely unknown. A recent study published online May 2 in*Science* from the groups of Christope Benoist at Harvard Medical School, Barbara Stranger at University of Chicago and Philip de Jager at the Brigham and Women's Hospital, together with colleagues from the Broad Institute, Stanford and Massachusetts General Hospital, presents an extensive analysis of the relationship between gene expression changes in the adaptive and innate immune system and genetic risk factors of disease. The researchers, led by postdoctoral scholar Towfique Raj, analyzed expression of >19,000 genes in T cells and monocytes (adaptive and innate immune cells, respectively) from a multi-ethnic cohort of 461 healthy, young individuals, and cross-referenced the genomic data from these cells with genetic risk factors for diseases. They found that risk factors for autoimmune disease are associated with changes in T-cell gene expression, whereas high risk genetic variants for Alzheimer's and Parkinson's diseases are more tightly related to changes in monocyte function. These finding provide new insight into how genetic variation contributes to changes in innate immune system function, and uncovers new targets for potentially attenuating development of these neurodegenerative diseases.
Click here to read more.

Drug News

ALS Patients Create First-of-a-Kind Investment Fund for ALS

Three recently diagnosed ALS patients have created the first ever ALS-specific investment fund targeted at developing a cure for the debilitating and fatal disease. The founders are also seasoned entrepreneurs, including a serial entrepreneur whose company received an award last year for fastest growing company in Holland, the managing director of an investment company, and an experienced advisor to Fortune 500 companies. The team aims to raise €100 million from impact investors rather than the traditional pharmaceutical/biotech venture capital investors. Although they are just getting started, they have already successfully launched the most extensive global genetic research study in ALS called Project MinE. Click here to read more.

iPierian Acquired by Bristol-Myers Squib in a $725m Deal

Bristol-Myers Squib (BMS) announced the acquisition of biotechnology compsny iPierian in a $725M deal aimed at further strengthening BMS's position in Tau biology and neurodegenerative diseases. iPierian is applying stem cell technologies to help treat neurodegenerative diseases, in particular, Alzheimer's disease, spinal muscular atrophy, and ALS. Their lead compound, IPN007, is a preclinical stage monoclonal antibody that is expected to enter Phase I clinical trials in 2015 for progressive supranuclear palsy (PSP), a rapidly progressing neurodegenerative disorder associated with Tau dysfunction. In the future, development plans for the drug could extend to other Tauopathies such as frontotemporal dementia and Alzheimer's disease. Click here to read more about the terms of the partnership.

Winners of Sanofi-US Innovation Challenge to Conduct Big Data Genetic Analysis on ALS

Veterans Advancing ALS/MND, a partnership between Innovative Solutions Consortium and Johns Hopkins University, had won $100k and access to subject matter experts, as winners of the Sanofi-US Innovation Challenge: Collaborate Innovate. The goal of the challenge was to give voice to patients in the drug development process. Veterans Advancing ALS/MND plans to conduct large-scale genetic analysis of ALS patients to identify underlying causes of the higher incidence of ALS in veterans. Click here to read more.

Cytokinetics Publishes Preclinical and Clinical Data on Candidate Therapy for ALS

Last month, Cytokinetics announced the failure of its candidate therapy for ALS, tirasemtiv, to meet primary endpoints in the BENEFIT-ALS (Blinded Evaluation of Neuromuscular Effects and Functional Improvement with Tirasemtiv in ALS)Phase IIb clinical trial (see April 2014 Drug News Story). Tirasemtiv enhances troponin function in skeletal muscles, leading to increased muscle force in response to input from motor neurons. Although the drug did not improve motor function based on the ALS functional rating scare (ALS-FRS), tirasemtiv appeared to have beneficial effects on respiratory muscle function. Cytokinetics is now addressing some questions raised by the outcome of BENEFIT-ALS in three publications describing preclinical and clinical studies conducted in support of the tirasemtiv as a candidate therapy for ALS. The papers appear in PLOS ONE, Muscle & Nerve, and the American Journal of Respiratory and Critical Care Medicine. Click here to read more.

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