THE ALS FORUM

Discovering a Common Goal, Discovering a Cure

ALS Forum e-Newsletter Volume 103 **May 12, 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)

ALSA Clinical Management Grants

Upcoming Meetings:

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

May 21-23, 2014: Boston, MA: The 13th Annual World Pharma Congress: Tackling Translational

Conference News

April was an exciting month full of conferences! In this newsletter, we tell you about some of the highlights from 9th Annual Neurotech Investing & Partnering Conference and the American Medical Informatics Association, Joint Summits on Translational Science. Keep tuned in the next volume for a report on discussions at Translational CNS 2014!

Prize4Life Covers Recent Advances Presented at the 2014 Neurotech Conference

Representative's from government, investors, pharma and biotech came together at the 9th Annual Neurotech Investing & Partnering Conference, hosted by the Neurotechnology Industry Organization (NIO) and NeuroInsights in April 23-24 in Boston, Massachusetts. The primary goals were to discuss trends in drug, device and diagnostics development for neurological diseases, and to identify partnering opportunities to help accelerate development of new diagnostic and therapeutic options for patients. Prize4Life's Executive Director, Dr. Sara Shnider, attended the meeting and reported on the session on "Parkinson's and Other Movement Disorders". Although the session focused on Parkinson's disease, the challenges of therapy development raised in the session, such as drug delivery to the central nervous system and evaluating clinical trial results with subjective outcome measures, are common to other neurodegenerative diseases including ALS. Click here to read the in-depth report of this intriguing session.

Highlights from the American Medical Informatics Association, Joint Summits on Translational Science 2014

Dr. Neta Zach, Chief Scientific Officer of Prize4Life-Israel recently presented a talk about the PRO-ACT (Pooled Resource Open-access ALS Clinical Trials) platform, which houses the largest ALS clinical trials dataset developed to date, at the American Medical Informatics Association, Joint Summits on Translational Science. The conference, held April 7-11 in San Francisco, California, brought together attendees to discuss recent advances in translational bioinformatics and medical informatics with potential to open new research avenues, especially in the area of rare diseases such as ALS where scarcity of clinical data is a major limiting factor in developing

Challenges

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

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

novel therapies. Click here to read the about these cutting-edge initiatives.

Research News

C9ORF72 Repeats Implicated in New Disorders

The hexanucleotide repeat expansion in the chromosome 9 open reading frame 72 gene (C9ORF72) is the most common disease-causing mutation for familial amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Affected patients carry hundreds to thousands of repeats in the intronic regions of C9ORF72, whereas healthy individuals carry only on the order of 30 repeats. Although the function of the C9ORF72 gene is unknown, a recent study reported that the repeat expansions fold into a G-quadruplex, which disrupts gene expression and leads to translation of potentially-toxic dipeptide fragments (see March 2014 news). Now, two publications in *JAMA Neurology* implicate C9ORF72 in two additional disorders. The paper published on April 14 from Dennis Dickson's laboratory at the Mayo Clinic in Jacksonville, Florida reports the association of this gene with depressive pseudodementia, a type of dementia thought to be triggered by psychiatric disorders. The second paper, published on April 21 from Sheng-Han Kuo's group of Columbia University, New York, reports the association with multiple system atrophy (MSA), a movement disorder caused by cerebellar neurodegeneration. To read more about how mutations in this mysterious gene are tied to a variety of neurodegenerative diseases, click here.

In Situ Cellular Reprogramming Offers a New Avenue for Repair of Neuronal Circuitry

Therapeutic approaches for ALS based on stem cell transplantation into the spinal cord have shown promise, and are already being tested in the clinic (see, for example, this issue). The beneficial effects of the transplanted cells appear to be mediated primarily by production of trophic factors and reduction of inflammation and astrogliosis. However, efforts to repair dying motor neurons have proven challenging, as the transplanted cells often fail to extend long axonal projections and integrate into the complex motor neuronal circuitry. A new proof of concept study from Chun-Li Zhang's group at University of Texas Southwestern Medical Center in Texas, published February 25 in *Nature Communications*, demonstrates that resident astrocytes in the spinal cord can be reprogrammed by expression of SOX2 into doublecortin-positive neuroblasts. These stem cells gradually differentiate into motor neurons in the spinal cord, and exhibit electrophysiological activity indicative of synapse formation. These findings open a new avenue for replacing damaged motor neurons in ALS by *in situ* reprogramming of endogenous astrocytes. Further research is needed to determine whether the newly-generated motor neurons are able to improve motor function following injury or disease. To read more about their approach and the remaining open questions, click here.

Selective Ablation of Microglia Reveals a Hidden Microglial Progenitor Population

Motor neuron degeneration in ALS is a non cell-autonomous process, involving contributions from surrounding non-neuronal cells such as

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microglia. These resident immune cells of the central nervous system respond to signals released from dying motor neurons by releasing proinflammatory cytokines that further aggravate the disease. A new study from Kim Green's group at the University of California, Irvine, describes a small molecule inhibitor of colony-stimulating factor 1 receptor (CSF1R), which selectively ablates microglia, and provides a powerful research tool to investigate the contribution of microglia to disease. Since the small molecule is already being tested in clinical trials for several cancers, including glioblastoma and leukemia, there is also a clear path towards applications in human therapy. In addition, the researchers describe an intriguing finding following elimination of >95% of resident microglia: within 3 days after treatment withdrawal, the microglial population was replenished from progenitors in the CNS. Subsequent maturation of these progenitors into microglia provides conclusive evidence of the existence of a widespread microglial progenitor pool in the CNS. To read more about microglial progenitors in the CNS and potential applications of this small molecule inhibitor, click here.

A Neuroprotective Role for Protein Aggregates?

Neuropathological protein aggregates are a hallmark of ALS pathology and are commonly thought to exert detrimental effects on motor neuron survival. Two disruptive studies, published in *Nature Communications* and *Plos One* from Prof. Gerardo Lederkremer and Dr. Julia Leitman of Tel Aviv University's Department of Cell Research and Immunology, in collaboration with Prof. Ulrich Hartl of the Max Planck Institute for Biochemistry, demonstrate an opposite function for these protein clusters. The researchers found that in both striatal cell lines expressing mutant huntingtin and in the striatum of Huntington's disease mouse models, striatal neurons are particularly sensitive to endoplasmic reticulum (ER) stress. Mutant huntingtin triggers the ER stress response well before the protein accumulates as protein aggregates. Surprisingly, the protein aggregates appear to exert a protective effect on the stressed striatal neurons. These findings call into question the current therapeutic strategies directed at disrupting protein aggregation, and reveal novel therapeutic targets for attenuating the ER stress response. To read more about these potentially groundbreaking studies, click here.

Drug News

Muscle-Enhancing Therapy Fails to Meet Expectations in Phase IIb Trial for ALS

South San Francisco based Cytokinetics presented results of their Phase IIb clinical trial of tirasemtiv in ALS to an eager audience of researchers and clinicians at the 2014 American Academy of Neurology Meeting in Philadelphia. The novel candidate drug is thought to act by targeting troponin and enhancing muscle sensitivity to calcium, thereby increasing muscle responsiveness to progressively weaker signals from motor neurons. The candidate therapy had shown promise for enhancing muscle function in ALS patients in earlier clinical studies, but the Phase IIb study did not meet the primary endpoints - no significant improvement in motor function, as assessed by the ALS Functional Rating Scale in its revised form (ALSFRS-R) was detectable. Some of the patients appeared to exhibit improvements in secondary endpoints, such as slow

vital capacity (SVC) and muscle megascore. Although 711 patients with ALS enrolled in the study, only 473 completed it, and the drop-out was primarily due to low tolerability of the drug. The company plans to continue analysis of the trial data and will reassess the path forward. Click here to read more.

Brainstorm to Begin Phase II Trial of NurOwn Stem Cell Therapy for ALS

The U.S. Food and Drug Administration (FDA) has approved the initiation of a Phase II safety and efficacy trial of Brainstorm's stem cell therapy for ALS. This landmark study is the first Phase II double-blinded stem cell study to be conducted for ALS. Brainstorm's NurOwn stem cells are autologous, adult mesenchymal stem cells that have been induced to differentiate into cells producing neurotrophic factors. NurOwn cells, which appear to be safe based on earlier clinical studies, will be administered to ALS patients via intramuscular and intrathecal injections. The study will enroll 48 patients at Massachusetts General Hospital, Boston, the University of Massachusetts Memorial Hospital, Worcester and the Mayo Clinic in Ohio. For more about this promising new clinical trial for ALS, click here.

Corporate Update from Q-Therapeutics: IND Filing for ALS Targeted for 2014

Salt Lake City, Utah-based Q-therapeutics has released its formal corporate update on the research and development status of the company. Q Therapeutics is developing a cell-based therapeutic product, called Q-cells®, to restore or preserve normal neuronal function by replacing astrocytes, and oligendendrocytes, the "support" cells of the nervous system. In 2013, Q-Therapeutics obtained Orphan Drug Designation from the FDA for *Q-Cells* for treating ALS, which provides financial incentives and regulatory support for developing these cells into an ALS therapy. The company aims to complete investigational new drug (IND)-enabling studies required by the FDA for initiation of clinical trials in 2014. Click here to read about Q-therapeutics' recent R&D progress.

Genervon Successfully Completes Phase IIb Clinical Trial for ALS

Genervon Biopharmaceuticals received FDA approval for a Phase IIb trial of GM604 in ALS last June (for more information see June 2013 Drug News) and has now announced the successful completion of the trial. GM604 is a hexapeptide derived from neurotrophic factor motorneuronotrophic factor (MTNF), which confers its effect by regulating multiple ALS-associated genes and pathways. Preliminary analysis of the trial data shows that seven out of eight patients exhibited attenuation of disease progression within ten weeks after completion of dosing. The full results of the study will be released later in 2014. Click here to read the full press release.

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Identified content provided through a partnership with Alzforum.