THE ALS FORUM

Discovering a Common Goal, Discovering a Cure

ALS Forum e-Newsletter Volume 101 **April 11, 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:

Horizon 2020: Funding opportunity : New therapies for rare diseases

Horizon 2020: Funding opportunity: Clinical research on regenerative medicine

Upcoming Meetings:

April 9-12, 2014: Magdeburg, Germany: 8th International Symposium on Neuroprotection and Neurorepair

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

Research News

Matrin 3: New Genetic Mutation Further Implicates RNA Processing Defects in ALS

A new ALS-associated genetic mutation has been identified, further implicating defects in RNA processing in ALS disease pathology. The study, published on March 30th online in *Nature Neuroscience* from Bryan Traynor's group at the National Institute of Aging and Adriano Chio's group at the University of Turin, Italy, identified mutations in the Matrin 3 (*MATR3*) gene in two families suffering from ALS and dementia. The mutation was also identified in one case of sporadic ALS. The investigation revealed that MATR3, an RNA and DNA-binding protein that is important for RNA processing, binds another ALS-associated protein, TDP-43, and the mutation affects its ability to bind TDP-43. Interestingly, MATR3 pathology was found even in the spinal cord of ALS patients without *MATR3* mutations. Exome sequencing data from the study have been made publicly available.
Click here to read more

Don't Forget to Switch REST On

In a surprise re-appearance, the regulatory gene repressor element 1-silencing transcription factor (REST) has been found to re-emerge in the aging brain and protect it from a variety of stressors. It was previously thought that REST is expressed only in the developing brain, where it represses neuronal genes by modifying chromatin structure. A new study led by Bruce Yanker and colleagues at Harvard Medical School, published on March 20 in *Nature*, directly correlates REST expression in the aging human brain to preservation of cognitive abilities, even in presence of amyloid plaques and neurofibrillary tangles characteristic of Alzheimer's disease. In an in-depth study spanning neural cell lines, primary neuronal cultures, *C. elegans* and REST conditional knockout mice, the investigators demonstrated that absence or downregulation of REST leads to neuronal death in the face of stressors, while upregulation of REST rescues neurons. Interestingly, abnormal REST expression was also found in other neurodegenerative diseases involving dementia, including frontotemporal dementia (FTD) and dementia

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 28-29, 2014: London, UK: Astrocytes in Health and Neurodegenerative Disease

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 8-11, 2014: Berlin, Germany: The 8th World Congress of Controversies in Neurology

May 9, 2014: New York, NY:The Biology of Aging: Novel Drug Targets for Neurodegenerative Diseases

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

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

with Lewy bodies. Click here to read more.

Microglial NF-kB Regulates ALS Disease Progression in Mouse Model

Microglia, macrophages of the brain and spinal cord, are critical for protecting the central nervous system against invading pathogens. However, they are also central contributors to neuroinflammation and motor neuron death in ALS. A new study, published in *Neuron* on March 5th online from Brian Kaspar's laboratory at the Research Institute at Nationwide Children's Hospital in Columbus, Ohio, describes a novel mechanism for microglia-induced inflammation via NF-κB. This proinflammatory transcription factor is upregulated in the spinal cord of ALS patients and of SOD1-G93A mice. The researchers demonstrate that selective inhibition of NF-κB in microglia slows disease progression in the ALS mouse model by 47%, while inhibition in astrocytes alone has little effect. Interestingly, NF-κB has already been implicated in ALS through interactions with the ALS-associated protein, TDP-43 (see December 2011 story). Together, these finding suggest that NF-κB may be a promising therapeutic target for inhibiting microglia-induced inflammation in ALS. Click here to read more.

Pseudobulbar Affect is Common in Older ALS Patients

Uncontrollable outbursts of crying and laughter in neurologic disorders are termed pseudobulbar affect (PBA). PBAs are thought to occur due to injury to pathways that regulate emotional expression, and are a secondary consequence of several neurological disorders. In the largest study to screen for PBA to date, led by David Crumpacker from the Baylor University Medical Center, Dallas, it appears that this condition is more common than previously thought. The study, reported at the annual meeting of the American Association for Geriatric Psychiatry, screened 5,290 patients with one of six neurological conditions: ALS, Parkinson's disease, Alzheimer's disease, multiple sclerosis, stroke and traumatic brain injury. Prevalence of PBA symptoms in patients over 65 year old was 27.4%, with the highest rate among ALS patients, while in patients younger than 65 years the prevalence was as high as 49.5%. The FDA approved medication Nuedexta can partially alleviate these symptoms. Click here to read more.

Drug News

ALSTDI CEO Urges More Preclinical Testing Before Human ALS Trials

Each new candidate ALS therapy that is tested in patients sparks overwhelming hope across the ALS community. However, often these drugs are tested in human trials without sufficient preclinical validation, leading to repeated failures in the clinic, states Steve Perrin, CEO of ALS Therapy Development Institute (ALSTDI) in Cambridge, Massachusetts. In a Comment in the March 26 issue

May 22-24, 2014: Leuven, Belgium: European Network for Cure of ALS (ENCALS) Meeting

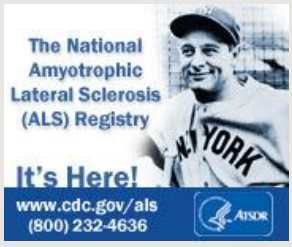
June 14-15, 2014: New London, NH: Gordon Research Seminar: Barriers of the CNS, The Neurovascular Unit: Partners for Life

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



of *Nature*, ALSTDI reports testing over one hundred compounds in ALS mouse models that had been previously identified as potential drugs for ALS. Strikingly, the researchers were unable to reproduce the reported efficacy of these candidate therapies, including several that had progressed to clinical testing and subsequently failed. Perrin reiterated the need to sufficiently characterize aspects of the mouse model that correspond to human ALS and to use mathematical simulations to help guide the statistical analyses (for guidelines on using the ALS mice see *Working with ALS Mice*). Perrin also underscored the need for public and private funding specifically for studies to better characterize the animal models. Click here to read more.

$17M Series A Financing towards Ataxias Drug Development

Cambridge, MA-based Ataxion has secured $17M in series A financing from Biogen Idec and Atlas Venture. This new startup biotech company is focused on rare neurodegenerative diseases called orphan hereditary ataxias, a group of hereditary disorders associated with loss of motor coordination due to degeneration of Purkinje cells in the cerebellum (see related story from January 2013). Ataxion's therapeutic approach aims to alleviate the symptoms of the disease by normalizing firing patterns of Purkinje cells, rather than providing a genetic or protein-based cure. Interestingly, a genetic link between ataxias and ALS has been found in form of the ataxin-2 gene (see story from August 2013). Click here to read more.

NeuroQuest's New Biomarker Technology Soon Coming to SC

An Israeli start-up company developing biomarkers for early detection of ALS and Alzheimer's disease (AD) will establish its clinical development base in Charleston, South Carolina. NeuroQuest's blood- based biomarker technology is based on the research of Michal Schwartz at the Weizmann Institute of Science, which identified cellular components of the immune system that are required for normal brain function. By measuring immune biomarkers in patients' blood, NeuroQuest's technology can recognize neurodegenerative disease-specific immune responses at their early stages. In initial trials, the biomarker demonstrated up to 85% diagnostic accuracy for both AD and ALS. NeuroQuest recently closed two investment rounds with SCRA Technology Ventures. Click here to read more.

Alector and Johnson & Johnson to Collaborate over Alzheimer's Disease Antibody Drug

Alector, a San Francisco based biotech start-up, will join forces with Johnson & Johnson's (J&J) Innovation Center to conduct research on new antibody-based therapies for Alzheimer's disease (AD). Alector is designing monoclonal antibodies against key targets associated with AD, using current scientific understanding of the sporadic form of the disease. To achieve this goal, Alector is leveraging the expertise of Adimab, the top yeast display antibody company. J&J will be fund the research, hoping for better performance than their own bapineuzumab, which failed to outperform the placebo in treating AD.
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