THE ALS FORUM
Discovering a Common Goal, Discovering a Cure

ALS Forum e-Newsletter Volume 106 **June 20, 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 at www.ALSDatabase.org

NEALS Biofluid Repository Available to Researchers

NINDS Fibroblast Repository

VABBB Tissue Request Information Site

Funding Opportunities:

Frick Foundation for ALS Research Grants

The Association for Frontotemporal Degeneration RFPs

ALS Association ALS Clinical Research Training Fellowship

Blueprint Neurotherapeutics Network (BPN): SBIR Small Molecule Drug Discovery and Development for Disorders of the Nervous System (U44)

Bernice Ramsay Innovation

Research News

DNA Damage Causes FUS to Relocate

Many neurodegenerative diseases exhibit an increase in neuronal DNA damage early in the course of disease (see Feb 2013 Conference News, and Sept 2013 Paper Alert). We recently reported on new findings about the underlying defect in DNA repair mechanisms in ataxia telangiectasia (A-T) and spinocerebellar ataxia with axonal neuropathy 1(SCAN1) (seeJune 2014 News). A new paper, published online June 4 in *Journal of Neuroscience*, sheds light on mechanisms linking DNA damage to two adult onset neurodegenerative diseases tied to defects in protein fused in sarcoma (FUS), ALS and frontotemporal lobar degeneration (FTLD). The study, led by Thomas Kukar and colleagues at Emory University School of Medicine in Atlanta, shows that double-stranded breaks in DNA trigger phosphorylation of the protein FUS and its translocation from the nucleus to the cytoplasm. Cytoplasmic accumulation of FUS in neurons is characteristic of a subset of familial ALS and FTLD cases. However, precisely how these changes contribute to neurodegeneration is yet to be unraveled. Click here to read more.

TDP-43 Disrupts Mitochondria-ER Bonding

A new pathological mechanism for TAR DNA-binding protein 43 (TDP-43) has been identified. The RNA-binding protein has been a hot topic in ALS research ever since TDP-43 containing cytoplasmic aggregates were tied to the majority of ALS cases (for some recent TDP-43-related discoveries see Nov 2012 News, Dec 2013 News, and Feb 2014 News). A new study published June 3 in *Nature Communications* suggests that TDP-43's toxic effect is due to its role in uncoupling mitochondria and the endoplasmic reticulum (ER). The transient bridges that form between mitochondria and the ER, called mitochondria-associated ER membranes (MAMs), play a central role in regulation of calcium homeostasis and in synthesis of cholesterol and phospholipids. Christopher Miller and colleagues from Kings College London report that the TDP-43 expression interferes with MAMs, likely through activation of GSKβ. To read more about TDP-43's effect on MAM's and how this may be linked to ALS, click here.

Grants: 2014 Discovery Grant

Webinars:

July 10, 2014: ALSTDI Pipeline Update

Upcoming Meetings:

June 22-27, 2014: Waterville Valley, NH: Cell Biology of the Neuron: Mechanistic Insight into Neuronal Development, Plasticity, Disease and Regeneration

June 27-28, 2014: Cracow, Poland: Advanced in Clinical Neuroimmunology ACN 2014

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

July 2014

July 5-10, 2014: Nice, France: The 13th International Congress on Neuromuscular Diseases - ICNMD 2014

July 6-11, 2014: Easton, MA: Gordon Research Conference: Intrinsically Disordered Proteins, Understanding Intrinsically Disordered Regions (IDRs) at Different Scales: From Single Molecules to Complex Systems

July 12-17, 2014: Copenhagen, Denmark: Alzheimer's Association International Conference

July 13-15, 2014: Prince Edward Island, Canada: Biotechnology &

Early Changes in Brain MRI Precede ALS

Presymptomatic changes detectable by MRI that precede onset of neurodegenerative disease have been described for genetic forms of Alzheimer's, Parkinson's and Huntington's disease. However, such changes in ALS patients have not emerged until now. A recent study, led by Michael Benatar and colleagues at the University of Miami in Florida and presented at the AAN 2014 in April, identified changes in a small cohort of ALS patients with SOD1 mutations that occur in brain white matter prior to the onset of motor symptoms. Surprisingly, the changes are visible in MRI diffusion tensor imaging of the right temporal lobe rather than in motor areas. These intriguing results will need further validation in a larger cohort of patients, but if confirmed, could potentially be leveraged for early therapeutic interventions geared towards disease prevention or delay of onset. For more on these promising results, click here.

Copper Therapy Extends Lifespan of ALS Mice

A new candidate therapy for ALS based on copper delivery to the brain and spinal cord extends lifespan and improves locomotor function in ALS mice. Mutations in copper, zinc superoxide dismutase (SOD1) are thought to cause familial ALS through a toxic gain-of-function mechanism, although precisely how SOD1 mutations lead to selective motor neuron death is not fully understood. A recent report published June 4 online in*Journal of Neuroscience* and led by Peter Crouch and colleagues at the University of Melbourne, Australia and Joseph Beckman at Oregon State University, demonstrates that restoring the copper content of mutant SOD1 by oral delivery of a an organic molecular containing copper, called Cu-ATSM, improved locomotor function and extended lifespan by 26% in a mutant SOD1 mouse model of ALS. Intriguingly, the treated mice express higher levels of misfolded mutant SOD1 than untreated mice, challenging the accepted view that the abundance of mutant SOD1 determines disease severity. Cu-ATSM has also shown therapeutic promise in Parkinson's disease (see April 2011 Conference News). Click here to read more.

Drug News

Neuralstem to Offer Experimental Stem Cell Therapy in Colorado

Neuralstem plans to offer its experimental stem cell therapy to ALS patients in Colorado under the new "right-to-try" law recently passed in Colorado. According to this law, demonstrating safety is sufficient for administering the drug to terminal patients. As Neuralstem's human spinal cord-derived stem cell therapy called NSI-566, has been shown in a Phase I trial to be safe in humans (see March 2014 news) it qualifies under the new law. The company has already begun training surgeons on delivery of the therapy. Whether patients will pay for the treatment is yet to be determined. Click here to read more.

Critics Claim European Medicines Agency Wavering on Clinical Trial Transparency

Datasets from completed clinical trials offer a wealth of untapped

Human Health Symposium

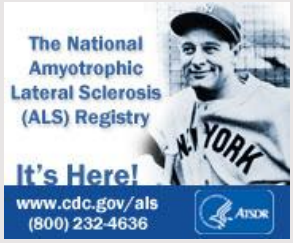
July 27 - August 1, 2014: Girona - Costa Brava, Spain: Gordon Research Conference: Neurobiology of Brain Disorders, Neurodegeneration and Aging-related Disorders of the Nervous System

August 2014

August 3-8, 2014: Andover, NH: Gordon Research Conference: Musculoskeletal Biology & Bioengineering, Identifying and Overcoming Barriers to Translation

August 3-8, 2014: Waterville Valley, NH: Gordon Research Conference: Synaptic Transmission, Synapses in Networks

August 10-15, 2014: Newport, RI: Gordon Research Conference: Neural Development, From Stem Cells to Circuits



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information about patients, their underlying disease and the effects of treatments on disease pathways. In order to create such a resource for the ALS research and drug development community, Prize4Life has partnered with the NCRI at Massachusetts General Hospital to create thePRO-ACT (Pooled Resource Open-access ALS Clinical Trials) platform, the largest public ALS clinical trials dataset developed to date. In Europe, the European Medicines Agency (EMA) recently passed a law to require publication of clinical trial results to make them publicly accessible (seeNovember 2013 News). The EMA is the first major regulatory agency to pass such a law to increase transparency of clinical trial data. However, pressure from pharmaceutical companies has caused the EMA to waver on the initial proposal, according to criticism from the British Medical Journal. Where will the final policy stand? The EMA met on June 12th to finalize it, so keep your ears peeled for more soon. To read more about the new law and the responses from different stakeholders, click here andhere.

Voyager and ReGenX Partner to Treat Neurodegenerative Diseases

Cambridge, MA-based Voyager Therapeutics has entered into a licensing deal with ReGenX Biosciences, a Washington, DC-based gene therapy company, to use ReGenX's NAV® vectors. Voyager plans to use these vectors to develop new gene therapies for neurodegenerative disease, such as ALS, Huntington's and Friedreich's Ataxia (for more background, seeFeb 2014 News). ReGenX's technology uses recombinant adeno-asociated viral (AAV) vectors optimized for efficient delivery of genetic material into cells of interest. Voyager obtained a non-exclusive license for an undisclosed up-front fee and milestone payments. Click here to read more.

CEOi, Sage Bionetwork and DREAM Launch Alzheimer's Disease Challenge

The DREAM project (Dialogue for Reverse Engineering Assessments and Methods) is a veteran of big data challenges for neurodegenerative diseases. Back in 2012, DREAM partnered with Prize4Life to launch theDREAM-Phil Bowen ALS Prediction Prize4Life, with the goal to develop algorithms to predict disease progression in ALS patients based on large clinical datasets from the PRO-ACT database. This year, DREAM is partnering with Sage Bionetworks and the Global CEO Initiative on Alzheimer's Disease (CEOi) to launch a big data challenge aiming to spur diagnostic innovation and to accelerate identification of Alzheimer's disease biomarkers. The challenge solutions will be exciting to see - they are likely have applications for other neurodegenerative diseases too. Click here to read more.

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