DISCOVERING A CURE

THE ALS FORUM

ALS Forum e-Newsletter Volume 82 **March 22, 2013**

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 PRO-ACT Database at www.ALSDatabase.org

NEALS Biofluid Repository Available to Researchers

NINDS Fibroblast Repository

Upcoming Meetings:

April 9-11, 2013: Washington, DC: 3rd Annual World Orphan Drug Congress

April 14-19, 2013: Les Diablerets, Switzerland: Oxidative Stress & Disease, Program: The Metabolic-Inflammatory Axis in Brain Aging and Alzheimer's Disease

April 21-24, 2013: Washington, DC: MDA Scientific Conference: Therapy Development for Neuromuscular Diseases: Translating Hope Into Promise

May 1-2, 2013: Bethesda, MD: NIH workshop on Alzheimer's Disease-Related Dementias:

Research News

Disease Mutations Zip Lock Stress Granules in Proteinopathy, ALS

In what is sure to be hailed as a landmark paper, researchers recently put forward a model that begins to tie together the growing list of RNA-binding proteins associated with ALS and other complex neurodegenerative disorders. The results of these findings were published online on March 3 in *Nature*. Many RNA-binding proteins contain unstructured protein domains that appear to be critical for mediating the assembly of proteins within stress granules. Mutations in these unstructured or prion-like domains seem to profoundly influence the kinetics of assembly and disassembly of stress granules, and a growing number of proteins associated with ALS, including TDP-43, FUS, VCP, TAF15, and now hnRNPA2B1 and hnRNPA1, seem to be involved in this process. You won't want to miss the details of this exciting and complex story, click here now!

Protein Destroying Muscle, Bone, Nerves Parks on Mitochondria

But stress granules aren't the whole story. Two recent papers suggest that mutations in valosin-containing protein (VCP), which played a starring role in the theory covered above, could also be contributing to the development of multisystem proteinopathy, ALS, and FTD through a separate mechanism. Both papers, published online on March 14 in the journal *Neuron,* suggest that mutations in VCP can also affect mitochondria. One paper suggests that mutations in VCP somehow lead to a reduction in the membrane potential of mitochondria, reducing the efficiency of ATP production. The second paper suggests that mutations in VCP may influence the clearance of damaged mitochondria. To learn more of the exciting details of these two studies, as well as how defects in the normal function and clearance of mitochondria may lead to neurodegeneration (hint: it may involve the Parkinson's disease-linked protein parkin), click here.

Researchers Discover New Gene That Triggers Motor Neuron Death

Mutations in CLP1, the first mammalian RNA kinase to be identified, could be contributing to the loss of motor neurons in motor neuron diseases such as ALS. In a surprising new study recently published in *Nature*, researchers discovered that mice carrying a mutant CLP1 gene

Research Challenges and Opportunities

May 3-5, 2013: San Francisco, CA: Targeted Drug Delivery for Pain and Neurologic Disease

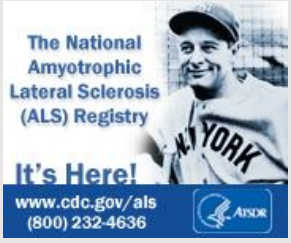
May 6, 2013: New York, NY: The New York Academy of Sciences, Translating Natural Products into Drugs for Alzheimer's and Neurodegenerative Disease

May 6-8, 2013: Philadelphia, PA: 9th Annual Biomarker World Congress

May 18-24, 2013: Les Diablerets, Switzerland: Gordon Research Conference: Dendrites: Molecules, Structure & Function

May 19-22, 2013: Boston, MA: Society for Clinical Trials 34th Annual Meeting

May 21-23, 2013: Boston, MA: Translational CNS Summit



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had motor neuron loss leading to paralysis and sometimes death. The researchers found that when CLP1 was no longer functional, it increased the sensitivity of motor neurons to oxidative stress apparently through the accumulation of tRNA fragments. The CLP1 kinase-inactive neurons responded to oxidative stress by activating p53, which caused the motor neurons to die. Removing p53 from mice with the CLP1 mutation prevented these motor neurons from dying. One of the researchers that worked on the study, Dr. Stefan Weitzer, said "We've discovered a new mechanism that leads to the death of motor neurons. If this holds true for other neuronal disease, our results could be one day used to drive the development of treatments for previously incurable diseases." Read more about these unexpected and interesting findings here.

New Role of Hsp90 Discovered - Could Lead to New Treatments for ALS and Other Conditions

Researchers at the University of Central Florida's College of Medicine recently found that when Hsp90 is damaged by a form of oxidative stress, called tyrosine nitration, the protein becomes a "cell executioner" and causes these cells to die. These findings were published in the March 19 issue of *Proceedings of the National Academy of Sciences.* "The concept that a protein that is normally protective and indispensable for cell survival and growth can turn into a killing machine, and just because of one specific oxidative modification, is amazing," said Maria C. Franco, co-author of the study. This discovery may help researchers to develop future treatments for a variety of medical conditions including ALS, stroke, cancer, spinal cord injuries, and more. Read more about this interesting discovery here.

Drug News

Exciting New Developments for BrainStorm - Including Clinical Trial Results from Their Phase I/II Trial

Earlier this year BrainStorm Cell Therapeutics Inc. announced that their Phase I/II clinical trial to test the tolerability and safety of their ALS treatment was fast tracked to a Phase IIa dose-escalating trial by the Israeli Ministry of Health. BrainStorm presented the results from their Phase I/II clinical trial at the 65th Annual Meeting of the American Academy of Neurology (AAN) Conference held this week in San Diego, California. BrainStorm plans to begin a Phase II trial in the United States later in 2013. This month it was announced that the Mayo Clinic would be the third clinical trial site, joining the University of Massachusetts and Massachusetts General Hospital (MGH).

Drug Development For Rare Diseases - Have We Gone Too Far?

In this provocative Xconomy commentary, Dr. Stewart Lyman, Owner and Manager of Lyman BioPharma Consulting LLC in Seattle, Washington, raises the question of whether BioPharma has shifted their focus too far in the direction of developing therapies for rare and orphan diseases. There are many reasons why BioPharma is currently incentivized to invest in drug development for rare diseases, but Lyman challenges "do we want to encourage work on diseases where effective treatments will provide the greatest benefit to the most people, or the ones that are the "easiest" to get approved and reimbursed?" Click here to read the full thought-provoking commentary and decide for yourself.

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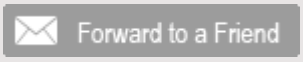

[Amorfix Makes Advance Towards Development of Potential ALS Diagnostic Tool]

In January, Amorfix Life Sciences announced they were in the process of developing a blood test that could be used to diagnose ALS. The blood test builds on initial findings by Dr. Neil Cashman, Amorfix Chief Scientific Officer and Professor of Medicine at the University of British Columbia, and other researchers at the University of British Columbia, which showed that ALS patients have misfolded SOD1 circulating in their blood. Now, Amorfix announced that they have successfully cloned "ultra-high affinity antibodies" against misfolded SOD1. Cashman said "The generation of these high quality antibodies significantly advances the development of a highly sensitive and simple blood test to diagnose ALS by measuring misfolded SOD1 in the plasma of patients." Read more about the development of this blood test and Amorfix' other ALS initiatives here.

[Neuralstem CEO Reflects on FDA Public Hearing on ALS - Blog Highlights the ALS "Crisis"]

The Maryland-based company Neuralstem Inc. recently completed a Phase I clinical trial testing spinal cord neural stem cells for the treatment of ALS and they are currently gearing up for a Phase II study. Neuralstem's CEO Richard Garr regularly shares his thoughts on the progress of their clinical trials and the current ALS landscape by contributing blogs to his company's website. Following the emotional and riveting testimony of ALS patients and advocates at the February 25 FDA public hearing on ALS, Mr. Garr shared his thoughts: "Let us hope that the FDA takes the opportunity that this crisis presents to change the way they approach our trial, and any other novel therapy that has the potential to help this population." Garr also makes the key point that the FDA should not be viewed as an enemy but rather as a potential partner. Read this insightful blog post here.

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