DISCOVERING A CURE

THE ALS FORUM

ALS Forum e-Newsletter Volume 81 **March 8, 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

New Workshop Announced:

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

Upcoming Webinar:

March 12, 2013, 4-5 pm EST: ALS Association / NEALS PALS Webinar: BENEFIT-ALS Blinded Evaluation of Neuromuscular Effects and Functional Improvement with *Tirasemtiv* in ALS

Upcoming Journal Club:

Conference News

The following three part series highlights hot research topics covered at the Keystone Symposium "New Frontiers in Neurodegenerative Disease Research" held in Santa Fe, New Mexico from February 4-7, 2013.

Part 1: Exploring Genome Fragmentation in Neurodegeneration
Genome instability and its link to neurodegeneration was a hot topic at the Keystone Symposium "New Frontiers in Neurodegenerative Disease Research." As attendees of the symposium found out, unrepaired double-stranded DNA breaks seem to be common in adult neurodegenerative diseases such as ALS and Alzheimer's disease, and also in ataxia telangiectasia (AT), a neurodegenerative disease that affects children. It is thought that these DNA breaks may somehow contribute to neurodegeneration in these diseases. Surprisingly in each of these diseases, mutations in key disease-linked proteins seem to negatively influence the DNA repair process. This includes APP in Alzheimer's disease and ataxia telangiectasia mutated (ATM) in AT. Interested in finding out which unlikely protein was proposed to be the culprit in ALS? Click here.

Part 2: Does ALS Gene Police RNA, Keep Strands From Entangling?
New research out of Dr. Christopher Link's laboratory at the University of Colorado at Boulder shed some intriguing new light on the potential biological role of the RNA binding protein TDP-43. Tassa Saldi, a student in Dr. Link's laboratory, described these findings during the recent Keystone Symposium. Saldi knocked out the TDP-43 orthologue, TDP-1, in *Caenorhabditis elegans* and looked for changes in the transcriptome. She identified a number of genes that were either underexpressed, overexpressed, or spliced differently as compared to the transcripts in wild type worms. Frustratingly, as others have reported, these differentially expressed and spliced transcripts did not group into any obvious gene categories. But that didn't stop Saldi from looking for a more subtle trend within the data. In an incredibly clever intuitive leap she identified a completely unexpected commonality among these transcripts. Click here to read this fascinating story.

March 12, 2013, 6:30-8 pm: Harvard NeuroDiscovery Center Student/Faculty Journal Club paper discussion: Unconventional Translation of C9ORF72 GGGGCC Expansion Generates Insoluble Polypeptides Specific to c9FTD/ALS, Neuron, 2013 Vol 77 Issue 4

Funding News:

NINDS Institutional Center Core Grants to Support Neuroscience Research (P30)

2013 AAN Foundation ALS-Richard Olney, MD Clinician Scientist Development Three Year Award

Upcoming Meetings:

March 16-23, 2013: San Diego, CA: 65th Annual American Academy of Neurology Meeting

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 3-5, 2013: San Francisco, CA: Targeted

Part 3: Up-and-Coming ALS Mice Leave Scientists ConFUSed

ALS researchers have been actively searching for an alternative to the SOD1 mouse model for preclinical studies and basic research in hopes of better emulating sporadic and non-SOD1 mediated disease. Unfortunately, although many attempts have been made to generate alternative ALS mouse models based around TDP-43, all of these models to date have failed to recapitulate the disease phenotype as completely as the SOD1-based models. Now this appears to also be the case for several new FUS models that were unveiled at Keystone. Dr. Eric Huang from the University of California, San Francisco, and Dr. Shuo-Chien Ling from the University of California, San Diego, separately presented their results around several new FUS-based mouse models they have developed. Although these new FUS models do recapitulate some ALS pathology, both groups unexpectedly found that none of these mice had massive motor neuron death. Read the full story about these new FUS models here.

Research News

Paper Alert: Zebrafish Say TDP-43 Causes ALS by Loss of Function

The mechanism of how mutations in TDP-43 cause ALS and FTLD is still highly debated - are aggregates of TDP-43 toxic or is it loss of TDP-43 function that contributes to cell death? Now a recent paper published online in the *Proceedings of the National Academy of Sciences* provides evidence to suggest that the TDP-43 mechanism is most likely loss of function. The researchers, led by Dr. Bettina Schmid and Dr. Christian Haass at the German Center of Neurodegenerative Diseases, knocked out the two TDP-43 orthologues, TARDBP and TARDBP-like, in zebrafish. The authors found that zebrafish embryos with this double knockout barely survived for a week. They identified that these double mutant embryos had defects in the formation of blood vessels, blood circulation, and showed significant muscle degeneration as compared to wild type zebrafish embryos. To learn what was happening at the molecular level click here.

Drug News

Does TauRx Drug Work by Oxidizing Tau?

In 2008, TauRx Therapeutics reported positive results from their Phase II study of Rember (which also happens to be methylene blue) in Alzheimer's disease. In a small study, TauRx found that Rember reduced cognitive decline in people with Alzheimer's disease by over 80 percent. Although results from the Phase II study showed that Rember worked by breaking up aggregates of tau, it was unclear how this compound was working at the molecular level to break up these aggregates. Now, researchers from the Max Planck Institute for Biophysical Chemistry in Germany believe that they know how this dye works to break up the tau aggregates -- and even prevent the aggregation of tau in the first place. In the fall of 2012, TauRx Therapeutics announced they received approval from both the United States and Europe to test a modified version of methylene blue, called LMTX, in two Phase III studies, one in behavioral-variant frontotemporal

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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dementia (bvFTD) and one in Alzheimer's disease. TauRx just secured an investment of $10.5 million from Dundee Corporation of Toronto to support these Phase III studies.

Is the Future Outlook of ALS Treatments Grim?

Many companies, including Biogen Idec and now Novartis, are investing in drug development for rare and orphan diseases. This looks like a safe bet. Based on the recently published IMS Institute for Health Informatics report, "The Global Use of Medicines: Outlook Through 2016," the number of new molecular entities (NMEs) for the treatment of rare and orphan diseases is projected to account for about 33% of all NMEs by 2016. However, despite this good news, if nothing is done to resuscitate the ALS drug development pipeline, the projected outlook for ALS therapies is grim. In GlobalData's recent report "Amyotrophic Lateral Sclerosis (ALS) - Analysis and Market Forecasts to 2019," the projected market for ALS is expected to decrease from $112 million in 2011 to $70 million by 2019. The report cites the lack of late stage therapeutics in the current pipeline, the recent failure of Biogen's Phase III study of dexpramipexole, and Sanofi's Rilutek patent expiration this upcoming year as key contributors to the market decline. Prize4Life's $1M ALS Treatment Prize and Mouse Colony initiatives were launched to change this gloomy picture by providing some life support to the ALS drug development pipeline.

Recent FDA Hearing Highlights ALS Drug Development Concerns

On February 25, 2013 the FDA held the first ever public hearing on ALS. The hearing included testimony from clinicians, scientists, various ALS organizations, industry representatives, as well as patients and families. Prize4Life Scientific Advisory Board Member and ALS Association Chief Scientist Dr. Lucie Bruijn discussed the need to work collaboratively to accelerate treatments and a cure for ALS. "It is absolutely critical that the FDA and the ALS community come together to not only identify the obstacles and challenges of ALS drug development but also to find the solutions," said Dr. Bruijn. Dr. Jonathan Glass, director of the Emory ALS Center and site investigator on the recently completed Neuralstem Phase I clinical trial, echoed Dr. Bruijn's comments and offered some potential solutions. Dr. Glass suggested "In order to move faster toward effective therapeutics, it may be necessary to develop short, less-expensive trials to determine if a drug can hit a therapeutic target in order to test therapeutic hypotheses, prior to the initiation of efficacy trials. This will give a quicker answer to whether a potential therapeutic has any chance of success in treating ALS."

ALS Patients Needed to Test ALS Biomarker Device

In 2011, Prize4Life awarded its $1M ALS Biomarker Prize to Dr. Seward Rutkove for his discovery of a biomarker for ALS - a technology called electrical impedance myography (EIM). EIM measures the flow of a small painless electrical current through healthy and diseased muscle tissue, and by comparing the size and speed of the electrical current, EIM can accurately measure ALS progression. Convergence Medical Devices, a start-up company founded by Dr. Rutkove, is currently seeking ALS patients to participate in a study to help further develop and refine their EIM device. The study involves a single 45-minute visit to Convergence headquarters in Boston, Massachusetts where basic EIM measurements are taken. For more information on this study please

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Identified content provided through a partnership with the Alzheimer Research Forum.

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