THE ALS FORUM
Discovering a Common Goal, Discovering a Cure

ALS Forum e-Newsletter Volume 117 **December 5th, 2014**

We hope you all had a wonderful Thanksgiving holiday! We are now back after the holiday with more conference and R&D news!

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:

The ALSGene tool: www.ALSGene.org

The PRO-ACT Database: www.ALSDatabase.org

NEALS Biofluid Repository Available to Researchers

NINDS Fibroblast Repository

VABBB Tissue Request Information Site

Funding Opportunities:

ALS ACT, ALSA, NEALS and the ALS Finding a Cure Foundation RFP: Phase II Clinical Development of Novel, High-Potential Treatments for People with ALS.
Letter of Intent due January 9, 2015.

Webinar:

NEALS Webinar: Mexiletine Study - Results Overview.Nov 21, 2015, 3-4pm EST.

Upcoming Meetings:

Conference News

More Exciting News from the International Conference on Frontotemporal Dementias
Last issue we reported one news story on the 9th the International Conference on Frontotemporal Dementias (ICFTD), which convened on Oct. 23-25 in Vancouver, British Columbia. We now have full coverage of the conference, with nine (!) exciting stories from Alzforum's Gabrielle Strobel and Jessica Shugart. Click here to read more about the latest findings on FTLD proteins, clinical studies, and biomarkers!

Advances in ALS and FTD Genetics Workshop Emphasizes Integration and Data Sharing
In conjunction with the Society for Neuroscience Annual Meeting in Washington, D.C., the ALS Assocation (ALSA), the National Institute of Neurological Disorders and Stroke, and the Association for Frontotemporal Degeneration sponsored a one-day workshop to discuss the latest research on ALS and frontotemporal dementia (FTD) Genetics. The workshop provided a unique opportunity for cross-fertilization between the ALS and FTD researchers and clinicians, and for initiating conversation surrounding data harmonization between these groups. For ALSA's full report on the stimulating meeting click here.

Research News

New Evidence for Role of Upper Motor Neurons in Disease Onset and Motor Neuron Survival in ALS
In mouse models of ALS, motor neuron death in the spinal cord and denervation at the neuromuscular junction (NMJ) are evident prior to onset of behavioral symptoms, but the timing of upper motor neuron (UMN) degeneration and its contribution to disease is not well understood (see related news of May 2013). A new study published Nov 12 in *Journal of Neuroscience* online suggests that UMN health can shape the course of ALS. Researchers from Clive Svendsen's laboratory at the Cedar Sinai Medical Center in Los Angeles, CA, and colleagues

November 2014

November 15-19, 2014: Washington, DC: The Annual Society for Neuroscience Meeting

November 16-18, 2014: New York, NY: Partnering for Cures

December 2014

December 3-5, 2014: San Antonio, TX: World Stem Cell Summit

December 3-6, 2014: Cold Spring Harbor, NY:Neurodegenerative Diseases: Biology & Therapeutics

December 5-7, 2014: Brussels, Belgium:International Conference on ALS/MND

December 17-20, 2014: Hotel Vila Galé Coimbra, Portugal: Mitochondria, Metabolism and Disease

January 2015

January 13-17, 2015: Hokkaido, Japan: Society for Neuromuscular Sciences 8th Annual Scientific Meeting

January 25-30, 2015: Taos, New Mexico:Neuroinflammation in Diseases of the Nervous System

February 2015

February 1-3, 2015: Cambridge, UK: Biomarkers for Brain Disorders: Challenges and Opportunities

Feb 17-19, 2015: Boston, MA: World CNS Summit 2015

Feb 23-24, 2015:

used viral vectors to selectively reduce mutant SOD1 expression presymptomatically in the motor cortex of an ALS rat model overexpressing SOD1. Remarkably, this selective knockdown led to delayed disease onset, improvement in motor neuron survival and retention of NMJ integrity. Click here to read more about this work and its implications for human ALS.

Mathematical Models Adopted from Cancer Shed Light on ALS

Despite being very different diseases, ALS and some forms of cancer have shared characteristics: complex genetics, mostly frequently adult onset, and onset commonly followed by rapid disease progression (see July 2014 news story). These shared features led Ammar Al-Chalabi at King's College, London and Neil Pierce at the London School of Hygiene and Tropical Medicine to team up with an international team of researchers to adapt mathematical models from cancer to ALS. In the October 7 *Lancet Neurology*, the researchers apply a multistep model of ALS to epidemiological data from five different European registries, and conclude that ALS is caused by a sequence of six steps. The accumulation of these steps over a lifetime, one of which can be an inherited mutation, ultimately ends in disease. This thought-provoking approach provides further support for the contribution of environmental risk factors to ALS. Click here to read more.

Impaired Clearance of Oxidized mRNA May Contribute to Neurodegenerative Disease

DNA damage likely contributes to neuronal degeneration in ALS, but does RNA damage also play a role? A growing body of evidence implicates RNA oxidation as an early contributor to ALS (*Chang et. al., 2008*), and now a new study published November 13 in *Cell Reports*describes the molecular mechanism by which the cell normally rids itself of oxidized messenger RNA (mRNA). Using both bacterial and yeast translation systems, researchers from Hani Zaher's laboratory at Washington University in St. Louis, Missouri demonstrate that oxidative damage to mRNA causes ribosomal stalling and blocks translation. The no-go decay system, a recently discovered surveillance system for removing non-functional RNA species, effectively degrades oxidized mRNA and prevents toxic RNA builds up in the cell. Click here to read the full story on the intricate cellular machinery that tackles RNA oxidative damage, and what happens when this system go awry.

Multiple Rare Variants of ALS Genes May Accelerate Disease Onset

The identity of susceptibility genes that contribute to the risk of familial and sporadic ALS is a subject of intense investigation. We recently reported on a genetic study that estimated genetic heritability as underlying at least 21% of the risk of developing ALS (see July 2014 news story). Now, a report in the November 7 *Annals of Neurology*online identifies rare of new variants in known ALS genes in more than a quarter of sporadic ALS and over 60% of familial ALS cases in the study. Intriguingly, the researchers, led by Matthew Harms at Washington University in St. Louis, Missouri and Robert Baloh of Cedars-Sinai Medical Center in Los Angeles, California, calculated that carrying two or more variants in these ALS risk genes accelerates symptom onset by approximately 10 years. Click here to read more about the creative approaches used and the implications of these findings.

Manchester, UK: 10th Annual Biomarkers Congress

Feb 25-26, 2015: La Jolla, CA: Biocom Global Life Sciences Partnering Conference

March 2015

March 1-3, 2015: San Diego, CA: 9th Annual Drug Discovery for Neurodegeneration Conference

April 2015

April 7-11, 2015: Soelden, Austria: The 17th International Neuroscience Winter Conference

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Drug News

Isis Pharmaceuticals Initiates Phase III Study in Spinal Muscular Atrophy
Isis Pharmaceuticals, a California-based pharmaceutical company that specializes in antisense based drug development, has announced the initiation of a Phase III trial of ISIS-SMN_{Rx} in 120 non-ambulatory children with Spinal Muscular Atrophy (SMA; for more about their ALS program see Jan 2013 news story). Patients with SMA express low levels of the survival of motor neuron protein (SMN) due to a mutated SMN1 gene, and ISIS-SMN_{Rx} functions by increasing production of SMN through a closely related gene, SMN2. In parallel to this study, Isis is conducting a Phase III study in infants with the disease. Isis will receive a $27M milestone payment from its development partner, Biogen Idec, for launching this trial. Click here to read more.

International Partnership of Foundations Invests in Drug Development for Neurodegenerative Diseases
An international collaboration of medical charities and foundations led by MRC Technology will invest over £30 million (~$47 million) into developing therapies for brain diseases. The initiative, calledNeurodegeneration Medicines Acceleration Programme (Neuro-MAP) will focus on developing promising new therapies for ALS and other neurodegenerative diseases by repurposing approved drugs or testing drug candidates previously shelved by pharmaceutical companies. Promising candidates will be delivered back to pharmaceutical companies for later stage development. Click here to read more about the Programme participants and their goals for the initiative.

Novartis' Gilenya Fails to Ameliorate Severe Form of Multiple Sclerosis
Gilenya, a sphingosine 1-phosphate receptor modulator also known as fingolimod, was the first FDA-approved oral disease modifying therapy for relapsing forms of multiple sclerosis (MS) upon approval in September 2010. Novartis' drug is also under development as a candidate ALS therapy in partnership with ALSTDI (see also March 2013 news story). Now Novartis has announced that the drug failed to improve disability measures in a more rare form of MS called primary progressive multiple sclerosis (PPMS). The severe and irreversible central nervous system damage cause by PPMS is thought to be mediated by distinct pathways from the relapsing forms of MS, and the divergent drug effects of Gilenya between these two indications further support this hypothesis. Click here to read more.

Cystic Fibrosis Foundation to Receive $3.3 Billion for Kalydeco Rights
Fifteen years ago, the Cystic Fibrosis Foundation (CFF) partnered with Vertex Pharmaceuticals and funded the company's drug development program for cystic fibrosis (CF). A total of about $150M were invested in developing therapies for CF, successfully leading to the 2012 FDA approval of Kalydeco, the first disease-modifying therapy for CF, and two more in the pipeline. The CFF has now announced the sale of its royalty rights in the drug to Royalty Pharma for $3.3 billion, 20 times the Foundation's annual budget, and is planning to inject the funds into further CF research. This success story is not without controversy, as some believe it has created a conflict of interest. Click here to read

more about the pros and cons of venture philanthropy in the medical arena.

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