



ALS Forum e-Newsletter Volume 140

November 20, 2015

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Resources:

[ALS Drugs in Development Database](#)

[ALSGene](#)

[The PRO-ACT Database](#)

[NEALS Biofluid Repository Available to Researchers](#)

[VABBB ALS CNS Tissue Request Information Site](#)

[TargetALS Cores](#)

Funding Opportunities:

[ALSA, ALS ACT, ALS Finding a Cure, NEALS Phase II Clinical Development RFP](#). Letter of Intent due Nov 30, 2015.

[MDA Venture Philanthropy](#). Letter of intent due Dec 1, 2015.

[NCATS Pre-clinical Research Based on Existing Repurposing Tools \(R21\)](#). Letter of intent due December 13, 2015.

[MDA Research Grants](#). Letter of Intent due

Conference News

[More Highlights from the "RNA Metabolism in Neurological Disease" Conference](#)

The RNA Metabolism in Neurological Disease conference, co-organized by Paul Taylor of St. Jude Children's Research Hospital in Memphis, Tennessee, and Fen-Biao Gao of the University of Massachusetts Medical School in Worcester, was recently held in Chicago just prior to the annual Society for Neuroscience meeting. This week we bring you two more articles from Alzforum's Amber Dance on highlights from the meeting:

[Listen Up, Gene Silencing Strikes a Chord at RNA Meeting](#)

Efforts to develop therapeutics that target toxic RNA and proteins in ALS span a range of approaches including silencing of transcription, reducing gene expression, and increasing expression of chaperones that can reshape misfolded proteins. Don Cleveland from the University of California, San Diego, in collaboration with Clotilde Lagier-Tourenne of Massachusetts General Hospital in Charlestown and [Isis Pharmaceuticals](#), has been testing antisense oligonucleotides (ASOs) targeting C9ORF72 to reduce RNA expression from the toxic repeats. In addition, Isis and Biogen are collaborating on second generation ASOs for silencing SOD1 that are slated to enter human testing in 2016 (see [May 2013 news](#)). Other RNA-silencing approaches include microRNAs targeting SOD1 and C9ORF72, being developed in Robert Brown's laboratory at University of Massachusetts Medical School in Worcester, MA, while approaches being developed in Aaron Gitler's group at Stanford

Dec 15, 2015. More information coming soon!

[MND Association, Chief Scientist of Scotland, Marie Curie. Palliative Care Research RFP.](#) Applications due Jan 14, 2016

[California Stem Cell Agency \(CIRM\) 2.0 Inception Awards.](#) Applications due January 15, 2016.

Upcoming Meetings:

November 2015

Nov 29-Dec 4, 2015: Cambridge, UK: [Molecular Neurodegeneration.](#)

December 2015

Dec 10-12, 2015: Atlanta, GA: [World Stem Cell Summit.](#)

Dec 11-13, 2015: Orlando, FL: [International Symposium on ALS/MND.](#)

2016

January 2016

Jan 12-16, 2016: Hokkaido, Japan: [The Society of Neuromuscular Sciences Inc., 10th Annual Scientific Meeting.](#)

Jan 24-27, 2016: Santa Fe, New Mexico: [Keystone Symposium on Molecular and Cellular Biology: Axons: From Cell Biology to Pathology.](#)

February 2016

Feb 25-26, 2016: Manchester, UK: [11th Annual Biomarkers Congress.](#)

March 2016

University in Palo Alto, CA, are aiming to go upstream and inhibit transcription of C9ORF72 hexanucleotide repeats. James Shorter from University of Pennsylvania shared findings on new chaperones that can disaggregate misfolded proteins. Click [here](#) to read the full report.

[New RNA-binding Protein Resides in Nuclear and Cytoplasmic Stress Granules](#)

Researchers led by Robert Bowser from the Barrow Neurological Institute in Phoenix, Arizona, have identified a novel protein in cerebrospinal fluid of ALS patients called RNA-binding motif 45 (RBM45). Little is known about RBM45, but studies presented by Bowser and colleagues at the RNA Metabolism in Neurological Disease meeting are uncovering a new stage of pathology in ALS that involves RBM45-containing nuclear inclusions. These are distinct structures from the cytoplasmic stress granules that are pathological hallmarks of ALS. These nuclear structures contain heat shock transcription factor 1 (HSF1), a protein thought to play a key role in cellular protection against stress. In parallel, the researchers examined the binding partners of RBM45, and found evidence that RBM45 and TDP-43 bind the same RNA species in the cytoplasm. Click [here](#) to read more about this intriguing protein and the new biology it is revealing about ALS.

Research News

[Vascular Defects May Contribute to Spinal Muscular Atrophy](#)

Spinal muscular atrophy is a fatal childhood motor neuron disease, which affects approximately 1 in 6000 infants. According to a report in the Oct 27 *Annals of Neurology* online, impaired blood supply to skeletal muscles and the spinal cord may play a major role in disease pathophysiology. Simon Parson from the University of Aberdeen in the UK, together with colleagues from Oxford University, University College London, and University of Edinburgh in Scotland, examined the vasculature in the skeletal muscle and spinal cord of mouse models of SMA, as well as in muscle biopsies from human SMA patients. The vasculature was depleted in both mice and humans, and in the SMA model mice these findings were accompanied by evidence of hypoxia and a disrupted blood spinal cord barrier. These findings open a new line of inquiry beyond the nervous system that could shed light on the mechanisms of neurodegeneration in SMA.

[New Findings Highlight Mechanism for Selective Neurodegeneration in Charcot-Marie-Tooth](#)

Charcot-Marie-Tooth (CMT) disease, also known as hereditary motor and sensory neuropathy, is one of the most common inherited neurological disorders, affecting approximately 1 in 2500 people in the US. Mutations in glycyl-transfer RNA synthetase (GlyRS) are known to cause one subtype of CMT, but how this

March 6-8, 2015: Miami, FL: [Annual Drug Discovery for Neurodegeneration Conference](#).

April 2016

Apr 2-6, 2016: Sölden, Austria: [18th International Neuroscience Winter Conference](#).

April 5-7, 2016: Boston, MA: [BioIT World Conference & Expo](#).

April 6-7, 2016: Boston, MA: [11th Neurotech Investing and Partnering Conference](#).

April 16-23, 2016: Vancouver, Canada: [American Academy of Neurology \(AAN\) Annual Meeting](#).

June 2016

June 5-9, 2016: Whistler, British Columbia, Canada: [Keystone Symposia, Autophagy: Molecular and Physiological Mechanisms](#).

June 12-16, 2016: Keystone, Colorado: [Keystone Symposia, Common Mechanisms of Neurodegeneration](#).

June 12-16, 2016: Keystone, Colorado: [Keystone Symposia, Microglia in the Brain](#).

July 2016

July 2-6, 2016: Copenhagen, Denmark: [10th FENS Forum of Neuroscience](#).

ubiquitously expressed protein leads to selective degeneration of peripheral axons has been unclear. In the October 29th *Nature*, researchers led by Samuel Pfaff at the Salk Institute and Xiang-Lei Yang of The Scripps Research Institute in La Jolla, CA, describe a potential mechanism that could underlie this selective vulnerability. The researchers report that GlyRS-mutant enzymes bind to the neuropilin 1 (Nrp1) in motor neurons and inhibit binding of vascular endothelial growth factor (VEGF) to these receptors, thereby blocking a key pathway for motor neuron survival. Increasing VEGF expression improved muscle strength in a CMT2D mouse model, while genetic reduction of Nrp1 exacerbated the CMT phenotype in mice. These findings point to a critical pathway that contributes to selective neuronal death in CMT, and could present a new avenue for targeted therapies.

Drug News

[New ALS Clinical Trial to Start for MediciNova's Ibudilast](#)
[MediciNova](#), Inc., a biopharmaceutical company in La Jolla, California, has received FDA approval for a new Phase IIa clinical trial protocol for treating ALS patients with the small molecule, phosphodiesterase inhibitor MN-166, also called ibudilast (see [April 2014 news](#), [Sept 2015 news](#)). This study will examine the drug's effect on reducing brain microglial activation using a novel imaging biomarker for ALS called positron emission tomography (PET) [11] C-PBR28. The drug will be tested in 15 ALS patients over the course of 36 weeks and will be conducted in collaboration with Massachusetts General Hospital's Neurological Clinical Research Institute and Harvard Medical School.

[Avalon and GSK Launch New Startup Focused on ALS](#)
[GlaxoSmithKline \(GSK\)](#) and [Avalon Ventures](#) have partnered to fund a new ALS-focused start-up company called Iron Horse Therapeutics (not to be confused with the ALS diagnostics company, [Iron Horse Diagnostics](#)). Based on research showing that the protein-tyrosine kinase ephrin type-A receptor 4 (EphA4) is a modifier gene in ALS, and mice and humans with lower EphA4 expression have a less aggressive course of disease (see [Aug 2012 news](#)), Iron Horse Therapeutics is moving forward with development of small molecule inhibitors of EphA4. Iron Horse will receive up to \$10 million in seed funding as well as R&D support from the partners, up until the stage of lead drug candidate selection, when the partners will decide whether to acquire the company.

[Amylyx Targets Inflammation and Oxidative Stress with ALS Drug Combo](#)

Cambridge, MA-based [Amylyx Pharmaceuticals](#) has received \$600k in funding from the ALS Finding a Cure Foundation and the Cure Alzheimer's Fund to advance preclinical development

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of its lead candidate, AMX0035. The drug is a proprietary combination of two compounds, which have shown potent anti-inflammatory and neuroprotective effects in preclinical studies in ALS, Alzheimer's and other neurodegenerative diseases. The compounds act by synergistically blocking mitochondrial and ER stress. Amylyx plans to enter clinical trials in ALS in 2016, and with the help of the recent grants will fund IND-enabling studies to advance toward this goal.

[New IPOs Put Spotlight on Two Companies Combating Neurological Diseases](#)

Two Boston-area biotech companies priced IPOs last week, raising millions of dollars for the development neurological disease therapies. [WaVe Life Sciences](#) produces "stereopure" RNA-based drugs proposed to confer improved safety and potency over other RNA-based therapies. The company is focusing on Huntington's disease (HD) and Duchenne muscular dystrophy. [Voyager Therapeutics](#) is developing gene therapies for CNS diseases, including ALS, HD, and spinal muscular atrophy (see [Feb 2014 news](#)). The company is developing optimized adeno-associated viral vectors (AAV) for delivery into the brain or spinal cord, a challenging task fraught with safety risks. The company's pipeline includes a Parkinson's disease gene therapy in clinical development, while other candidates will likely not enter clinical trials until 2017.

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