



ALS Forum e-Newsletter Volume 134

August 21, 2015

The ALS Ice Bucket Challenge is back! To learn more visit [www.alsicebucketchallenge.org](http://www.alsicebucketchallenge.org). To support the ALS Forum click [here](#). Your contributions will help enrich this resource!

Visit the [ALS Forum website](#) to read the complete stories featured in this e-newsletter. Please let your friends and colleagues know about the ALS Forum. It is easy to sign up for the newsletter [here](#).

#### Resources:

[ALS Drugs in Development Database](#)

The ALSGene tool:  
[www.ALSGene.org](http://www.ALSGene.org)

The PRO-ACT Database:  
[www.ALSDatabase.org](http://www.ALSDatabase.org)

[NEALS Biofluid Repository Available to Researchers](#)

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

#### Funding Opportunities:

[ALS Association Clinical Management Grants](#). Letter of Intent due September 14, 2015.

[Clinical and Translational Science Award \(CTSA U54\)](#). Applications due Sept 25, 2015.

[ALS Therapy Alliance \(ATA\) RFP](#). Applications due Oct 15, 2015.

[California Stem Cell Agency \(CIRM\) 2.0](#)

## Research News

### [TDP-43 Keeps Cells Healthy by Repressing Cryptic Exons](#)

Cytoplasmic inclusions of the RNA-binding protein TDP-43 are a major hallmark of ALS and frontotemporal dementia (FTD). A new study led Philip Wong at Johns Hopkins University School of Medicine in Baltimore, MD, describes a new function for TDP-43: suppressing splicing of cryptic exons, segments of intronic RNA that contain exon splice sites. As reported in the August 7 *Science*, in the absence of TDP-43, these aberrant exons appear in the mature mRNA, leading to translation of dysfunctional proteins, and ultimately cell death. Interestingly, in mouse embryonic stem cells expressing a conditional TDP-43 knockout, the phenotype could be rescued by expressing a hybrid protein with TDP-43 RNA binding sites and a splicing repressor. Future research will characterize the faulty transcripts and protein products in neurons from iPS cells derived from ALS patients, and their potential as biomarkers of TDP-43 pathology.

### [Fly Model of Neurodegeneration Reveals Novel Suppressor Genes of TDP-43 Toxicity](#)

Scientists have developed a new approach to study motor neuron degeneration by tracking single motor axons in the legs of adult *Drosophila*, allowing them to image age-related changes in synaptic and axonal morphology. Researchers led by Jemeen Sreedharan of the Babraham Institute in Cambridgeshire, UK, and Marc Freeman of University of Massachusetts Medical School in Worcester, MA overexpressed the ALS-causing mutant protein,

[Awards](#). Due last business day of each month.

#### Webinars:

[ALSA Research Update Webinar](#). Aug 25, 2015, 4:00-5:00pm EST.

#### Upcoming Meetings:

##### September 2015

Sept 3-6, 2015: Prague, Czech Republic: [2nd World Congress on Neurotherapeutics](#)

Sept 9-11, 2015: Philadelphia, PA: [CNS Diseases World Summit](#)

Sept 19-20, 2015: Montreal, Canada: [10th Annual Symposium of the Fondation Andre-Delambre](#)

Sept 27-29, 2015: Chicago, IL: [American Neurological Association Annual Meeting](#)

Sept 24-25, 2015: Ottawa, Canada: [Ottawa International Conference on Neuromuscular Biology, Disease and Therapy](#)

Sept 27-29, 2015: Chicago, IL: [American Neurological Association Annual Meeting](#)

Sept 30 - Oct 4, 2015: Brighton, UK: [20th International World Muscle Society Congress](#)

##### October 2015

Oct 15-16, 2015: Chicago, Illinois: [10th Brain Research Conference RNA Metabolism in Health and Disease](#).

Oct 17-21, 2015: Chicago, Illinois: [The Society for Neuroscience Annual Meeting](#).

TDP-43Q331K, in the fly leg model, and then conducted forward genetic screens to identify mutants with resistance to TDP-43-mediated neurodegeneration. As reported in August 17 *Current Biology*, the researchers identified three suppressor genes - hat-trick and xmas-2, and the known modifier of neurodegeneration, shaggy/GSK3 (see [April 2013 news](#)). Interestingly, these suppressors did not suppress Wallerian degeneration, suggesting that TDP-43 kills neurons via a distinct process. The researchers are currently validating these results in mammalian models.

#### [Making Muscles in a Dish Could Pave the Way for New Therapies](#)

Understanding the cross-talk between degenerating neurons and their target muscles could aid in the development of new therapies for motor neuron disease, but deriving skeletal myocytes *in vivo* had proven to be challenging. Led by Olivier Pourquie, investigators from Harvard Medical School, Brigham and Women's Hospital in Boston, and the Harvard Stem Cell Institute, were able to successfully differentiate mouse and human stem cells through each stage of muscle development into functional muscle fibers capable of contracting and multiplying in large numbers. As reported in the August 3 *Nature Biotechnology* online, the researchers then used their protocol to derive and study muscle fibers from a mouse model of Duchenne muscular dystrophy (DMD). This myocyte-generating protocol might in the future provide a platform to study neuromuscular diseases by co-culturing muscle cells and neurons derived from animal models or from patient-derived stem cells.

## Drug News

#### [New Study Finds Detrimental Effect of Guanabenz in ALS Mouse Model](#)

A new study led by scientists from the [ALS Therapy Development Institute](#) (ALS TDI) underscores the complexity of therapeutic interventions that perturb ER stress and the unfolded protein response (UPR), two important pathways in ALS. Guanabenz is an alpha2 adrenergic receptor agonist approved for use in humans, which also inhibits de-phosphorylation of the alpha subunit of eukaryotic initiation factor 2 (eIF2alpha) and prolongs activation of the UPR (see [April 2015 news](#)). Although earlier studies have shown that guanabenz treatment ameliorates survival in the mSOD1 mouse model of ALS, a new study published Aug 19 in *PLOS ONE* presents efficacy data with two different guanabenz treatment protocols suggesting that the drug accelerates onset of paralysis and shortens lifespan in this preclinical model, despite beneficial effects in cellular models of ER stress. Although differences in study design may underlie some of the discrepancies, these findings also suggest that the

Oct 31-Nov 5, 2015:  
Santiago, Chile. [World  
Congress of Neurology](#)

#### November 2015

Nov 14-18, 2015: San  
Francisco, CA: [American  
Medical Informatics  
Association \(AMIA\) Annual  
Symposium](#)

#### December 2015

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

#### 2016

##### January 2016

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

##### March 2016

March 21-22, 2016: San  
Francisco, CA: [AMIA Joint  
Summits on Translational  
Science](#)

##### April 2016

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

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

##### July 2016

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

timing and target-selectivity are particularly important when perturbing the intricate network of pathways involved in the UPR.

#### [ProGas Study Finds Benefit in Earlier Gastrostomy for ALS patients](#)

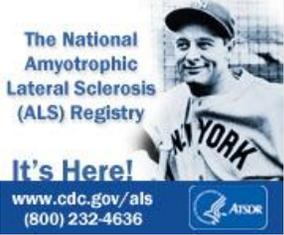
As ALS progresses and impairs patients' ability to maintain sufficient oral intake of nutrients, patients often require long-term nutritional support via gastrostomy, a procedure for inserting a feeding tube directly into the stomach. The [ProGas study](#), a multi-center longitudinal, prospective cohort study in the UK, led by Christopher McDermott at the University of Sheffield, UK, compared over 300 ALS patients who had undergone gastrostomy by percutaneous endoscopy, radiological insertion, or per-oral image-guidance. As published in the July *Lancet Neurology*, no significant difference in the safety of the three methods was identified, based on 30-day mortality following the procedure. However, patients who received gastrostomy prior to losing 10% of their weight at diagnosis survived significantly longer than patients who had lost more than 10% of their diagnosis weight, suggesting that earlier intervention would benefit patients.

#### [Ice Bucket Challenge Dollars Fund Expanded Collaboration Between Biogen and Columbia University](#)

The Boston-area based biotech company, [Biogen](#), is expanding its \$30 million collaboration with Columbia University Medical Center (CUMC) (see [Feb 2015 news](#)). With funding from the ALS Association, Biogen and CUMC are launching a new project to map the genomes of 1,500 ALS patients who are currently being seen at ALS clinics. The study is unprecedented in that it will combine next generation sequencing with detailed clinical phenotyping of patients, in order to identify genes that shape clinical features of ALS. This collaborative project will provide the foundation for tailored therapies for ALS patients, where drug development and testing will be geared to subgroups of ALS patients based on shared genetic mutations. This three-year project is supported by \$3.5 million raised by the ALS Association in last summer's Ice Bucket Challenge.

#### [Kadimastem's Stem Cell Therapy Shows Benefit in ALS Rat Model](#)

Following promising results of their stem cell therapy in ALS rat models, the Israeli biotechnology company [Kadimastem](#) is preparing for a Pre-Investigational New Drug (IND) Meeting with the US FDA to pave the way for Phase I clinical trials in humans. Kadimastem, which focuses on stem cell therapies for diabetes and neurodegenerative diseases, has developed a proprietary technology for treating ALS with human embryonic stem cell-derived astrocyte precursors (see [July 2014 news](#)). Injecting the derived astrocytes into the spinal fluid of an ALS rat model



The National Amyotrophic Lateral Sclerosis (ALS) Registry

It's Here!

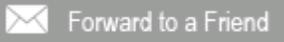
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increased survival, improved motor function, delayed disease onset, and inhibited ALS progression. The company hopes that its treatment could be an effective off-the-shelf stem cell therapy for ALS that does not require immuno-suppressive drugs.

### [Chaperone Therapeutics and ALS TDI Partner to Tackle Protein Misfolding](#)

North Carolina-based biotechnology company [Chaperone Therapeutics](#) and the nonprofit biotechnology company, the [ALS Therapy Development Institute](#) (ALS TDI), have entered into a research partnership to develop therapies for ALS that target protein misfolding and aggregation. Chaperone Therapeutics has identified small molecules that dissolve aggregates of misfolded proteins, a characteristic of many neurodegenerative diseases. One of the targets of these lead compounds is heat shock factor protein 1 (HSF1), a transcription factor that regulates activity of the chaperone proteins that assist with protein folding in the cell (see [Feb 2010 news](#)). ALS TDI is conducting preclinical experiments to test the ability of these lead compounds to reverse protein misfolding in cell-based assays and to ameliorate disease in vivo ALS models.

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