DISCOVERING A CURE

THE ALS FORUM

**ALS Forum e-Newsletter Volume 69** **August 30, 2012**

*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:**

Upcoming ALSA and NEALS Webinar September 11th: Trial of Resistance and Endurance Exercise in ALS

Upcoming Workshop October 2 and 3: Applying to the NIH SBIR Phase I Program for First-Time Applicants

**Upcoming Registration Deadline:**

September 12th for the Keystone Symposia: Multiple Sclerosis in January

Register Now for the 23rd International Symposium on ALS/MND, December 5-7, 2012: Chicago, IL. The program was just released.

**Upcoming Meetings:**

September 5-7, 2012: Manchester, UK: 8th International Conference on Frontotemporal Dementias

## Research News

ALS Modifier: Ephrin Receptor Loss Delays Onset, Progression

The question of why some ALS patients live for only 2 to 3 years after diagnosis and some can live 10 or more years after diagnosis still puzzles clinicians and researchers alike. A new finding may provide at least part of the answer. Researchers at the University of Massachusetts Medical School (UMMS), the Vesalius Research Center and the University of Leuven, Belgium, have identified a gene, *EPHA4*, that has been shown to influence survival time in ALS patients. Their findings, published August 26 online in *Nature Medicine*, suggest that mutation or deletion of the ephrin receptor EphA4 extends survival time in ALS patients. Similar to the newly ALS-linked gene *profilin 1*, EphA4 regulates the actin cytoskeleton. EphA4 was first identified in a screen for genetic modifiers of ALS. Using various approaches, the researchers were able to confirm their findings in zebrafish, mice, and rats. Further, Dr. Robert Brown's lab at UMMS identified two new mutations in EphA4 in two ALS patients. In one case, an ALS patient with a truncation of EphA4 lived for seven years. In the second case, the ALS patient had a missense mutation in EphA4 and is still living twelve years after diagnosis.

Could Sortilin Be a Sweet Spot for FTD Therapy?

Progranulin, sortilin, and TDP-43 have all been linked to frontotemporal dementia (FTD), but understanding the relationship among these proteins and how they contribute to FTD has been a challenge. At the Alzheimer's Association International Conference in Vancouver, Canada, Leonard Petrucelli of the Mayo Clinic in Jacksonville, Florida, presented new findings suggesting a mechanism for how these three proteins may interact and lead to FTD.

Meeting Mulls Over Use of Complex Medical Data

In Part 1 of a two-part Alzforum series covering the Meaningful Use of Complex Medical Data (MUCMD) conference held at the Children's Hospital Los Angeles in California, researchers, statisticians, engineers, clinicians, and business people came together to discuss using electronic medical records to answer many unanswered clinical questions. For example, Prize4Life has partnered with the Northeast

September 6-7, 2012: Dublin, Ireland: Neurons Under Stress 2012

September 8-11, 2012: Stockholm, Sweden: 16th European Federation of Neurological Societies Congress

September 21-22, 2012: Quebec, Canada: Annual Foundation Andre-Delambre ALS Symposium: Causes and Therapeutic Perspectives

October 2, 2012: Rockland, MD: 3rd Annual Conference on Clinical Research for Rare Diseases

**Training Program:**

Interested in drug discovery and development for nervous system disorders? Apply to the NIH Blueprint-funded training program! Application deadline: October 1, 2012.

**Funding News:**

ADDF/AFTD: Accelerating Drug Discovery for Frontotemporal Dementias: Letter of Intent Due September 6, 2012

MJFF: Target Validation and Therapeutic Development Initiative Programs: Proposals Due September 12, 2012

MGH's Neurology Clinical Trials Unit Calls for ALS Clinical Trial Applications: Application Due September 17, 2012

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ALS Consortium (NEALS) and the ALS Therapy Alliance (ATA) to create the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database. The PRO-ACT database, which is scheduled to go live this December, will provide access to data collected from over 18 Phase II and Phase III clinical trials for ALS, totaling nearly 8,500 clinical records - the largest ALS clinical record database in existence. Before the full PRO-ACT database goes live, researchers are getting to preview a sample of the data. In July, Prize4Life launched the DREAM-Phil Bowen ALS Prediction Prize4Life, which offers $25,000 to the individual/team who develops the best algorithm to predict the rate of disease progression for a given ALS patient. Interested in solving this challenge? Register here. While Part 1 of this series highlights the "Big Data" vision, Part 2 of the series, Big Data Present Big Challenges for Researchers, suggests many challenges still lie ahead.

FTD Risk Factor Confirmed, Alters Progranulin Pathways

In a recent *Journal of Neuroscience* article, researchers from the Chen-Plotkin, Lee, and Trojanowski labs at the University of Pennsylvania in Philadelphia, report an overabundance of the transmembrane protein 106B (TMEM106B) in patients who died from frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP). Two years ago, a genome-wide association study (GWAS) of 515 FTD patients indicated that TMEM106B might be a risk factor for FTD. However, complications in the GWAS data made the association difficult to confirm. Then TMEM106B popped up again, this time in an analysis of microRNA changes in FTD patients. Chen-Plotkin found that TMEM106B mRNA transcripts were upregulated in patients with FTD and even further overexpressed in FTD patients with mutations in progranulin. Chen-Plotkin's working hypothesis is that TMEM106B localizes to the endosomes and lysosomes, and TMEM106B overexpression disrupts normal endocytic trafficking and the lysosomal degradation of proteins. Disruption of such critical cellular processes may contribute to the progression of FTLD-TDP.

## Drug News

Proteostasis Therapeutics Presents Novel Approach for Treating Neurodegenerative Diseases

Proteostasis Therapeutics, Inc. is using a novel approach to treat orphan and neurodegenerative diseases, including ALS, by regulating protein homeostasis. The company recently presented their latest findings at the Alzheimer's Association International Conference (AAIC). At AAIC, the company showed that their promising lead compound could decrease toxic protein aggregates in neurons, and rescue the neurons from cell death. In certain cases of ALS, the ALS-associated protein, TDP-43, accumulates inside of neurons and forms protein aggregates. Proteostasis' approach to target clearance of such aggregates might rescue these neurons from death and may be a viable therapy for ALS patients.

Biogen Idec and Regulus Therapeutics Team Up for MS

A few weeks ago, Harvard researchers Drs. Oleg Butovsky and Howard Weiner announced the discovery of a potential miRNA-based biomarker

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

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for ALS. This week, Biogen Idec announced that it was teaming up with Regulus Therapeutics to identify a microRNA biomarker in blood for MS. A spokesperson for Regulus said the biomarker would be used to identify "optimal patient segments in clinical trials, to develop companion diagnostics, and to monitor disease progression or relapse." Biogen Idec has a vested interest in using the biomarker for learning more about MS patient populations, as Biogen markets three MS drugs, Avonex, Fampyra and Tysabri. You can read more about the ALS biomarker discovery here.

Neuralstem Treats 18th Patient and Concludes Phase I Clinical Trial

Neuralstem, Inc. just treated their 18th and final patient in their Phase I ALS clinical trial. The goal of the Phase I study was to determine if Neuralstem's stem cell therapy was safe to inject into the spinal cords of patients. The results of this initial study appear to be promising. Dr. Eva Feldman, the lead investigator of the trial, commented, "In some patients, it appears that [ALS] is no longer progressing, but it is too early to know if the result from that small number of patients is meaningful." If the stem cell therapy is deemed safe by the FDA, Neuralstem will begin enrolling for their Phase II clinical trial. Read more about the story of one of the patients participating in the Neuralstem Phase I clinical trial here.

NeuRx Diaphragm Pacing System Enters Phase II Trials

The ALS Association has partnered with the MDA to fund a Phase II clinical trial of the NeuRx Diaphragm Pacing System (DPS). NeuRx DPS regulates breathing by stimulating the diaphragm. Diaphragm pacing may help people with chronic breathing problems, including those with ALS, regulate their breathing. The Phase II trial will enroll 180 people with ALS, with 120 receiving the NeuRx DPS and 60 receiving the current standard of treatment.

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