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DISCOVERING A CURE

THE ALS FORUM

ALS Forum e-Newsletter Volume 74 **November 8, 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.

In observance of Thanksgiving, the ALS Forum e-Newsletter will not be published on November 22. We will return to our normal bi-weekly publication schedule on Thursday, November 29.

Resources:

NEALS Biofluid Repository Available to Researchers

NINDS Fibroblast Repository

Upcoming Registration Deadline:

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

Upcoming Meetings:

November 28-30, 2012: New York, NY: Partnering for Cures

November 28 - December 1, 2012: Cold Spring Harbor, NY: Neurodegenerative Diseases

November 29, 2012: New York, NY: NYAS Symposia Targeting Metals in Alzheimer's and

Research News

Growth Factor Stabilizes Cell Skeleton, Rescues Motor Neurons
Researchers at the University of Wuerzburg in Germany finally know how a protein called CNTF (ciliary neurotrophic factor) works to protect axons from degenerating. In a paper published online on October 29 in the *Journal of Cell Biology*, the researchers reported that CNTF stimulates the activation of the transcription factor STAT3. Once activated, instead of translocating to the nucleus, STAT3 remains in the cytosol, where it binds and inhibits the protein stathmin. Stathmin normally binds tubulin monomers, preventing their polymerization into microtubules, which limits axon growth. The group studied the effects of CNTF treatment in neurons isolated from a mouse model of progressive motor neuronopathy (PMN). As compared to axon length in a wild type mouse, axon growth is stunted in the neurons from the PMN mouse. However, the researchers found that CNTF treatment increased axon length in the PMN neurons - and this increase in axon length was associated with an increase in the number of STAT3-stathmin binding interactions. CNTF was previously tested in a clinical trial for the treatment of ALS. Unfortunately the treatment was found to have side effects leading to discontinuation of the clinical trial. Now, 15 years later, new research has revealed the key step in how CNTF is capable of protecting axons of neurons from degenerating. Now that we know the molecular pathway by which CNTF works, we may have a safer drug target to pursue for ALS therapy development. This warrants a revisiting of the original CNTF trial data, which Regeneron has graciously donated to the PRO-ACT project.

Researchers Lasso TDP-43 With RNA Lariats
In certain cases of ALS and FTD, the RNA-binding protein, TDP-43, accumulates in toxic cytosolic protein aggregates. In these diseases,

Other Neurodegenerative Diseases

November 29-30, 2012: Geneva, Switzerland: 3rd Annual World Orphan Drug Congress

November 29, 2011: Boston, MA: Harvard NeuroDiscovery Center Annual Symposium: The Synapse: Basic Biology and Functional Consequences

December 3-5, 2012: West Palm Beach, FL: The World Stem Cell Summit

December 5-8, 2012: Cold Spring Harbor, NY: Blood Brain Barrier

December 5-7, 2012: Chicago, IL: 23rd International Symposium on ALS/MND

December 17, 2012: London, UK: Mitochondria and the Central Nervous System

January 11-16, 2013: Big Sky, MT: Keystone Symposia: Multiple Sclerosis

January 15-19, 2013: Hokkaido, Japan: The Society of Neuromuscular Sciences Incorporated 7th Annual Scientific Meeting

February 3-8, 2013: Santa Fe, NM: Keystone Symposia Joint Meeting: Neurogenesis & New Frontiers in Neurodegenerative Disease Research

February 10-12, 2013: San Francisco, CA: 7th Annual Drug Discovery for Neurodegeneration Conference

eliminating the toxicity associated with these aggregates could be a beneficial therapeutic strategy. However, not much was known about how to prevent the toxicity associated with TDP-43 aggregates, until now. In a paper published on October 28 in *Nature Genetics*, researchers at the Stanford University School of Medicine and the Gladstone Institutes in San Francisco identified a genetic modifier that prevents TDP-43 toxicity. Using a yeast model of TDP-43 toxicity, the scientists screened for genes that when deleted would suppress TDP-43 toxicity. The researchers found that deleting an RNA processing enzyme, Dbr1, prevented TDP-43 toxicity. Dbr1 is responsible for cleaving and linearizing RNA lariats that remain from pre-mRNA splicing events. Once linearized, these RNA pieces are degraded by RNA degrading enzymes. The researchers found that when Dbr1 is deleted, cytoplasmic TDP-43 binds to these unprocessed lariats, and this binding prevents toxicity. Some researchers have proposed that TDP-43 may bind and sequester important cellular RNA targets into TDP-43 aggregates, which may cause cellular toxicity. In the case of the Dbr1 deletion, the extra lariats may act as RNA "decoys," which prevents TDP-43 from binding and sequestering these important cellular RNA targets - thereby preventing cellular toxicity. Dbr1 might be another new target for drug development in ALS.

Genetics Project Update: Over 1,000 Genomes and Counting

In an open-access report published in *Nature*, the 1000 Genomes Project provided an update on their efforts to sequence 2,500 genomes from multiple geographic areas. The goal of the project is to " build a resource to help to understand the genetic contribution to disease." In their Phase I update, The 1000 Genomes Project Consortium reported on their findings from a combination of whole genome and exome sequencing of 1,092 individuals from 14 nations across the Americas, Europe, Africa, and Asia. Of the 1,092 genomes sequenced, the researchers identified a number of genomic variations - 1.4 million short deletions or insertions, 14,000 large deletions, and 38 million single nucleotide polymorphisms. Furthermore, the Consortium found that individual populations have their own defined set of common and rare variants. Gerard Schellenberg, a professor from the University of Pennsylvania in Philadelphia, said that these findings emphasize the importance of matching case and control populations, "Scientists studying a rare variant must take care to show it is truly linked to disease, and not simply the ethnicity or background of the population they are studying." It's clear that these data will be invaluable, and hopefully could lead to the identification of rare genetic variants that are associated with ALS.

Identification of a Gene Important for Nerve Cell Regeneration

In an article published online November 1 in *Cell Reports*, researchers reported the identification of a protein responsible for regenerating axons after injury. Researchers used RNAi to knockdown the levels of four proteins involved in microtubule severing in *Drosophila*: fidgetin, katanin-60, katanin-60L1, and spastin. They found that knocking down katanin-60 or spastin caused the largest defects in axon regeneration. However, when they tested axon regeneration in *Drosophila* that were heterozygous or null for mutations in either katanin-60 or spastin, it was the flies with either 1 or 2 mutant copies of spastin that showed the

February 19-20, 2013: Manchester, UK: 8th Annual Biomarkers Congress

Funding News:

Massachusetts Neuroscience Consortium Calls for Proposals. Proposal Deadline: November 16, 2012

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

HNDC and the MGH NCRI announced an RFA for the 2013 Neurodegenerative Disease Pilot Study Grant Program. Proposal Deadline: December 6, 2012

Rare Disease Challenge Be HEARD. Proposal Deadline: December 15, 2012

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greatest defects in axon regeneration. In addition, the team found that axon regrowth was sensitive to spastin dosing, as spastin overexpression reduced axonal regrowth. Dr. Melissa Rolls, an assistant professor of biochemistry and molecular biology at Penn State, and senior author of the study said, "We are hopeful that this discovery will open the door to new research related to spinal-cord and other neurological disorders in humans."

Drug News

Second Chance for Failed Drugs - Maybe One Could Be An ALS Therapy?

In an effort to find more therapies for both common and rare diseases, AstraZeneca (AZ) has released 22 of its failed drugs to academic researchers, with the hope that the drugs will have a second chance. The program is a collaboration between the United Kingdom's Medical Research Council (MRC) and AZ. The MRC is providing $11 million in funding to 15 labs that will investigate alternative uses of the failed drugs. The 15 research groups that will be participating in the program were selected from a field of 100 applicants. We are pleased to report that one of the research groups will be testing some of the failed compounds as potential therapies for ALS!

TauRx Therapeutics Begins Phase III Trials with Therapy That Targets Protein Aggregates

Singapore-based TauRx Therapeutics Ltd., just announced that they are beginning two global clinical trials for Alzheimer's disease. The trials will focus on the use of TauRx's Tau Aggregation Inhibitor (TAI) therapy, LMTX, which targets the disaggregation of protein aggregates of tau. In the Phase II clinical trial, LMTX reduced the rate of Alzheimer's disease progression by 90%. LMTX also targets the disaggregation of protein aggregates of TDP-43, which are found in certain cases of FTD and ALS. In September of this year, TauRx launched a Phase III clinical trial to evaluate the efficacy and safety of LMTX for the treatment of behavioural variant frontotemporal dementia (bvFTD). The study is enrolling 180 people in the US, UK, Canada, Germany, Australia, Singapore and the Netherlands. Learn more about the Phase III trial of LMTX in people with bvFTD here.

Neuraltus Pharmaceuticals Plans to Move Forward with Testing ALS Drug in Phase III Trial

Neuraltus Pharmaceuticals just announced the results from their Phase II clinical trial of NP001 in people with ALS. For the Phase II study, 136 people with ALS were treated either with the placebo or with one of two doses of NP001. Unfortunately, the results of the study did not reach statistical significance. However, a post hoc analysis of the data from just the patients receiving the highest dose of NP001 did reach statistical significance. Of those receiving the higher dose, 27% did not have any progression in their disease for six months. Dr. Robert Miller, of the California Pacific Medical Center, who led the study said "the results from this study with NP001 are most encouraging, as halting or slowing the rate of disease progression in a subset of patients, as this study suggests, would translate into a clear clinical benefit for these patients."

After discussions with the FDA, Neuraltus has decided to move forward with a Phase III study of their NP001 drug for the treatment of ALS. Neuraltus plans to start enrolling patients in the Phase III study in 2013.

An Interview with the CEO of Brainstorm Cell Therapeutics Inc.
BrainStorm Cell Therapeutics is currently conducting a Phase I/II clinical trial to test the tolerability and safety, as well as collect preliminary efficacy data on their NurOwn technology for the treatment of ALS. The study is being conducted at the Hadassah University Medical Center in Jerusalem. In July, BrainStorm reported that they had successfully treated 12 patients enrolled in the trial, with none of the 12 patients reporting any side effects. Upon FDA approval, BrainStorm plans to initiate a Phase II trial of NurOwn in people with ALS in the United States. Recently, Dr. Adrian Harel, the CEO of BrainStorm, was interviewed about their Phase I/II study of NurOwn. Read the interview with Dr. Harel here.

Cytokinetics Begins Enrollment for Phase IIb Trial of Tirasemtiv
Cytokinetics, Incorporated has started enrolling patients in their Phase IIb study of tirasemtiv (formerly CK-2017357) in people with ALS. The study, called BENEFIT-ALS (Blinded Evaluation of Neuromusclar Effects and Functional Improvement with Tirasemtiv in ALS), will be used to determine the tolerability, safety, and efficacy of tirasemtiv in people with ALS. Tirasemtiv works via a novel mechanism to reduce - and even prevent - muscle fatigue. The lead investigator in the study Dr. Jeremy M. Shefner, Professor and Chair of the Department of Neurology at the Upstate Medical University at the State University of New York, said "if successful, this novel mechanism therapy could improve the lives of many patients living with ALS." The trial will enroll 400 people with ALS from over 70 centers located in the United States, Europe, and Canada. You can learn more information about the trial here.

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