DISCOVERING A CURE

THE ALS FORUM

ALS Forum e-Newsletter Volume 73 **October 25, 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:

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:

October 31 - November 1, 2012: New York City, NY: Life Science Summit 2012

November 1, 2012: Boston, MA: 8th Annual ALS TDI Leadership Summit

November 9, 2012: London, UK: 12th Annual King's College Neuromuscular Disease Symposium

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

Research News

Microglial Progranulin Douses Neural Inflammation

In 2006, researchers found that null mutations in progranulin were associated with certain cases of hereditary FTD. Since then, researchers have been investigating the link between low levels of progranulin and the neuronal death observed in people with FTD. Now, researchers may have a better understanding of this link. In a paper published online on October 8 in the *Journal of Clinical Investigation*, researchers found that decreased levels of a certain type of progranulin - progranulin produced by microglia - are responsible for neuronal death. Using progranulin-knockout mice and wild-type mice, the researchers tested dopaminergic neuron survival when treated with MPTP, a toxin that causes inflammatory stress. After treatment with MPTP, wild-type mice lost 37% of their dopaminergic neurons in the substantia nigra, while the progranulin-deficient mice lost 66% of these neurons. The researchers repeated the same experiment using microglia-specific progranulin knockout mice. The results were surprising. "Getting rid of progranulin in the microglial compartment was sufficient to produce the same effect as the total body knockout," said senior author Robert Farese Jr. of the Gladstone Institutes, San Francisco, California. As it turns out, the researchers found that the progranulin-deficient microglia secreted more pro-inflammatory cytokines that seemed to "promote the death of wild-type neurons." The researchers are now looking for compounds that increase progranulin levels, and may prevent neuronal death.

Mutations in TREM2 Cause Frontotemporal Dementia

In a study published online on October 8 in *Archives of Neurology*, researchers announced the identification of a new genetic risk factor for FTD, known as TREM2. Mutations in TREM2 (triggering receptor expressed on myeloid cells 2) were originally linked to Nasu-Hakola disease, which causes changes in bone structure and dementia. Now, researchers have identified that TREM2 mutations can also cause FTD. In order to identify the new FTD risk factor, the researchers completed whole-exome sequencing on blood samples from 44 different Turkish

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 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

Funding News:

MND Association is Calling for Research Project Grants. Summary Applications are due November 2

Massachusetts Neuroscience Consortium Calls for Proposals. Proposal Deadline:

people with FTD. They found that three of the 44 people had mutations in TREM2, one with a nonsense mutation, and two with amino acid mutations. The three individuals harboring the TREM2 mutations all had early onset FTD, but did not have any bone abnormalities. Although not much is known about TREM2, it is thought to potentially control the microglial immune response. It seems that TREM2 mutations may be linked to an increase in the inflammatory response, potentially echoing the link between progranulin-deficiency and inflammation. Although we still need to learn more, it seems that inflammation might be a common pathway in FTD.

Neural Progenitors Talk Back to Microglia

Transplanted neural stem cells don't appear to create many new neurons, yet they have yielded promising results, especially in the treatment of models of spinal cord injury and MS. What is happening at the molecular level if new neurons aren't being generated? We now may have an answer. In a *Nature Neuroscience* article released online on October 21, researchers showed that neural progenitor cells (NPCs) signal to microglia, which respond by activating and proliferating. The researchers profiled the media from mouse NPCs to identify any potential secreted signaling molecules. They found that the NPCs secreted a variety of signaling molecules, and one of these was vascular endothelial growth factor (VEGF). VEGF was of particular interest to the researchers because it had previously been shown to stimulate microglial proliferation. The authors confirmed that VEGF was indeed a major component of the NPC-mediated proliferation of the microglia. The authors believe that NPCs play an important role in activating the microglial protective immune response. Regarding neuronal stem cell therapies, it may not be the neuronal stem cells themselves that are responsible for beneficial effects of the therapy, but rather the stimulated immune response of the microglia. Yet more support for neuroinflammatory targets for ALS therapy development!

Studying Neurodegenerative Diseases Using a "Brain on a Chip"

Scientists at the Draper Laboratory campus in Tampa, Florida, and at the University of South Florida have developed a "brain-on-a-chip." The study, led by Anil Achyuta, a scientist at Draper, commented that "our device is designed to be the most biologically realistic model of brain tissue developed in the lab thus far." The "brain-on-a-chip" was created by bringing together cultured neurons, microglia, astrocytes, and vascular cells that were isolated from vascular and neural layers in rats. These cells and vascular layers were combined on a chip in such a way that allowed the cells to communicate across a microporous membrane. The team was even able to connect this miniature brain to a microfluidic pump that circulated stimulants and nutrients through the vascular channels. This advance was driven by bringing together normally unrelated research areas, including tissue engineering, microfluidics, and neuroscience. The researchers are hoping to one day use the "brain-on-a-chip" to study neurodegenerative diseases and stroke. The results of this study were published September 26 online in the journal, *Lab on a Chip*.

Drug News

November 16, 2012

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

MNDA PhD Studentship

Wellcome Trust Seeding Drug Discovery. Proposal Deadline: November 9, 2012

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NeuroPhage Pharmaceuticals Has Positive Results With Neurodegenerative Disease Therapy

Many neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and ALS, are characterized by aggregates of proteins. Many companies have tried to target the disassembly of these protein aggregates; however, few have made progress using this approach, until now. Cambridge, MA-based NeuroPhage Pharmaceuticals just reported positive results in a pre-clinical study using their anti-protein aggregate therapy, NPT001. Neurophage tested NPT001 in a pre-clinical model of Parkinson's disease. In this model, NPT001, was able to clear the alpha-synuclein protein aggregates, as well as restore normal function to neurons. The studies were performed in the laboratory of Dr. Eliezer Masliah, a professor at the University of California San Diego. NeuroPhage is one of the newest teams competing for the $1M ALS Treatment Prize,
and hopefully, they will reproduce this positive result with NPT001 in ALS!

FDA Review Panel Extends The Review Period of Biogen Idec's MS Drug

The FDA just announced that they are extending the review period of Biogen Idec's MS drug, BG-12, by three months. The FDA extended three months past the original deadline of December 28. Biogen said that this three month extension is normal and that the FDA did not request any additional studies. If approved, BG-12 will be an alternative to Novartis' MS drug, Gilenya. Later this year, the ALS Therapy Development Institute plans to launch a Phase II clinical trial testing the safety and tolerability of Gilenya in people with ALS. Perhaps Biogen will consider testing BG-12 in ALS?

Missing Data From Clinical Trials May Skew Trial Results

Missing clinical trial data is a big problem that has not been discussed until recently. In cases where there is missing clinical trial data, statisticians do their best to control for this missing data. However, even with statisticians controlling for these missing data points, some assumptions need to be made about the outcome of the patient, which can introduce inaccuracies in the data and influence the credibility of the trial results. The National Research Council recently assembled a panel of experts to discuss ways to address and prevent missing clinical trial data. The panel identified a number of ways to help prevent missing data, including encouraging participants that have stopped taking a treatment to still participate in follow up visits, and shortening the follow-up period after the trial has ended. It's clear that trial participation is critical for the success and accuracy of the trial, and ultimately for the safety of people who might be taking the drug in the future!

Researchers Can Win Up To $400,000 Worth of Research Services In The Rare Disease Science Challenge

The Rare Genomics Institute and Assay Depot are combining forces to sponsor the Rare Disease Challenge: Be HEARD (Helping Empower and Accelerate Research Discoveries), which aims to accelerate research discoveries for rare diseases. The challenge offers a monetary prize of $10,000 and up to $400,000 in donated research services. The competition officially opened October 15 and the deadline for

submissions is December 15, 2012. To apply, researchers are asked to submit a proposal for their rare disease of interest (ALS is on the list of rare diseases), and specify any of the donated services that they would like to apply for (i.e. antibodies from Antibodies Incorporated). The finalists for the $10,000 prize (and their selected donated research services) will be announced on World Rare Disease Day, February 28, 2013. However, the winner will be selected by Facebook voters. The finalist with the most Facebook votes will win the $10,000 and their selected research services of choice. Find out more about the challenge here. Looks like Prize4Life has started a trend - using prizes to incentivize biomedical research!

The ALS Forum was developed by Prize4Life, Inc.
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www.prize4life.org

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