DISCOVERING A CURE

THE ALS FORUM

ALS Forum e-Newsletter Volume 72 **October 11, 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:

NINDS Fibroblast Repository

Upcoming Registration Deadline:

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

Upcoming Meetings:

October 13-17, 2012: New Orleans, LA: Society for Neuroscience Annual Meeting 2012

October 24, 2012: New York, NY: Michael J. Fox Foundation Annual PD Therapeutics Conference

October 24-26, 2012: Clearwater Beach, FL: 11th Annual NEALS Meeting

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

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

Research News

Compound to the Rescue in Parkinson's, ALS Models

Researchers at the University of Iowa and the University of Texas Southwestern Medical Center in Dallas have identified a new class of compounds, called P7C3, that protect neurons from cell death. They tested this class of compounds in animal models of both Parkinson's disease and ALS, and the results of these studies were published online on October 1 in two back-to-back articles in the *Proceedings of the National Academy of Sciences*. The researchers identified that one of these compounds, P7C3A20, prevented motor neuron death in the spinal cord of SOD1 mice. Additionally, the mice that were treated with this compound could hold on to a rotarod for longer periods of time and had a more normal walking gait, as compared to untreated animals. Although these findings are encouraging, P7C3A20 did not extend the life of these mice. The authors are currently looking for ways to further improve the molecule for increased bioavailability and reduced toxicity.

Friends of FUS: Protein's Many RNA Buddies Point to Disease

In a study published online on September 30 in *Nature Neuroscience*, researchers in the Department of Cellular and Molecular Medicine at the University of California, San Diego School of Medicine proposed a new mechanism for how ALS-linked proteins FUS and TDP-43 may contribute to disease progression. Both FUS and TDP-43 are RNA binding proteins and are normally localized to the nucleus where they bind and regulate RNA levels. Using previously published RNA-binding data for TDP-43, as well as new data for FUS' RNA targets, the researchers found that FUS and TDP-43 primarily bind and regulate different RNAs; however, there are a subset of these RNAs that are bound by both proteins. FUS and TDP-43 are responsible for regulating the expression of 112 of the same RNAs, and 45 of these RNAs require both FUS and TDP-43 for expression. Of these 45 genes, the researchers found that most of them had very long introns (nearly 160 kilobases), and many were important for regulating neuronal function. The researchers found that in cases where FUS or TDP-43 function is compromised, such as in ALS, the levels of these critical RNAs are reduced, as well as the levels of their corresponding protein products. Although they are not sure of the exact mechanism, the researchers

Summit

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

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 Other Neurodegenerative Diseases

Funding News:

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

Massachusetts Neuroscience Consortium Calls for Proposals. Proposal Deadline: 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

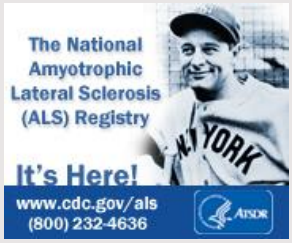
suggest that these decreased protein levels may contribute to neuronal death and disease pathology in ALS.

TDP-43 Controls Blood Vessels in Fish, Is Phosphorylated in Worms
At the 8th International Conference on Frontotemporal Dementias, held September 5-7 in Manchester, United Kingdom, researchers discussed the role of TDP-43 in both FTD and ALS. TDP-43 is critical for development, which makes it difficult to study its role in mammals. As an alternative, many groups have turned to model systems, such as *C. elegans* and zebrafish, to study the role of TDP-43. Nicki Liachko of the Veterans Affairs Puget Sound Healthcare System in Seattle, Washington, overexpressed a mutant version of TDP-43 in the nematode. Liachko previously showed that phosphorylation of mutant TDP-43 increased toxicity in the worm. Using short interfering RNAs, Liachko screened for kinases that when knocked down rescued the movement defect in the TDP-43 worms. She identified 12 kinases that rescued the phenotype, and found that one of these, CDC7, was responsible for directly regulating TDP-43 phosphorylation. Using zebrafish, Bettina Schmid and Christian Haass of the German Center for Neurodegenerative Diseases (DZNE) in Munich, Germany, showed the effects of fully knocking out TDP-43. In the fish, the researchers deleted the two homologues of the TDP-43 gene: TARDBP and the "TARDBP-like" (TARDBPl) gene. Although the TARDBP and TARDBPl embryos die eight days after fertilization, the embryos are fertilized outside of the mother and are translucent, allowing for the study of key developmental processes - including neuron and muscle formation. The researchers found that when they knocked out both TDP-43 homologues in the fish, the embryos had shorter neuronal axons, problems with blood vessel formation, and muscle degeneration. These model systems have already begun to provide critical advances in our understanding of the function of complex RNA binding proteins.

Can Epigenetics Explain Variable Progranulin Expression?
The role of epigenetics in FTLD was another hot topic discussed at the 8th International Conference on Frontotemporal Dementias. Julia Strathmann, of the German Center for Neurodegenerative Diseases in Munich, proposed an interesting model for how epigenetic regulation of the FTLD-linked gene, progranulin, may contribute to FTLD. Strathmann found that methylation of the progranulin promotor decreases progranulin expression. Strathmann, in collaboration with Christine Van Broeckhoven of the University of Antwerp, Belgium, measured the levels of progranulin promoter methylation in 10 people with FTLD and 5 controls. They observed a "small but significant" increase in methylation of the progranulin promoter in those with FTLD. Although these results are encouraging, the researchers suggest that epigenetic regulation of progranulin is most likely "not the sole cause of why these people developed FTLD." The progranulin story grows ever more complicated!

Drug News

Revalesio Attempts to Help One of Their Own With Potential ALS Therapy
Scientist Tony Wood was instrumental in developing oxygen-enriched saline to speed the growth of hydroponic plants in developing countries.



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In 2007, researchers at Stanford University showed that the oxygen-enriched saline had anti-inflammatory properties, and might also benefit people with neuro-inflammatory diseases, including multiple sclerosis (MS), Parkinson's, and Alzheimer's. Currently, plans are underway for a phase II clinical trial of Revalesio Corp.'s oxygen-enriched saline (RNS60) for the treatment of MS. In a strange turn of events, Wood was recently diagnosed with a rapidly-progressing form of ALS and requested to treat himself with the oxygen-enriched saline that he developed. The FDA approved Wood's request, and now he is in a single-patient trial at the UT Southwestern Medical Center testing RNS60 for the treatment of ALS.

Coyote Pharmaceuticals, Inc. Targets ALS and Alzheimer's with New Potential Therapy

Coyote Pharmaceuticals, Inc., has just announced that it is moving its lead compound, CNS-102, forward in clinical trials for ALS and Alzheimer's disease. Coyote plans to begin the first phase of the clinical program in 2013, by treating people with ALS. In pre-clinical studies, CNS-102 showed promising results in animal models of neurodegenerative disease, rescuing neurons from death. Coyote hopes that these initial results will yield promising clinical trial results in humans. Coyote Pharmaceuticals was founded in 2009 and has a focus on neurodegenerative and orphan diseases.

AstraZeneca Goes Virtual for Neuroscience Research

This has not been the best year for drug companies developing therapies for neurodegenerative diseases. For example, this year alone there were the failed clinical trials of potential Alzheimer's therapeutics, bapineuzumab and solanezumab, as well as the failed trial of potential ALS therapeutic, Ceftriaxone. The message is loud and clear -- drug development for neurodegenerative diseases is difficult, and there are clear challenges preventing advancement. Big pharma AstraZeneca has announced it is taking a virtual approach to neuro R&D. AstraZeneca has created the 'Virtual' Neuroscience Innovative Medicines Unit (iMed). The iMed team, which consists of about 40 scientists, uses several different programs to search external resources in order to identify new developments in neuroscience and find contract research organizations that will perform pre-clinical studies. AstraZeneca hopes to minimize costs and maximize the potential for lead drugs by using iMed to manage their pipeline and relationships with their external research partners. To learn more about iMed, read an interview with Menelas Pangalos, AstraZeneca's Executive Vice President for Innovative Medicines, here.

President's Council of Advisors on Science and Technology Recommends Faster Drug Approval Process

The President's Council of Advisors on Science and Technology (PCAST) wants to double the output of "innovative new medicines that meet critical public health needs over the next 10 to 15 years, while continuing to increase drug safety." PCAST suggested that one approach to achieving this goal would be to use the FDA's Accelerated Approval Program for certain candidate drugs. These candidate drugs include drugs that either meet an unmet medical need or treat serious diseases (ALS checks both boxes). This approach could have the potential to benefit people with ALS. However, we need to proceed

carefully. Although this approach has the potential to increase the number of available drugs, the increased speed of the approval process may potentially compromise drug safety. Read more about the PCAST report here.

An Update on Neuralstem's Phase I Trial

Dr. Eva Feldman, principle investigator of the Neuralstem Phase I clinical trial, presented an update about the trial results on October 8 at the American Neurological Association annual meeting in Boston, MA. Neuralstem's Phase I trial was designed to test the safety of injecting stem cells directly into the spinal cord for the treatment of ALS. So far, 15 people have been treated and three of the 15 have received two treatments. The Phase I part of the trial is set to conclude six months after the last patient is treated (August, 2012). Dr. Feldman said that "this has been a very successful trial so far. We have demonstrated that intraspinal transplantation is feasible and well-tolerated. Although this phase of the trial was not powered to demonstrate efficacy, we appear to have interrupted the progression of the disease in one subgroup of patients. We are anxious to move to future trial phases to examine therapeutic efficacy."

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