THE ALS FORUM

Discovering a Common Goal, Discovering a Cure

ALS Forum e-Newsletter Volume 96 **November 19, 2013**

Be sure to check out our newly redesigned ALS Forum website. We hope you like what you see and we would love to know what you think. Please email jgoodman@prize4life.org with any feedback you may have.

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:

Visit the PRO-ACT Database at www.ALSDatabase.org

NEALS Biofluid Repository Available to Researchers

NINDS Fibroblast Repository

VABBB Tissue Request Information Site

Funding News:

The National Center for Advancing Translational Sciences (NCATS) is accepting applications for the National Institutes of Health's Bridging Interventional Development Gaps (BrIDGs) program. The application deadline is January 10, 2014.

Young Investigator Scholarships are available for the ADDF's 8th Annual Drug Discovery for Neurodegeneration Conference. Click here to learn more and apply.

Upcoming Meetings:

December 4-5, 2013:

Research News

Sense, Antisense: C9ORF72 Makes Both Forms of RNA, Peptides

Two years after the initial discovery of the hexanucleotide repeat expansion in C9ORF72, researchers are working to figure out if the mutation in C9ORF72 causes amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) through one or more of three potential mechanisms: 1) a loss of function haploinsufficiency mechanism that reduces transcription, 2) a toxic gain of function through the sequestration of important RNA binding proteins into RNA foci, or 3) a separate gain of toxic mechanism involving dipeptide repeat (DPR) proteins generated via repeat-associated non-ATG (RAN) translation of C9ORF72. Now to add to the already complex C9ORF72 story, four different research groups have shown that C9ORF72 is transcribed and translated in both the sense (forward) and antisense (backward) directions. This finding has important implications for designing targeted antisense oligonucleotide therapies (for more information, read the following *Neuron* and *Science Translational Medicine* stories) and for understanding which, if any, DPR proteins might be toxic. Click here to read the details of these new C9ORF72 findings.

In Second Study, Antisense Oligos Bust RNA Aggregates

In our last issue of the ALS Forum e-Newsletter we highlighted the exciting discovery that RNA transcribed from the hexanucleotide repeat in C9ORF72 might sequester a number of important RNA-binding proteins into RNA foci, preventing these RNA-binding proteins from performing their normal cellular functions. Antisense oligonucleotides (ASOs) against C9ORF72 significantly decreased the RNA foci and were protective in cell death assays. Now a team from the Cedars-Sinai Medical Center in Los Angeles, California, led by Dr. Robert Baloh, has shown similar results in a separate study, the findings of which were published in *Science Translational Medicine* on October 23. Dr. Baloh, along with first author Dr. Dhruv Sareen and colleagues, transformed skin fibroblasts isolated from ALS patients harboring C9ORF72 hexanucleotide repeats into motor neurons. The team observed changes in gene expression and identified that C9ORF72 RNA foci sequestered important RNA binding proteins in these motor neurons. Motor neurons

Milan, Italy: 21st Annual Meeting of the International Alliance of ALS/MND Associations

December 6-8, 2013: Milan, Italy: 24th International Symposium on ALS/MND

February 2-4, 2014: Miami, FL: ADDF's 8th Annual Drug Discovery for Neurodegeneration Conference

April 23-24, 2014: Boston, MA: The Neurotech Investing & Partnering Conference
2014 Advances in Drugs, Devices and Diagnostics for the Brain and Nervous System

April 23-25, 2014: Boston, MA: Stem Cell Summit 2014

April 26 - May 3, 2014: Philadelphia, PA: American Academy of Neurology 2014 Annual Meeting

June 14-15, 2014: New London, NH: Gordon Research Seminar: Barriers of the CNS, The Neurovascular Unit: Partners for Life

June 15-20, 2014: New London, NH: Gordon Research Conference:Barriers of the CNS. Expanding the Understanding of CNS Barriers in Health and Disease

June 22-27, 2014: Waterville Valley, NH: Cell Biology of the Neuron: Mechanistic Insight into Neuronal Development, Plasticity, Disease and Regeneration

treated with ASOs targeted against C9ORF72 no longer had RNA foci and gene expression patterns were restored to normal. These findings are further evidence in support of a "gain-of-toxicity" mechanism for C9ORF72 in ALS and FTD. Click here to read the full story.

Brain Stimulation Turns Paralyzed Rats into Walkers, Swimmers - Potential Application in ALS?

Research out of the Swiss Federal Institute of Technology in Zurich, Switzerland, and published online in *Science Translational Medicine* on October 23, suggests that deep brain stimulation (DBS) therapy might one day be a therapeutic option for people with spinal cord injuries, and potentially even people with amyotrophic lateral sclerosis (ALS). The researchers tested whether stimulating a region in the brainstem that controls motion, the mesencephalic locomotor region (MLR), using DBS would stimulate remaining intact nerve fibers to restore partial or complete movement following spinal cord injury. To test their hypothesis, the researchers stimulated the MLR region in rats four weeks after the rats experienced a spinal cord injury that damaged 80% of their spinal cord. Following the spinal cord injury the rats had severely compromised hind-limb function. However, DBS treatment restored the rats' ability to walk and swim to nearly pre-injury levels. It is theoretically possible that DBS treatment could be an option to slow symptom progression in people living with ALS. However, additional research and testing will be needed before we will know for sure. Let's hope some of the funds from the new five-year, $70 million U.S. Defense Advanced Research Projects Agency (DARPA) initiative to support the study of DBS and other brain devices will go towards the study of DBS in ALS.

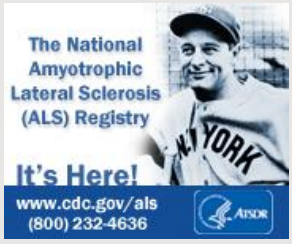
Numb Regulates Muscle Stem Cell Proliferation

In new research published online on November 4 in the *Proceedings of the National Academy of Sciences (PNAS)* a team of researchers from the University of Arizona, Arizona State University, and Stanford University identified a key protein involved in the "activation and proliferation" of adult muscle stem cells known as satellite cells. Led by senior authors Dr. Jeanne Wilson-Rawls, associate professor in the Arizona State University School of Life Sciences, and Dr. Thomas Rando, professor in the Department of Neurology and Neurological Sciences at the Stanford University School of Medicine, the researchers identified that Numb, a protein involved in regulating protein degradation, normally suppresses Myostatin. Cells lacking Numb have increased levels of Myostatin and fail to proliferate. Numb-mediated Myostatin suppression promotes satellite cell differentiation and expansion after injury. This finding has implications for identifying novel approaches to stimulate satellite cell "activation and proliferation" to enhance muscle regeneration in diseases such as ALS.

Drug News

Dr. David Lowe Joins Amarantus' Board of Directors

San Francisco, California based Amarantus Bioscience Holdings, Inc. just announced that Dr. David Lowe has joined their Board of Directors. Dr. Lowe is currently the President & CEO of a Switzerland-based neuroscience consulting firm called NeuroAssets, and brings over 35 years of expertise in the identification of investment opportunities in central nervous system (CNS) disorders and the development of therapeutics for CNS diseases. Amarantus' lead drug candidate is



Download your free copy:

SUPPORT THE ALS FORUM

Send the ALS Forum e-Newsletters to your colleagues!

Forward to a Friend

MANF, a highly potent growth factor that has anti-apoptotic activity. Amarantus is currently investing in the development of MANF for the treatment of Parkinson's Disease and Ischemic Heart Disease. However, now that Dr. Lowe is "on-board" we may see a "reprioritizing [of] the MANF pipeline." Dr. Lowe is especially interested in testing MANF in orphan indications. Multiple groups have shown the importance and potential therapeutic potential ofgrowth factors and anti-apoptotic therapeutics in ALS, let's hope that Dr. Lowe has ALS on his short list for orphan indications.

Teaching an Old Dog (Drug) New Tricks

AB Science just announced that their Phase II clinical trial of masitinib for the treatment of Amyotrophic Lateral Sclerosis (ALS) has been advanced into a Phase III trial. Masitinib (marketed as Kinavet in the US) is an inhibitor of the c-kit kinase and was originally developed for the treatment of tumors in dogs. Now, masitinib is being tested in humans for the treatment of multiple indications, including in cancer, inflammatory diseases, and in central nervous system disorders, such as ALS. Masitinib works by targeting and inhibiting "the survival, migration and activity of mast cells," which are involved in the inflammatory response and regulate the permeability of the blood-brain barrier. Neuroinflammation is a hallmark of ALS, and potentially reducing neuroinflammation viamasitinib might provide some therapeutic benefit in ALS. The original Phase II study in ALS involved the recruitment of 45 patients, and the Phase III will expand the recruitment to 210 patients. The Phase III will evaluate the safety and efficacy of masitinib for the treatment of ALS and the results are expected in 2015.

Talk of Innovation, Breakthroughs at NEALS 2013

At the annual Northeast ALS (NEALS) Consortium meeting in October, the discussions focused on some of the latest ALS treatments currently (or almost) in trials, including devices and drugs from Neuralstem's stem cell therapy to a diaphragm pacing system that aims to help ALS patients keep breathing for longer. Click here to read about all of the exciting developments covered at the NEALS meeting.

Partnership Could be a Model for Orphan Disease "Adoption"

Rare and orphan disease treatments could be fostered by a newly formed collaboration between Fidelity Biosciences, a subsidiary of Fidelity Investments, and Regenx Biosciences. Together, the companies have formed Dimension Therapeutics, a gene therapy company focused on "developing novel treatments for rare diseases." With Series A financing and rights to a portfolio of over 100 patents and patent applications, Dimension Therapeutics will focus on innovations in gene therapy, "a fundamental method of disease intervention, changing a patient's genetic code to treat genetic disease, and in some cases providing a potential lifelong benefit following a single treatment." With Dimension Therapeutics focusing on developing treatments for rare and orphan diseases, let's hope they are thinking about ALS as a potential indication of interest!

The ALS Forum was developed by Prize4Life, Inc.
P.O. Box 425783 Cambridge, MA 02142
www.prize4life.org

Identified content provided through a partnership with the Alzheimer Research Forum.