DISCOVERING A CURE

THE ALS FORUM

ALS Forum e-Newsletter Volume 79 **February 8, 2013**

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.

BREAKING NEWS: ALS Gains A New Champion!
Prize4Life applauds a brand new $25M ALS initiative launched yesterday by Daniel Doctoroff, CEO of Bloomberg L.P., New York City Mayor Michael R. Bloomberg, and David M. Rubenstein, Managing Director of the Carlyle Group. The $25 million will be used to fund a new initiative called Target ALS, which will bring together laboratories working on ALS, including some at Bloomberg's alma mater, John Hopkins, as well as at Columbia University. Both Doctoroff and Bloomberg are longtime supporters of Prize4Life. Read the press release here.

Resources:

NEW Resource Added!! Visit the PRO-ACT Database at www.ALSDatabase.org

NEALS Biofluid Repository Available to Researchers

NINDS Fibroblast Repository

Funding News:

The MDA announced that they have awarded 12 grants for the study of ALS, totaling $3.6 million. Want to know more about the research that was funded? Watch the MDA's Grants at a Glance slideshow here.

2013 AAN Foundation ALS-Richard Olney, MD Clinician Scientist

Research News

C9ORF72 Function: Is the ALS Protein a Membrane Traffic Cop?
C9ORF72 may one day have a new and easier to pronounce name, DENNL72, also known as DENN-like 72! Two recent bioinformatics studies both classified C9ORF72 as a member of the DENN (Differentially Expressed in Normal and Neoplasia) protein family. DENN proteins are GDP-GTP exchange factors that function to activate Rab GTPases. These proteins regulate events that happen at the membrane, including membrane fusion and vesicle budding. Although the field is still actively debating whether the disease mechanism for the hexanucleotide repeats within C9ORF72 is gain of function (RNA-mediated) or loss of function, the suggestion that the protein has potential roles in membrane trafficking echoes the emerging role of vesicular trafficking defects in neurodegenerative diseases. Read more about these two bioinformatics studies here.

Low Calcium Jams Neuron-Muscle Communication in ALS Fish
In a study published in the January 23 issue of the *Journal of Neuroscience*, researchers proposed that defects in calcium entry into nerves following an action potential may lead to one of the earliest events in ALS, denervation of muscle. Using zebrafish expressing a mutant version of TDP-43, researchers in Dr. Pierre Drapeau's laboratory at the University of Montreal, Canada found that there was "poor communication" between motor neurons and muscles. First author Dr. Gary Armstrong attributed this "poor communication" to a potential defect in calcium signaling during action potentials. Dr. Armstrong gave these fish two different calcium channel agonists and observed that

Development Three Year Award

Upcoming Meetings:

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

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

March 6-7, 2013: Washington, DC: The Traumatic Brain Injury Conference

March 16-23, 2013: San Diego, CA: 65th Annual American Academy of Neurology Meeting

April 9-11, 2013: Washington, DC: 3rd Annual World Orphan Drug Congress

April 14-19, 2013: Les Diablerets, Switzerland: Oxidative Stress & Disease, Program: The Metabolic-Inflammatory Axis in Brain Aging and Alzheimer's Disease

April 21-24, 2013: Washington, DC: MDA Scientific Conference: Therapy Development for Neuromuscular Diseases: Translating Hope Into Promise

Upcoming Webinar:

Register for the ALS TDI Gladstone Institutes Collaboration Webinar on February 26, 2013 at 4:00 PM EST

these compounds rescued the fish's swimming defect, as well as restored normal neuron-muscle signaling. Read more about the implications this work has for the role of calcium channels in ALS here.

Astrocytes Turn Bad In ALS

A new set of studies led by Dr. Hemali Phatanani in Dr. Tom Maniatis' laboratory at Columbia University Medical Center, New York in collaboration with the HudsonAlpha Institute for Biotechnology in Huntsville, Alabama, and published in *The Proceedings of the National Academy of Sciences USA*, provide the field with a better understanding of the dynamic and complex relationship between motor neurons and astrocytes in ALS. In normal healthy individuals, astrocytes secrete factors to support motor neurons. However, in ALS this supporting role "is profoundly disrupted." The researchers involved in the study performed a series of co-culture experiments, combining both normal and diseased motor neurons and astrocytes. Afterwards, they separated the motor neurons from the astrocytes, and looked at the changes in gene expression in each cell type. The results of these RNA profiling experiments were surprising - many pathways that are associated with motor neuron degeneration were upregulated in healthy motor neurons co-cultured with sick astrocytes, suggesting that the diseased astrocytes contributed to the activation of these pathways. Read more about these interesting findings here.

New Study Suggests Neural Reprogramming Could Lead to Potential Treatments for ALS

Dr. Paola Arlotta, an associate professor in the Department of Stem Cell and Regenerative Biology at Harvard, and her postdoc, Dr. Caroline Rouaux, recently discovered that it is possible to reprogram callosal projection neurons into neurons phenotypically similar to corticospinal motor neurons. Corticospinal motor neurons are one of the two types of neurons that progressively degenerate in people with ALS. Drs. Arlotta and Rouaux reprogrammed these neurons in the brains of live mice using the Fezf2 transcription factor. This work was recently published online in *Nature Cell Biology*. Read more about this intriguing approach here.

Is There a Link Between Cytoskeletal Proteins, Mitochondria Length and Neurodegenerative Diseases?

A recent discovery out of Dr. Henry Higgs' laboratory at Dartmouth's Geisel School of Medicine, and reported in the January 25th issue of *Science*, sheds light on the dynamics of mitochondrial fission and fusion. INF2 (Inverted Formin 2) normally regulates actin polymerization, so the researchers were surprised to find that INF2 could also influence mitochondrial length. Silencing INF2 using small interfering RNAs led to an increase in the average length of mitochondria. Furthermore, when the researchers overexpressed a mutant version of INF2, the mitochondria decreased in size. Mutations in INF2 have been associated with Charcot-Marie-Tooth Disease (CMTD), and this research provides additional insights into the role that cytoskeletal and mitochondrial dynamics may have in CMTD, as well as in other neurodegenerative diseases. As Dr. Higgs said, "before this discovery, no one thought the cytoskeleton played a role in mitochondrial division." Read more about these striking findings here.

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Drug News

BrainStorm Cell Therapeutics Inc. Appoints New CEO as Company's Stem Cell Technology Advances Closer to Commercialization
BrainStorm Cell Therapeutics has had a number of recent exciting announcements, including the news that their Phase I/II clinical trial studying stem cell technology for the treatment of ALS is being fast tracked to a Phase IIa. On the heels of these developments, BrainStorm Cell Therapeutics announced they have appointed well known biotech executive Alon Natanson as their new Chief Executive Officer. Before joining BrainStorm, Natanson served as the Director of Marketing and Finance for Teva Pharmaceuticals Industries Ltd. in the Copaxone division where he helped to commercialize patented therapeutics for multiple sclerosis. Natanson replaces Dr. Adrian Harel who held the position since February 2011 and is transitioning to a scientific role within BrainStorm.

Collaborations Are The Key To Finding New Therapies
Todd B. Sherer, CEO of The Michael J. Fox Foundation, recently wrote an opinion article for *Nature Medicine* about the importance of collaboration for the advancement of translational research -- and the pharmaceutical companies are beginning to take this advice to heart. There has recently been a surge in the number of collaborations between pharmaceutical companies and academic labs. For example, Biogen Idec recently committed $10 million to support the formation of an academic research consortium with the long-term goal of identifying potential drugs to treat ALS. Now AstraZeneca (AZ) is also jumping on the industry-academia collaboration bandwagon with the announcement of two new collaborations. AZ has entered into a formal collaboration with The Lead Discovery Center (LDC) in Dortmund, Germany. This collaboration will be focused on the identification of new treatments for diseases "with high unmet medical need." AZ has agreed to contribute 250,000 compounds to LDC, which will screen the compounds against "high-potential targets" in a variety of disease areas including cancer, neuroscience, and inflammation. These targets have been identified by researchers at LDC's partner academic institutes including, most notably, the Max Planck Society. In addition to the AZ-LDC deal, AZ recently licensed the rights to compounds that are developed at the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD). Dr. Mike Poole, vice president of the AZ Neuroscience Innovative Medicines Unit, said "AstraZeneca is interested in pursuing research collaborations across all areas of neuroscience research where the science is compelling." Let's hope that some of the findings that come from these collaborations yield advances and therapies for ALS!

Changing How Potential ALS Drugs Get to ALS Patients
There is a new ALS non-profit in town, the ALS Emergency Treatment Fund (ALSETF), which is led by managing director, Jess Rabourn, and research director and PALS, Eric Valor. ALSETF's goal is to provide post-Phase II ALS therapies to ALS patients who might not qualify for clinical trials. Over 50% of people with ALS are not eligible to participate in clinical trials because their disease has progressed past the minimum inclusion criteria for the trial. ALSETF's goal is to help these ALS patients gain access to therapies that are in the later stages of the

clinical trial process by partnering with the government and industry under the Expanded Access Program (EAP). EAP allows people with life threatening conditions who have no other treatment opinions to be administered a therapy that has not yet been approved by the FDA. Rabourn said "We want to find ways of facilitating near-term access for patients. For a helluva lot of patients, there just is no access." Visit ALSETF's website to read more about their mission.

Tamoxifen Showed Promising Results in a Preclinical Duchenne Muscular Dystrophy Study

Tamoxifen was developed by AstraZeneca for the treatment of breast cancer. However, new research suggests that it might have application as a potential therapy for Duchenne muscular dystrophy. Researchers from the Geneva-Lausanne School of Pharmaceutical Sciences of the University of Geneva and University of Lausanne administered tamoxifen to a mouse model of Duchenne muscular dystrophy (DMD) for a little longer than a year. The study's lead author, Dr. Olivier M. Dorchies, said that treatment with tamoxifen "caused remarkable improvements of muscle force and of diaphragm and cardiac structure." The results of this study will be published in the February 2013 issue of the *American Journal of Pathology*. Tamoxifen is currently being tested as a potential therapy for ALS in an ongoing Phase II clinical trial. Learn more about this clinical trial here.

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