THE ALS FORUM

Discovering a Common Goal, Discovering a Cure

ALS Forum e-Newsletter Volume 110 **August 22, 2014**

This has been an exciting month for ALS awareness, with the Ice Bucket Challenge bringing the disease to the public eye and raising millions of dollars for ALS. This outpour of support will boost ALS research funding and drive breakthroughs in understanding and treating the disease. Prize4Life would like to extend thanks to all its donors for their generosity and for supporting ALS research. If you would like to support the ALS Forum, please donate here.

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:

The ALSGene tool: www.ALSGene.org

The PRO-ACT Database: www.ALSDatabase.org

NEALS Biofluid Repository Available to Researchers

NINDS Fibroblast Repository

VABBB Tissue Request Information Site

Funding Opportunities:

Blueprint Neurotherapeutics Network (BPN): SBIR Small Molecule Drug Discovery and Development for Disorders of the Nervous System (U44). Application due date: October 21, 2014.

Harvard NeuroDiscovery Center, 2014 NeuroBehavior LaboratoryPilot Project Research Program. Applications due September 15, 2014.

NIH Transformative Research Awards (RO1).Letter of Intent due

Research News

New ALS Therapeutic Target Validated in Stem Cells and Mouse Model

Motor neurons derived from human stem cells have been adopted as a powerful tool for mechanistic studies in ALS, however, their utility as a predictive model for ALS translational research has yet to be validated. Kevin Eggan's laboratory at the Harvard Stem Cell Institute in Cambridge, MA has taken major steps in that direction this year. Earlier this year, Eggan's group published work that is providing the foundation for an ALS clinical trial of an epilepsy drug, retigabine (see April 2014 news story). A second study, published August 6 in *Science Translational Medicine* has validated another potential therapeutic target, the microglial prostanoid receptor DP1. In cells culture, pre-treatment of glial cells from mutant SOD1 (mSOD1) mice with a DP1 inhibitor protected motor neurons derived from human stem cells from the toxicity of mSOD1 glia. Importantly, these findings were corroborated in an animal model of ALS, where genetic ablation of the receptor extended lifespan and increased motor neuron survival. Since two drug companies already have a development program surrounding the DP1 receptor for a condition called niacin induced flushing, there is potential for testing existing drugs against this target in ALS patients. Click here to read more about this exciting research.

Computational Modeling Sheds Light on Motor Neuron Vulnerability in ALS

In a first-of-its-kind study, published July 31 in *Neuron* online, researchers have used computational modeling of neurons to elucidate underlying mechanisms of motor neuron degeneration in ALS. The collaborative work between Gwendal Le Masson from University of Bordeaux, France and Serge Przedborski and Larry Abbot at Columbia University in New York, modeled how neuronal ATP shortage impairs the function of ATP-dependent sodium/potassium transporters and disrupts calcium homeostasis. The ionic instability leads to abnormal neuronal activity and further energy shortage, which are thought to sensitize motor neurons to degeneration. The computational model can explain the greater vulnerability of fast-fatiguable motor neurons to

September 1, 2014.

Frick Foundation ALS Research Grants.Applications due September 30, 2014.

Upcoming Meetings:

August 2014

August 10-15, 2014: Newport, RI: Gordon Research Conference: Neural Development, From Stem Cells to Circuits

September 2014

September 8-10, 2014: Philadelphia, PA: 3rd International Conference and Exhibition on Neurology & Therapeutics

September 17-20, 2014: Minneapolis, MN: 1st ALS Research Group Meeting

October 2014

October 12-14, 2014: Baltimore, MD: American Neurological Association's 2014 Annual Meeting

October 23-25, 2014: Vancouver, Canada: The 9th International Conference on Frontotemporal Dementias

November 2014

November 13-14, 2014: Arlington, VA: 24th Neuropharmacology Conference

November 13-14, 2014: Arlington, VA: 9th Brain Research Conference Neuroprotection: Basic mechanisms and translational potential

November 15-19, 2014: Washington, DC: The Annual Society for Neuroscience Annual

degeneration, as well as how in ALS energy imbalance at the axon terminal detrimentally affects the whole cell. Next, predictions arising from the simulations will be tested experimentally in cell culture. Click here to read more about how computational models can improve our understanding of motor neuron degeneration in ALS.

DipeptideToxicity Causes Degeneration in C9ORF72 ALS

Since the discovery of an intronic hexanucleotide repeat expansion in the C9ORF72 gene that is the most common known form of inherited ALS (see Sept 2011 news story), extensive research efforts have focused on how the expansion causes motor neuron degeneration. Several hypotheses exist (see Nov 2013 news story, and this newsletter), but the relative contribution of RNA vs. protein-based mechanisms is still being unraveled. New findings published August 7 in*Science Express* by Adrian Isaacs and colleagues at University College London, UK implicate dipeptides translated from C9ORF72 RNA via repeat-associated, non-ATG-initiated (RAN) translation (see also Feb 2013 news story). The researchers generated genetically modified fruit flies that expressed RNA only with no dipeptides, dipeptides alone, or both RNA and protein species. Surprisingly, the dipeptides were necessary to cause eye degeneration in the fly and eventually death. Although this paper does not rule out the contribution of RNA toxicity, it puts RAN translation "in the center of the field". Click here to read more.

Tailored Chaperones Reverse Toxicity of Mutant TDP-43 and FUS

TAR DNA-binding protein 43 (TDP-43) and fused in sarcoma (FUS) are two ALS-linked RNA binding proteins that form pathological cytoplasmic protein aggregates in ALS and whose mutant forms cause the disease. Researchers are employing a variety of strategies to destroy these aggregates or prevent their formation as ALS therapeutic approaches (see Nov 2011 news story). A new study published July 25 online in*Disease Models and Mechanisms* by Meredith Jackrel and James Shorter at the University of Pennsylvania in Philadelphia describes generation of optimized mutant variants of the yeast heat shock protein 104 (Hsp104), that are capable of selectively breaking down aggregates of TDP-43 and FUS and reducing their cellular toxicity. The team is now validating these results in animal models, and planning to develop variants of human chaperones with specificity for disease proteins. Click here to read more.

Drug and Device News

RNA-targeting Small Molecules Show Promise for C9ORF72 ALS and FTD

C9ORF72 hexanucleotide expansions are the most common known genetic cause of ALS and frontotemporal dementia (FTD), and account for up to 6% of sporadic ALS cases. The C9ORF72 mutation is hypothesized to cause neuronal toxicity through accumulation of RNA transcripts that inhibit critical RNA-processing proteins and promote repeat-associated non-ATG (RAN) translation of toxic dipeptides called c9RAN proteins (see Jan 2013 news story). A new study published online August 14 in *Neuron* provides a proof of principle demonstration that C9ORF72 RNA transcripts can be successfully targeted by small

Meeting

December 2014

December 3-5, 2014: San Antonio, TX: World Stem Cell Summit

December 3-6, 2014: Cold Spring Harbor, NY:Neurodegenerative Diseases: Biology & Therapeutics

December 5-6, 2014: Brussels, Belgium:International Conference on ALS/MND

December 17-20, 2014: Hotel Vila Galé Coimbra, Portugal: Mitochondria, Metabolism and Disease

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molecules. Leonard Petrucelli and colleagues at the Mayo Clinic in Jacksonville, Florida together with Matthew Disney and colleagues from the Scripps Research Institute in Jupiter, Florida identified asmall molecule that successfully targets the detrimental RNA species and reduces production of c9RAN proteins in a cellular model of C9ORF72 ALS. In addition, c9RAN proteins were detected in the cerebrospinal fluid of patients carrying C9ORF72 mutations, suggesting they can serve as a potential pharmacodynamic biomarker for drugs that target this cause of ALS and FTD. To read more, click here.

Lauren Sciences to Develop V-Smart Therapeutics for ALS

Lauren Sciences LLC, a New York based biotechnology company, announced the award of a grant from the ALS Association (ALSA) to its collaborating research team at Ben Gurion University (see April 2012 news story) to develop the V-Smart technology for therapeutic applications in ALS. The technology is based on blood-brain-barrier (BBB) permeable nanovesicles that can encapsulate a desired small molecule, peptide or protein and deliver it to the brain in a controlled manner. The ALSA funding is aimed at developing this platform to deliver a neurotrophic factor with therapeutic potential that would otherwise not cross the BBB to degenerating motor neurons in the brain. Preclinical studies using this approach in Parkinson's disease have demonstrated beneficial effects. Click here to read more.

Neuralstem to Begin Phase I Trial of Stem Cell Therapy for Spinal Cord Injury

Neuralstem, Inc. is launching a Phase I safety trial of its proprietary NSI-566 stem cell therapy for treating chronic spinal cord injury (cSCI). Neuralstem has already completed Phase I studies and initiated Phase II studies of NSI-566 for treating ALS, (see Sept 2013 news story). Now that the treatment has been shown to be safe in ALS patients, and preclinical studies have demonstrated locomotor improvements following treatment in spinal cord injured rats (see Sept 2012 news story), Neuralstem is ready to tackle this second therapeutic indication. The trial will recruit 8 patients and will be conducted at University of California, San Diego (UCSD), where much of the preclinical work was performed. Click here to read more.

Intel and MJFF Partnership Uses Smartwatches to Study Parkinson's Disease

Large datasets of information about patient symptoms, disease progression and drug effects can be a goldmine for understanding complex diseases. Aiming to better understand Parkinson's disease (PD) and its clinical progression, Intel and the Michael J. Fox Foundation (MJFF) have partnered to collect such data from thousands of PD patients via smartwatches. In order to make sense of all the data, Intel has developed analytics platforms to collect, store and manage the data. This is not the first 'big data' initiative from the MJFF - in 2010, they created the Parkinson's Progression Markers Initiative (PPMI), an observational clinical study to generate a comprehensive clinical database and biorepository for PD. These types of initiatives are also sprouting up in the ALS space and are facilitating new insights into the disease (see for example, the PRO-ACT database). Click here to read more.

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