ALS Research Forum e-Newsletter Vol. 160 **September 30, 2016**

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What would like to hear your opinion!

As we explore ways to improve the ALS Research Forum, we would like to hear your input on the **content and resources you would find most useful**. Please let us know by answering 5 brief questions here: https://www.surveymonkey.com/r/2016_ALSRF **Thank you** for your input!

Conference News

FTD Conference Highlights Biomarkers and Clinical Trials

At the International Conference on Frontotemporal Dementias, held August 31 to September 2 in Munich, Germany, researchers and clinicians convened to share advances in research and therapy development for frontotemporal lobar degeneration. Discussions revolved primarily around the molecular mechanisms underlying the different clinical syndromes that comprise FTD and developing reliable biomarkers to improve clinical trials. Read the full conference coverage brought to you through our partnership with Alzforum:

Part I: Frontotemporal Dementia: The Hard Work of Pushing Toward Trials

Part II: First Round of FTD Therapeutics Fell Short, But Many More Are Up and Running

Part III: Fluid NfL Shines, Tau PET Dims, in the Hunt for FTD Biomarkers

Research News

Loss of Optineurin Triggers Inflammation, Oligodendrocyte Death

The ALS-linked protein optineurin (OPTN) normally shields oligodendrocytes from a

form of programmed cell death called necrotopsis, and thus keeps axons healthy and tightly wrapped in insulating myelin, according to a study in the August 5 issue of Science. Mice lacking OPTN expression exhibited marked demyelination of motor axons and increased expression of the necrotopsis mediators RIPK1, RIPK3 and MLKL. In mouse models of SOD1-ALS, RIPK1 levels were also elevated, and treatment with a RIPK1 inhibitor delayed axon demyelination and onset of motor dysfunction. The authors propose a model whereby OPTN normally promotes RIPK1 degradation, but in the absence of functional OPTN, RIPK1 levels increase, triggering an inflammatory response, necroptosis of oligodendrocytes, and dying back of unmyelinated axons.

Stabilizing Mutant SOD1 Prevents Aggregation, Improves Cell Survival

Over 100 ALS-associated mutations in superoxide dismutase 1 (SOD1) have been identified, the majority of which yield a destabilized protein product with a propensity to form neurotoxic protein aggregates. Researchers from the University of North Carolina, Chapel Hill, have now developed an approach to mutate SOD1 and prevent its aggregation. As reported online in the September 17 Structure, mutations that mimicked a physiological modification to SOD1, T2-phosphorylation, helped stabilize the SOD1 protein. This modification prevented aggregation of the SOD1 protein, even in variants harboring ALS-associated mutations, and improved motor neuron survival in cell-based assays. These findings point to a possible new therapeutic approach for SOD1-ALS.

Impaired BMP Receptor Trafficking Linked to TDP-43 Pathology in Drosophila Models

Mutations in the RNA-associated protein TDP-43 cause ALS and frontotemporal dementia (FTD), but how these aberrant forms cause neurodegeneration remains unclear (see Feb 2016 news, Jul 2016 news). A report in the August 17 Molecular Biology of the Cell online implicates impaired Bone Morphogenic Protein (BMP) signaling, which controls synaptic growth and function. Activated BMP receptors are typically internalized into early endosomes, where they regulate cytoskeletal architecture and downstream targets to modify transcription. In Drosophila models of both gain- and loss-of-function of TDP-43, BMP receptor distribution was shifted to recycling endosomes, which limit receptor signaling. Rerouting BMP receptors out of recycling endosomes by inhibiting Rab11 partially restored synaptic growth and larval motor function in the TDP-43 mutant larvae.

Peptide-conjugated Oligonucleotides Offer New Approach for SMA Therapy

Loss-of-function mutations in the survival motor neuron 1 (SMN1) gene cause the infant neurodegenerative disease spinal muscle atrophy (SMA). The majority of gene therapy-based therapeutic approaches to SMA rely on splice-switching oligonucleotides (SSOs) that modify splicing of a similar gene, SMN2, to generate functional SMN protein. However, these drugs require direct delivery into the CNS due to limited blood-brain barrier (BBB) penetration of SSOs. In the Sep 12 PNAS, researchers report on a novel peptide-conjugated SSO, Pip6a-PMO, which effectively crosses the BBB. In newborn SMA model mice, two intravenous injections of Pip6a-PMO were sufficient to restore SMN protein expression, neuromuscular junction morphology, and motor

coordination. The treated mice survived for 200 to 400+ days, whereas their untreated siblings died within two weeks. The team is now planning a clinical study in SMA patients.

SOD1 Chaperone Alleviates Mutant SOD1 Toxicity in ALS Mouse Models
The majority of ALS-associated mutations in the superoxide dismutase 1 (SOD1) protein cause it to misfold and form toxic aggregates. In motor neurons (MNs) specifically, the misfolded protein accumulates on the surface of mitochondria and the ER and inhibits their normal function (see July 2011 news). Why the specificity for MNs? Researchers have proposed that the chaperone macrophage migration inhibitory factor (MIF) may play a role, since it promotes proper folding of mutant SOD1 (mSOD1) but is not expressed in MNs (see March 2015 news). A report in the September 6 PNAS provides further support for the importance of MIF. Mutant SOD1 mice lacking MIF expression accumulated higher levels of misfolded SOD1 and had a shorter lifespan as compared to MIF-expressing mSOD1 mice. Augmenting MIF expression in neuronal cultures reduced mSOD1-induced cell death. These findings suggest that MIF could provide a potential therapeutic target for SOD1-ALS.

Drug News

Neuraltus Begins Phase II Confirmatory Study of NP001 in ALS
The biotechnology company Neuraltus Pharmaceuticals is initiating a second Phase II clinical trial of its candidate ALS therapy called NP001 (see April 2016 news). The drug is a small molecule that regulates activated macrophages and reduces inflammation. In a previous Phase II trial, post-hoc analysis suggested NP001 was beneficial in a subgroup of patients with elevated levels of a marker of systemic inflammation called C-reactive protein (CRP). The current study aims to test and confirm the prior results in a randomized, double-blind, placebo-controlled clinical trial of up to 120 patients in the U.S. and Canada. Drug effects will be assessed based on changes from baseline in the score of the ALS Functional Rating Scale-Revised (ALSFRS-R) and in measures of respiratory function.

Biogen and IONIS Pharmaceuticals Submit New Drug Application for SMA Therapy
Biogen and IONIS Pharmaceuticals have submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for the approval of nusinersen, an investigational treatment for spinal muscular atrophy (SMA). Nusinersen is an antisense oligonucleotide that is designed to modify the splicing of survival of motor neuron 2 (SMN2) gene, a gene closely related to the mutated SMN1 gene that causes SMA.Nusinersen treatment was found to significantly improve achievement of motor milestones following interim analysis of the ongoing Phase III clinical trial (see Aug 2016 news). In addition to the NDA submission to the FDA, Biogen plans to submit a Marketing Authorization Application to the European Medicines Agency in the coming weeks.

Deals & Partnerships

MDA and Target ALS Partner to Support Young ALS Investigators

The Muscular Dystrophy Association (MDA) and Target ALS Foundation have announced a partnership focused on supporting young investigators dedicated to ALS research. The MDA awards competitive three year Development Grants to select post-doctoral fellows who are transitioning to independent research careers in academia. The new partnership will help provide the MDA-supported young investigators with the critical tools needed for their research studies, by granted them reduced cost access to the Target ALS core facilities, including human postmortem tissue, human stem cells and viral vector cores. Through this alliance, MDA and the Target ALS Foundation aspire to attract talented researchers to the field of ALS and accelerate their research efforts.

Funding Opportunities:

October 2016

NEW! MNDA Biomedical Research Project Grants. Summary Application due by Oct 28, 2016.

NEW! CReATe Clinical Research Scholars Program. Application due by Oct 31, 2016.

CIRM Accelerating Therapies: Public-Private Partnership Program (ATP3). Application due Oct 31, 2016.

December 2016

MDA Investigator-Initiated Research Grants. Letter of Intent due Dec 15, 2016.

MDA Young Investigator Development Grants. Letter of Intent due Dec 15, 2016.

Full List of Funding Opportunities >>

Job Opportunities:

NEW! Biostatistician, Research Fellow, University of Dublin, Ireland.

NEW! Director of Neurodegeneration Disease Models, Allector, San Francisco, CA.

Postdoctoral Position, Roger Sher Lab, Stony Brook University, Stony Brook, NY.

Postdoctoral Position, Joe Lewcock Lab, Denali Therapeutics, South San Francisco, CA.

Full List of Job Opportunities >>

Upcoming Meetings:

Please note the abstract submission deadline for AAN is Oct 24, 2016.

October 2016

Oct 16-18, 2016: Baltimore, MD: American Neurological Association Annual Meeting.

Oct 19-21, 2016: London, UK: The Lancet Neurology Conference: Preclinical Neurodegenerative Disease.

November 2016

Nov 10-11, 2016: San Diego, CA: RNA Metabolism in Neurological Disease.

Nov 12-16, 2016: San Diego, CA: Society for Neuroscience Meeting.

December 2016

December 7-9, 2016: Dublin, Ireland: International Symposium on ALS/MND.

March 2017

Mar 29-Apr 2, 2017: Vienna, Austria:International Conference on Alzheimer's and Parkinson's Diseases.

April 2017

Apr 22-28, 2017: Boston, MA. American Academy of Neurology Annual Meeting. **Abstracts due October 24, 2016.**

Full List of Upcoming Meetings>>

Resources:

ALS Drugs in Development Database

ALSGene

Alzforum ALS Mouse Model Database

The PRO-ACT Database

NEALS Biofluid Repository Available to Researchers

VABBB ALS CNS Tissue Request Information Site

Target ALS Core Facilities