
**ALS Research Forum e-Newsletter Vol. 155** **July 8, 2016**

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## Conference News

Highlights of the Joint Keystone Symposia on Neurodegeneration/Microglia in the Brain

At the joint Keystone Symposia on Common Mechanisms of Neurodegeneration/Microglia in the Brain held June 12-16 in Keystone, Colorado, enthusiastic scientists convened to share news discoveries and ideas surrounding the role of microglia in health and disease. The concurrent meetings provided a productive platform to foster collaboration between fields that are becoming increasingly intertwined. Researchers presented discoveries spanning a wide-range of topics, including embryonic origins of macrophages, advances in methods for culturing microglia, and sex- and age-dependent differences in microglia.

Keystone Features Advances Toward Human Microglia in a Dish

At the "Microglia in the Brain" Keystone Symposium, held last month in parallel to "Common Mechanisms of Neurodegeneration", scientists greeted with enthusiasm three new approaches for creating induced microglia in a dish. In one method, induced microglia were generated from primitive hematopoietic progenitors derived from induced pluripotent stem cells (iPSCs). Following transplantation into the brains of mice, the induced microglia exhibited molecular and functional hallmarks of native cells (Marsh et al., 2016). In an attempt to recapitulate the *in vivo* development process, another group generated microglia by co-culturing iPSC-derived yolk sac macrophages with neurons *in vitro*. A third research team presented an approach that combined iPSC-derived primitive macrophages with a unique culture medium, and expanded on strategies for further improving microglial differentiation using a three-dimensional culture system.

## Research News

Cytoplasmic TDP-43 Disrupts Mitochondrial Function in ALS and FTD

Cytoplasmic aggregates of the RNA-binding protein TDP-43 are a hallmark of ALS and frontotemporal dementia (FTD), by how this mislocalized protein causes neuronal death has remained unclear. A new study published in the June 27 Nature Medicine demonstrates a novel mechanism for cytoplasmic TDP-43 toxicity: direct interference with mitochondrial function. Once in the mitochondria, TDP-43 sequesters mitochondrial mRNAs that encode respiratory chain complex I proteins, essential components in the cell's energy-generating process. Injection of an inhibitory protein that blocks mitochondrial import of TDP-43 prevented motor deficits and neuron loss in a transgenic model of mutant TDP-43. These findings suggest that inhibiting mitochondrial localization of TDP-43 could be a novel therapeutic approach for ALS.

Single Cell RNA Sequencing of The Human Brain Reveals Neuronal Subtypes and Diversity

In the June 24 *Science* online, researchers present a detailed single cell transcriptional analysis of over three thousand cells from six regions of the human brain, exposing remarkable neuronal diversity and genetic heterogeneity. This tour de force experiment was achieved through single-nucleus RNA sequencing (SNS) of neurons from the postmortem brain of a healthy adult, which enabled targeted selection of cells from regions with distinct anatomical and physiological properties. The gene expression profiles distinguished excitatory and inhibitory neurons, and revealed diversity between different cortical regions and layers, as well as within them. The postmortem SNS approach can now be applied to examine additional brain regions, and to characterize changes that occur in neurodegenerative diseases, such as ALS and FTD.

Twin Study Reveals Epigenetic Changes Associated with Immune Function in ALS

Monozygotic twins differentially affected by ALS/FTD can shed light on environmental or epigenetic contributors to disease (see Sep 2014 news). A report in *The FASEB Journal*
published July 1 online describes epigenetic and transcriptional differences in peripheral blood mononuclear cells from monozygotic twins discordant for an ALS diagnosis. Using bisulfite sequencing to measure abundance of different immune cell types based on their methylation signatures, the researchers identified an increase in CD14 macrophages and reduction in T cells in the ALS affected twin. In addition, cytokine production differed between the PBMCs of the twins, with a higher level of IL-6 and TNF-alpha production by ALS PBMCs.These findings could provide clues to epigenetic changes that affect disease progression in ALS.

ALS Stem Cell Treatment Reported Safe Following Phase II Trial

In the June 29 Neurology, researchers report results of the Phase II clinical trial in ALS of NSI-566, human spinal cord-derived neural stem cells developed by Neuralstem, Inc.(see March 2015 news). In an open-label, dose-escalation study of 15 patients who received bilateral cervical spinal cord injections, of which a subset also received lumbar spinal cord injections, the treatment appeared safe and well-tolerated, with adverse events mostly linked to the surgery and immunosupressant medications. Although the rate of disease progression did not differ between the treated patients and historical controls, larger studies will be needed to evaluate efficacy of the treatment in ALS.

## Funding Opportunities:

NINDS Clinical Trial Readiness for Rare Neurological and Neuromuscular Diseases. LOI due Jul 18, 2016.

The ALS Assistive Technology Challenge. LOI due by Jul 29, 2016.

**August 2016**

***NEW!*** The Judith and Jean Pape Adams Foundation ALS Research Grants. Application due Aug 12, 2016.

***NEW!*** Accelerating Drug Discovery for Frontotemporal Degeneration. LOI due Aug 12, 2016.

**September 2016**

Frick Foundation for ALS Research Grants. Applications due Sept 30, 2016.

Full List of Funding Opportunities >>

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## Job Opportunities:

***NEW!*** Stem Cell/Molecular Biology Researcher, UC San Diego, San Diego, CA. Applications due Jul 13, 2016.

Director, Neuroscience Research & Drug Discovery, Verge Genomics, San Francisco, CA.

***NEW!*** Scientist I - Electrophysiology, Research, Biogen, Cambridge, MA.

Full List of Job Opportunities >>

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## Upcoming Meetings: *Don't miss the abstract submission deadlines listed below!*

**August 2016**

Aug 7-12, 2016: Girona, Spain: Gordon Research Conference on Neurobiology of Brain Disorders. Abstracts due Jul 10, 2016.

**September 2016**

***NEW!*** Sept 7-9, 2015: Baltimore, MD: Neurological Disorders Summit.

***NEW!*** Sept 25-28, 2016; Bar Harbor, ME: Molecular Mechanisms of Axon Degeneration.

**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.

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


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