ALS Forum e-Newsletter Volume 128 **May 29, 2015**

Visit the ALS Forum website to read the complete stories featured in this e-newsletter.

May is ALS Awareness Month! Please use this opportunity to let your friends and colleagues who may be interested in learning more about ALS know about the ALS Forum. It is easy to sign up for the newsletter here.

Resources:

ALS Drugs in Development Database

The ALSGene tool: www.ALSGene.org

The PRO-ACT Database: www.ALSDatabase.org

NEALS Biofluid Repository Available to Researchers

VABBB ALS CNS Tissue Request Information Site

Funding Opportunities:

CreATE Consortium ALS Biomarker RFA. Letter of Intent Due: June 26, 2015.

ALS Therapy Alliance (ATA) RFP. Applications due Oct 15, 2015.

California Stem Cell Agency (CIRM) 2.0 Awards. Due last business day of each month.

Webinars:

ALSA Research Webinar: The CreATE Consortium. May 29, 2015. 4:00-5:00 PM EST.

Research News

New Mouse Model of C9ORF72 ALS and FTD Exhibits Hallmarks of Human Disease

Researchers led by Leonard Petrucelli from the Mayo Clinical in Jacksonville, Florida have created the first mouse model for C9ORF72 ALS and frontotemporal dementia (FTD) that exhibits behavioral and pathological hallmarks of the human disease. Hundreds to thousands of GGGGCC (G4C2) repeats in the C9ORF7 gene are the most common genetic cause of ALS and FTD, but previous attempts at developing mouse models of C9ORF72 mutations have not succeeded at recapitulating disease-associated degeneration and motor phenotypes (see Nov 2013 news). First author Jeannie Chew created this model by artificially expressing only 66 copies of the G4C2 repeat rather than the full gene or full number of repeats seen in patients. In addition, rather than using germline transgenes, which are expressed during embryonic development, the researchers expressed the transgene in the CNS only after birth. According to the report in the May 14 *Science,* within six months the mutant mice exhibited key behavioral and molecular indicators of ALS/FTD, including motor deficits, dipeptide aggregates, and cytoplasmic inclusions of TDP-43. Next, the researchers plan to express antisense versions of the repeats to investigate their role in these diseases. Click here to read more.

No FUS, No Muss?

More than a dozen different ALS-causing mutations in the RNA-binding protein FUS have been identified (see Oct 2012 news;Ishigaki et al., 2012), but it is unclear whether a toxic property of the mutated protein or rather absence of normal, functional FUS leads to motor neuron demise. In support of the gain-of-function model, mouse models that overexpress wild-type

Upcoming Meetings:

June 2015

June 7-10, 2015: London, Ontario, Canada.International Research Workshop on Frontotemporal Dementia in ALS.

June 14-17, 2015: Heidelberg, Germany:EMBO Symposium on Mechanisms of Neurodegeneration.

June 14-18, 2015: San Diego, CA: 19th International Congress of Parkinson's Disease and Movement Disorders.

June 19 - 24, 2015: Breckenridge, Colorado:Keystone Symposia: Autophagy

June 20-23, 2015: Berlin, Germany: 1st Congress of the European Academy of Neurology.

June 24-27, 2015: Stockholm, Sweden:International Society for Stem Cell Research Meeting.

July 2015

July 6-7, 2015: San Francisco, CA: Neurological Disorders Summit.

July 15-18, 2015: Bilbao, Spain: XII European Meeting on Glial Cells in Health and Disease.

July 27-29, 2015: Rome, Italy: 4th International Conference and Exhibition on Neurology and Therapeutics.

September 2015

or mutant FUS exhibit progressive motor deficits (see Feb 2013 news; Mitchell et al., 2013). However, until now, FUS null mice have not survived past their first day after birth, likely due to an essential role for FUS, a fact which has precluded any studies on its role in neurodegeneration (Hicks et al., 2000). Recent studies led by Nobuyuki Nukina of Doshisha University in Kyoto, Japan, have tackled this problem by creating a FUS null strain on a more genetically diverse background. As reported in the April 25 *Acta Neuropathologica Communications*, first author Yoshihiro Kino and colleagues were able to monitor these mixed-background FUS null mice through late adulthood and observed normal physical activity, motor function, and motor neuron survival in these mice through 90 weeks of age. These findings support the gain-of-function hypothesis for how mutated FUS causes ALS. Has the debate been fully resolved? Find out more here.

Making Sense of C9ORF72 RNA Regulation in ALS

The most common genetic cause of familial ALS is an expansion of a hexanucleotide repeat in the first intron of the C9ORF72 gene. Normally the gene contains two dozen or less of the GGGGCC repeats, but in individuals with with ALS, this sequence can be repeated over 1,000 times (see Sep 2011 news). Intriguingly, the repeats undergo transcription in both the sense and antisense directions (see Nov 2013 news), and this RNA aggregates in potentially toxic RNA foci. A recent paper in the May 6 *Acta Neuropathologica* online from the laboratory of Pamela Shaw at the University of Sheffield, UK, reports that motor neurons of patients who died of ALS had a greater proportion of antisense C9ORF72 RNA than the sense transcripts. First author Johnathan Cooper-Knock and colleagues found that it was the antisense RNA foci, and not the sense ones, that correlated with cytoplasmic mislocalization of the transcriptional repressor, TDP-43 (transactive response DNA binding protein 43 kDa), a pathological hallmark of ALS (see Feb 2014 news). The authors suggest that overproduction of the antisense transcripts and dipeptides by motor neurons triggers TDP-43 mislocalization and toxicity, and they plan to test it in the newly published C9ORF72 mouse model. To read more, click here.

Meta Analysis Reveals Ethnic Differences in ALS

Two new meta analyses of ALS patients reveal relationships between patient ethnicity and ALS disease characteristics. Benoît Marin from the University of Limoges in France and colleagues investigated ethnic differences in the onset, incidence, and phenotype of the disease in a dataset combining 78 ALS population-based studies including over ten thousand ALS patients. Using subcontinent as a surrogate for ethnicity, and accounting for genetic admixture, the authors reported a positive association between ALS incidence and European ancestry. No such correlations were seen in patients of Asian ancestry. In a

Sept 3-6, 2015: Prague, Czech Republic: 2nd World Congress on Neurotherapeutics.

Sept 19-20, 2015: Montreal, Canada: 10th Annual Symposium of the Fondation Andre-Delambre.

Sept 27-29, 2015: Chicago, IL: American Neurological Association Annual Meeting.

Sept 30 - Oct 4, 2015: Brighton, UK: 20th International World Muscle Society Congress.

October 2015

Oct 15-16, 2015: Chicago, Illinois: 10th Brain Research Conference RNA Metabolism in Health and Disease.

Oct 17-21, 2015: Chicago, Illinois: The Society for Neuroscience Annual Meeting.

Oct 31 - Nov 5, 2015: Santiago, Chile. World Congress of Neurology.

December 2015

Dec 11-13, 2015: Orlando, FL: International Symposium on ALS/MND.

2016

January 2016

Jan 24-27, 2016: Santa Fe, New Mexico: Keystone Symposium on Molecular and Cellular Biology: Axons: From Cell Biology to Pathology.

April 2016

Apr 2-6, 2016: Solden, Austria: 18th International

second study, Marin and colleagues found that the median survival time for ALS patients after onset was also significantly dependent on ethnicity, with a difference of two years between patients of North European and South Asian ancestry. The findings were presented at the 2015 Annual Meeting of the American Academy of Neurology. Find out more here.

Efficient Method to Convert Adult Blood Cells into Neurons Creates New Opportunity

New methods for deriving pluripotent stem cells from ALS patient tissue have created a promising new resource for investigating disease mechanisms and screening for new candidate therapies (see April 2015 news). However, these approaches suffer from limitations with respect to ease of tissue collection, storage and generation of large numbers of reprogrammed cells. In the May 21 *Cell Reports* online, researchers from McMaster University in Ontario, Canada led by Mickie Bhatia report on a new method for directly reprogramming adult blood cells into glia and a variety of neuronal subtypes of the central and peripheral nervous systems. By combining a previously published direct reprogramming approach using the transcription factor OCT4 (Mitchell *et. al.*2014) with chemical inhibition of SMAD4 and GSK3, co-first authors Jong-Hee Lee and Ryan Mitchell were able to directly reprogram adult blood cells into neural progenitor cells without an intermediate pluripotent state. The approach was successful with both fresh and cryopreserved blood, opening the doors to a wealth of stored patient samples previously collected in the context of clinical trials. Click here to read more.

Drug and Device News

Small Molecule Inhibitor of TGF-beta Rejuvenates Neural and Muscle Stem Cells

Transforming growth factor-β1 (TGF-β1) produced by astrocytes is an important component of the deadly signaling cascades that accelerate motor neuron death in ALS (see April 2015 news). Now is has also been implicated as a factor contributing to aging and reduced regenerative potential of stem cells in the brain and skeletal muscle. In the May 6 *Oncotarget,* researchers from the University of California, Berkeley led by Irina Conboy and David Schaffer, report that systemic administration of an inhibitor of TGF-β1 signaling, currently in clinical development as an anticancer drug, simultaneously rejuvenates hippocampal neurogenesis and skeletal myogenesis. In addition, the inhibitor reduces tissue inflammation in the brain and muscle, based on normalized expression of inflammatory markers such as β2-microglobulin. These findings suggest that this inhibitor may merit further exploration as a candidate therapy for ALS with potential

Neuroscience Winter Conference.

April 16-23, 2016: Vancouver, Canada:American Academy of Neurology (AAN) Annual Meeting.

July 2016

July 2-6, 2016: Copenhagen, Denmark:10th FENS Forum of Neuroscience

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for beneficial effects on motor neuron survival as well as in supporting muscle cell regeneration. Click here to read more.

Denali Brings Together Genentech Heavy Hitters to Tackle Neurodegenerative Disease

A new startup company, Denali Therapeutics of South San Francisco, is setting out to tackle ALS, Alzheimer's, Parkinson's disease, and other neurodegenerative diseases. Denali will focus on new drug targets emerging from the vast data on human genetics, as well as on targets tied to neuroinflammation. The new company has already successfully raised a record-breaking series A, with $217 million in venture capital (see Forbes magazine). The founding team is composed of all former top Genentech researchers who are pooling their vast neuroscience expertise and biotechnology experience to discover new drugs for neurodegenerative diseases. The company plans to hire scientists from a diverse number of fields - from molecular genomics to pharmaceutical development to enable development of novel therapies from bench to bedside. Click here to read more.

Virtual Reality Headset Uses Eye Tracking Technology, Potential Applications for PALS

A new cutting-edge virtual reality (VR) headset that uses eye-tracking technology is gaining traction on Kickstarter and has already exceeded its fundraising goal. The headset, developed by Tokyo-based startup, FOVE, uses infrared sensors to detect the position and orientation of users' eyes, which can control games and programs through movement and blinking. Considering how transformative eye-tracking technologies have been in assistive communication devices for ALS patients and others with motor disabilities, this device has potential for exciting therapeutic applications. For example, in collaboration with University of Tsukuba's Special Needs Education School for the Physically Challenged, FOVE developers created a program for a teenager with ALS to play an electric piano by selecting chords through eye movements. Nevertheless, Dr. Albert Rizzo, a Director of Medical Virtual Reality at University of Southern California, stated that "he would want to see a clearly defined value proposition before predicting that FOVE will be revolutionary in the field". The headsets will be distributed in Spring of 2016 once the eye-tracking technology is improved and the safety of the infrared lights is confirmed. Click here to read more.

The ALS Forum was developed by Prize4Life, Inc.

Identified content provided through a partnership with Alzforum.