SPOTLIGHT

Prize4Life, Sage Bionetworks and DREAM Launch the ALS Stratification Challenge

Prize4Life, Sage Bionetworks and DREAM are proud to announce the launch of the DREAM ALS Stratification Prize4Life Challenge (or ALS Stratification Challenge). The challenge invites competitors to develop computational solutions to stratify ALS patients into meaningful subgroups based on disease progression or survival, to help shed light over disease heterogeneity. This the second ALS computational challenge to use the PRO-ACT database (see Nov 2014 news; Nov 2012 news; Kueffner, R. et. al., 2015).

Click here to read more - and to join, click here!

Research News

Neurofilaments Come to Light as Promising Biomarkers

Neurofilament light chain is emerging as a promising prognostic biomarker for ALS. Neurofilament proteins are composed of three subunits and provide crucial cytoskeletal support in neurons, particularly within axons. Following injury, neurofilament subunits leak from injured neurons into the CSF and then into the blood. In the June 2 Neurology, researchers led by Martin Turner and Andrea
Malaspina from University of Oxford, U.K., report that blood concentrations of neurofilament light chain (NfL) were nearly four times higher in patients with sporadic ALS compared to healthy controls. In individual patients, NfL levels were stable and correlated with rate of disease progression. These findings support NfL as a minimally-invasive biomarker of ALS progression, as well as a potential pharmacodynamic biomarker for clinical trials.

**Profiling Profilin Reveals Unstable Cavities**
Approximately 1 to 2% of cases of familial ALS are caused by mutations in the profilin-1 gene (see July 2012 news). Researchers from have now found that some of these mutations cause cavities within the profilin protein and destabilize it. In the June 8 Proceedings of the National Academy of Sciences, researchers led by Daryl Bosco at the University of Massachusetts Medical School in Worcester analyzed the stability of four different profilin mutations associated with ALS. Normally profilin helps the polymerization of actin, but the mutated proteins are more likely to form aggregates or be rapidly degraded, leading to loss-of-function of the protein. Understanding the structural abnormalities of the aberrant profilins could pave the way for targeted treatments aimed at structural stabilization.

**Short Expansions May Predispose Progeny to ALS**
The most common cause of familial ALS is the expansion of a non-coding hexanucleotide repeat in the C9ORF72 gene (see Sept 2011 news). But how many GGGGCC repeats are necessary to trigger the disease? According to a paper in the June 4 American Journal of Human Genetics, the key predictor may be methylation of the repeats, which shuts down gene expression (see March 2015 news). Scientists led by Ekaterina Rogaeva and Lorne Zinman from the University of Toronto, Canada studied a family in which four of five adult siblings carried the expanded version of the gene. Two of them had developed ALS, yet none of their parents or grandparents had been
afflicted. Interestingly, one of the father's copies of the C9ORF72 gene contained 70 unmethylated repeats, which expanded in the offspring to a methylated, high copy repeat gene. These findings could provide a new allele to help predict predisposition to ALS.

**C9ORF72 Null Mice Root for the Gain-of-Function Hypothesis**

Mice lacking C9ORF72 expression in neurons and glia display no overt neurological or motor phenotype, a new study published in the June 5*Annals of Neurology* online reports. Researchers led by R. Jeroen Pasterkamp and Leonard van den Berg from the University Medical Center Utrecht in the Netherlands describe mice with normal motor function, the expected number and size of motor neurons and no signs of gliosis. These findings suggest that hexanucleotide repeat expansions in the C9ORF72 gene, the most common known cause of inherited ALS, are unlikely to be causing ALS and/or FTD due to haploinsufficiency. Further support for the toxic gain-of-function hypothesis for C9ORF72 mutations was recently provided by the striking behavioral and pathological phenotype of mice overexpressing the repeat expansions (see May 2015 news). Interestingly, in nematodes and zebrafish, C9ORF72 knockdown does cause motor dysfunction. Why is there a discrepancy?

**Drug News**

**New Findings on SOD1 Protein Properties Are Key Step For Antisense Clinical Trials**

Mutations in the superoxide dismutase (SOD1) gene are the second most common cause of inherited ALS, and account for approximately 2% of ALS cases. Antisense oligonucleotides designed to reduce levels of SOD1 represent a promising therapeutic approach that has already proven safe in Phase I clinical trials (see May 2013 news). However, in order to determine the treatment regimen most likely to be effective in humans, characterization of the kinetic properties of SOD1 is essential. A new study led by Timothy Miller and Randall Bateman from
Washington University in Saint Louis, Missouri and published in the June 15 *Journal of Clinical Investigation* determined the turnover rates of SOD1 in the CSF and CNS of rats expressing human SOD1, as well as in healthy humans. These findings are an important step in advancing the SOD1 antisense clinical trial, as well as other trials for therapies targeting SOD1 expression.

**Gene Therapy Prevents Limb Paralysis in Mice**
A candidate gene therapy for ALS delivering an RNA helicase shows promise in preclinical models, according to papers in the June 8 *Proceedings of the National Academy of Sciences* and the January *Gene Therapy*. The helicase human upframeshift protein 1 (hUPF1) is a part of a master complex that initiates nonsense-mediated mRNA decay (NMD), a pathway by which the cell destroys unwanted RNA transcripts. As recently reported in two separate studies, hUPF1 has a significant neuroprotective effect in rat neuronal cultures and *in vivo* rodent models of ALS (see [Nov 2011 news story](#)). Both of these models mimic ALS pathology, in part, by over-expressing TDP-43, which causes cell death in culture and induces limb paralysis in rats. Gene therapy with hUPF1 successfully prevented the development of forelimb paralysis, and negated TDP-43-associated neurotoxicity.

**LRP4 Identified as Potential Serum Biomarker and Therapeutic Target in ALS**
A team of researchers from the Hellenic Pasteur Institute in Athens, Greece, have identified antibodies to an important neuromuscular protein in the serum of twenty percent of ALS patients. The protein, called LDL receptor-related protein 4 (LRP4), is a transmembrane protein that is important in development and function of the neuromuscular junction. *In vitro*, antibodies to LRP4 reduce neuronal survival and synaptic function, suggesting that the anti-LRP4 antibodies may be contributing to the pathophysiology of ALS in this subgroup of ALS patients. These findings require further corroboration in a larger cohort with more
diverse control groups, but if confirmed, could point to LRP4 antibodies as a potential biomarker of this ALS patient subgroup that could enable early detection and therapeutic intervention. These findings were reported at the 2015 American Academy of Neurology Annual Meeting in April.

Resources:
ALS Drugs in Development Database
ALSgene
The PRO-ACT Database
NEALS Biofluid Repository Available to Researchers
VABBB ALS CNS Tissue Request Information Site

Funding Opportunities:
CDC RFP: Establishing a Biorepository of ALS. Applications due July 17, 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.

Upcoming Meetings:
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
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

October 2015
Oct 15-16, 2015: Chicago, IL: 10th Brain Research Conference RNA Metabolism in Health and Disease
Oct 17-21, 2015: Chicago, IL: 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

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 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