THE ALS FORUM
PRIZE4LIFE
Discovering a Common Goal, Discovering a Cure

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Research News

Dietary BMAA Reproduces Aspects of ALS/PDC Brain Pathology in Monkeys
Monkeys fed a diet of the cyanobacterial toxin BMAA develop neuropathology similar to Guamanian ALS/parkinsonism dementia complex (ALS/PDC), and simultaneous consumption of L-serine can partially prevent that neuropathology. According to a study published Jan 20 in Proceedings of the Royal Society B., chronic administration of BMAA to vervet monkeys was associated with formation of neurofibrillary tangles and amyloid deposits in multiple brain regions in a dose-dependent manner. The study provides evidence for a link between BMAA exposure and the high incidence of ALS/PDC among the Chamorro people of Guam, but whether it contributes to sporadic ALS remains unclear.

Panel of Mouse Models Agree: Mutated FUS Gains Toxic Function
New ALS mouse models harboring FUS mutations support a gain-of-function model for mutant FUS toxicity. In the Feb 4 Nature Communications, researchers describe new FUS mouse models carrying a single copy of human FUS, rather than the multiple copies of prior models. Mice expressing the P525L FUS variant, which is associated with juvenile-onset disease in humans, exhibited motor neuron degeneration that progressed more rapidly that in mice expressing the adult-onset R251C FUS mutation. These mouse lines also recapitulated the selective vulnerability of motor neurons observed in human ALS, with neuromuscular junction denervation occurring first in fast-twitch muscles. In contrast, loss-of-FUS function after birth does not cause degeneration, suggesting that FUS function is not necessary for motor neuron health.

Presymptomatic IL-10 Expression in Microglia Helps SOD1 Mice Stay in Shape
In mouse models expressing ALS-causing SOD1 mutations, glial cells accelerate disease progression and exacerbate motor neuron degeneration. However, how

they shape different phases of the disease are not well understood. New findings published in the Jan 20 Journal of Neuroscience show that microglial production of interleukin-10, a cytokine that damps down the immune response, is dramatically elevated in presymptomatic mouse models of SOD1-ALS. Blocking IL-10 hastens disease onset, while increasing its expression delays onset and prolongs survival. These findings suggest that targeting the immune properties of microglia at the earliest stages of disease may have disease-modifying effects in SOD1-ALS.

Highly-Structured Repeat RNAs Cause Neuritic Defects

Hexanucleotide repeat expansions in the C9ORF72 gene cause the majority of familial cases of ALS and FTD, and evidence suggests that both the RNA and its protein products can damage neurons (see Oct 2013 news, Dec 2015 news). A paper in the Dec 9, 2015, eLife points again to RNA, and implicates highly-structured repeat RNAs, such as C9-RNA G-quadruplexes, in neuritic defects. Results from cultured neurons and*Drosophila* models show that these RNA species associate with transport granules and travel into neurites, where they disrupt local mRNA translation and cause dendritic branching defects. These findings provide a mechanistic link to several other ALS-FTD mutations through dysfunction of transport granules.

Somatostatin Interneurons Trigger Cortical Hyperexcitability in TDP-43 Mice

Overactive somatostatin interneurons trigger upper motor neuron excitotoxicity in mouse models expressing mutant TDP-43, according to a report in the Feb 23 Nature Neuroscience online. In cortical layer 5 pyramidal neurons (L5PN) of mice co-expressing the A315T variant of TDP-43 and YFP, the researchers identified signs of excitotoxicity prior to motor symptoms or appearance of ubiquitin inclusions. Electrophysiological studies revealed that disinhibition of L5PNs was caused by hyperactive somatostatin (Sst) interneurons. By manipulating activity of Sst interneurons, using optogenetics or targeted ablation, the researchers were able to repair the circuit activity and alleviate symptoms of neurodegeneration in these mice.

Assistive Technology

Minimally-Invasive Microelectrode Array Could Enable Brain Control of an Exoskeleton

A minimally-invasive stent electrode array ('stentrode') can record brain electric signals of sufficiently high quality to control an assistive mobility device, such as an exoskeleton. According to a paper in the Feb 8 Nature Biotechnology online, the stentrode can be safely implanted via angiography, alleviating the requirement for a risky craniotomy. In studies conducted in healthy sheep, insertion of the stentrode into a cortical vein overlying the motor cortex enabled acquisition of electric recordings comparable to epidural surface arrays overlying the dura mater. The team is planning a clinical trial to test whether the device can be used to control an exoskeleton in paralyzed patients.

Deals and Partnerships

AbbVie Joins UK Dementia Consortium
The pharmaceutical company AbbVie is the most recent member to join the UK Dementia Consortium, a £4 initiative to identify new treatment for dementia, including Alzheimer's disease, ALS and frontotemporal dementia (FTD). Other participants are the pharmaceutical companies Eisai, Lilly and Astex, the research charity MRC Technology, and the non-profit organization Alzheimer's Research UK (see Sept 2015 news). The consortium has already funded several projects, including a study developing novel approaches to target TDP-43 toxicity in ALS and FTD.

Funding Opportunities:

Department of Defense ALS Research Program (ALSRP) Funding Opportunities. Pre-announcement.

NEW! ALS Canada Hudson Translational Team Grant. Letter of Intent due March 11, 2016.

California Institute of Regeneration Medicine (CIRM) Quest 2.0 Awards. Applications due March 15, 2016.

NEW! Translational Research Advancing Therapy for ALS (TREAT ALS) Drug Development Contract. Letter of Intent due March 21, 2016.

ALSA, ALS Finding a Cure Grand Challenge: Generation of a PET Tracer for TDP43 Aggregates. Letter of Intent due March 22, 2016.

NEW! ALS Canada Discovery Grants. Full application due June 3, 2016.

All funding opportunities >>

Upcoming Meetings:

March 2016

March 6-8, 2016: Miami, FL: Annual Drug Discovery for Neurodegeneration Conference.

March 20-23, 2016: Arlington, VA: MDA Clinical Conference.

March 22-23, 2016: Oxford, UK: UK Neuromuscular Translational Research Conference.

April 2016

April 2-6, 2016: Solden, Austria: International Neuroscience Winter Conference.

April 5-7, 2016: Boston, MA: BioIT World Conference & Expo.

Full list of upcoming meetings>>

Resources:

ALS Drugs in Development Database

ALSGene

The PRO-ACT Database

NEALS Biofluid Repository Available to Researchers

VABBB ALS CNS Tissue Request Information Site

TargetALS Cores

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