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

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Resources:

ALS Drugs in Development Database

ALSGene

The PRO-ACT Database

NEALS Biofluid Repository

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.

Research News

ALS Worm Model Implicates Innate Immune Response

New studies in *Caenorhabditis elegans* models of ALS have revealed a pathway by which the putative ALS genes, SARM1 and UNC-13, activate the innate immune response and exacerbate neurodegeneration. UNC-13, a protein involved in neurotransmitter release, and the kinase SARM1 were first linked to ALS through separate genetic studies (see Sep 2009 news; Jun 2012 news) but their link to the innate immune response in ALS had not previously been shown. In the June 10 *Nature Communications*, scientists led by Alex Parker at Université de Montréal in Canada, report that loss-of-function of either UNC-13 or the SARM1 worm homolog, TIR-1, resulted in a decreased innate immune response and improved motility in *C. elegans*models expressing either human mutant TDP-43 or FUS. Inhibition of downstream kinases also had similar results, making them candidate targets for future therapies. The next step will be to link these findings to pathways in humans.

Worm Model Reveals Granulin's Role in Neurodegeneration

In humans, loss of one copy of progranulin (PGRN) typically leads frontotemporal dementia (FTD), while loss of both copies causes a different disease called neuronal ceroid lipufuscinosis. However, how progranulin deficiency leads to these conditions is not well understood. A new study sheds light on this question by pointing to a critical role for the progranulin cleavage products called granulins in exacerbating neurodegeneration. As reported in the June 24 *Journal of Neuroscience*, researchers led by Aimee Kao at the University of California, San Francisco, found that granulins exacerbate motility defects in *C. elegans* expressing human wild-type TDP-43 and lead to accumulation of the toxic protein. Furthermore, brain tissue of FTD patients with TDP-43 proteinopathy contained more granulin fragments in affected regions than controls. More work on the link between progranulin

Upcoming Meetings:

Call for Papers - deadline Sept 24, 2015! See AMIA 2016 Joint Summits on Translational Science and listing below.

July 2015

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 9-10, 2015: Philadelphia, PA: Biotechnology Transfer and Commercialization

Sept 9-11, 2015: Philadephia, PA: CNS Diseases World Summit

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

Sept 24-25, 2015: Ottawa, Canada: Ottawa International Conference on Neuromuscular Biology, Disease and Therapy

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

deficiency and increased granulin activity could directly impact therapeutic strategies for FTD (see Nov 2014 news).

Computational Approaches Reveal Master Regulators in ALS
How do glial cells, which normally help maintain neuronal health, become sources of toxic factors that promote neuronal necrotopsis in ALS? What are these toxic factors? A collaborative project led by Serge Przedborski and Andrea Califano at Columbia University in New York set out to identify these key pathways by applying computational analysis to gene expression data from cultured motor neurons (MNs) undergoing necrotopsis, in order to infer master regulators of this transcriptional response. Amongst the regulators described in the July 2 *Cell Reports*, the team identified NF-κB, a pro-inflammatory transcription factor previously linked to ALS (see Dec 2011 news ; Mar 2014 news). Inhibition of NF-κB protected motor neurons (MN) from toxicity of conditioned media from mSOD1-expressing astrocytes or astrocytes from sporadic ALS patients. Further corroboration in human ALS would further support these intriguing findings.

Gut Bacterial Diversity is Necessary for Microglial Health
Microglia, the resident immune cells of the brain, undergo changes in the face of ALS that can exacerbate neuroinflammation and accelerate disease progression (see Apr 2007 news; Aug 2014 news). A paper in the June 1 *Nature Neuroscience* highlights a new player needed to support microglial health and maturation: a diverse gut microbiome. Researchers led by Marco Prinz from the University of Freiburg, Germany found that microglia from germ-free mice exhibit gene expression profiles and morphology indicative of an immature state. These cells regain their normal shape and number only when a diverse gut flora is added back to these mice. Short-chain fatty acids produced by intestinal bacteria may be the key signaling molecule mediating this cross-talk. This work raises the intriguing possibility of a role for the gut microbiome in ALS.

Drug and Device News

Mitsubishi Tanabe Pharma Gains Approval of RADICUT for ALS in Japan
Mitsubishi Tanabe Pharma Corporation has received approval from the Japanese regulatory agency, the Pharmaceutical and Medical Device Agency (PMDA), to market RADICUT for treatment of ALS in Japan. Also known as edaravone or MCI-186, RADICUT is a free radical scavenger discovered by MTPC that is also marketed for treatment of the acute phase of cerebral infarction, a type of ischemic stroke. The company reports that a series of clinical trials in ALS patients show reduced functional loss with drug treatment as compared to placebo. The company

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.

November 2015

Nov 14-18, 2015: San Francisco, CA: American Medical Informatics Association (AMIA) Annual Symposium

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.

March 2016

March 21-22, 2016: San Francisco, CA: AMIA Joint Summits on Translational Science

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

has not yet applied for drug approval in the U.S., however, it was granted Orphan Drug Designation for RADICUT from the FDA in 2015. Interestingly, earlier this year, Treeway also gained Orphan Drug Designation in the U.S. for their reformulated version of the drug, called TW001 (see March 2015 news).

ALSA Boosts Phase II Clinical Trial of NP001 With $1.5M Grant

The ALS Association has awarded a $1.5M grant to Robert Miller, Director of the Forbes Norris MDA/ALS Research Center at Sutter Health's California Pacific Medical Center in San Francisco, to support a Phase II trial of NP001 in ALS. NP001 is an anti-inflammatory drug under development by Neuraltus Pharmaceuticals that regulates activated, inflammatory macrophages. The clinical trial, expected to begin later this year, will aim to confirm evidence from a previous Phase II study of potential clinical benefits of NP001 in ALS patients. Importantly, the trial will examine two biomarkers of inflammation identified in the prior study in greater detail - interleukin-18 and lipopolysaccharide (LPS). The $1.5M in funding from the ALS Association, combined with the $1.2M in funding from Neuraltus, will help accelerate clinical development of NP001.

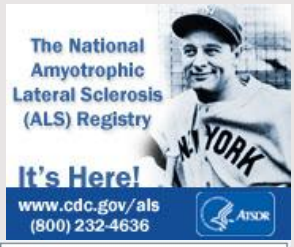
Multi-institutional French and UK Collaboration to Initiate Clinical Trial of IL-2 in ALS

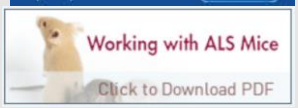
An ambitious, multi-institutional clinical trial of low dose interleukin-2 (IL-2) in ALS has received funding from Motor Neuron Disease Association in the UK, the French government and the European Commission's Horizon 2020 Program. The joint clinical trial between France and the UK, called Modifying Immune Response and Outcomes in Amyotrophic Lateral Sclerosis (MIROCALS), will examine whether low dose IL-2, an anti-inflammatory drug used at higher doses to treat cancer, will slow disease progression and exert beneficial effects in ALS (see March 2014 news). The trial will also include a comprehensive companion biomarker study to monitor drug effects and identify drug-responsive patient subgroups. The groundwork for the study will begin in September 2015 with a pilot study in France, followed by recruitment for the main trial in 2016.

Injectable Nanoelectronics Faithfully Record Neurons

A major technological breakthrough in devices for recording neuronal activity *in vivo* comes in the form of a mesh electronic device that is smaller than a micron. Developed by scientists led by Charles Lieber at Harvard University, the device is small and flexible enough to be inserted into a syringe, yet still creates a sturdy scaffold for the 16-channel electrode. As published in June 9 *Nature Nanotechnology*, following injection into the brain, the device unfolds and records activity from surrounding cells without

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





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triggering an inflammatory response, which can easily occur upon injections of a foreign substance. The researchers successfully recorded responses from the same neurons for over three-months. These new injectable electronics could eventually be used to measure neural activity in the diseased CNS and track responses to therapeutic interventions. Click here to read more about this remarkable advance.

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