
**ALS Research Forum e-Newsletter Vol. 149** **April 15, 2016**

*Visit the ALS Research Forum to read the complete stories featured in this e-newsletter. Friends and colleagues can sign up for the newsletter here. Follow us on Facebook and Twitter for the latest updates.*

## Research News

TAM Receptors Regulate Microglial Phagocytic Function in Health and Disease

Clearance of neuronal debris in the CNS is an important function of microglia, both during normal neurogenic processes and following injury. According to a report in the April 6 *Nature*, two TAM receptor tyrosine kinases, called Mer and Axl, are expressed in microglia and regulate this critical phagocytic function. Mice lacking these receptors not only failed to clear cellular debris in neurogenic regions of the brain, but also exhibited marked accumulation of new neurons in the olfactory bulb, suggesting that microglia may engulf a subset of compromised newborn neurons prior to apoptosis. Surprisingly, in a mouse model of Parkinson's disease, Axl expression was elevated, and deletion of Mer and Axl increased lifespan, suggesting that in the diseased brain, TAM receptors may cause excessive clearance of unhealthy neurons and thereby exacerbate disease. Further work is needed to characterize these the role of these microglial receptors in other neurodegenerative diseases, including ALS.

Pesticides Induce Gene Expression Changes Similar to Autism and Neurodegenerative Diseases

Several studies have explored the association between environmental toxins and ALS, but a causal link between the two has not been established (Trojsi et al., 2013). An experimental approach described in the March 31 *Nature Communications* could provide a strategy to prospectively screen for pesticides and other chemicals that may be linked to neurodegenerative diseases, including ALS. Researchers from University of North Carolina, Chapel Hill, exposed mouse cortical neuron-enriched cultures to 294 environmentally-used chemicals, and profiled the subsequent transcriptomic changes. They next clustered the compounds associated with similar transcriptional signatures, and compared these to gene expression patterns from postmortem brains from people with autism or neurodegenerative diseases, including ALS. Intriguingly, a cluster of compounds triggered transcriptional changes observed not only in autism,

but also in Alzheimer's, Huntington's disease and ALS. Additional compounds mimicked changes observed in ALS mouse models expressing human TDP-43, providing interesting leads for further investigation at the mechanistic and epidemiological level.

AB Science Announces Promising Interim Phase III Results of Masitinib in ALS
AB Science has announced promising interim outcomes in their Phase III trial of masitinib in ALS, however the data will not be shared until the trial is complete. Based on preclinical studies, masitinib is protein kinase inhibitor that acts by blocking pathological mast cell and microglial activation, and thereby reduces neuroinflammation. The company conducted interim analysis of its ongoing double-blind, placebo-controlled Phase II/III clinical trial in ALS once almost 200 subjects had reached the designated 48-week time point since treatment initiation. The company reports that ALS patients treated with masitinib and riluzole exhibited statistically significant improvements over placebo and riluzole-treated patients based on several endpoints, including change from baseline in Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) and the secondary endpoint of change from baseline in forced vital capacity (FVC).

Neuraltus Plans Second Phase II Study of NP001 Using Biomarker-Driven Patient Selection
Biopharmaceutical company Neuraltus Pharmaceuticals has announced plans to initiate a second Phase II ALS clinical trial of NP001, a regulator of inflammatory monocytes and macrophages. In the first Phase IIa study, NP001 caused a clinically meaningful decrease in the rate of disease progression in a subset of patients treated with high dose NP001 who also had elevated baseline inflammation (Miller, RG et al., 2015). Secondary analysis of the Phase IIa data suggested that the inflammatory marker C-reactive peptide (CRP) may be a biomarker of the patient subgroup most likely to benefit from high-doses of NP001. The company is now developing a new Phase II study protocol to validate the initial findings and test CRP as a biomarker to enrich patient selection for future NP001 trials.

The US FDA Grants Orphan Drug Designation to Anavex 3-71 for FTD
The US FDA has granted orphan drug designation to Anavex 3-71 to treat frontotemporal dementia. The small molecule drug, developed by Anavex Life Sciences, is an activator of sigma-1 receptors and modulator of the M1 muscarinic receptors. In 3xTg transgenic mouse models of Alzheimer's disease, Anavex 3-71 improved cognition, reduced amyloid and tau pathology, and reduced neuroinflammation. Anavex 2-73, the company's lead compound, is also a sigma-1 receptor agonist and is being tested in Phase II trials in AD.

## Assistive Technology

Brain Computer Interface Enables Voluntary Control Over Hand Movements in Quadreplegic Patient

A 24 year-old quadriplegic patient with a cervical spinal cord injury has been able to move his hand, pour the contents of a glass, and play Guitar Hero with the aid of an implanted chip that transmits signals directly to his arm muscles. In the April 13 Nature, researchers led by Ali Rezai from Ohio State University in Columbus report that by combining a motor cortical multi-electrode array with a neuromuscular electric stimulation system worn as a sleeve, a paralyzed patient could control six different hand and finger movements that involved grasping, manipulating and releasing objects. After 15 months of training, this neural bypass system was able to help the patient regain movement similar to a lower cervical spinal cord injury. Further testing would be necessary to explore whether this type of device could be adapted for ALS patients, who also exhibit cortical motor neuron degeneration.

## Funding Opportunities:

NINDS Program Project Grant (P01). Applications due May 25, 2016.

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

CIRM Partnering Opportunity for Translational Research Projects. Applications due July 15, 2016.

Full List of Funding Opportunities >>

## Upcoming Meetings:

**May 2016**

May 9-11, 2016: Seoul, Korea: International Conference on Molecular Neurodegeneration.

May 16-19, 2016: Philadelphia, PA: Biomarkers and Diagnostics World Congress.

May 19-21, 2016: Milan, Italy: Annual ENCALS Meeting.

**June 2016**

June 5-9, 2016: Whistler, BC: Keystone Symposium: Autophagy, Molecular and Physiological Mechanisms.

Full List of Upcoming Meetings>>

## Resources:

ALS Drugs in Development Database

ALSGene

Alzforum ALS Mouse Model Database

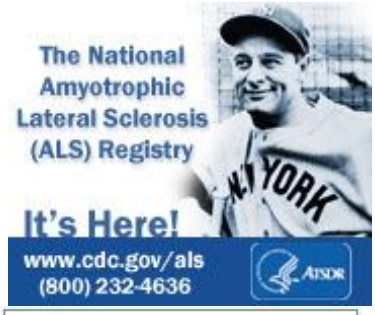
The PRO-ACT Database

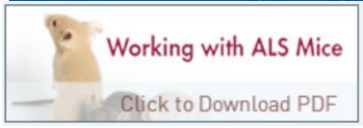
NEALS Biofluid Repository Available to Researchers

VABBB ALS CNS Tissue Request Information Site

TargetALS Cores

---




v