

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:

[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.

Upcoming Meetings:

May 2015

May 21-23, 2015: Verbania, Italy: [European Network for the Cure for ALS \(ENCALS\) Annual Meeting](#).

May 31 - June 4, 2015: Jerusalem, Israel: [EMBO Workshop, Macromolecular Assemblies at the](#)

Research News

[Friend or Foe: How TGF-beta May Contribute to Nerve Damage](#)

How can an immune response normally serve a protective role in the central nervous system (CNS) yet contribute to the pathology of ALS? The key to this conundrum may be transforming growth factor- β 1 (TGF- β 1), which has neuroprotective effects (see [Nov 2007 news story](#); [Katsuno et al., 2010](#)), yet is elevated in the cerebrospinal fluid of people with ALS ([Itzecka et al., 2002](#)). According to a paper published April 16 in *Cell Reports* online, TGF- β 1 secreted from astrocytes, but not from neurons, may be the culprit. First author Fumito Endo and senior author Koji Yamanaka of Nagoya University in Japan and colleagues overexpressed TGF- β 1 in astrocytes of the mutant SOD1 (mSOD1) ALS mouse model. This resulted in a decreased number of T-cells in the spinal cord and a reduction in microglia-activating cytokines, including IL-4. Microglial production of insulin-like growth factor-1 (IGF-1) was also blunted. When mSOD1 mice were injected with a TGF- β 1 inhibitor after disease onset, the treated mutant mice lived longer. The authors are now trying to unravel how TGF- β 1 inhibition affects both microglia and T cells. Click [here](#) to find out more.

[Vaccination-Induced Choroid Plexus Activation Proves Beneficial in ALS Mice](#)

Activation of the immune system can have both beneficial and detrimental effects in ALS, depending on the cellular and spatial context (see [April 2015 news story](#); [Sept 2009 news story](#)). According to a study in the April 22 *Journal of Neuroscience* from the laboratory of Michal Schwartz at the Weizmann Institute of Science in Rehovot, Israel, peripheral macrophages and T-cells, which could exert protective effects in the CNS are blocked from entry in ALS due to alterations in the choroid plexus (CP), the epithelial barrier between the blood and cerebrospinal fluid (CSF). As a result, the anti-inflammatory response is diminished and the neurotoxic immune responses dominate. First authors Gilad Kunis and Kuti Baruch aimed to test this hypothesis by promoting leukocyte infiltration into the CNS through interferon- γ (IFN- γ), which facilitates trafficking of immune cells across the CP ([Kunis et al., 2013](#)). The researchers demonstrate that injection of mutant SOD1 ALS mice with a fragment of myelin

[crossroads of cell stress and function.](#)

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

oligodendrocyte glycoprotein (MOG), which stimulates T cells to secrete IFN- γ , leads to an increase in peripheral immune cells and neurotrophic factors in the spinal cord parenchyma. Though the immunized mutant mice exhibited motor neuron loss similar to vehicle treated controls, they had an increased life expectancy, better grip strength, and healthier motor neurons. Could this type of immunization prove to be an effective means to help combat neurodegeneration? Find out more [here](#).

[Axonal Destruction Cascade Targets Cellular Energy Reserves](#)

Following axonal injury, severed axons trigger degeneration distal to the injury in a process called Wallerian degeneration. This self-destruction process is in part initiated by the protein called sterile alpha and TIR motif-containing 1 (SARM1, see [Feb 2015 news story](#); [June 2012 news story](#)). The essential cofactor nicotinamide adenine dinucleotide (NAD⁺) also is also involved in this process, as its concentration plummets in dying axons, and blocking its decrease attenuates axonal degeneration ([Wang et al., 2005](#)). Researchers led by Jeffrey Milbrandt of Washington University Medical School in St. Louis have found that it is SARM1 that initiates the reduction of NAD⁺. As they report in the April 24 *Science*, the authors expressed a protease-sensitized SARM1 in mouse dorsal root ganglion (DRG) neurons, and found that without SARM1 activity, axons survived post injury. Further experiments showed that the Toll-interleukin receptor (TIR) domain of SARM1, which promotes dimerization, is sufficient to initiate axon destruction. Can these findings have implications for ALS? Potentially, since blocking SARM1 function in ALS mice overexpressing mutant human SOD1 (mSOD1) prolongs lifespan and improved motor neurons survival (see [April 2013 news story](#)), and enhancing NAD⁺ synthesis also improves symptoms in ALS mice (see [Oct 2012 news story](#)). To read more about this work click [here](#).

[Researchers Develop Improved Approach for Generating Motor Neurons in the Lab](#)

Stem cell therapies have long-since been a promising approach for treating neurodegenerative diseases, but the complexities of the different types and functions of nerve cells continue to pose substantial challenges. The limb-innervating motor neurons (MN) of the lateral motor column (LMC), which control movement of arms and legs and are often the first to degenerate in ALS, have proven to be particularly difficult to properly replicate. Previous research from Bennett Novitch's laboratory at the University of California, Los Angeles has shown that the key may lie in the transcription factor forkhead box protein P1 (Foxp1). Foxp1 is necessary for generation of limb-innervating MNs but is rarely expressed in MNs derived from stem cells in the lab (see [Aug 2002 news story](#)). In a publication in the 14 April *Nature Communications*, first author Katrina Adams and colleagues

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

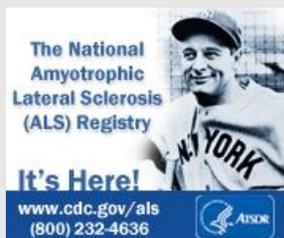
Oct 15-16, 2015: Chicago, Illinois: [10th Brain Research Conference RNA Metabolism in Health and Disease](#).

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](#).



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demonstrate that expression of Foxp1 in mouse and human embryonic stem cells drives stem cell-derived MNs toward an LMC identity. The Foxp1-differentiated MNs express molecular markers of LMC neurons, and project to distal limb muscles following transplantation into developing chick embryos. Next, the researchers plan to investigate how these MNs identify their specific target muscles and whether they can be used therapeutically. Click [here](#) to read more.

Drug News

[Transthyretin Shows Promise as Biomarker for C9ORF72 ALS and FTD](#)

A new study led by Marka van Blitterswijk from the Mayo Clinic in Jacksonville, Florida found elevated levels of the protein Transthyretin (*TTR*) in the cerebellum of ALS or frontotemporal dementia (FTD) patients carrying C9ORF72 mutations, as compared to disease patients not carrying the mutation or patients with other neurological conditions. At the [Annual American Academy of Neurology Meeting](#) in Washington, D.C., the researchers presented data of both elevated RNA expression in C9ORF72 ALS patient autopsies, as well as increased protein levels in the cerebrospinal fluid (CSF) and plasma collected from living patients. The role of TTR in ALS is unclear, but its presence in the CSF may confer neuroprotective properties, since the cerebellum does not degenerate in ALS. The ability to detect TTR in biofluids suggests that TTR holds promise as readily detectable biomarker for this subgroup of ALS patients. Longitudinal studies are underway to evaluate whether TTR can also serve as a biomarker of disease progression, and have utility in ALS clinical trials. Click [here](#) to read more.

[USC, Sanofi and DRVision Partner to Identify New Candidate ALS Drugs](#)

A new partnership between University of Southern California (USC), [Sanofi](#), and startup company [DRVision Technologies](#), with funding from the Department of Defense, aims to identify new candidate drug for treating ALS. Led by Justin Ichida from USC, the research partners will leverage a platform developed by Ichida to screen compounds on motor neurons generated from induced pluripotent stem cells (iPSCs) derived from ALS patients with a C9orf72 mutation, the most common known genetic cause of ALS. Ichida will screen 2,000 FDA-approved compounds in his laboratory, while Sanofi will test over 40 thousand additional compounds. The most promising 'hits' may be further developed by Sanofi chemists into safe drugs to enter human trials. Click [here](#) to read more.

[MRF and NIH Launch Clinical Testing of Guanabenz in MS](#)



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Multiple sclerosis (MS) is a disease in which the immune systems attacks myelin surrounding axons in the central nervous system, leading to impaired neurotransmission and progressive axonal degeneration. Currently approved treatments for MS primarily target the immune response, but a new clinical trial is testing what could be the first therapy to reduce damage to the myelin sheath and protect the oligodendrocytes that form it. The drug, called guanabenz, is FDA-approved to treat high blood pressure, but has been discontinued due to development of improved drugs. A recent study, published March 13 in *Nature Communications* ([Way, S et. al., 2015](#)), demonstrates that guanabenz treatment prevents oligodendrocyte cell death, delays disease onset and reduces paralysis in mouse models of MS. The MRF is now supporting the Phase I clinical trial to test safety and tolerability of guanabenz in relapsing-remitting MS patients in combination with the FDA-approved anti-inflammatory drug for MS, Copaxone. Guanabenz, as well as a newer derivative called Sephin 1, is also beneficial in mouse models of ALS (see [April 2015 news story](#)), so the outcome of these trials will also be of utmost interest to the ALS community. Click [here](#) to read more.

[MJFF Partners with Imago to Study Parkin Protein](#)

The Michael J. Fox Foundation for Parkinson's Research (MJFF) has acquired research tools from [Imago Pharmaceuticals](#) (originally developed by Elan Pharmaceuticals) to accelerate research and drug development surrounding the therapeutic target parkin. Mutations in the parkin (*PARK2*) gene lead to early onset Parkinson's disease (PD) caused by dysfunction of the parkin protein, a component of the E3 ubiquitin ligase complex. Although it is most well known for its role in PD, it is also linked to ALS through the mitophagy pathway and optineurin (see [Oct 2014 news story](#)) and though its effect on TDP-43 (see [Jan 2013 news story](#)). The newly acquires research tools include cell lines, plasmids and compounds, which will initially be integrated into MJFF-funded studies, but will be available to the broader research community later this year. Click [here](#) to read more.

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