DoD Amyotrophic Lateral Sclerosis Research Program (ALSRP)

Each year, the Department of Defense's office of the Congressionally Directed Medical Research Programs (CDMRP) assesses scientific opportunities to advance research in specific areas. The investigators supported by individual programs are making significant progress against targeted diseases, conditions, and injuries. This list is not intended to be a full representation of accomplishments, but rather a sampling of the broad portfolio of research and advances resulting from congressional appropriations.

Year	ALSRP Research Contributions	Additional Information and Hyperlinks
2007	Dr. Ole Isacson of McLean Hospital developed a screening method for identifying compounds that can upregulate expression of IGF-II and that may have neuroprotective properties. The FDA-approved and widely used phosphodiesterase 5-inhibitor (PDE5i) vardenafil HCl stood out as a lead candidate drug for further in vitro and in vivo testing.	• Hedlund E, Karlsson M, et al. 2010. Global gene expression profiling of somatic motor neuron populations with different vulnerability identify degenerative and protective processes. Brain 133(Pt 8):2313–30. • ALSRP Research Highlight
2007	Dr. Serge Przedborski from Columbia University successfully developed a rapid, high-throughput cell-based screen that uses astrocyte-conditioned medium and embryonic stem motor neurons (ES-MNs) to screen large drug libraries of already existing compounds. JNK2/3 inhibitors and Necrostatin-1 emerged as the main protective finds for both primary motor neurons and ES-MNs.	• Re DB, Le Verche V, et al. 2014. Necroptosis drives motor neuron death in models of both sporadic and familial ALS. Neuron 81(5):1001-8. • ALSRP Research Highlight – 2009 • ALSRP Research Highlight – 2012
2009	Dr. Nicholas Maragakis of Johns Hopkins University initiates preclinical studies of induced pluripotent stem cell-derived astrocyte transplantation as a possible therapy for ALS.	• Haidet-Phillips AM, Roybon L, et al. 2014. Gene profiling of human induced pluripotent stem cell-derived astrocyte progenitors following spinal cord engraftment. Stem Cells Transl Med 3(5):575-85. • ALSRP Research Highlight
2009	Dr. Richard Silverman from Northwestern University developed a high-throughput screening system to identify compounds that protect cells against the toxic effects of aggregated SOD1 proteins and identified lead compounds for entry into GMP and GLP IND-enabling studies.	• Zhang Y, Benmohamed R, et al. 2013. Arylazanylpyrazolone derivatives as inhibitors of mutant superoxide dismutase 1 dependent protein aggregation for the treatment of amyotrophic lateral sclerosis. J Med Chem 56(6):2665-75.
2010	Dr. James Connor from Penn State discovered that intracerebroventricular infusion of artificial cerebrospinal fluid (CSF) or H-ferritin delays onset of ALS symptomatology and increases lifespan in SOD1G93A mice. In addition, motor neuron survival is increased in animals receiving a CSF infusion compared to untreated controls.	
2010	Dr. Pierre Drapeau from the University of Montreal performed a large-scale drug screen of chemical modifiers of the TDP-43 gene and found a number of neuroleptic compounds, including the antipsychotic drug pimozide, are successful in their ability to restore mobility in ALS model systems. A collaboration to begin a Stage IIb randomized clinical trial of pimozide in patients with ALS was initiated.	• Tauffenberger A, Julien C, and Parker JA. 2013. Evaluation of longevity enhancing compounds against transactive response DNA-binding protein-43 neuronal toxicity. Neurobiol Aging 34(9):2175-82.

Year	ALSRP Research Contributions	Additional Information and Hyperlinks
2010	Dr. Piera Pasinelli and colleagues at Thomas Jefferson University demonstrated improvement of the bioavailability and effectiveness of Riluzole therapy in a mouse model of ALS by blocking the membrane transporter P-glycoprotein (P-gp) with the known P-gp/BCRP-inhibiting drug, Elacridar.	• Jablonski MR, Markandaiah SS, et al. 2014. Inhibiting drug efflux transporters improves efficacy of ALS therapeutics. Annals of Clinical and Translational Neurology 1(12):996-1005. • ALSRP Research Highlight
2011	Dr. Nicholas Cosford of Sanford-Burnham Medical Research Institute evaluated the effectiveness of enzyme inhibitors of apoptosis as novel treatments to halt the progression of Amyotrophic Lateral Sclerosis (ALS).	• Limpert AS, Mattmann ME, and Cosford ND. (2013) Recent progress in the discovery of small molecules for the treatment of amyotrophic lateral sclerosis (ALS). Beilstein J Org Chem 9:717-32.
2011	Dr. Jeffrey Rothstein from Johns Hopkins University demonstrated that human ALS oligodendroglia appear to cause the axon degeneration of human ALS motor neurons, which confirmed the studies derived from an ALS mouse model and from human postmortem tissue.	
2012	Dr. Michael Benatar of the University of Miami found that an epigenetic strategy targeting the unexpanded C9orf72 allele may be useful for rescuing C9orf72 haploinsufficiency.	• Zeier Z, Esanov R, et al. 2015. Bromodomain inhibitors regulate the C9ORF72 locus in ALS. Exp Neurol 271:241-50.
2013	Dr. Clive Svendsen of Cedars-Sinai Medical Center pursed the use of an ex-vivo gene therapeutic approach based on the intramuscular transplantation of mesenchymal stem cells (MSC) secreting GDNF. This MSC-GDNF based cell therapy has reproducibly improved motor function, motor neuron survival and neuromuscular innervation in ALS rats. These essential preclinical studies aim to establish optimal dose and safe procedures for translating this progenitor cell and growth factor therapy into human patients.	
2013	Dr. Leonard Petrucelli and his team at the Mayo Clinic College of Medicine create a mouse model that reflects the neuropathological changes and neurodegeneration of c9ALS/FTD. These mice offer an attractive model for identifying diagnostics and testing potential therapeutics targeted towards C9ORF72 mutation carriers.	• Chew J, Gendron TF, et al. 2015. C9ORF72 repeat expansions in mice cause TDP-43 pathology, neuronal loss, and behavioral deficits. Science 348(6239):1151–54. • ALSRP Research Highlight
2014	Dr. Joseph Beckman of Oregon State University is funded to complete pre-IND studies preparing CuATSM for FDA approval. His initial success in the ALS mouse model quickly led to more advanced development. The ALS Association is supporting studies in dogs and an early clinical trial of CuATSM in ALS patients was initiated in Australia.	• Williams JR, Trias E, et al. 2016. Copper delivery to the CNS by CuATSM effectively treats motor neuron disease in SODG93A mice co-expressing the Copper-Chaperone-for-SOD. Neurobiol Dis 89:1-9. • ALSRP Research Highlight
2015	Building on Dr. Piera Passinelli's finding in the ALS mouse model (see 2010 Dr. Piera Passinelli), Dr. Antonius Bunt of Izumi Biosciences, Inc. proposes to develop IZ10023, a manufacturable, stable, orally bioavailable nanoparticle formulation of Elacridar for ALS. Dr. Bunt will advance the novel formulation of IZ10023 to an IND.	