



Amyotrophic Lateral Sclerosis Research Program

Amyotrophic lateral sclerosis (ALS) impacts U.S. Service members and Veterans: Research supports the conclusion that people who have served in the military are at a greater risk of developing ALS than those with no history of military service. In 2006, the National Academy of Medicine (formally Institute of Medicine) conducted a review and concluded that there was sufficient evidence to support an association between military deployment and risk of developing ALS. Subsequently, the Department of Veterans Affairs implemented regulations to establish a presumption of service connection for ALS. Importantly, the regulation acknowledges the link between military service and increased risk for ALS. The benefits of the treatment focused research supported by the Amyotrophic Lateral Sclerosis Research Program (ALSRP) extend to Service members, Veterans and their family members living with ALS today.

VISION

Improve treatment and find a cure for ALS

MISSION

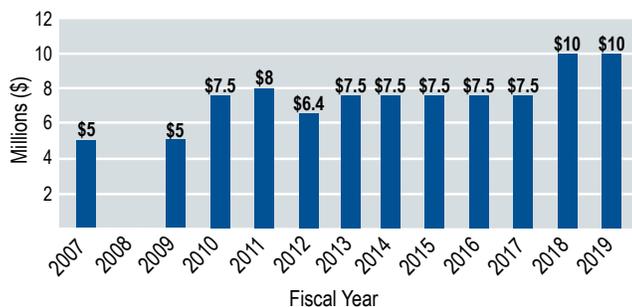
Fund innovative preclinical research to develop new treatments for ALS for the benefit of Service members, Veterans, and the general public

PROGRAM HISTORY

The ALSRP was created in 2007 when the DoD redirected \$5 million (M) of Army Research, Development, Test, and Evaluation funding for the CDMRP to initiate the ALSRP as a broadly competed, peer-reviewed research program. Although the ALSRP was not funded in fiscal year 2008 (FY08), Congress appropriated funding in FY09

and has continuously provided funding since, with a total appropriation of more than \$80M. The overall goal of the program has been to expedite the pathway from bench science to clinical trials for

new therapeutic approaches in ALS. From the inception of the program, the portfolio has been narrowly focused on therapeutic discovery and preclinical validation research projects, with the intent to identify new ALS drug candidates and move them into advanced drug development. The ALSRP's Programmatic Panel includes program directors from other federal funding agencies, such as the National Institutes of Health and the U.S. Department of Veterans Affairs (VA). These panel members provide information regarding the research being funded in related areas by their organizations to ensure synergy and prioritization of the most promising leads.



ALSRP consumer reviewer: Matt Bellina had been a naval aviator flying the EA-6B Prowler out of Naval Air Station Whidbey Island on Washington's Puget Sound when the twitching and loss of coordination began. By the time he was given a preliminary diagnosis of ALS, Matt had already been grounded due to his worsening symptoms. The diagnosis was confirmed a little over a year later when Matt was only 30 years old. Matt found the opportunity to serve as a peer reviewer for the

CDMRP ALSRP and welcomed the prospect of immersing himself further in therapeutic development efforts.

STRATEGIC PLAN

In 2018, the ALSRP developed a Strategic Plan outlining the overall goals of the program, how those goals will be addressed, and how research outcomes will be tracked.

Details of the Strategic Plan can be found at

<https://cdmrp.army.mil/alsrp/pdfs/ALSRP%20Strategic%20Plan.pdf>

Program Priorities

Preclinical Treatment Discovery

- High-throughput screens
- Identify candidate drug leads
- Measure drug-target engagement

Preclinical Treatment Validation

- Secondary validation and drug delivery
- Optimization of drug properties
- Collect data for Food and Drug Administration (FDA) submission
- Develop Good Manufacturing Practices methods

Research Mechanisms

Therapeutic Idea Award

- FY10–present
- Identify candidate drugs in high-throughput screens
- Validate novel drug candidates, assess pharmacological properties, and demonstrate effect on intended molecular targets

Therapeutic Development Award

- FY07–present
- Ready candidate drugs for clinical trials through secondary validation, optimization of pharmacological properties, development of manufacturing processes, and compilation of data for FDA submissions
- Develop markers to demonstrate drug actions on intended molecular targets

PROGRAM ACCOMPLISHMENTS

Over 70 projects have been funded through FY18, many of which are still in progress. From these funded efforts, four promising new ALS drug candidates have gained industry support and are being further advanced and three others have advanced to early-phase clinical trials through other funders.

ALSRP-funded therapeutics advancing along the development pipeline:

- **Riluzole + Elacridar:** The ALSRP funded a combination therapy, riluzole with elacridar (a cellular pump inhibitor), to increase penetration and bioavailability of riluzole in an ALS animal model. The ALSRP has continued support of this combination approach through a separate award to the pharmaceutical development company Izumi Biosciences to develop their own elacridar formulation.
- **CuATSM:** Use of the copper carrier CuATSM in a mouse model of ALS revealed that treated mice lived longer than controls. Because of this interesting finding, the ALSRP is funding the development of three novel classes of copper carriers, all of which have low toxicity, are easily synthesized and are effective at low dosages. The ALSRP-funded investigator has secured collaborative follow-on funding from the ALS Association and is now moving forward with submission of an Investigational New Drug (IND) and has plans to open a trial in the United States.
- **Mir-155:** Mir-155 is a microRNA associated with ALS. Under an ALSRP award, genetic manipulation of miR-155 in an ALS animal model was shown to delay disease onset and extend survival. Based on these findings, a therapeutic development company has invested in a therapeutic strategy to target miR-155 as a treatment for ALS.
- **Apo-H-Ferritin:** Under an ALSRP award, infusion of apo-h-ferritin at the time of motor disease onset was shown to extend life span in several ALS animal models. Development of this strategy is being further supported by the ALS Association, and the researchers are working with a medical device company to develop an implantable device that can deliver the apo-h-ferritin solution directly into the spinal lumbar space.

ALSRP-funded therapeutics now in clinical trial:

- **Pimozide:** The ALSRP funded large-scale screens of thousands of FDA-approved drugs to identify chemical modifiers of TDP-43 in preclinical models of ALS. A class of neuroleptics was identified, with pimozide being the most potent compound, as confirmed in all models tested. A national clinical trial has started in Canada (funded by ALS Canada and Brain Canada) to determine the potential for pimozide as a therapeutic (NCT03272503).
- **Human neural progenitor cells (hNPCs) secreting glial cell-derived neurotrophic factor (GDNF):** The ALSRP funded preclinical studies to deliver the growth factor GDNF to motor neurons. Delivery of GDNF, through hNPCs, enhanced motor neuron function and extended survival in ALS animal models. These results, as well as additional results outside of the ALSRP, contributed to a California Institute of Regenerative Medicine grant moving this approach into clinical trials in patients (NCT02943850).
- **AT-1501:** The ALSRP funded pharmacokinetic and toxicology studies using the antibody, AT-1501, which is designed to block the protein activity of CDL40. These preclinical studies showed that AT-1501 successfully prevented the molecular signaling that normally activates an inflammatory response in ALS. In response to these successful outcomes, as well as further development efforts by the ALS Therapy Development Institute, the FDA granted Orphan Drug Designation and IND approval of AT-1501. A therapeutic development company has provided funding for a Phase I clinical trial to determine the safety of AT-1501 as an ALS treatment strategy.

