Congressionally Directed Medical Research Programs

CDMRP

Department of Defense

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Amyotrophic Lateral Sclerosis Research Program

Amyotrophic lateral sclerosis (ALS) impacts U.S. Service members and Veterans: Research supports the idea 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 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 (VA) 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. Resources are needed to care for Service members, Veterans, their family members living with ALS today. 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

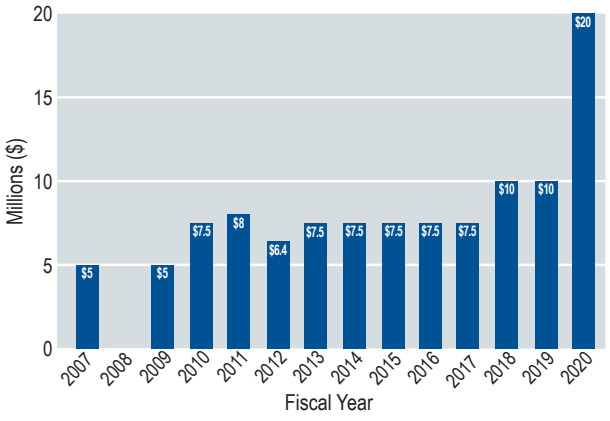
Fund innovative and impactful research to develop new treatments for ALS

PROGRAM HISTORY

The ALSRP was created in fiscal year 2007 (FY07) when the DoD redirected $5 million (M) of Army Research, Development, Test, and Evaluation funding to the Congressionally Directed Medical Research Programs (CDMRP) to create the ALSRP as a broadly competed, peer-reviewed research program. Although not funded in FY08, Congress re-started funding in FY09 and has since provided continuous funding, for a cumulative total of $109.4M in appropriations. The overall goal of the program has been to speed the progression of new ALS therapies from the lab bench to clinical trials. Since FY07, the program has focused narrowly, on preclinical studies to identify new ALS drug candidates and move them into advanced development. In FY20, the Congress doubled the ALSRP appropriation from 10M to $20M. This has enabled the ASLRP to expand its mission to include clinical research as well as increasing its investment in preclinical studies of innovative new therapeutic approaches. The new clinical mission is implemented in a new Clinical Development Award mechanism that supports use of data and samples from ALS patients to foster biomarker development, optimize existing protocols for ALS care, and enrich ongoing clinical therapeutic development efforts.

PROGRAMMATIC PANEL

The ALSRP's Programmatic Panel includes program directors from other federal funding agencies, such as the National Institutes of Health and the 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 embraced the opportunity to serve as a peer reviewer for the CDMRP ALSRP and welcomed the prospect of immersing himself further in therapeutic development efforts.

Program Priorities

Preclinical Treatment Discovery
- Develop animal and cell models
- Construct high-throughput screens
- Identify candidate drug leads
- Measure drug-target engagement

Preclinical Treatment Validation
- Conduct secondary validation and drug delivery
- Optimize drug properties
- Collect data for FDA submission
- Develop Good Manufacturing Practices methods

Clinical Development
- Encourage use of established ALS patient repositories
- Promote correlation of patient samples with clinical outcomes
- Optimize current ALS clinical care strategies

Research Mechanisms

Therapeutic Idea Award
- FY10–present
- Ideas in the early stage of development
- Identification of candidate drug leads
- Co-develop markers to demonstrate drug actions

Therapeutic Development Award
- FY07–present
- Secondary drug validation and optimization studies
- Ready candidate drugs for clinical trials
- Investigational New Drug application (IND) enabling studies
- Continued development of markers to demonstrate drug actions

Clinical Development Award
- New in FY20
- Leverage patient based ALS resources
- Correlative clinical research to better define subtypes, predict therapeutic response, or assess prognosis
- Optimize components of current ALS clinical care
- Correlate clinical trial-related biosamples, imaging, or epidemiological data with clinical outcomes

PROGRAM ACCOMPLISHMENTS

Over 80 projects have been funded through FY19, many of which are still in progress. From these funded efforts, four promising new ALS drug candidates have moved into advanced drug development and three have advanced to early-phase clinical trials.

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 industry 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 lifespan 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.

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