



Amyotrophic Lateral Sclerosis



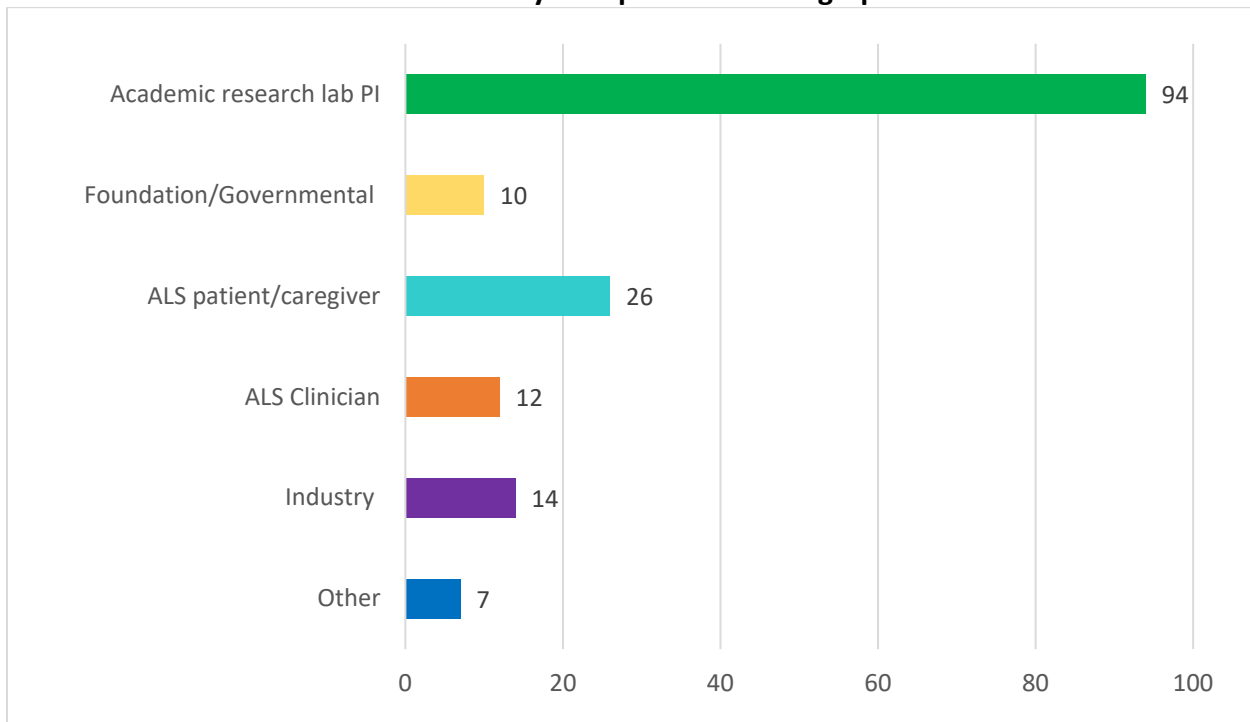
Vision - Improve treatment and find a cure for ALS

The appropriation for the FY20 Department of Defense (DOD) ALS Research Program (ALSRP) increased to \$20M. A hallmark of the ALSRP is the inclusion of ALS patients and family members, researchers, clinicians and representatives from other ALS research funding agencies in every aspect of our program cycle. In this spirit, the ALSRP crowd-sourced the collective wisdom of the entire ALS community via a **Mechanisms and Priorities Survey** to ask:

1. Is there a good understanding of the current ALSRP funding mechanisms and review process?
2. How can the existing funding mechanisms be improved?
3. Are there suggestions for new priorities/mechanisms?

We are exceptionally grateful for the thoughtful and important feedback received from our stakeholders. In this **Frequently Asked Questions** document, we provide an overview of the ALSRP program cycle, and summarize the survey data and the actions we have taken in response – as we work to improve and accelerate ALS therapy development together.

ALSRP Mechanisms and Priorities Survey - Respondent Demographics



Why does the DOD fund ALS research?

In 2007, the ALS advocate community heightened political awareness of the connection between military service and the risk of ALS, and encouraged Congress to commit resources and funding to finding treatments for veterans and the American public afflicted with ALS. In fiscal year 2007, Congress

appropriated \$5 million for ALS-specific research funding via the DOD to initiate the ALSRP as a broadly competed, peer-reviewed research program managed by the Congressionally Directed Medical Research Program (CDMRP). Guidance from stakeholders resulted in an overarching goal for the program of expediting the pipeline from bench science to new clinical therapeutics for ALS.

Why are veterans 60% more likely than civilians to develop neurodegenerative diseases such as ALS, and is the ALSRP funding research investigating this military connection?

A variety of factors from head trauma and excessive physical activity to environmental exposures are implicated in possibly increasing the risk of ALS in veterans. The causes are likely multifactorial, resulting from a combination of genetic factors and environmental triggers. Research on the relationship between ALS and military service is summarized in a white paper published by the ALS Association (<http://www.alsa.org/als-care/veterans/military-white-paper.html>).

The strategic guidance for the ALSRP is focused specifically on funding research which directly promotes novel therapeutic development, an identified gap in the ALS research continuum. Thus, both epidemiological studies and pure mechanistic basic science without a viable therapeutic development strategy are outside of the ALSRP scope. Other Federal agencies have ongoing research programs investigating the connection between military service and ALS, including CDC efforts through the [National ALS Registry](#).

What are the steps of the ALSRP program cycle and who is involved?

The ALSRP is funded via annual Congressional legislation known as the Defense Appropriations Act. The CDMRP recognizes the value of firsthand experience with a disease and is a leader in integrating **Consumers** (patients, family members or caregivers) into every aspect of program design and execution. Consumers vote side by side with scientists and clinicians on the Peer Review and Programmatic Panels, and have since the inception of the ALSRP.

The ALSRP [Programmatic Panel](#) is comprised of expert scientists, clinicians, Consumers, and representatives of the DOD, National Institutes of Health (NIH), Department of Veterans Affairs, and representatives from ALS research foundations and industry (<https://cdmrp.army.mil/alsrp/panels/panels20>). This enables the ALSRP to establish an investment strategy by comparing research portfolios and award mechanisms within the organization as well as with other federal and nonfederal agencies.

The ALSRP follows five major steps for soliciting, reviewing, and funding applications as summarized below:

- 1. Vision Setting:** Conducted by the Programmatic Panel in the first 1-4 months of the annual program cycle, Vision Setting identifies current ALS research priorities and funding gaps, assesses portfolio needs, and defines an investment strategy by refining and prioritizing the ALSRP award mechanisms.
- 2. Program Announcement Release:** Within 2–5 months of Vision Setting, Program Announcements are released which detail each funding opportunity, including the submission requirements and review criteria. Applications may be submitted to ALSRP only in response to a program announcement; no investigator-initiated applications are accepted.
- 3. Pre-Application Screening and Invitation to Submit Full Application:** Pre-Applications are evaluated by the Programmatic Panel based on requirements described in each Program

Announcement, in order to generate a list of projects to invite for submission of full applications.

4. **Peer Review:** All CDMRPs employ a two-tiered review process, consisting of independent Peer and Programmatic Review steps. Full applications first undergo Peer Review – a detailed assessment of scientific and technical merit by panels comprised of scientific and consumer reviewers. There are no standing panels; reviewers are recruited each year based on the expertise needed. Identities are unknown to applicants and contact between applicants and reviewers is not permitted. Peer Review is criteria-based and does not compare proposals to each other. Summary Statements for each proposal (both numeric scores and narrative summaries) are then submitted to the Programmatic Panel.
5. **Programmatic Review:** The same Programmatic Panel responsible for Vision Setting and Pre-Application Screening then conducts a comparison-based Programmatic Review, which incorporates the scientific and technical merit evaluations from Peer Review with consideration of programmatic relevance, overall portfolio composition, and adherence to the intent of each award mechanism. This second tier of the two-tier review process generates the final list of applications recommended for funding. Awards then move into the negotiation and management phases.

ALSRP Funding Mechanisms

What program announcements/funding mechanisms are used by the ALSRP?

The Therapeutic Idea Award (TIA) mechanism supports high risk/high reward hypothesis-driven therapeutic ideas in an early stage of development. Proposed research should introduce a new paradigm, challenge current paradigms, or introduce novel technologies. Preliminary data is not required, but a strong scientific rationale is important.

The Therapeutic Development Award (TDA) mechanism supports post-discovery validation and development of candidate therapeutics agents through the many steps required before U.S. Food and Drug Administration (FDA) approval as an investigational new drug (IND). This can include studies on drug production, purity, stability, toxicology, pharmacokinetics, pharmacodynamics, and efficacy in cell and animal models.

Over the past few years, the ALSRP has instituted changes to the TIA and TDA mechanisms to 1) include the development of new preclinical model systems, 2) encourage academic and industry partnerships, and 3) incentivize incorporation of biomarker development/validation into proposals.

From Survey - What are specific ideas about how existing funding mechanisms could be improved?

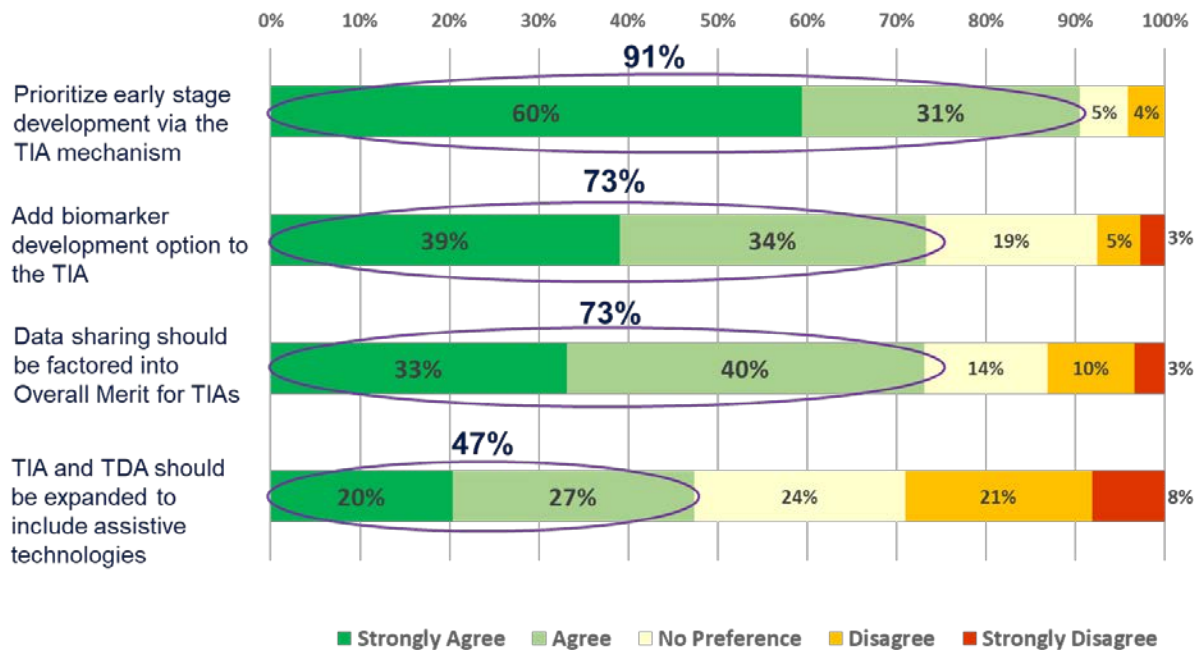
Overall community feedback about the ALSRP Funding Opportunities was very positive.

- “ALSRP is an excellent program for early and novel ALS drug development”
- “Priorities are clear and right where they should be”
- “Overall this seems to be a well conceptualized program”
- “Continue to fund unconventional approaches. True innovation with little more than a good idea and risk taking are hard to fund in the current environment”

- “Keep the focus on innovative ideas. Some may progress to TDA , others not, and that is OK”
- “New mechanisms are great, but it is important the funding to the TIA and TDA is retained”

Suggestions to improve the **TIA** included further emphasizing hypothesis-driven novel therapeutic development, incorporating biomarker development through the use of existing human sample repositories, and placing more importance on data sharing plans. Ideas to improve the **TDA** included better clarification of the research starting point/research scope, a stronger focus on the use of validated ALS models, and making biomarker availability/development a fundamental requirement rather than an optional component of the mechanism.

ALSRP Mechanisms and Priorities Survey –Improvements to the Current Mechanisms



Based on these survey responses and extensive deliberations, we made the following changes for FY2020:

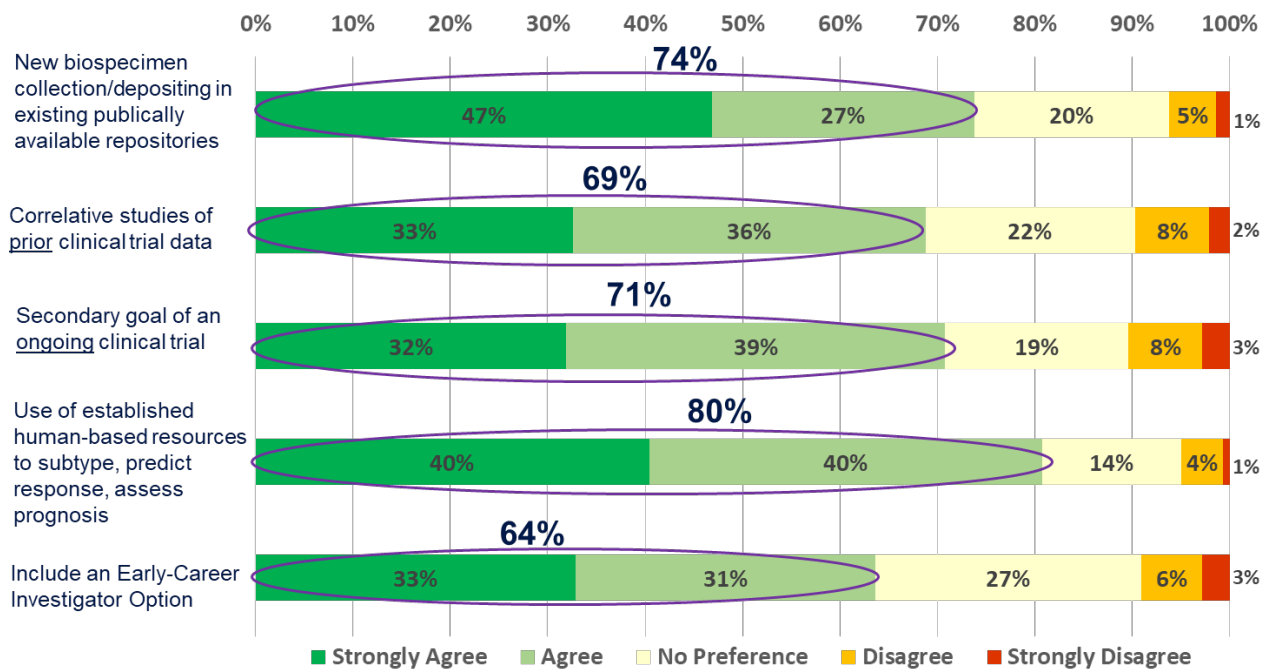
- Prioritized funding of **novel innovative ideas** through the Therapeutic Idea Award (**TIA**) mechanism.
- Provided greater emphasis on **biomarker development** in parallel to therapeutic discovery research, to improve and **de-risk** eventual clinical trials.
 - Added a “**biomarker option**” with **increased funding** to the TIA.
 - Made biomarker existence/development a **required component** of the TDA.
- Emphasized **open data and resource sharing plans**, so advances can be rapidly leveraged by the entire research community.

We also asked whether assistive technologies should be included as an additional area of interest, however there was not strong enthusiasm from the community and therefore the TIA and TDA remain focused on therapeutic development.

Suggestions to offer resources in addition to grant funding prompted the ALSRP to create a database of all publicly available ALS Research Resources, including animal models, biorepositories (including biofluids, cell lines, postmortem tissues), data sets and data visualization platforms, and research tools like antibodies and other reagents. This information is now available on the ALSRP webpage and will be regularly updated - <https://cdmrp.army.mil/alsrp/resources/ALSRResources>.

From Survey - Are there suggestions for new priorities/mechanisms in FY20?

While the current ALSRP budget is not sufficient to fund clinical trials directly in addition to our existing award mechanisms, , **67% of survey respondents** expressed enthusiasm for the ALSRP offering a new award mechanism designed to enrich/leverage ALS clinical trials. Respondents expressed high enthusiasm for such a mechanism to include:



Therefore, In FY20 the ALSRP introduced a new Clinical Development Award (CDA) to support leveraging of patient-based ALS resources (biosamples and data) to define subtypes, predict therapeutic responses, improve the value of ongoing clinical trials, and/or optimize components of current ALS clinical care.