

Amyotrophic Lateral Sclerosis Research Program

Strategic Plan

INTRODUCTION

The Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas.

In 2015, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine was assembled to evaluate the CDMRP's two-tier review process and its coordination of research priorities with the National Institutes of Health (NIH) and the Department of Veterans Affairs (VA). As part of their final report,¹ the committee recommended that each CDMRP program "... develop a strategic plan that identifies and evaluates research foci, benchmarks for success, and investment opportunities for 3–5 years into the future," and that these strategic plans "should specify the mission of the program, coordination activities with other organizations, research priorities, how those priorities will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives."

In response to these recommendations, this document presents the current strategy for the CDMRP's Amyotrophic Lateral Sclerosis Research Program (ALSRP). The ALSRP Strategic Plan identifies the high-impact research goals most important to its stakeholders while providing a framework that is adaptable to changes in the medical research environment to address those goals. This plan has been formulated to provide greater clarity of the program's goals over time to the public and other stakeholders. Funding for the ALSRP is Congressionally appropriated on an annual basis; therefore, there is no guarantee of future funding. The ALSRP Strategic Plan will be reviewed during the program's annual Vision Setting meeting and updated as necessary.

ALSRP BACKGROUND AND OVERVIEW

Shortly after the 1990-91 Persian Gulf War, two separate studies were conducted in response to reports that Amyotrophic Lateral Sclerosis (ALS) was occurring in Gulf War Veterans at an unexpected rate, particularly in young Veterans who were not yet of the age at which ALS is more common. The two studies used different methods to examine the issue, yet they produced similar conclusions: that Gulf War Veterans were approximately twice as likely to develop ALS as Veterans who had not served in the Gulf War. Following publication of these studies, the VA established a registry to identify cases of ALS in military Veterans. The VA also requested that the National Academies conduct an independent assessment of the relationship between military Service and the development of ALS. The Institute of Medicine (now the National Academies' Health and Medicine Division) noted that among the strongest evidence to show the connection between ALS and military Service was a Harvard study, which found an increased risk of the disease in Veterans from all eras, not just the 1991 Persian Gulf War.² In 2008, the VA implemented regulations to establish a presumption of Service connection for ALS. Under this regulation, the VA presumes that ALS was incurred or aggravated by a Veteran's Service in the military. As a result, Veterans with ALS and their survivors are eligible for Service-connected benefits. Later that year, Congress mandated a National ALS Registry to replace the VA registry, and the Centers for Disease Control and Prevention (CDC) launched the National ALS Registry in 2010. Two subsequent reports on data findings from the National ALS Registry reaffirmed that military Service is a risk factor; however, the etiology of ALS and its linkage to military Service remains uncertain.

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 the resources and funding necessary to find treatments for Veterans afflicted with ALS and to determine why and how military Service increases risk of the disease. In fiscal year 2007



FY07, Congress appropriated ALS-specific research funding, and the Department of Defense (DoD) redirected a \$5 million (M) appropriation from Army Research, Development, Test, and Evaluation funding to initiate the ALSRP as a broadly competed, peer-reviewed research program managed by the CDMRP. Recommendations from stakeholders/ Programmatic Panel members resulted in a focus on leveraging new ALSRP funds with other mechanisms of federal and non-federal funding to promote development of ALS therapeutics. The benefits of the research from this program extend to Warfighters and their family members, as well as retirees and other beneficiaries of the Military Health System.

Since the initial appropriation in 2007, the goal of the program has been to expedite the pathway from bench science to clinical trials for new therapeutic approaches and to fund scientifically meritorious research in accordance with directives received from Congress.

The overarching Vision and Mission of the ALSRP are as follows:

VISION: Improve treatment and find a cure for ALS

MISSION: Fund innovative and impactful research to develop new treatments for ALS

The ALSRP is conducted according to the two-tier review model recommended by the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine. Consumers participate as full members on all peer review panels and on the Programmatic Panel. The ALSRP Programmatic Panel includes major stakeholders in the ALS research field, as well as program directors from other federal funding agencies, such as the NIH and VA. These panel members provide information about the research being funded in related areas by their organizations.

Appropriations for the ALSRP from FY07-FY20 total \$109.4M. Through FY19, funds have supported a total of 84 awards to multiple recipients through a competitive peer review process. The ALSRP has funded research at for-profit, non-profit, public, and private organizations, such as universities, colleges, hospitals, laboratories, and companies. Award data and abstracts of funded research proposals can be viewed on the CDMRP website (<http://cdmrp.army.mil>).

RESEARCH AND FUNDING ENVIRONMENT

ALS RESEARCH LANDSCAPE

ALS Incidence

The National ALS Registry of the CDC Agency of Toxic Substances and Disease Registry recently reported an estimated prevalence of 1-3 cases per 100,000 rising to 3-4 cases per 100,000 in persons over age 60. The age groups with the lowest number of persons with ALS were 18–39 years and more than 80 years. Males had a higher prevalence rate of ALS than females overall and across all data sources.

ALS Deaths

Life expectancy following diagnosis is estimated to be 3 to 5 years from the onset of symptoms. Ten percent of ALS patients live more than 10 years after diagnosis.

ALS Risk Factors

It is estimated that 5 to 10% of all ALS cases are inherited (familial disease). Sporadic ALS comprises 90% to 95% of ALS cases. Risk factors for sporadic ALS are unclear; however, links have been made between ALS onset and occupational exposures, military Service, infectious agents, physical activity, and trauma. To date, mutations in over 15 genes have been found to cause familial ALS. Some of these genes are also implicated in apparently sporadic forms of the disease. The most common mutation associated with ALS discovered to date is a hexanucleotide repeat expansion in the C9orf72 gene. This gene mutation is present in approximately 40% of familial and 8-10% of apparently sporadic ALS cases. It is also associated with some forms of familial frontotemporal dementia. Knowledge of environmental/demographic/behavioral risk factors is still emerging; so far, no definite non-genetic risk factor has been identified.

ALS Treatment

There are currently no known therapies to effectively halt the progression of ALS, although two Food and Drug Administration (FDA)-approved drugs, riluzole and edaravone, have been shown to modestly slow ALS progression in clinical trials. A third drug, Nudexa, has been used to control emotional dysfunction, and improve speech, swallowing and control of salivation. Progress has been made in clinical management of the disease, including respiratory and nutritional support (percutaneous endoscopic gastrostomy/nutrition, inspiratory positive pressure/NIPPY, dexamethorphan).



ALS Drug Development

Researchers have identified molecular biomarkers that appear to differentiate progression rates or have diagnostic potential. Recent work has focused on neurofilaments (neurofilament light [NFL] and neurofilament heavy [NFH]), p75NR, TDP43, and C9orf72. Further validation of these biomarkers is underway. Research on imaging and electrophysiological biomarkers for ALS is also advancing. Overall, development of sensitive disease progression biomarkers, as well as biomarkers for patient stratification or pharmacodynamic markers, is expected to enhance and facilitate future interventional clinical trials in ALS.

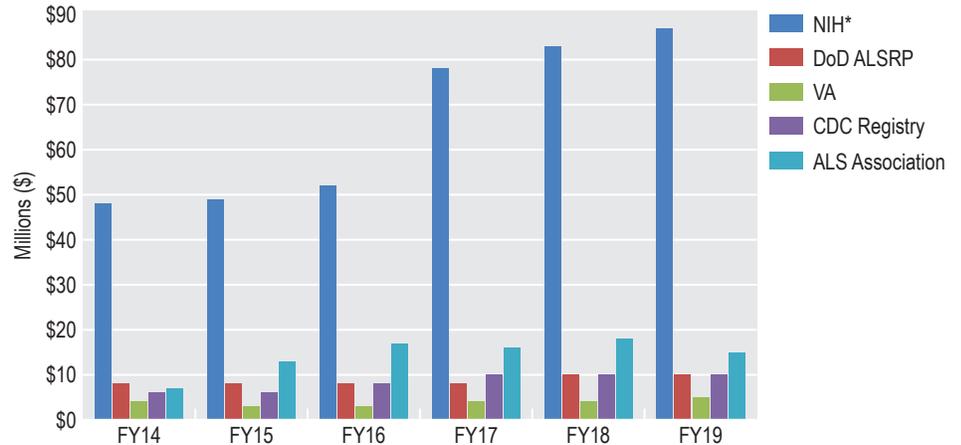
ALS FUNDING LANDSCAPE

Many ALS research funding opportunities for scientists and clinicians are made possible through support from the Federal Government (i.e., the NIH, CDC, VA, and DoD); industry; and non-profit organizations. A query of the NIH Research Portfolio Online Reporting Tools (RePORT) database returned 181 distinct ALS-related projects receiving funding in FY18. The National Institute of Neurological Disorders and Stroke (NINDS) funded a majority of the awards.

ALS research can be broadly categorized into five focus areas:

Epidemiology/Surveillance, Underlying Pathobiology, Biomarkers, Therapeutic Discovery and Preclinical Validation, and Clinical Trials. Research investments among the major funders prioritize unique knowledge gaps within these areas, while remaining complementary and synergistic.

The following table shows how major funders fill the gaps among the broadly defined ALS research areas. **It should be noted that this list is not all inclusive, and organizations such as the NIH and ALS Association fund across research areas. The information in this table depicts the major funder in a particular focus area, the amount of funding in a single year (FY18), and the funders' goals and objectives for addressing knowledge gaps.**



* NIH funding by institute: 69% National Institute of Neurological Disorders and Stroke, 20% National Institute on Aging, 4% National Center for Translational Sciences, 8% Other.

Focus/Gap Area	Major Funder (FY18 funding)	Goal/Vision	Objective/Mission
Epidemiology/Surveillance	CDC (\$6.8M)	Collect, manage, and analyze data about people with ALS	Estimate cases, understand who, examine connections, improve care
Underlying Pathobiology	NINDS (\$35.9M)	Shape the future of brain disease research Build collaborations Develop neuroscientists Translate scientific discoveries	Seek fundamental knowledge about the brain and nervous system and use that knowledge to reduce the burden of neurological disease
Biomarkers	ALS Association (\$0.6M)	Create a world without ALS	Improve diagnosis, follow disease progression, and track response to therapy
Therapeutic Discovery and Preclinical Validation	ALSRP (\$10.0M)	Improve treatment and find a cure for ALS	Innovative preclinical research to develop new treatments for ALS
Clinical Trials/Clinical Management	ALS Association (\$1.7M)/Industry	Advancing treatments	Advancing treatments to patients through clinical trials, precision medicine, and assistive technology



Epidemiology/Surveillance

Progress

Research approaches to epidemiology and surveillance of ALS in the United States are conducted primarily by the CDC. After the VA ALS Registry identified over 3,000 Veterans with ALS from 2003 to 2007, the CDC National ALS Registry³ has identified over 60,000 additional individuals with ALS since 2010. Annual appropriations of \$5-7M per year allow the CDC Agency for Toxic Substances and Disease Registry to fund state and metropolitan area-based surveillance projects to support the National ALS Registry. To date, CDC ALS funding has totaled more than \$50M.

Challenges

There are several limitations to epidemiology and surveillance efforts in ALS research, including the modest incidence, poor prognosis, and inability to recruit sufficient numbers of ALS patients for clinical trials.

Opportunities

In 2008, the U.S. Congress passed the ALS Registry Act, which authorized creation and maintenance of the CDC National ALS Registry. Establishment of this registry, as well as the newly launched National ALS Biorepository, provides an opportunity to fill knowledge gaps by providing estimates of prevalence and facilitating further study of risk factors and etiology.

Underlying Pathobiology

Progress

In FY18, underlying pathobiology research accounted for 63% of the NINDS portfolio and use 40% of the ALS Association portfolio. With advances in sequencing and “omics” technologies, there has been an exponential discovery of ALS genes and pathobiological pathways over the past decade. Building on these discoveries, a growing number of new ALS model systems have been engineered to enable research aimed at defining the molecular and cellular mechanisms of ALS.

Challenges

The major limitation in ALS pathobiology research is that most currently available animal models focus on the inherited forms of ALS, and the inability to model and predict the human disease, especially sporadic ALS, remains problematic. There is a need for additional fully characterized and validated models that represent the complex spectrum of ALS phenotypes.

Opportunities

Technical advances and new knowledge about the genetic etiology of ALS are providing opportunities to develop better in vivo and in vitro models of ALS. These opportunities include ALS patient-derived cell lines, such as induced pluripotent stem cell lines that can be differentiated into any cell type of interest, as well as three-dimensional tissue models and animal models based on CRISPR/Cas9 engineering. High-quality ALS patient biospecimens, such as autopsy tissue and biofluids, also serve as valuable tools for ALS research. Computational and discovery approaches, as well as high-throughput technologies and assays continue to bring new ideas forward. The NIH and several private foundations/non-profit groups are invested in developing and expanding such resources and funding research on the underlying pathobiology of ALS that harnesses the opportunities afforded by these new approaches, model systems, and patient-derived resources.

Biomarkers

Progress

In FY18, research approaches to identify biomarkers accounted for 16% of the ALS Association portfolio and 5% of the NINDS portfolio. Biomarker research includes both diagnostic and prognostic biomarkers. The focus is on not only biomarkers detected in plasma and serum, but also imaging and measures of functional strength and motor neuron survival, as determined by electro-impedance myography and motor unit number estimation. Significant progress has been made in identifying fluid markers (NFH and NFL) that determine prognosis, and efforts are underway to validate these markers in multi-center studies. Examples of funding initiatives enabling biomarker research include focused biomarkers requests for proposals and the TDP-43 Biomarker Grand Challenge Program (specifically released to identify a positron emission tomography ligand for TDP43). Efforts to centralize important resources such as cerebrospinal fluid, plasma, and urine for biomarker discover include CReATe and NeuroBANK, which are open-access repositories housing well-annotated samples. A listing of ALS repositories can be found at <https://cdmrp.army.mil/alsrp/resources/alsrpresources>. In addition, the FDA released a guidance document in 2018 for open comments that is based on efforts initiated by the ALS Association and is intended to engage the broader ALS community.⁴



Challenges

In the absence of well-validated biomarkers, diagnosis is delayed and clinical trials are very challenging because they require large numbers of people with ALS. In addition, it is very likely that there are responders and non-responders to a specific treatment approach due to the complex of the disorder. Improved biomarkers would enable improved stratification in clinical trials.

Opportunities

Appropriate biomarkers for a specific therapeutic approach should be developed at the same time as the treatment approach itself.

Therapeutic Discovery and Preclinical Validation

Progress

In FY18, therapeutic discovery and preclinical validation accounted for 100% of the DoD ALSRP portfolio and 10% of the NINDS portfolio. The research approaches in this area include preclinical testing to discover and validate potential drug candidates, exploiting previously characterized pathways to bridge basic and applied research, and collecting data for FDA Investigational New Drug (IND) applications. According to a recent BioCentury Collections report on ALS, 50 compounds are in the commercial ALS drug development pipeline.⁵ The most advanced therapies in development include small molecules, stem cell therapies, biologics, antisense inhibitors, and gene therapies. A large gap in the drug development pipeline exists between the discovery of a therapeutic candidate and getting it into first-in-human trials. This preclinical space is under-resourced and consequently slow. The ALSRP recognized this gap at the program's inception in FY07 and focused its mission on accelerating drug discovery. This niche is not filled by any other agency. Out of 84 projects funded through FY19 supported by the ALSRP, 48% of which are still in progress, four promising new ALS drug candidates have moved into advanced drug development, and three have advanced to early-phase clinical trials.

ALSRP-Supported Products Advancing to Further Development

- **Riluzole + Elacridar:** Under an ALSRP Therapeutic Idea Award, treatment with Elacridar (efflux pump inhibitor) + Riluzole in a mouse model of ALS was found to increase retention of Riluzole in the central nervous system; improve behavioral measures, including muscle function; and significantly extend survival of the mice. Under a follow-on ALSRP Therapeutic Development Award, Izumi Biosciences is developing their own Elacridar formulation and continuing detailed pharmacokinetics, toxicology, and large-scale compound manufacturing. Izumi plans to submit an IND application for human clinical trials.
- **CuATSM:** CuATSM is a copper chaperone that transfers copper from a carrier molecule to misfolded SOD1 and accelerates its maturation and function. Under an ALSRP Therapeutic Development Award, treatment with CuATSM in a mouse model of ALS demonstrated that mice lived longer than controls. Procypra Therapeutics filed the paperwork required to initiate a clinical trial of their derivative form of CuATSM in Australia. The ALSRP has funded a different study to develop three novel classes of copper carriers that have reduced toxicity, are easily synthesized, and are effective at low dosages. The ALSRP-funded investigator has collaborative funding through the ALS Association, is moving forward with submission of an IND application to the FDA, and plans to open a trial in the United States.
- **Targeting Mir-155:** Mir-155 is a microRNA associated with ALS. Under an ALSRP Therapeutic Idea Award, genetic manipulation was shown to delay disease onset and extend survival in a mouse model of ALS. MiRagen Therapeutics, Inc., is now developing a strategy to target miR-155 as a treatment for ALS.
- **Apo-H-Ferritin:** The ALSRP funded a Therapeutic Idea Award for the use of Apo-ferritin, specifically the development of apo-H-ferritin encapsulated by liposomes for delivery in ALS mouse models, to study the effects of removal and redistribution of iron. Infusion at the time of disease onset was shown to be associated with extension of lifespan. Development of this strategy is being continued through the ALS Association, and a device company has been engaged to develop a delivery method involving surgical implantation of a pump that would deliver a trophic solution into the lumbar spinal space.

ALSRP-Supported Products in Clinical Trials

- **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. Anelixis Therapeutics launched and completed a Phase I clinical trial to study AT-1501



safety and has secured funds for a Phase IIa study to explore dosing levels. This Phase IIa study will begin in 2020 and is anticipated to enroll 54 patients from 12 treatment sites over an 11-month periods (NCT04322149).

- **Pimozide:** The ALSRP funded large-scale screens of thousands of FDA-approved drugs under a Therapeutic Development Award to identify chemical modifiers of TDP-43 in preclinical models of ALS. A class of neuroleptics was identified, and pimozide was the most potent compound, as confirmed in all models tested. Because pimozide is already FDA-approved, it was able to move quickly into a small Phase IIb randomized clinical trial (NCT02463825) to look at the effects of a brief treatment of patients with sporadic ALS. Patients in ALS clinics in Canada were enrolled (sponsored by the University of Calgary and Alberta Health Services). Treated patients showed stabilization of motor activity, whereas untreated patients declined as expected. A national Phase IIb trial has started in Canada (funded by ALS Canada and Brain Canada) to determine the potential for pimozide as a therapeutic; 100 patients will be recruited and treated over a 6-month period (NCT03272503).
- **Human neural progenitor cells (hNPCs) secreting glial cell-derived neurotrophic factor (GDNF):** The ALSRP funded preclinical studies to foster the use of growth factors, specifically GDNF, delivered to motor neurons as a therapeutic approach. Under a Therapeutic Development Award, hNPCs that secrete GDNF were generated from post-mortem brain tissue and injected into the spinal cord or directly into the cortex of rodent and non-human primate ALS models. Using this method resulted in enhanced motor neuron function and extended survival. The California Institute of Regenerative Medicine expressed interest in these preliminary results and has initiated an \$18M grant to move this approach into clinical trials in patients (NCT02943850).

Challenges

Limitations to preclinical validation include an incomplete understanding of pathophysiology and therapeutic mechanism of action, limited translation to humans, and inadequate evidence that a single drug will be sufficient for the complex disorder of ALS. As ALS is mostly sporadic, identifying environmental factors contributing to or causing ALS remains an important challenge.

Opportunities

Most of the genes causing familial ALS have been identified in recent years (since the inception of the ALSRP) due to an explosion in ALS genetics. Based on this genetic information, animal models are being generated that will offer opportunities to discover and validate potential drug candidates, exploit previously characterized pathways to bridge basic and applied research, and collect data for FDA IND applications. New genetic insights and models may also allow candidate toxins to be evaluated. In particular, the better the (1) rationale for a particular target, (2) biomarkers that can confirm target engagement, and (3) model systems that are closely tied to human data to identify therapeutic effect after target engagement, the more likely the treatment will be effective in clinical trials.

Clinical Correlative Research

New for ALSRP in FY20

In FY20, the ALSRP developed a new funding mechanism to support correlative clinical research and has budgeted approximately 8% of the DoD ALSRP FY20 budget for this approach. The intent of this approach is to fund clinical studies that leverage 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. Though neither the NIH nor the ALS Association specifically tag clinical correlative research projects, examination of projects active in FY18 suggest that for both organizations, approximately 3% of FY18 funding was directed to projects that could be construed to be clinical correlative research. As of this writing, awards for this new FY20 mechanism have not yet been announced; projects of this type have yet to be awarded.

Challenges

There are few FDA approved treatments available to ALS patients. For these and other therapeutic strategies, endpoints related to a variety of domains and testing modalities are being used to capture efficacy, however, the choice of trial endpoints is constrained in practice. Lack of a unifying underlying molecular paradigm (common to more than a small percentage of cases) suggests a broad diversity in driving mechanisms in the ALS population. It is likely treatment approaches specific to individual subtypes will be needed. While many treatment protocols and clinical practice guidelines do consider systematic reviews of clinical evidence, objective effectiveness evidence and subtype distinctions are lacking. There also has been little research focused on optimization and personalization of existing treatment strategies or on development of new multidisciplinary treatment management practices. Clinical trials and other studies of ALS patients have generated many sets of well-annotated patient samples and data, but these sets are often unavailable or unknown to researchers who might otherwise use them for further analyses.



Opportunities

Increasingly, sets of ALS patient data and samples are being made available in several growing composite ALS sample and data banks. The ALSRP is publicizing these resources on its web site (<https://cdmrp.army.mil/alsrp/resources/alsrpresources>) in an effort to make these broadly available to the research community. Data sets or biosamples from clinical trials (or other sources) could underpin discovery of predictive/cohort-selective markers that indicate whether therapies are effective in an individual patient or patient subgroup. This type of marker could provide a basis for precision medicine, making treatments effective only in small subgroups of ALS patients, viable candidates for development and approval. Correlative studies based on trial data, or other clinical data sets, could help generate further evidence-based guidelines for existing treatments or new multidisciplinary treatment management practices. Projects leveraging ongoing clinical trials could substantiate drug effects using additional endpoints, including molecular indicators of on-target effects, providing more effectiveness evidence for FDA approval.

Clinical Trials

Progress

In FY18, 24% of the ALS Association portfolio and 11% of the NINDS portfolio were dedicated to clinical studies. Over \$1 billion has been invested by 19 companies investigating compounds through 20 clinical trials. Still, only three distinct drugs have been marketed in the United States. Riluzole, marketed as Rilutek, was approved to treat ALS in 1995. An easier-to-swallow liquid form of Riluzone called Tigtutik was approved in 2018. Edaravone, sold under the brand names, Radicava and Radicut, was recently approved as an ALS therapeutic in 2017. Nuedexa, approved in 2010 specifically targets the pseudobulbar effect quelling emotional outbursts and improving speech. Thus, progress is being made, albeit slowly.

Challenges

The major limitations are cost and risk/benefit tradeoffs, given the severity and rapid progression of ALS.

Opportunities

In cases of rapidly progressing and life-threatening diseases with unmet medical needs, such as ALS, flexibility and innovation in all aspects, including selection of control groups, outcome measures, and statistical approaches, should be considered. Surrogate endpoints or intermediate clinical endpoints should be strongly considered to accelerate the drug approval process and save time. Drug Development Guidance for Industry, published in 2018 by the FDA and composed with input from industry, sponsors, academia, and the ALS patient and caregiver community, offers “best practices” for clinical trial design, providing structure and direction for the design and conduct of clinical trials in ALS.⁶

STRATEGIC DIRECTION

The short- and long-term objectives of the ALSRP remain focused on translational research for the benefit of Service members, Veterans, and the general public. Six thousand persons in the United States die each year from ALS⁷, and it is projected that there will be 400,000 cases of ALS in the world in 2040 due to aging of the population.⁸ As the molecular mechanisms underlying ALS and the connection to military Service continue to be discovered, the ALSRP aims to assist researchers in building on these research findings to pursue translational research on therapeutic discovery and development.

DEFINITION OF TRANSLATIONAL RESEARCH

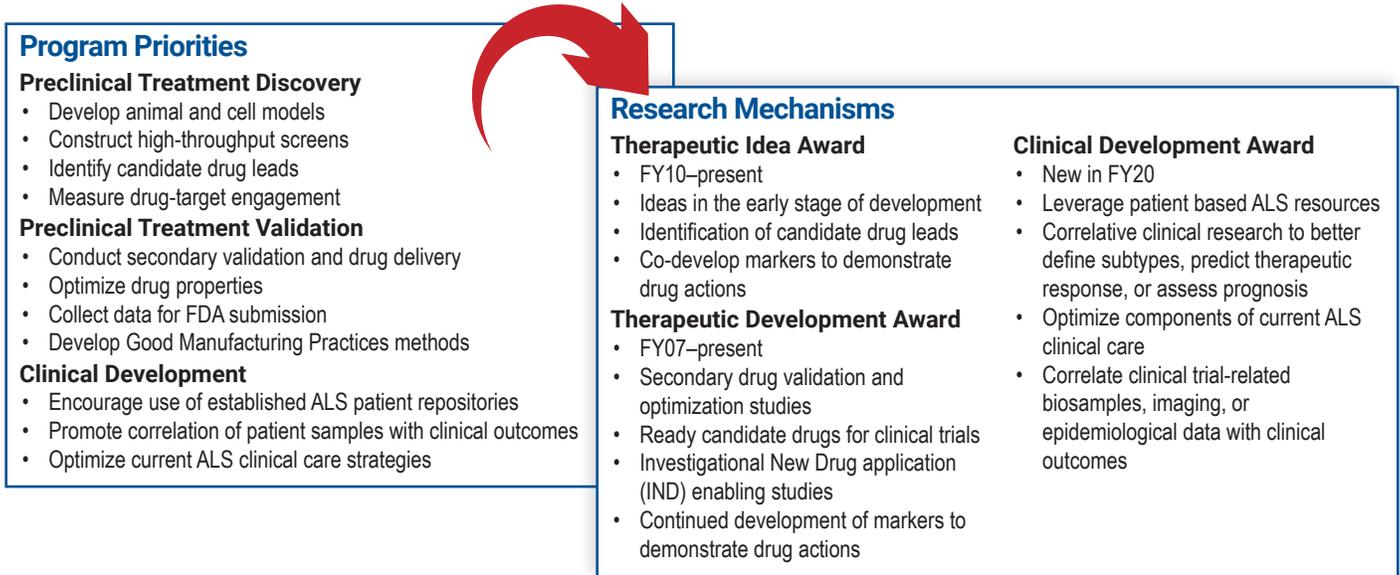
Translational research can be defined as development of effective disease intervention based on understanding of disease mechanisms. Translational research relies on target identification and validation and includes small molecules and biologics, gene and cell therapy, devices, surgery, and behavioral interventions. Any research designed to identify or test an interventional strategy in relevant biochemical, cellular, or animal models is also included.

CHARACTERISTICS OF A TRANSLATIONAL RESEARCH PROGRAM

- Target has already been linked to disease and is a tractable target for drug development.
- Clear therapeutic rationale and/or proof-of-concept data in appropriate preclinical model systems of ALS, including whole animal and cellular model systems, or informative clinical data from a related human disease are available.
- Methods to adequately measure target binding and proximal downstream effects (target engagement) and the potential for undesirable activities at related but unintended targets (selectivity) are defined.
- Correlational research for identifying best implementations for new (and existing) treatments.
- Time to achieving milestones is realistic and acceptable.



The following figure illustrates how the ALSRP Translational Research Program’s funding mechanisms address program priorities.



The ALSRP’s strategic goals are defined below. These goals outline the program’s priorities toward maintaining a bridge through which discoveries made in the laboratory can lead to advanced industry development and clinical trials. The ALSRP seeks to invest in these priorities/goals; however, the program enables investigators to propose their best ideas. The program does not define what types of products will be funded.

1. Direct resources toward prospectively identified and impactful areas related to preclinical treatment discovery.
 - a. Support research generating rigorous data towards the hypothesis that modulating the putative drug target/ affected pathway will produce a desirable outcome for ALS.
 - b. Support research to discover novel therapeutic delivery approaches.
2. Direct resources toward strategically relevant preclinical treatment validation.
 - a. Support research to validate promising leads targeting druggable or tractable pathways in appropriate model systems to enable more advanced drug or device development.
 - b. Support research toward advanced development of therapeutic delivery methods in appropriate model systems.
3. Direct resources toward leveraging patient-based ALS Resources for correlative clinical research to better define subtypes, predict therapeutic response or assess prognosis.
 - a. Support research to optimize components of current ALS clinical care.
 - b. Support research to correlate clinical trial-related biosamples, imaging or epidemiological data with clinical outcomes.

INVESTMENT STRATEGY

The ALSRP’s investment strategy outlines the program’s approach to soliciting the type of research that will facilitate accomplishment of its strategic goals in the short term, while ensuring its investments remain synergistic with other funders. The program will invest Congressional appropriations in distinct steps along the therapeutic development pipeline through a small number of stepwise translational award mechanisms. This investment strategy will be re-evaluated and updated as necessary during the program’s Vision Setting meeting.



1. Treatment discovery mechanism to accelerate therapeutic ideas and identification of therapeutic agents.
 - a. Enable grantees to build on innovative basic science findings and initiate preclinical drug discovery.
 - b. Emphasize innovation and impact as primary criteria.
2. Treatment validation mechanism supporting optimization of therapeutic strategies showing promise.
 - a. Advance therapeutic approaches/compounds with significant preliminary data through more advanced preclinical development and toward IND/clinical testing.
 - b. Support development of markers to improve the drug development process in parallel with the main therapeutic advancement effort.
3. Clinical correlative research mechanism to improve the development and implementation of treatments and treatment strategies.
 - a. Improve clinical treatments and practice by research leveraging existing human studies and data such as ongoing clinical trials or established data or samples.
 - b. Supports enrichment of ongoing clinical trial, optimization of existing treatments and multidisciplinary treatment strategies and development of markers of ALS subtypes or indicators of clinical effects and responses.
4. For all funding mechanisms, focus on projects with the highest probability for impact, i.e. strategically important targets.
 - a. Projects with impacts in areas of unmet needs will be prioritized over those where significant other effort/funding is already available within the NIH and/or the biotechnology and pharmaceutical industry setting.
 - b. Projects that are in the funding gap stage between academic and industrial research and require necessary preclinical risk mitigation will be prioritized.
 - c. Establish an award period of performance appropriate for the assessment of progress and potential for continued funding along the program pipeline.

MEASURING PROGRESS

The ALSRP anticipates measuring the following outcomes over the next 1 to 5 years to gauge its progress toward meeting its strategic goals:

SHORT-TERM OUTCOMES (1-3 YEARS)

1. Anticipated contributions to Preclinical Treatment Discovery, as evidenced by portfolio analyses.
 - a. Investments in the development of biochemical, cellular or animal models for therapeutic screening.
 - b. Investments in novel approaches to therapeutic delivery.
2. Anticipated contributions to Preclinical Treatment Validation, as evidenced by portfolio analyses.
 - a. Investments in preclinical treatment research with a clearly defined path to clinical proof of concept.
 - b. Parallel investments in development of surrogate markers to monitor progression in animal model systems to serve as early readouts of efficacy.
3. Anticipated contributions to Correlative Clinical Research as evidenced by portfolio analyses.
 - a. Investments in augmentation of ongoing clinical trials.
 - b. Investments in indicators of clinical effects or characterization of ALS subtypes.
 - c. Investments in optimization of treatments or multidisciplinary treatment strategies.

LONG-TERM OUTCOMES (3-5+ YEARS)

1. Anticipated contributions to Preclinical Treatment Discovery, as evidenced by portfolio analyses.
 - a. Contributions to the scientific community (publications, patents, etc.) describing identification of bioactive compounds that modulate a putative drug target/affected pathway in preclinical ALS model systems.
 - b. Contributions to the scientific community (publications, patents, etc.) describing optimization of therapeutic delivery methods in in vivo model systems.



2. Anticipated contributions to Treatment Validation, as evidenced by portfolio analyses.
 - a. Preclinical optimization and development research contributing to IND applications to the FDA and/or advanced development by federal or non-federal partners.
 - b. Availability of surrogate markers to monitor progression in model systems to serve as early readouts of efficacy.
 - c. 5+ years: Post-award engagement of federal and non-federal partners for advanced therapeutic development.
 - d. 5+ years: Completed projects contributing to the planning of early phase treatment trials for ALS.
3. Anticipated contributions to Correlative Clinical Research, as evidenced by portfolio analyses.
 - a. 5+ years: FDA approval of candidate pharmaceuticals based on efficacy and marker evidence.
 - b. 5+ years: Trials of practical ALS subtype markers as guides for treatment planning.
 - c. 5+ years: Publication of evidence-based guidelines for treatment protocols and multidisciplinary care management.

REFERENCES

1. *Evaluation of the Congressionally Directed Medical Research Programs Review Process, a Report of the National Academies of Sciences, Engineering, and Medicine*. 2016. The National Academies Press, Washington, DC. (<http://nationalacademies.org/hmd/reports/2016/cdmrp.aspx>).
2. Weiskopf, et al. 2005. Prospective Study of Military Service and Mortality from ALS. *Neurology*. 64(1).
3. CDC National ALS Registry and Biorepository, <https://www.cdc.gov/als/Default.html>.
4. *Guidance for Industry. Drug Development for Amyotrophic Lateral Sclerosis* (<http://www.alsa.org/advocacy/fda/assets/als-drug-development-guidance-for-public-comment-5-2-16.pdf>).
5. *Cytokinetics and Brainstorm Cell Therapeutics*. 2016. White Paper. BioCentury Collections Amyotrophic Lateral Sclerosis (ALS) Collection.
6. *Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment. Guidance for Industry*. 2018. U.S. Department of Health and Human Services, Food and Drug Administration (<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM596718.pdf>).
7. Hirtz D, et al. 2007. How common are the “common” neurological disorders? *Neurology*. 68:326-337.
8. Arthur KC, et al. 2016. Projected increase in amyotrophic lateral sclerosis from 2015 to 2040. *Nat. Commun.* 7:12408 doi: 10.1038/ncomms12408.