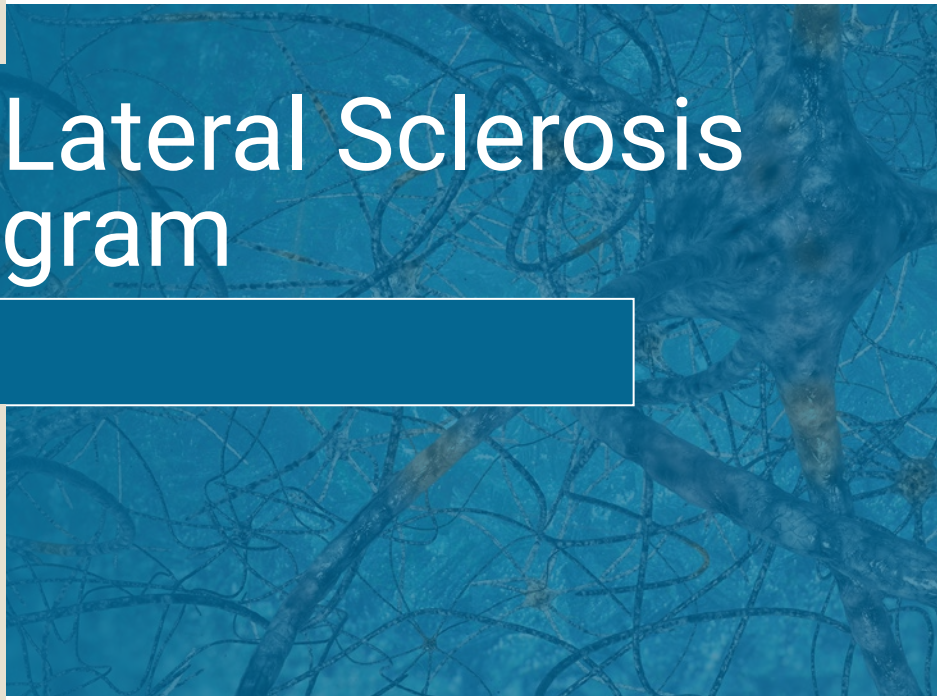
CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

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 annually during the program's Vision Setting meeting and updated as necessary.

ALSRP BACKGROUND AND OVERVIEW

Shortly after the 1990-1991 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 through the VA. 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 largely unknown.

In 2007, the ALS advocate community heightened political awareness of the connection between military service and the risk of ALS. They encouraged Congress to commit the resources and funding necessary to find treatments for Veterans afflicted with ALS and 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 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 ALSRP 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 Vision and Mission of the ALSRP are as follows:

VISION: *Improve treatments and find cures for people with ALS*

MISSION: *Fund impactful research to develop ALS treatments*

The ALSRP, like all CDMRP programs, 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. Of particular interest, consumers, patient advocates, care givers, and/or survivors participate as full members on the peer review and programmatic panels. The ALSRP Programmatic Panel includes a diverse group of basic and clinical scientists and patient advocates, as well as program directors in the ALS research field and from other federal funding agencies such as the NIH and CDC. These panel members provide information about the research being funded in related areas by their organizations.

Appropriations for the ALSRP from FY07-FY23 total $229.4M. Thus far, funds have supported a total of 189 awards to multiple recipients through a competitive two-tier review process. The ALSRP has funded research nationally and internationally at for-profit, non-profit, public, and private organizations such as universities, colleges, hospitals, laboratories, industry, and small, start-up pharmaceutical companies. Award data and abstracts of funded research proposals can be viewed on the CDMRP website (https://cdmrp.health.mil/).

RESEARCH AND FUNDING ENVIRONMENT

ALS RESEARCH LANDSCAPE

ALS Prevalence and Incidence

In 2022, the National CDC ALS Registry published a report estimating an average ALS prevalence of 5.5 persons per 100,000 within the U.S. population and a total of 32,000 new cases each year[3] The prevalence data was compiled in 2017 from the CDC Registry. Of those diagnosed, there has been a rising trend in prevalence of ALS in cohorts between persons aged 70-79. The lowest occurrence of ALS was found in persons in the age group of 18-39, with males diagnosed at higher rates than females overall. ALS affects persons of every race and ethnicity; however, whites, non-Hispanics, males, and persons over the age of 60-79 make up the largest percentages of those diagnosed.

ALS Deaths

ALS is a fatal neuromuscular disease; the most recent CDC Registry data from calendar year 2017 indicate that there were 24,328 total ALS deaths, which converts to an overall age-adjusted mortality rate of 1.70.[4] Unfortunately, the prognosis for most ALS cases is grim, and after official diagnosis, most patients succumb to the disease within 2-5 years. However, there is a subset of ALS patients that comprises about 10% of those diagnosed and lives more than 10 years after their diagnosis. Within that subset, there is a smaller subset, around 5%, who may live an additional 20 years past their diagnosis. It is not understood why this subset of ALS patients have this increased life expectancy, but it is a subject of scientific inquiry.

ALS Risk Factors

It is estimated that 5% to 10% of all ALS cases are inherited or familial-linked; thus, this subtype is referred to as “gene-positive ALS.” 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. To date, mutations in more than 15 genes have been found to cause gene-positive ALS. The sporadic subset of ALS is referred to as gene-negative ALS and comprises 90% to 95% of ALS cases. Risk factors for gene-negative ALS are unclear; however, links have been made between ALS onset and occupational exposures, military service, infectious agents, physical activity, and trauma. It is also associated with some forms of familial frontotemporal dementia. Knowledge of environmental, demographic, and behavioral risk factors is still emerging; so far, no definite non-genetic risk factor has been identified.

ALS Underlying Pathology

ALS is characterized by progressive degeneration of the motor neurons of the central nervous system. Pathogenesis of ALS remains widely unknown. Pathological features and gene mutations associated with ALS have offered essential insights into etiology. Most knowledge about disease mechanisms has been learned from the analysis of genetic forms of ALS as well as both cellular and animal models. These approaches have elucidated multiple cellular and molecular processes that are dysfunctional in ALS. These include abnormal regulation of RNA biogenesis and metabolism, neuroinflammation, disturbances in mitochondrial function, altered synaptic transmission, protein dyshomeostasis, and disturbances in subcellular structures such as the nuclear pore complex, among others. Understanding the molecular and cellular mechanisms underlying ALS is crucial for the development of therapeutic approaches tailored to different forms of ALS.

ALS Biomarker Development

Biomarkers can be used as indicators of disease states and/or biological changes in response to treatment or disease progression. Researchers have identified molecular biomarkers that appear to differentiate progression rates or have diagnostic potential. Recent work has focused on neurofilaments (neurofilament light [NF-L] and neurofilament heavy [NF-H], 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.

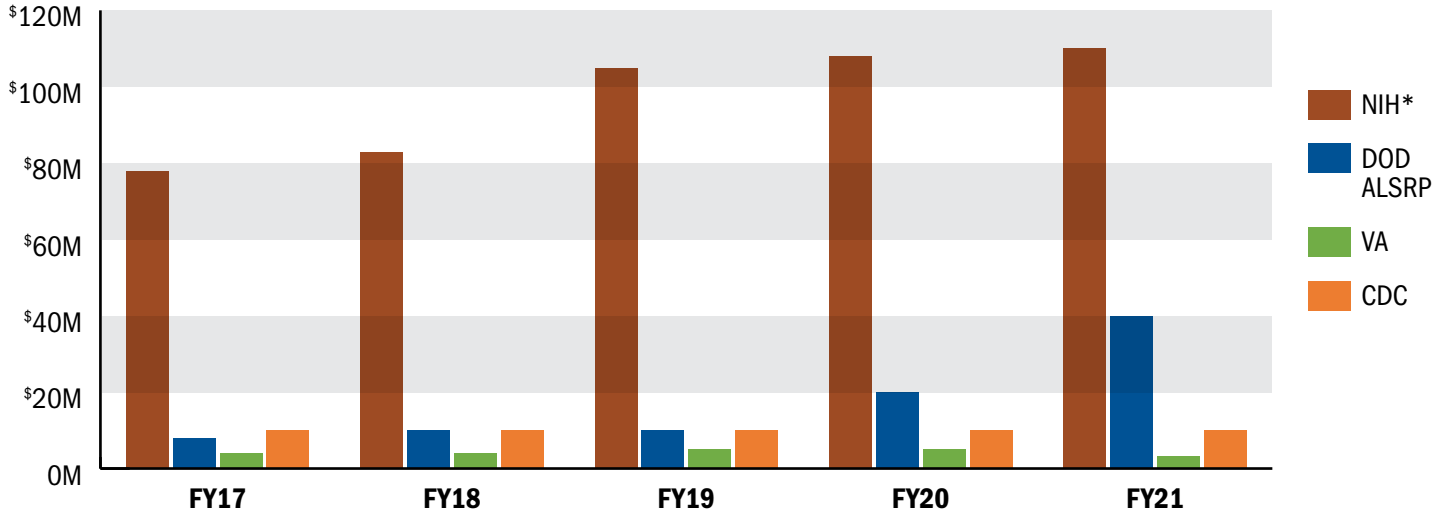
ALS Treatment

Currently, there are no known therapies to effectively halt the progression of ALS, although two U.S. Food and Drug Administration (FDA)-approved drugs, Riluzole and Edaravone (Radicava), have been shown to modestly slow ALS progression in clinical trials. In 2022, the FDA approved Radicava for oral administration, allowing patients to seek treatment for ALS from the comfort of their own home. A third drug, Nudexa, has been used to control emotional dysfunction and improve speech, swallowing, and control of salivation. Most recently, in 2022, AMX0035 (Relyvrio) was approved by the FDA as a fourth drug to help slow disease progression and prevent neuronal cell death. Progress has been made in clinical management of the disease, including respiratory and nutritional support (e.g., percutaneous endoscopic gastrostomy/nutrition, NIPPY™ a pressure controlled, positive pressure ventilator, and dextramethorphan).

ALS FUNDING LANDSCAPE

Many ALS research funding opportunities for scientists and clinicians are made possible through support from the federal government (i.e., NIH, CDC, VA, and DOD), industry, and non-profit organizations. Funding data for the ALSRP and other federal sources are shown in the figure below.

Figure 1: Federal Funding in ALS



*NIH funding by institute: 52% National Institute of Neurological Disorders and Stroke (NINDS), 31% National Institute on Aging, 2% National Institute of Environmental Health Sciences, 2% National Center for Advancing Translational Sciences, 13% other

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.

New in 2021 was funding for the Accelerating Access to Critical Therapies for ALS Act, more commonly known as "ACT for ALS." The bill is intended to enact changes in how research for ALS is funded and who can access ongoing investigational therapies. In addition, Congress provided $1M to support a National Academies of Sciences, Engineering, and Medicine study that brought together experts to devise a blueprint to make ALS a livable disease. The blueprint is expected to be released in 2024.

The following table (Table 1) shows how major funders are currently filling 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 fund across research areas. The information in this table depicts the major funders in a particular focus area and the funders' goals and objectives for addressing knowledge gaps.

TABLE 1: FUNDERS OF ALS RESEARCH BY FOCUS/GAP AREA

Focus/Gap Area	Major Funder(s)	Goal/Vision	Objective/Mission
Epidemiology/ Surveillance	**CDC**	Collect, manage, and analyze data about people with ALS	Estimate cases, understand who, examine connections, improve care
Underlying Pathobiology	**NINDS**	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
Clinical Biomarkers	**ALSRP**	Improve clinical trials through parallel biomarker development	Develop and improve clinical biomarkers to enrich clinical trials in ALS
Therapeutic Discovery and Preclinical Validation	**ALSRP**	Improve treatments and find cures for people with ALS	Fund impactful research to develop ALS treatments
Clinical Trials/ Clinical Management	**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 Registry[5] expanded ALS surveillance outside the Veteran population and most recently identified over 17,000 adult persons having definite ALS in 2017. The estimated new incidence of ALS in the United States recorded for the years 2014 to 2016 was between 4,800 to 6,045. Annual appropriations of $5M-$10M 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 studies.

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 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

Underlying pathobiology research accounts for the largest portion of the NINDS portfolio. With advances in sequencing and "omics" technologies, discovery of ALS genes and disease pathways has grown exponentially over the past decade. Building on these discoveries, a growing number of ALS model systems have been engineered to enable research to help determine 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 etiology of ALS is providing opportunities to develop better in vivo and in vitro models of ALS. These opportunities include using microbial clustered regularly interspaced short palindromic repeats (CRISPR) engineering, which allows scientists to "rewrite" DNA sequences in any type of cell. For example, researchers can take cells from ALS patients and induce or change them into pluripotent stem cell lines that can then be differentiated into any cell type of interest. CRISPR technology can even be used to develop three-dimensional tissue models and animal models.

High-quality ALS patient biospecimens, such as autopsy tissue and biofluids, curated in biorepositories and tissue cores also serve as valuable tools for ALS research. Biorepositories then can be mined using a variety of scientific approaches, from computational/systems biology to lab bench hypothesis-driven discovery approaches such as high-throughput screens and everywhere in between, all to bring new ideas forward to be fed through the pipeline. To harnesses the opportunities afforded by these new approaches, model systems, and patient-derived resources, the NIH and several private foundations/non-profit organizations are invested in developing and expanding these resources and technologies to better understand underlying ALS pathobiology.

Biomarkers

Progress

Research approaches to identify biomarkers account for about 5% of the NIH portfolio and include both diagnostic and prognostic biomarkers. The focus is on biomarkers detected in plasma and serum, as well as imaging and measures of functional strength and motor neuron survival, which scientists can determine by using electro-impedance myography and motor unit number estimation. Significant progress has been made in identifying cerebrospinal fluid markers (NF-H and NF-L) that determine prognosis of ALS disease severity, and efforts are underway to validate these markers in multi-center studies. Examples of funding initiatives enabling biomarker research include biomarker-focused requests for proposals and the TDP-43 Biomarker Grand Challenge Program (specifically released by the ALS Association to identify a biomarker to track TDP43 aggregation, which will facilitate ALS biomarker research by allowing scientists to directly trace and identify this common ALS mutation in their samples). Efforts to centralize important resources such as cerebrospinal fluid, plasma, and urine for biomarker discovery include CReATe and NeuroBANK, which are open-access repositories housing well-annotated samples. A listing of ALS repositories can be found at https://cdmrp.health.mil/alsrp/resources/alsrpresources.aspx. 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. The ALSRP, with its ALS-specific mission, is increasing the federal investment in clinical ALS biomarker research through its Clinical Biomarker Development Award. This type of mechanism was offered for the first time in FY20, and through FY21, a total investment of over $8M has been dedicated to this space. The goal of these investments is to support development or improvement of clinical biomarkers to enrich clinical trials in ALS. Across mechanisms, the ALSRP emphasizes therapeutic strategies need to be developed simultaneously with the molecular tools (biomarkers) that will be needed to guide their use in eventual clinical trials. Predictive, prognostic, and pharmacodynamic biomarkers are critical to improving trial design and interpretation. Additionally, balancing broad inclusion with ensuring that a given therapeutic strategy is being tested on the appropriate patients' needs to be considered. As an incentive for biomarker development, even at the earliest stage of therapeutic development, the ALSRP offers additional funding under the Therapeutic Idea Award to applicants that include a plan to develop a biomarker in parallel with their therapeutic research.

Challenges

While biomarkers are recognized as a priority, mechanism-specific, predictive, and pharmacodynamic biomarkers remain elusive. Only ~50% of ongoing clinical trials as of the writing of this report appear to be incorporating biomarkers beyond traditional endpoints and/or actively collecting samples for new biomarker validation/discovery. The vast majority of clinical trials for sporadic ALS patients are recruiting broad patient populations, despite targeting specific biological pathways that may only have therapeutic relevance to specific patient subsets. Of further note, predictive and pharmacodynamic biomarkers are lacking in trials other than gene-targeting strategies for specific familial mutations.

Opportunities

Collaborative, openly accessible repositories, and generating synergies that leverage existing resources are all opportunities to expand biomarker research. Investment in the development of markers, such as enrollment criteria and clinical endpoints, will significantly enable development of effective and ALS-specific therapeutics. Furthermore, new therapeutic strategies need to be developed simultaneously with the biomarkers that will be needed to guide their use in eventual clinical trials.

Therapeutic Discovery and Preclinical Validation

Progress

Types of 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. 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 moving it into first-in-human trials. This preclinical space is under-resourced; consequently, the ALSRP recognized this gap at the program's inception in FY07 and focused its mission on accelerating drug discovery. This preclinical niche is not filled by any other agency. Out of 189 projects supported by the ALSRP, over 60% of which are still in progress, several promising new ALS drug candidates have moved into advanced drug development, and four have advanced to early-phase clinical trials.

Each year, the NIH invests in therapeutic research; however, there is no predetermined investment strategy for ALS research. In recent fiscal years, ALS therapeutic discovery and preclinical validation accounted for roughly 18% of the NIH portfolios. The ALSRP, with its ALS-specific mission, has been the major funder of preclinical and therapeutic validation studies through its Therapeutic Idea Award (TIA) and Therapeutic Development Award (TDA). To date, 84% of the portfolio is dedicated to these types of studies, representing a total investment of $120M.

The TIA supports the initial exploration of innovative, high-risk, high-gain ideas aimed at drug or treatment discovery. The studies supported are hypothesis-driven and generate preliminary data for future avenues of therapeutic investigation. The TIA biomarker option supports preclinical efforts such as the development of target engagement biomarkers, objective pharmacodynamic biomarkers to measure the biological effect of an investigational therapeutic, or predictive/cohort-selective biomarkers that indicate whether a specific therapy will be effective in an individual patient or patient subgroup. This funding mechanism emphasizes hypothesis-driven therapeutic development and is designed to promote new ideas aimed at drug or treatment discovery that are still in the early stages of development. The ALSRP prioritizes this development stage, and the TIA continues to be the largest investment area for the program.

The TDA supports therapeutic validation studies that are empirical in nature and product-driven. Activities supported by this award include confirming candidate therapeutics that can optimize the potency, pharmacological properties, and testing of derivative and sister compounds; validating early pilot studies; formulation; and ensuring stability, leading to Good Manufacturing Practices certification and IND application-enabling studies. Development or further characterization of validated biomarkers, in parallel with the main therapeutic effort and for use in eventual clinical trials, is a critical component.

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.

Opportunity

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. The NINDS's recent strategy plan[7] for ALS highlights additional opportunities and priorities in the preclinical investigative space for ALS, including (1) enhancing the understanding of basic biology of motor neuron disease (there is a wide consensus that we must do more to understand the cellular and molecular events that underlie nonfamilial, sporadic ALS) and (2) translating novel disease pathways into clinical therapeutic development.

Examples of ALSRP-Supported Products Advancing to Further Development

- **Riluzole + Elacridar:** Under an ALSRP Therapeutic Idea Award, treatment with Elacridar (an efflux pump inhibitor) + Riluzole (a glutamate blocker) 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 to test their formulation in 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. Research conducted under an ALSRP Therapeutic Development Award showed that treatment with CuATSM in a mouse model of ALS increased the life span of the mice compared to mice that did not receive CuATSM. The ALSRP has funded an additional study to develop three novel classes of copper carriers that have reduced toxicity, are easily synthesized, and are effective at low dosages, and these formulations are moving quickly through the research pipeline. The ALSRP-funded investigator has secured additional 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. Furthermore, Procypra Therapeutics, an Australian company, is initiating a clinical trial of their derivative form of CuATSM.

- **Targeting miR-155**: miR-155 is a microRNA associated with ALS. microRNAs are important molecules because they help cells determine what genes are expressed, which then directs the amount and type of proteins that cells make. Protein errors are all hallmarks of the ALS disease state, so treatments that have the potential to target or manipulate key steps in protein synthesis, like microRNA can, are of great interest therapeutically. Specifically, in a study carried out under an ALSRP Therapeutic Idea Award, genetic manipulation via microRNA was shown to delay ALS disease onset and extend survival in a mouse model of ALS. MiRagen Therapeutics, Inc., is now developing a therapeutic optimized to target miR-155 in humans as a treatment for ALS.
- **Apo-H-Ferritin:** The ALSRP funded a Therapeutic Idea Award to encapsulate apo-H-ferritin in liposomes in order to help increase the viability and bioutilization of the apo-H-ferritin, which could be a potential treatment for ALS; apo-H-ferritin has the ability to capture iron and safely sequester and redistribute the iron away from regions like the brain and spinal cord. Excess iron is extremely reactive and oxidizing. It has been noted clinically for years that ALS patients have much higher levels of free and deposited iron compared to healthy controls, which is thought to contribute to the accelerated degradation of motor neurons, the hallmark of ALS. The ALSRP study looked at several different routes of apo-H-ferritin infusion in a mouse model of ALS, and then, in addition to studying the different formulation's ability to remove and redistribute iron in their model, they observed the onset of ALS symptoms and the life span of mice receiving different formulations. They found that the infusion that had apo-H-ferritin safely encapsulated in liposomes and was given at the time of symptoms onset extended the lifespan of the mice. Development and refinement of these formulations are being continued through the ALS Association, and a medical device company has been engaged to develop a delivery method involving surgical implantation of a pump that would deliver a solution into the lumbar spinal space.
- **Apilimod:** Under an ALSRP-supported Therapeutic Development Award, a chemical screen of small molecules that were known to target various cellular processes revealed that Apilimod is a powerful inhibitor of the protein PIKFYVE, which helps direct what enters and exits the cell via its role in cellular trafficking. The ALSRP investigator found PIKFYVE inhibition via Apilimod improved ALS-disease symptoms in several different animal models as well as in human iPSC cells. The researchers believe that PIKFYVE inhibition can remove the harmful protein aggregates common in ALS cells by increasing cellular exocytosis, the term used to describe how a cell disposes of harmful waste products. Since Apilimod was found to help eliminate these toxic proteins' aggregations in ALS models, it is thought that the molecule will help protect cells from further neurodegeneration; in fact, the researchers found that suppression of the *Pikfyve* gene in ALS mouse models reduced disease symptoms and extended the survival of the mice. In order to make results more applicable to the human situation, researchers also studied the effect of chronic suppression of the PIKFYVE protein, since it plays a role in other cellular processes, and found that consistently low levels of the protein were well tolerated in ALS mouse models at extended time points, thus adding further value to potential treatments such as apilipomid that decrease or inhibit PIKFYVE production. Based on these findings and in conjunction with the company, AcuraStem, Inc., a novel PIKFYVE inhibitor is now advancing toward ALS clinical trials. The ALSRP-supported work additionally developed analysis software with a partner, DRVision Technologies, which enabled automated detection of neuron number and the rate of neurodegeneration during large-scale screens. This software is now moving toward commercialization.

Clinical Trials/ Clinical Management

Progress

Historically, the ALSRP has been focused on preclinical validation and therapeutic development; however, starting in FY21 with increased appropriations and new congressional direction, the ALSRP has expanded into the clinical trial space. In FY21, Congress added language encouraging prioritization of treatment research: *"The committee is aware of research that reports that people who served in the military are twice as likely to develop and die from Amyotrophic Lateral Sclerosis [ALS] as those with no history of military service, and therefore, it is especially important that this research be continued into early phase clinical trials. The committee encourages the Department of Defense to take a broad approach to the type of research projects it may support through the peer-reviewed approach to help advance potential treatments for people living with ALS. The committee recommends $40,000,000 for a peer-reviewed ALS research program."* In response, the ALSRP offered the Therapeutic Biomarker Pilot Trial Award (TBPTA), which transitioned to the Pilot Clinical Trial Award (PCTA) in FY22 and FY23, becoming the first mechanism to support clinical trials. The current PCTA supports rapid implementation of clinical trials with the potential to have a significant impact on the treatment or management of ALS. The intent is to fund clinical studies that aim to de-risk and inform the design of more advanced trials by investigating safety, feasibility, biomarker application, and therapeutic efficacy in relevant patient populations. Projects may range from phase 1 to small-scale phase 2 clinical trials and may be designed to evaluate promising drugs, biologics, or devices with anticipated therapeutic impact that are supported by strong scientific rationale and existing preclinical data. Potential impact is not whether a therapy is ready at the conclusion of the

trial, but rather, whether the outcomes will improve and accelerate future larger trials. The PCTA incorporates parallel biomarker validation, which can include target engagement biomarkers, pharmacodynamic biomarkers to measure the biological effect of an investigational therapeutic, and/or predictive/cohort-selective biomarkers to indicate whether a specific therapy will be effective in an individual patient or patient subgroup. The ALSRP has funded five Pilot Trial studies (two TBPTAs and three PCTAs) thus far, and the CDMRP is expected to allot approximately $9.6M to fund PCTAs in FY23.

There are currently no known therapies to effectively halt the progression of ALS, and more than 50 drugs are under investigation for the treatment of ALS. The most funding in clinical trial management to date has been through industry, pharmaceutical companies, and venture capitalism. However, to date, only four distinct drugs have been marketed in the United States, with AMX0035 (Relyvrio) very recently approved in 2022 after demonstrating a reduction in disease progression. Riluzole, marketed as Rilutek, was approved to treat ALS in 1995. An easier-to-swallow liquid form of Riluzone, Tiglutik, was approved in 2018, and an oral film formulation, Exservan, was subsequently approved in 2019. The next distinct ALS therapeutic Edarovone, sold under the brand names, Radicava and Radicut, was approved decades after Riluzole in 2017. Last, Nuedexa, approved in 2010, specifically targets the pseudobulbar region of the brain and helps control some ALS symptoms by quelling emotional outbursts and improving speech in patients with ALS. Thus, progress is being made in the field of ALS treatment, albeit slowly.

Challenges

There are only a 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 that treatment approaches specific to individual subtypes will be needed. While many treatment protocols and clinical practice guidelines 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. Other major limitations are cost and risk/benefit tradeoffs, given the severity and rapid progression of ALS.

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 website (https://cdmrp.health.mil/alsrp/resources/alsrpresources.aspx) to make these broadly available to the research community. Data sets or biosamples from clinical trials and 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 continued investment in precision medicine by making treatments that are only effective in small subgroups of ALS patients viable candidates for further investment. 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. For example, since its development in 1995 with nine academic clinical centers, the Northeast Amyotrophic Lateral Sclerosis (NEALS) Consortium has grown to over 130 research centers, internationally and nationwide, committed to the research of ALS and motor neuron disease (MND), and collaborations among investigators are encouraged to leverage ongoing research. The NEALS Consortium's mission is to translate scientific advances into new treatments for people with ALS and MND as rapidly as possible. With established funding from the ALS Association, NEALS creates training opportunities for research experts at their highly equipped member sites to initiate new trials and produce high quality data. Faculty from the Sean M. Healey and Affiliated Managers Group, Inc. (AMG) Center for ALS at Mass General, in partnership with the NEALs Consortium, designed a first-of-its-kind platform trial for ALS. This multicenter, adaptive platform trial is testing multiple investigational products in parallel to find safe and effective treatments for people living with ALS and has increased the chance of finding an effective treatment.

In cases of rapidly progressing and life-threatening diseases with unmet medical needs, such as ALS, factors such as 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 are being considered to accelerate the drug approval process and to save time. *Drug Development Guidance for Industry*, published in 2019 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]

ALSRP-Supported Products in Clinical Trials

- **Tegoprubart (formerly known as AT-1501):** The ALSRP funded a Therapeutic Development Award to perform preclinical studies of the antibody AT-1501 and found that it blocked specific immune cell activation and protected nerves from damage caused during the progression of ALS. These studies showed that AT-1501 successfully prevented the molecular signaling that normally activates the inflammatory response seen in ALS patients. Because of these promising results and further efforts to refine AT-1501 by the ALS Therapy Development Institute, the FDA granted Orphan Drug Designation and IND approval of AT-1501. Tegoprubart was advanced through early clinical trials by Anelixis Therapeutics, a for-profit clinical-stage development company, with phase 1 trials concluding in 2019. Next, in May 2022, Eledon Pharmaceuticals, the company that acquired Anelixis Therapeutics in 2020, announced their results from the phase 2a trial, an open-label, dose-escalating, safety, and biomarker study of Tegoprubart. The endpoints of the study were safety and tolerability, and changes in pro-inflammatory biomarkers, and the results demonstrated that the drug was well tolerated and there were no drug-related serious adverse events. As reported, the researchers found that Tegoprubart reduced pro-inflammatory biomarkers and noted that the reduction was associated with a trend toward slowing disease progression (Clinical trial number: 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, a protein that, when mutated, causes neurodegenerative diseases like ALS in ALS animal models. A class of neuroleptics, drugs that block dopamine receptors, were identified, and the molecule pimozide was the most potent, as confirmed in all models tested. Because pimozide is already FDA-approved, it was able to move quickly into a small phase 2b 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 and sponsored by the University of Calgary and Alberta Health Services. Treated patients showed stabilization of motor activity, whereas untreated patients did not show a stabilization in the progression of their disease. Because of the results of the smaller phase 2b trial, a national phase 2b trial is now underway 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 examine the effect of growth factors, specifically GDNF, on the health of motor neurons to determine growth factor potential as a possible novel therapeutic approach to protect motor neurons. Under a Therapeutic Development Award, researchers used ALS patient post-mortem brain tissue to generate hNPCs that secrete GDNF and injected the cells into the spinal cord and brain cortex of rodent and non-human primate ALS models to see whether they could get the cells to secrete GDNF in the animals, and whether the growth factors in fact helped protect motor neurons. Indeed, the researchers were successful and were able to demonstrate enhanced motor neuron function and an increased survival in the animals receiving the injection. The California Institute of Regenerative Medicine has expressed interest in these preliminary results and has initiated an $18M grant to move this approach into clinical trials in patients (NCT02943850).
- **Prosetin:** The ALSRP funded a Therapeutic Idea Award to investigate neuroprotective agents as potential therapeutics for ALS. The award resulted in the identification of the potential therapeutic, prosetin, a brain-penetrant kinase inhibitor that is orally bioavailable, metabolically stable, and well-tolerated in long-term administration paradigms, making it a prime candidate for the treatment of ALS. The work to move this potential treatment closer to clinical trials was a collaborative effort with Project ALS, a non-profit entity that pursued orphan drug designation for prosetin from the FDA. In early 2022, Project ALS partnered with ProJenX, which obtained the license to prosetin from Columbia University, to initiate a first-in-human phase 1 clinical trial of this drug in healthy volunteers and ALS patients. The overall goal of the clinical trial is to determine the optimal dose of prosetin and acquire biomarker data to inform the design of future late-stage trials (NCT05279755).

STRATEGIC DIRECTION

The short- and long-term objectives of the ALSRP remain focused on translational research for the benefit of Service Members, Veterans, and all others living with ALS. Approximately 6,000 people in the United States die each year from ALS, and 400,000 cases of ALS in the world are projected in 2040 due to the aging population.[4] 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 advancing 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 to identify improved implementation strategies for new (and existing) treatments.
- Time to achieving milestones is realistic and acceptable.

STRATEGIC GOALS

The ALSRP's strategic goals are defined below. These goals outline the program's priorities of maintaining a bridge where discoveries made in the laboratory lead to advanced industry development and clinical trials. However, the ALSRP does not define what types of projects will be funded; rather, it encourages investigators to propose their best ideas that mirror the program's priorities and goals.

1. Direct resources toward innovative and impactful preclinical treatment discovery research.
    a. Support proof-of-concept drug discovery research.
    b. Support research generating rigorous data towards a hypothesis that modulating the putative drug target/affected pathway will produce a desirable outcome for ALS.
    c. Support research to discover novel therapeutic delivery approaches.
2. Direct resources toward strategically relevant preclinical treatment validation studies and projects that hold promise to advance towards clinical trials.
    a. Support research to validate promising leads; targeting druggable or relevant pathways in appropriate model systems to enable more advanced drug and/or device development.
    b. Support IND application-enabling research studies.
    c. Support advancement of therapeutic approaches driven by biomarker identification.
3. Direct resources toward leveraging patient-based ALS resources to better define subtypes, predict therapeutic response, or assess prognosis.
    a. Support research on the development or improvement of clinical biomarkers to enrich clinical trials in ALS.
    b. Support research to correlate clinical trial-related biosamples, imaging, or epidemiological data with clinical outcomes.
    c. Support research maximizing ALS clinical resources to validate clinical biomarkers.
4. Direct resources toward early-phase intervention trials that will generate compelling biomarker data that can then inform and de-risk more advanced trials for the treatment or management of ALS.
    a. Support the rapid implementation of biomarker-driven clinical trials with the potential to have a significant impact on the treatment or management of ALS.

TRANSLATING PRIORITIES INTO MECHANISMS

The following figure illustrates how the ALSRP funding mechanisms address program priorities.

PROGRAM PRIORITIES

Preclinical Treatment Discovery

- Hypothesis-driven drug development
- Identification of candidate drug leads
- Measurements of drug-target engagement

Preclinical Treatment Validation

- Secondary validation and drug delivery
- Optimization of drug properties
- Collection of data for FDA submission
- Development of Good Manufacturing Practices methods

Clinical Biomarker Development

- Use of established ALS patient repositories
- Correlation of patient samples with clinical outcomes
- Analysis of biosamples to better define subtypes or predict therapeutic response

Early Phase Clinical Trials

- Biomarker-driven approaches to improve the design of later-stage trials
- Demonstration of drug-target engagement, pharmacodynamics, or refinement of patient selection to de-risk future trials
- Optimization of established clinical care

RESEARCH MECHANISMS

Therapeutic Idea Award (TIA)

- FY10-present
- Ideas in the early stage of development
- Identification of candidate drug leads
- Co-development of biomarkers to demonstrate drug actions

Therapeutic Development Award (TDA)

- FY07-present
- Secondary drug validation and optimization studies
- IND application-enabling studies
- Continued development of markers to demonstrate drug actions

Clinical Biomarker Development Award (CBDA)

- FY20-present
- Leverage patient-based ALS resources
- Correlative clinical research to better define subtypes, predict therapeutic response, or assess prognosis

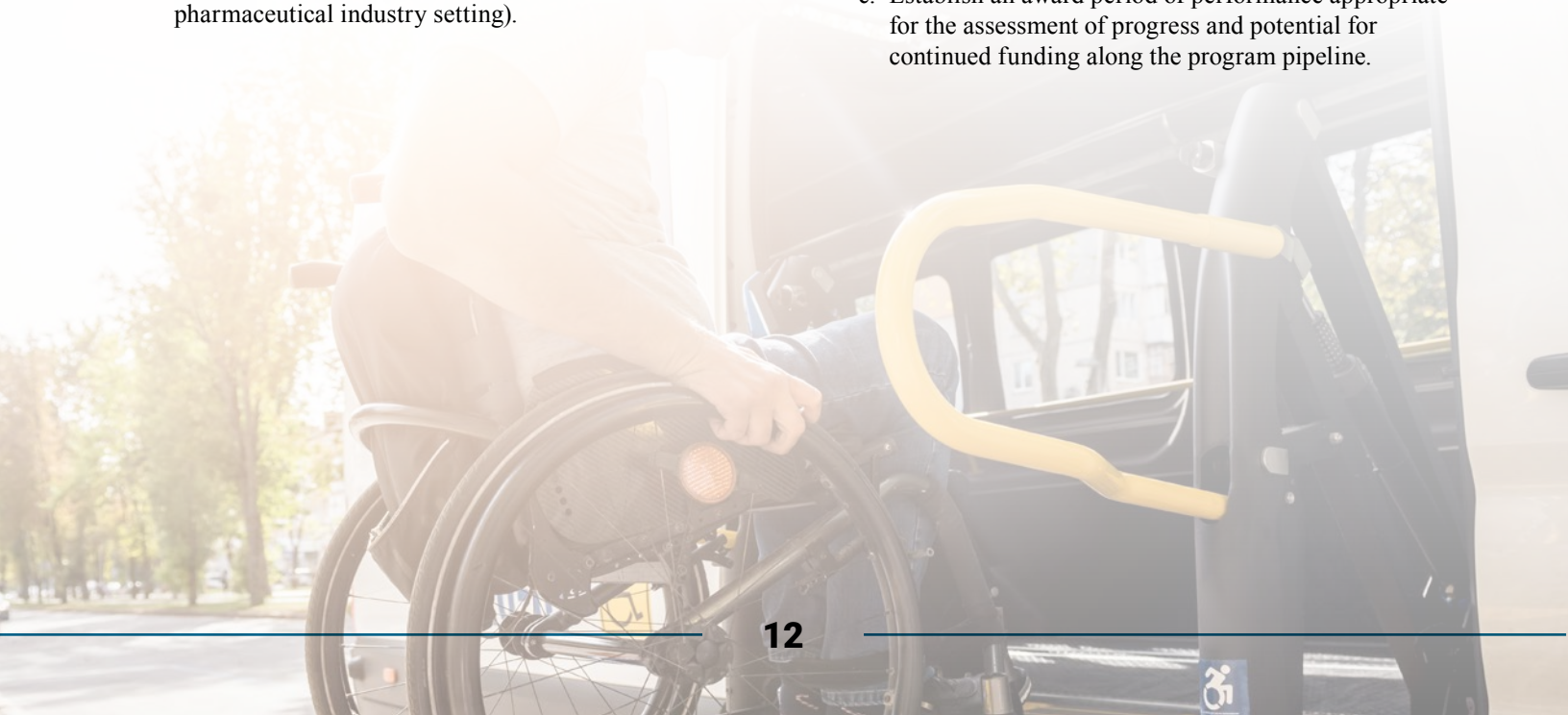
Pilot Clinical Trial Award (PCTA)

- FY21-present
- Exploratory clinical trials of novel therapeutics to demonstrate feasibility and inform the design of more advanced trials
- Requirement for plans to generate biomarker data
- Optimization of established clinical care, including improvements to assistive technologies and specific symptom management strategies

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 reevaluated and updated as necessary during the program's annual Vision Setting meetings.

1. Treatment discovery funding mechanism (the TIA) to accelerate therapeutic ideas and identification of therapeutic agents.
    a. Enable researchers to build on innovative basic science findings and initiate preclinical drug discovery.
    b. Emphasize innovation and impact as primary criteria.
2. Treatment validation funding mechanism (the TDA) supporting optimization of therapeutic strategies showing promise.
    a. Advance therapeutic approaches/compounds with significant preliminary data through more advanced preclinical development and toward IND application submission/clinical testing.
    b. Support development of biomarkers to improve the drug development process in parallel with the main therapeutic advancement effort.
3. Clinical biomarker mechanism (the CBDA) to develop and improve clinical biomarkers to enrich clinical care.
    a. Support research that leverages existing human studies and data such as ongoing clinical trials or established clinical repositories.
    b. Optimize existing treatment strategies and develop biomarkers of ALS subtypes or biomarkers of clinical effects and responses.
4. Early-phase clinical trial mechanism (the PCTA) to support rapid implementation of clinical trials with potential to have significant impact on people living with ALS.
    a. Support exploratory clinical trials of novel therapeutics to demonstrate feasibility and to inform the design of more advanced trials.
    b. Generate biomarker data measuring target engagement, pharmacodynamic effects, and/or be predictive/cohort-selective.
    c. Optimize current clinical care, such as respiratory care strategies, devices, and assistive technologies, as well as other symptom-management strategies.
5. For all funding mechanisms, the ALSRP will preferentially fund projects that will have the largest impact on people living with ALS.
    a. Projects with impacts in areas of unmet needs will be prioritized over projects where research efforts are ongoing and/or substantial dedicated funding (e.g., within the NIH and/or the biotechnology and pharmaceutical industry setting).
    b. Projects that are in the funding-gap stage between academic research and industrial partnership that require additional 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 early stage, hypothesis-driven therapeutic development, and screening.
    b. Investments in novel approaches to therapeutic delivery.
2. Anticipated contributions to Preclinical Treatment Validation, as evidenced by portfolio analyses.
    a. Investments in validation studies, advancing preclinical treatment research with a clearly defined path to clinical proof of concept.
    b. Parallel investments in biomarker-driven therapeutic development that serve as early readouts of efficacy or cohort selection.
3. Anticipated contributions to development and improvement of Clinical Biomarker Research as evidenced by portfolio analyses.
    a. Investments to maximize clinical ALS resources and biorepositories that better define subtypes, predict therapeutic response, or assess prognosis.
    b. Investments in the development and validation of biomarkers that enrich clinical trials in ALS.
4. Anticipated contributions to Clinical Trials as evidenced by portfolio analyses.
    a. Investments in early-stage clinical trials with compelling biomarker data.
    b. Investments in promising biologics and investigational devices with anticipated therapeutic impact.
    c. Investments in optimization of current clinical care and 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/disease pathway in preclinical ALS model systems.
    b. Contributions to the scientific community (publications, patents, etc.) describing optimization of therapeutic delivery methods of 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 biomarkers to monitor progression in model systems to serve as early readouts of efficacy or for cohort selection.
    c. Post-award engagement of federal and non-federal partners for advanced therapeutic development of potential therapeutics.
3. Anticipated contributions to Biomarker Development Research, as evidenced by portfolio analyses.
    a. Improved characterization of ALS subtypes and predictors of therapeutic response.
    b. Validated ALS biomarkers as guides for clinical trial planning.
    c. Biomarker evidence that aligns to FDA's biomarker qualification criteria and context of use for ALS.
4. Anticipated contributions to Early Phase Clinical Trial, as evidenced by portfolio analyses.
    a. New ALS treatments being considered for approval by the FDA.
    b. Precision or personalized medical therapeutics, i.e., therapies with specific effectiveness for patient subgroups or even individual patients.
    c. Publication of evidence-based guidelines for treatment protocols and multidisciplinary care management.

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