CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED
MEDICAL RESEARCH PROGRAMS

Amyotrophic Lateral Sclerosis Research Program

Impactful Research to Develop ALS Treatments

For more information, please visit
cdmrp.health.mil/alsrp

Congressionally Directed Medical Research Programs

In 1992, as a result of a powerful grassroots effort led by the breast cancer advocacy community, Congress appropriated funds for breast cancer research and created the CDMRP. This started a unique partnership among the public, Congress, and the military. Since then, the CDMRP grew to over 30 targeted programs and received over $19.4 billion in appropriations between FY92 and FY22. Congress adds funds for the CDMRP to the DOD budget to support and provide guidance to individual programs like the Amyotrophic Lateral Sclerosis Research Program.

APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for application evaluation, which is critical to ensuring that each of the research program portfolios reflects not only the most meritorious science, but also the research that best meets the program goals. The first tier of evaluation is a scientific peer review of applications, measured against established criteria determining their scientific merit. The second tier is a programmatic review, conducted by a Programmatic Panel, which is composed of leading scientists, clinicians, and ALS patients and advocates. In this tier, the Programmatic Panel compares applications and recommends funding based on scientific merit as determined in peer review, potential impact, portfolio balance, and relevance to overall program goals.

AMYOTROPHIC LATERAL SCLEROSIS RESEARCH PROGRAM

Vision: Improve treatments and find a cures for ALS

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

SCOPE OF PROBLEM

Average life expectancy is **2-5 years** from diagnosis

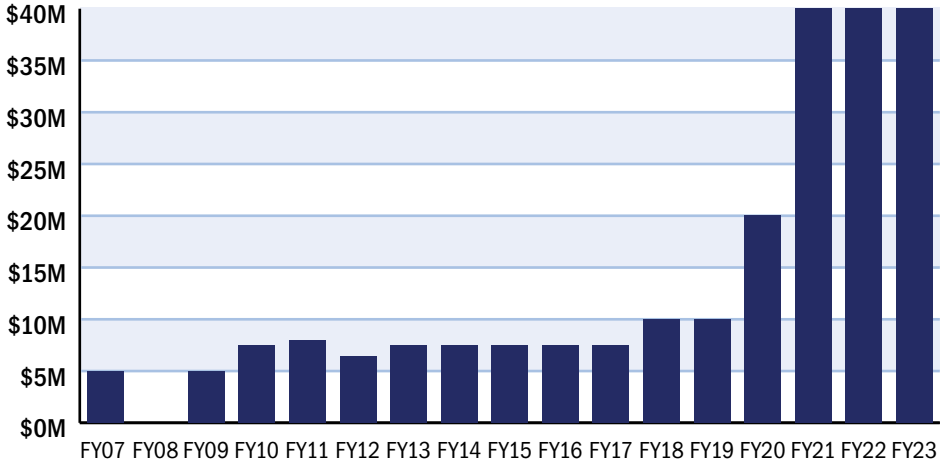
No known therapies to effectively stop or slow progression

ALS is fatal

"As a first-time ALSRP reviewer, I was thoroughly impressed by the process. My opinions after review of proposals were heard along with the scientific reviewers, and together I believe we came out with solutions that were in the best possible interest of ALS patients. The process was informative, educational and affirming for me to be able to share my knowledge and experience as a consumer. "

Lori Larson Heller,
I AM ALS, ALSRP Peer Reviewer

FUNDING HISTORY, TOTAL APPROPRIATION BY FISCAL YEAR



SERVICE MEMBERS ARE MORE LIKELY TO DEVELOP ALS

- Scientific evidence demonstrates that those who serve in the military—regardless of branch, location, or service era— are at a greater risk of dying from ALS than if they had never served
- Reasons for increased risk have been linked to chemical exposure, traumatic injury, viral infection, and intense physical activity; however, no definitive link has been established

1 in 6 people living with ALS are **Veterans**[1]

4,540 Veterans received care for ALS in 2020[1]

Over **1,000** Veterans per year recieve a new ALS diagnosis

The Department of Veterans Affairs implements regulations to establish a "Presumption of Service Connection" for ALS

RELEVANCE TO THE MILITARY

Shortly after the 1990-1991 Persian Gulf War, researchers investigated reports that there was an unexpectedly high rate of young Gulf War Veterans with new amyotrophic lateral sclerosis diagnoses. Two subsequent studies showed that Gulf War Veterans were approximately twice as likely to develop ALS than those of other combat eras. Following publication of these studies, the VA established a registry to identify cases of ALS in Veterans. The VA also requested 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-based study that 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 a Veteran's service contributed to their ALS diagnosis. 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 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, how military service contributes ALS remains largely unknown.

[1] Veterans Health Administration data

[2] Weisskopf, et al. 2005. Prospective Study of Military Service and Mortality from ALS. Neurology. 64(1).

ALSRP'S THERAP

The ALSRP supports a therapeutic development pipeline to find new treatments for ALS. From early ideas to cli

INVESTIGATING EARLY IDEAS

Therapeutic Idea Award

Generating new ideas and knowledge to support advanced research:

- Highly innovative, hypothesis-driven, preclinical therapeutic development in ALS
- Proof-of-concept drug discovery

Targeting miR-155: Errors in how cells make or clean up proteins are all hallmarks of ALS, so treatments that potentially target or manipulate key steps in protein synthesis are of great interest therapeutically. MicroRNAs are important molecules because they help cells determine what genes to express. These genes then direct the amount and type of proteins that cell needs to create. MiR-155 is a microRNA associated with ALS. Recently, an ALSRP-supported study showed that genetic manipulation via microRNA delays ALS disease onset and extends survival in a mouse model of ALS. MiRagen Therapeutics Inc., is now developing a therapeutic to target miR-155 in ALS patients.

Apo-H-Ferritin delivery solutions: Clinical observations note that ALS patients have much higher levels of iron compared to people who do not live with ALS. Excess iron is extremely detrimental and may accelerate the degradation of motor neurons. The ALSRP-supported study looked at several different routes of apo-H-ferritin infusion in a mouse model of ALS and how the subsequent iron distribution impacted symptoms and life span. apo-H-ferritin can capture iron and safely sequester and redistribute the iron away from regions like the brain and spinal cord. The researchers found that highly bioavailable apo-H-ferritin in liposomes (small, lipid surrounded bubbles), given at the time of symptom onset, extended the life span of the mice. Investigators continue to refine this therapeutic with support from the ALS Association.

THERAPEUTIC DEVELOPMENT

Therapeutic Development Award

Developing treatments for clinical trials include:

- Evaluating therapeutic efficacy in at least one ALS-relevant model system
- Goal of this stage is FDA (or equivalent) approval, such as an Investigational New Drug, IND, designation

Pimozide: One approach to identifying a ready-to-go treatment for ALS is to repurpose FDA-approved treatments. One such ALSRP-supported project identified chemical modifiers of TDP-43, a protein associated with ALS, and found that a class of dopamine receptors-blocking drugs were key candidates. One such drug, pimozide, potently modified TDP-43. Since pimozide is already FDA-approved, testing moved quickly into a small phase 2b randomized clinical trial (NCT02463825) with sporadic ALS patients. The trial was successful; treated patients showed stabilization of motor activity. ALS Canada and Brain Canada are funding a larger, national phase 2b trial in Canada to determine the potential for pimozide as a therapeutic (NCT03272503).

Controlling neuronal traffic with Apilimod: Apilimod, a powerful inhibitor of the protein PIKFYVE, improves ALS symptoms in several different ALS animal models. PIKFYVE inhibition can remove the harmful protein aggregates common in ALS cells. Reducing levels of the Pikfyve gene that encodes the protein reduced symptoms and extended the survival of ALS mice. Maintaining consistently reduced levels was well tolerated in ALS mouse models at extended time points. A novel PIKFYVE inhibitor is now advancing toward ALS clinical trials.

PEUTIC PIPELINE

nical trials, the ALSRP funds new, promising and exciting research to find treatments for people living with ALS.

BIOMARKERS

Clinical Outcomes and Biomarkers Award

Clinical measures relevant for disease:

- Identify biomarkers key to understanding how well a drug works, who it works for, and what types of drugs to administer
- Supports the development and improvment of clinical biomarkers to enrich clinical trials

Analysis of Adaptive and Innate Immune Response in FUS-ALS Patients Treated with Antisense Therapy: The goal of this study is to understand the role of a subset of toxic inflammatory cells found circulating in the blood, brain, and spinal cord of ALS patients. This research generated single-cell sequencing data that include RNA at the single-cell level. Once complete, these data will be shared to the scientific community and available publicly for other researchers to use. This resource is a major push forward for the ALS research community.

A Search for Biomarkers to Track ALS Progression: This project aims to identify biological changes in ALS over time by longitudinally measuring byproducts of cellular metabolism in patient samples while integrating these readouts with previously collected clinical and molecular data. The team seeks to identify molecular biomarkers related to ALS progression. Results show metabolic markers that correlate with clinical measures of disease severity. The team also identified metabolic markers that indicate differences in fast and slow progressing patients.

CLINICAL TRIALS

Pilot Clinical Trial Award

Translating results to the clinic:

- Support for initial testing of promising therapeutics in early-phase intervention trials that include biomarker data
- Inform and de-risk more advanced future trials for the treatment or management of ALS
- Improve current aspects of ALS clinical care, such as improvements to assistive technologies, symptom management strategies, and telemedicine approaches

A Brain-Computer Interface for Voice Synthesis in People with ALS: This Pilot Clinical Trial Award, PCTA, will develop and test an implanted intracortical brain-computer interface that translates the speech motor cortex activity of a person with ALS trying to speak into instantaneous synthesized voice output.

Combined Respiratory Training to Improve Pulmonary and Cough Function in Persons with ALS: This PCTA – Clinical Care Tier will evaluate the impact of a combined lung volume recruitment and expiratory muscle strength training exercise regimen on cough and respiratory function in persons with ALS.

Awards through FY22*:

222

Follow-On Funding:

80

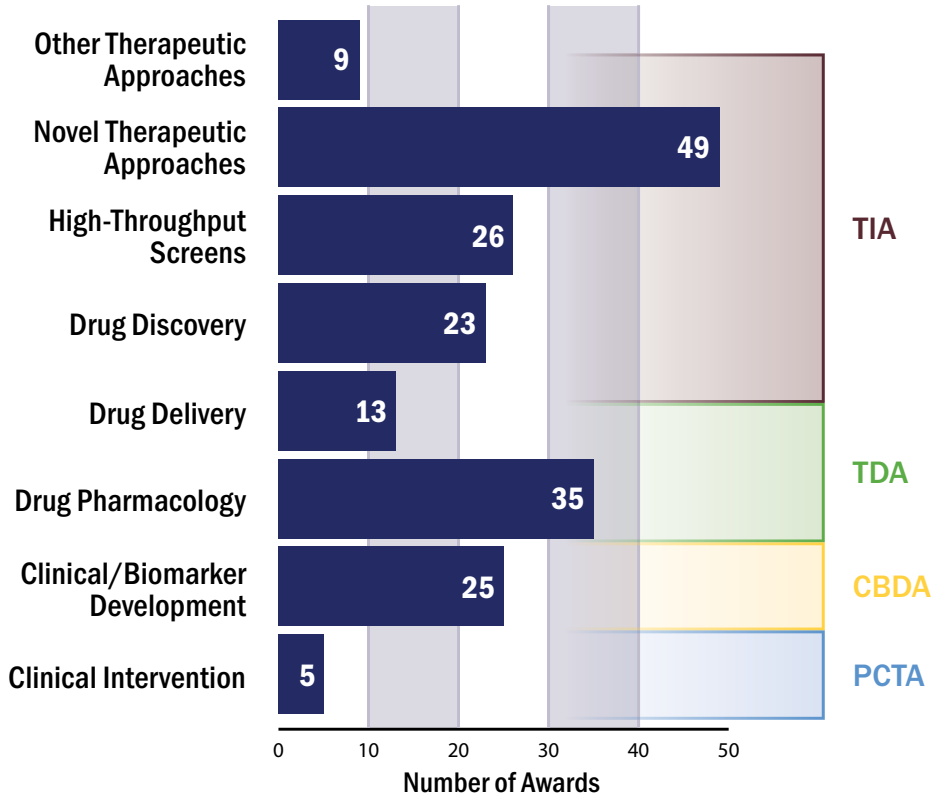
13 continuing along our pipeline:

- TIA to TDA: **7**
- TDA to PCTA: **1**
- TDA to clinical trial outside of our funding mechanisms: **5**

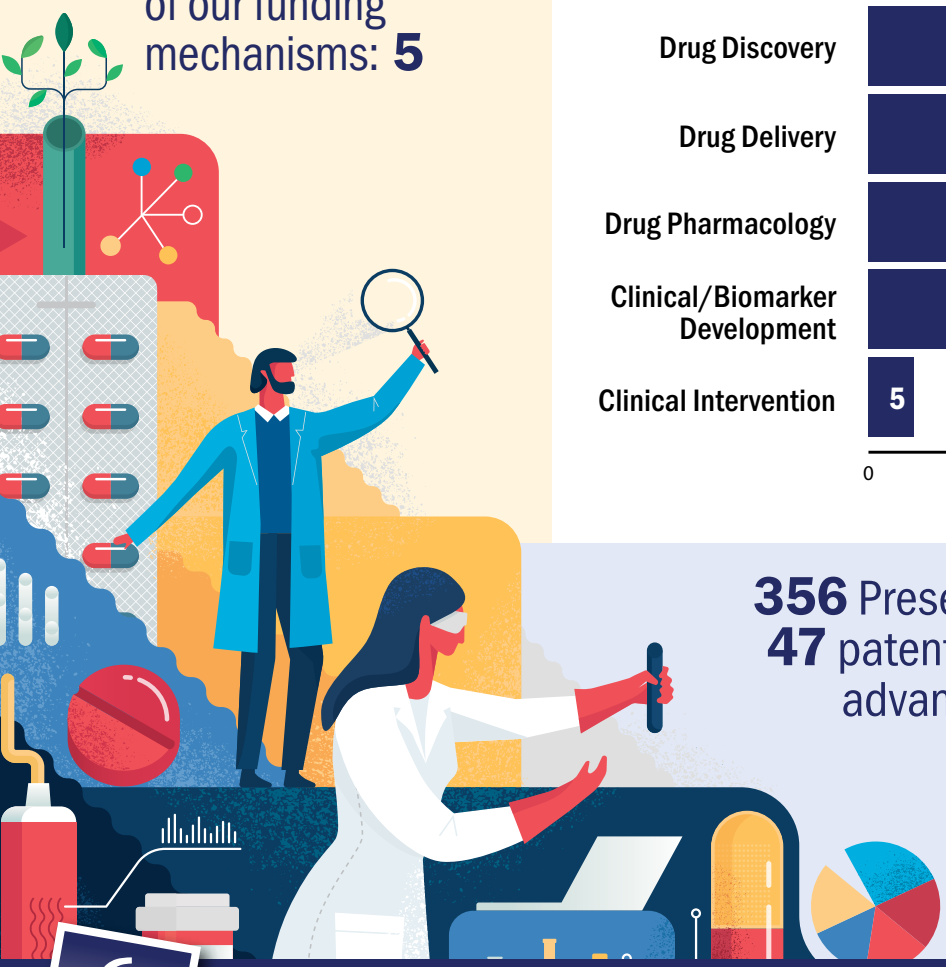
OUTCOMES

- New treatments advancing through clinical trials
- Numerous treatments in advanced development with industry partners
- Experimental therapeutics and markers
- New classes of small molecules
- New classes of biologicals
- New biological markers
- Methods and protocols
- Reagent production
- Therapeutic delivery methods
- Drug screens and testing
- Stem cells as regenerative therapeutics

Portfolio by Award Theme FY07-FY22



356 Presentations, **248** publications, **47** patents/applications, **5** treatments advancing through clinical trials, and **8** INDs and counting.



ADVANCING ALONG THE ALSRP PIPELINE

Teresa Dunn, Ph.D., Uniformed Services University of the Health Sciences , recieved an FY19 Therapeutic Idea Award, TIA, for her project, *"SPT-Associated ALS, a New Paradigm for Disease: Mouse and Fly Models for Identifying and Testing Therapeutic Targets."*

This study aims to develop cell and animal models of *SPTLC1*-associated ALS, for therapeutic development, and to investigate whether elevated sphingolipids will also prove to be useful biomarkers of disease in adult ALS patients. Researchers recently discovered that patients with an early-onset form of ALS have mutations in *SPTLC1*. *SPTLC1* is a gene that codes for a subunit of serine pamitoyltransferase (SPT), an endoplasmic reticulum-associated multi-subunit enzyme that catalyzes the first step of sphingolipid synthesis. The mutations cause high and unregulated SPT activity resulting in elevated sphingolipids. The sphingolipids are highly enriched in the nervous system and are well-known for causing neurological disease when not maintained at proper levels.

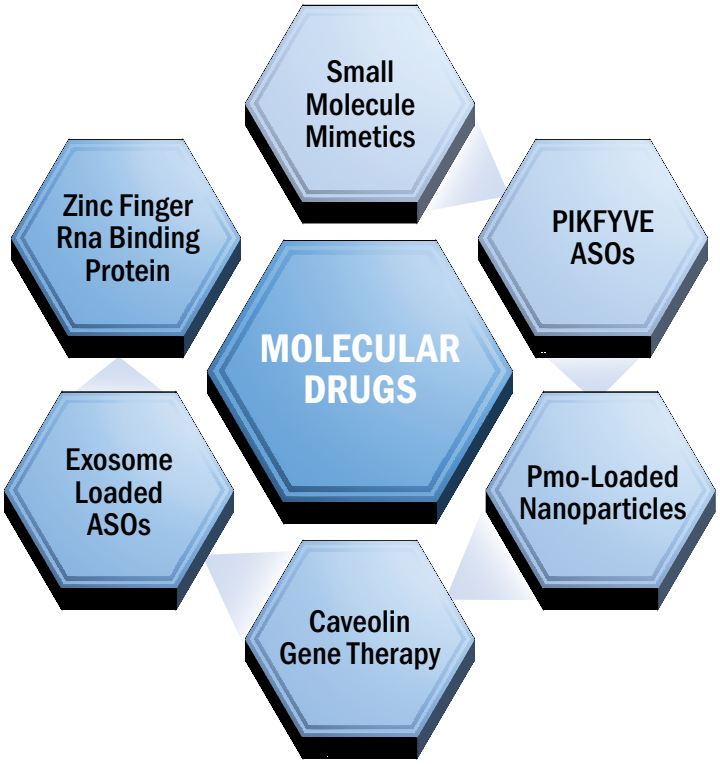
The research team, in collaboration with others, established that the *SPTLC1* mutations that cause ALS do so by impairing the normal feedback inhibition of SPT by the orosomucoid-like proteins. The resulting unrestrained SPT activity leads to elevated levels of sphingolipids, which are implicated in motor neuron death. The researchers hypothesized that allele-specific oligonucleotides, ASOs, directed against the *SPTLC1*-ALS alleles should restore normal sphingolipid homeostasis. Studies in patient fibroblasts indicate that this is the case and suggest these alleles as a potential target for a novel therapeutic strategy for the treatment of childhood-onset ALS resulting from *SPTLC1* mutations. This work defines excess sphingolipid biosynthesis as a fundamental metabolic mechanism for motor neuron disease. Dunn will use her ALSRP award to continue this line of investigation and move into therapeutic testing. Additional testing includes dietary, genetic, and pharmacological approaches that hope to demonstrate the role of sphingolipid perturbations in disease, as well as create robust mouse models for further therapeutic testing. The initial stages of this work were reported recently in *Nature Medicine*. This TIA led to a NEW FY22 Therapeutic Development Award, TDA, entitled, "Targeting Excessive Sphingolipid Synthesis for Treatment of ALS.

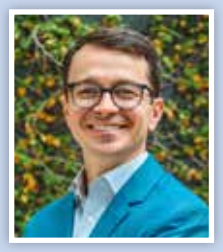
INVESTIGATING EARLY IDEA

The ALSRP encourages innovative, high-risk project ideas, know
The ALSRP offers the Therapeutic Idea Awa

"[We are] committed to ALS and neurodegeneration in our program and hope to continue to forge forward with progress toward clinical trials through the development of optimized small molecules, which are ready for clinical trials. We approach our work in ALS as a dedicated, multi-disciplinary research team and although it may be a Herculean task, I am very hopeful that we will get to the clinical studies."

Ann Marie Schmidt, M.D.,
New York University Langone Health, Grossman School of Medicine





New Nerve-on-a-Chip® System Could Revolutionize Therapeutic Development for ALS

J. Lowry Curley, Ph.D., AxoSim Technologies

With the multifaceted etiology of ALS, the current preclinical drug screening tools capable of measuring only a few markers at a time are simply insufficient. A 3D system comprised of neuronal stem cells and specialized brain cells is more physiologically relevant to brains and therefore represents a significantly superior clinical nerve pathology prediction tool. To address this hypothesis, the human Nerve-on-a-Chip®, NoaC, pilot project was developed featuring micro-engineered human motor nerve constructs. The objective of this pilot project is to establish the feasibility of obtaining structural and functional metrics that reliably differentiate healthy and ALS human motor nerve tissue in vitro.

The team-created NoaC constructs were electrically active, which is a sign of mature nerve cells. In addition, how the cells interacted with each other better mimicked the brain. This team performed the first known in vitro measurement of population-level electrophysiology of human neuron-astrocyte cocultures recorded in healthy human motor NoaC construct. Researchers noted differences in the how fast neurons grew and expression of ALS biomarkers in healthy versus ALS constructs. The team also identified potential key metrics to evaluate therapeutics for efficacy in preventing, slowing, or reversing ALS. This human cell-based preclinical model of ALS is an important tool to accelerate therapeutic development.

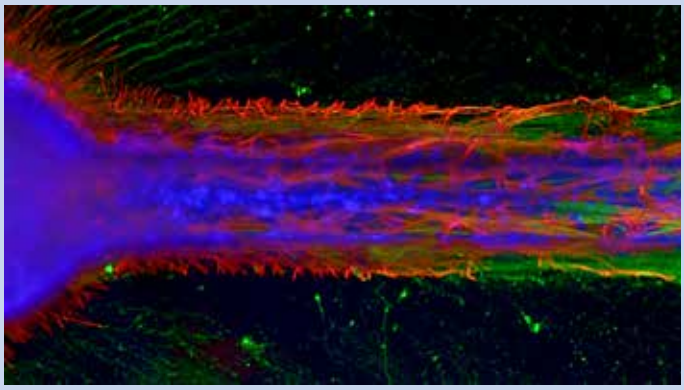


Figure 1: Micro-engineered motor nerve construct. The in vitro mini-nerve fiber tract shows the important developmental process of constrained axonal outgrowth (green) interacting with astrocytes (red) and includes migrating supportive cells (blue).

AS FOR ALS THERAPEUTICS

ing that sometimes the best solutions come from unlikely starts
rd to support new ideas for ALS treatments

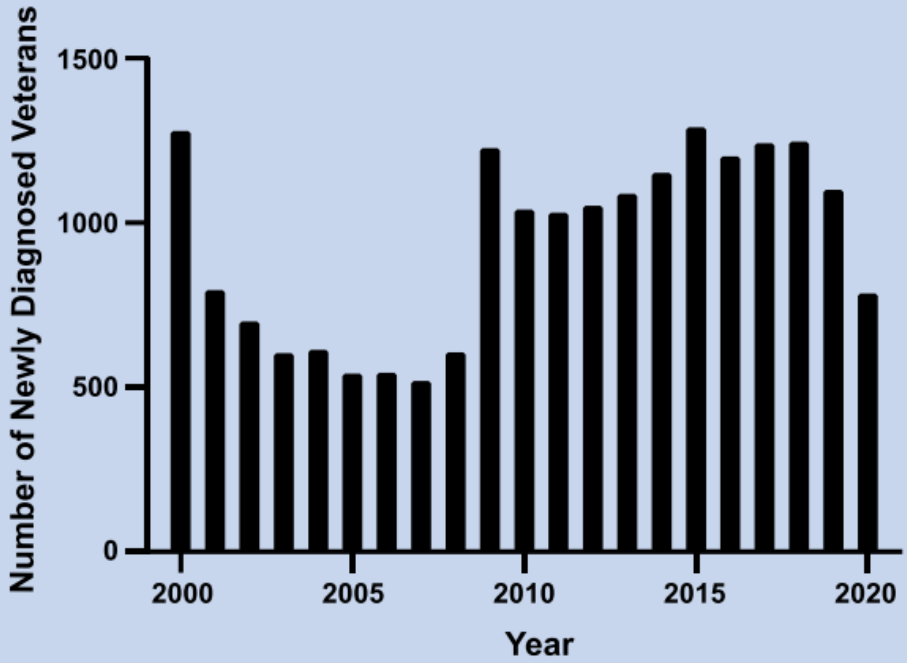
Using Machine Learning for Drug Repurposing to Impact ALS Treatment

Priyadip Ray, Ph.D., Lawrence Livermore National Laboratory

The research team aims to identify novel treatments for ALS in the form of repurposed current FDA-approved medications. The VA historical database 2010-2019 contains over 13,000 Veterans with an ALS diagnosis. This is likely the largest single longitudinal comprehensive dataset. Pathophysiological mechanisms underlying ALS onset and progression are still largely unknown. The team will use causal machine learning techniques on electronic health records to test the hypothesis that medications prescribed for other indications alter the risk for ALS and/or its progression.

Thus far, causal analysis with known confounders identified three classes of medications associated with longer survival in ALS for which a direct confounder is not readily evident (statins, alpha-adrenergic blockers, and non-steroidal anti-inflammatory drugs). The cohort included a greater than expected proportion of individuals whose branch of service at the time of separation was the Army, suggesting the possibility of a branch-specific risk factor for ALS.

Yearly Rise: Tracking the Number of Newly Diagnosed Veterans



An illustration of the number of Veterans newly diagnosed with ALS over the last two decades

EXAMPLES OF RECENTLY FUNDED TIA AWARDS

Justin Ichida Ph.D., University of Southern California
Using CSF1R Suppression to Reprogram Microglia to a Neuroprotective State in ALS

David Medina M.D., St. Joseph's Hospital and Medical Center
Retinoid-Activating Gene Therapy for the Treatment of Amyotrophic Lateral Sclerosis

Axtman Ph.D., University of North Carolina at Chapel Hill
A Novel Therapeutic Strategy to Reduce TDP-43 Expression in ALS

Davide Trotti Ph.D., Thomas Jefferson University
Senotherapy for ALS

Sarah Rea Ph.D., Murdoch University
Development of a Novel Treatment Strategy and Unique Methods of Delivery to the CNS for ALS

DEVELOPING TREATMEN

Following the development of new therapeutic targets, researchers must then fully verify and validate their findi The ALSRP supports Therapeutic Development Awards for projects in the final stages of preclinic

> "The support from ALSRP allowed us to do all of the small and large animal preclinical studies required to move to a new patient trial currently underway. ALS is a very tough disease to treat, and this research gives us hope that we are getting closer to finding ways to slow down this disease."
>
> **Clive Svendsen, Ph.D.**
> *Cedars-Sinai Medical Center*

A Combined Cell and Gene Therapy Approach for Preserving Motor Neuron Function in ALS

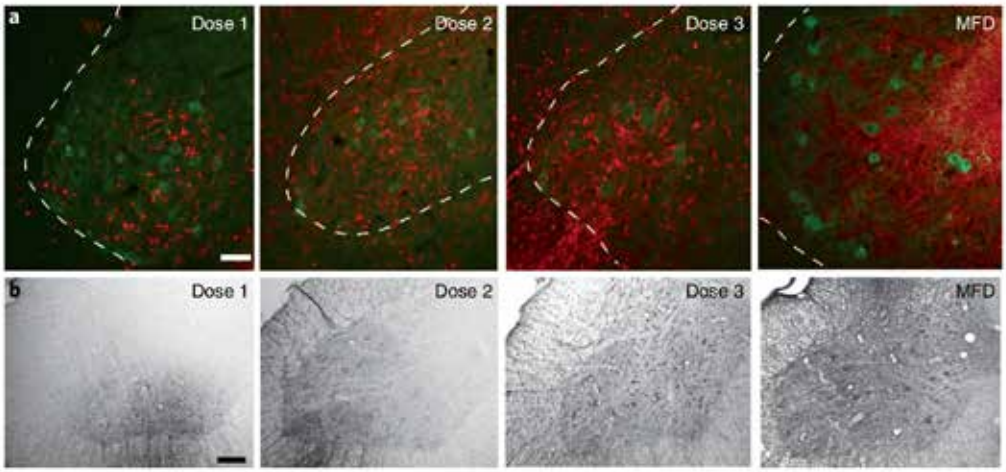
Clive Svendsen, Ph.D., Cedar-Sinai Medical Center

Studies have shown that a powerful growth factor called glial cell-line derived neurotrophic factor, GDNF, can slow disease progression in models of ALS.

One strategy to delay disease progression uses gene therapy to directly deliver GDNF to motor neurons. The Svendsen lab successfully delivered human neural progenitor cells that secrete GDNF into the cortex of ALS animal models. This approach resulted in enhanced motor neuron function and extended survival, suggesting it protects downstream motor neurons. Importantly, this treatment may have positive effects on disease onset and patient life span.

The Svendsen lab examined the safety of transplanting neural progenitor cells engineered to produce GDNF into the spinal cord of ALS patients. After the transplantation, researchers observed the 18 enrolled patients monitoring leg muscle strength.

In a *Nature Medicine* publication released in September 2022, the results of the trial showed there were no negative effects of the cell transplant on leg muscle strength, and the phase 1/2a trial reached its primary endpoint of safety. This is the first study to show that researchers can safely transplant allogenic neural progenitors, engineered to release GDNF, into the human central nervous system. This proof of concept, showing that a single delivery of genetically modified neural progenitor cells can sustain survival and release of a protein product, combined with the data from the ALSRP study, represents a novel therapeutic option for ALS and other neurodegenerative diseases, . The team can now use the same cells in a clinical trial focusing on delivery to the upper motor neurons.



Immunohistochemistry of the human-specific nuclear marker SC121(red) showed the GDNF engrafting around host spinal cord ChAT-positive motor neurons (green).

TS FOR CLINICAL TRIALS

ngs before regulatory agencies such as the FDA will approve the treatment to go forward in human ALS patients.
cal treatment validations; so far eight therapeutics/formulations have been approved by the FDA

Protecting Nerve Cells Against ALS Progression

Steve Perrin, Ph.D., ALS Therapy Development Institute, ALS TDI

[2016]

The ALS TDI previously discovered that targeting CD40 Ligand in the immune system delayed disease progression and extended the life span of ALS mice. The ALS TDI moved forward with development of a new antibody drug, AT1501, to target CD40L in patients with ALS. This was challenging because previous antibody drugs that targeted CD40L in humans were toxic and caused potentially fatal blood clots.

[2017]

With support from the ALSRP award, Perrin and the ALS TDI team showed that AT1501 did not cause platelets to clot in non-human primates, and it was safe enough to move into human phase 1 ALS clinical trials.

[2018]

In April, the FDA granted granted an Orphan Drug Designation and an IND approval of AT1501.

[2019]

Anelixis Therapeutics, a for-profit clinical-stage development company, pushed AT1501, now named Tegoprubart, through early clinical trials. Anelixis successfully completed phase 1 trials of Tegoprubart in 2019.

[2022]

In May 2022, Eledon Pharmaceuticals announced their results from the phase 2a trial, an open-label, dose-escalating, safety, and biomarker study of Tegoprubart. The goals of the study were safety, tolerability, and changes in pro-inflammatory biomarkers. Tegoprubart proved to be well-tolerated with no drug-related serious adverse events. The Revised ALS Functional Rating Scale showed a pro-inflammatory biomarker reduction associated with a non-significant trend toward slowing disease progression.

DRUGS APPROVED BY THE FDA AND SUPPORTED IN PART BY THE ALSRP

Over the years, the ALSRP has funded 42 advanced therapeutic development projects that have helped support 3 FDA drugs/formulations. This pivotal effort has significant implications for persons living with ALS, their caregivers, and their families. Advanced therapeutic development through the ALSRP holds promise for patients by enabling the field to bring more therapeutics to clinical trial, thereby bridgingthe gap between idea and treatment.

- Edaravone
- Prosetin
- Tegoprubart

ALSRP has supported **seven** INDs and **one** new drug formulation:

- AKV9 (2009)
- miR-155 (2012)
- GDNF (2013)
- Apilimod PIKfyve inhibitor (2014)
- Edaravone (2016)
- Tegoprubart (2016)
- Prosetin (2015, 2020)
- RASRx1902 (2021)

BIOMARKERS: CLINICAL MEAS

Biomarkers are key to understanding how well a drug works, who it
Since FY20, the ALSRP has supported projects to understanc

Proteomics Blood-Based Biomarker Discovery for ALS

Femando Vieira, M.D., ALS Therapy Development Institute

This team will analyze approximately 5,000 proteins in the blood samples of study participants using standard approaches and artificial intelligence approaches to identify patterns of blood proteins that predict faster or slower ALS. Blood proteins that that predict faster or slower disease could be considered as novel biomarkers.

Rasch-Built Outcome Measures to Improve ALS Clinical Trials

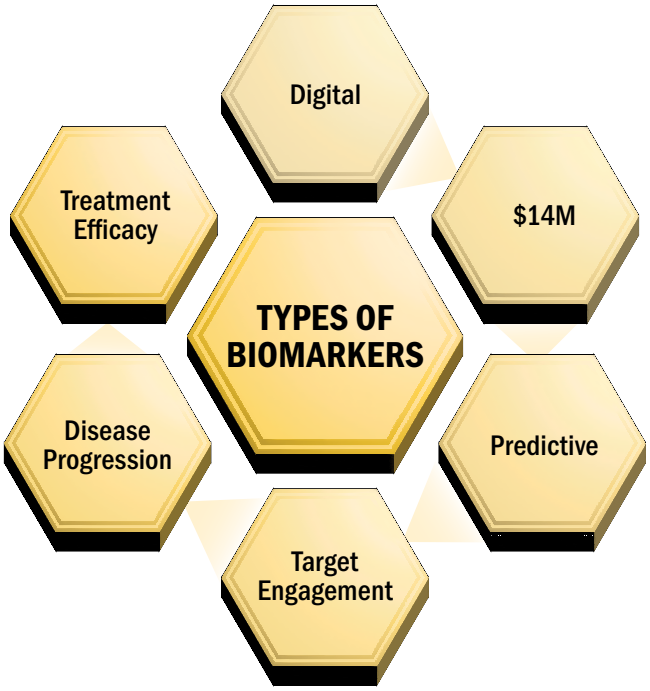
Christina Fournier, M.D., Emory University

The project builds and refines an ALS outcome measure toolbox containing a widely accessible, patient-reported questionnaire to assess overall disability and a novel objective exam-based scale to assess overall motor strength using Rasch methodology, known as the ALS Motor Observational Telemedicine Objective Rasch, ALS MOTOR,-built assessment, this new and accessible tool accurately measures ALS progression remotely. Beneficial for both clinical care and research studies, remote tools such as the ALS MOTOR assessment allow for reduced patient burden. Use of Rasch methodology for scale validation enabled for optimization of scale psychometric properties, which is particularly important when using the sum-score as an overall outcome measure

A Multimodal and Spatially Resolved Dissection of Antisense Oligonucleotide Therapy of FUS-Related ALS Disease Progression

Change to Tom Maniatis, Ph.D., Columbia University Medical Center

This project will use spinal cord samples to investigate FUS transcripts depletion as a measure of disease progression. Early results include the construction of a gene regulatory network and crucial regulators mediating homeostatic function, which is a first in the spinal cord and ALS community. Furthermore, the ability to profile and directly identify cellular communities within the human spinal cord and brain, tracking paracrine signaling cues, will have a dramatic impact on how the ALS community analyzes and interprets disease progression.



Home Telemonitoring of Bulbar Function by Acoustic Measurement of Swallowing and Speech Sounds in ALS

Andrew Geronimo, Ph.D., Pennsylvania State University, Milton S. Hershey Medical Centerr

A longitudinal home study of ALS patients to assess bulbar progression via a smart-phone based, self administered remote speech and swallow assessment. This study is currently enrolling participants.

Development of [11C]CPPC as a Clinical PET Radioligand Biomarker of Microglial Activation in ALS

Nicholas Maragakis, M.D., Johns Hopkins University

This study will explore [11C]CPPC PET uptake as a measure of neuroinflammation and attempt to correlate this activity with disease progression.

Discordant Protein RNA Expression as a Novel Metric of ALS Pathophysiology

Ritchie Ho, Ph.D., Cedars-Sinai Medical Center

This study will characterize how protein and RNA expression is regulated in distinct brain and spinal cord regions, providing a resource to understand the healthy baseline of this physiology and how ALS disrupts it.

URES RELEVANT FOR DISEASE

works for, what types of drugs to administer to someone, and more
d meaningful ways to evaluate biomarkers in people with ALS

Integrative Multimodal Communication for ALS Patients Using iPad

Fusheng Wang, Ph.D. Stony Brook University

The research team aims to develop a lightweight, cost-effective, multimodal-based assistive communication application, EyeCanDo, running on iPad Pro with an optional consumer-grade wireless EEG headset, to take full advantage of the available capabilities of an ALS patient, including eye gaze, facial expressions, and brainwaves, to assist patients with communication. EyeCanDo will be the first application on a tablet device supporting ALS patients with both eye gaze and brain-computer interfaces.

Functionality Added to EyeCanDo

NEW PROJECTS FUNDED IN FY22

Plasma Biomarkers in Amyotrophic Lateral Sclerosis
Katheryn Cousins, Ph.D. at the University of Pennsylvania

Development of Clinical Biomarkers for Molecular Subtypes of Sporadic ALS
Molly Gale Hammell, Ph.D. at Cold Spring Harbor Laboratory

RP-115: A Novel Biomarker of Astrocyte Dysfunction and Glutamate Dysregulation in Brain and Spinal Cord in ALS
Michael O'Sullivan, Ph.D. at University of Queensland

Ultrasensitive Plasma/CSF Immunoassays to Support ALS Clinical Trials
Martin Stengelin, Ph.D. at Meso Scale Diagnostics, LLC.

Clinical Development of ISGylation Diagnostic Biomarker for ALS
Shyamal Desai, Ph.D. at Louisiana State University Health Sciences Center

Characterizing Microbial Markers Predictive for ALS Onset and Progression
Michael Morrison, Ph.D. at Lawrence Livermore National Laboratory

Restriction Spectrum Imaging as a Biomarker for Amyotrophic Lateral Sclerosis
Iris Broce-Diaz, Ph.D. at University of California, San Diego

TDP43 in Circulating Neuron-Derived Extracellular Vesicles as Prognostic and Diagnostic ALS Biomarker
Erez Eitan, Ph.D. at Neurodex, Inc

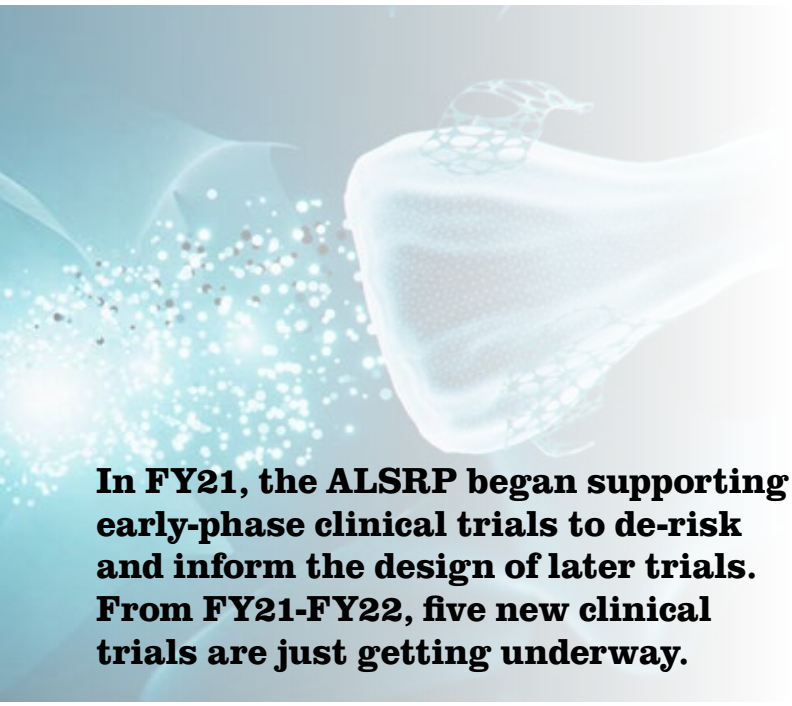
Longitudinal Neuroimaging and Molecular Biomarkers of Cerebrovascular Health in ALS
Nadine Bakkar, Ph.D. at St. Joseph's Hospital and Medical Center

"Biomarkers are critical for advancing therapeutic development from early preclinical studies through safety and efficacy clinical trials. Biomarkers can be used as different types of tools; for example, in preclinical studies, some biomarkers can be used to show that a therapeutic agent is hitting the intended mechanism of action. In later stages of therapeutic development, biomarkers for early diagnosis and to identify which patients are most likely to improve from a specific intervention improves the chances that a therapeutic will get regulatory approval. This is especially important in heterogeneous diseases like ALS, where different treatments may work better for some people than others and early interventions are needed."

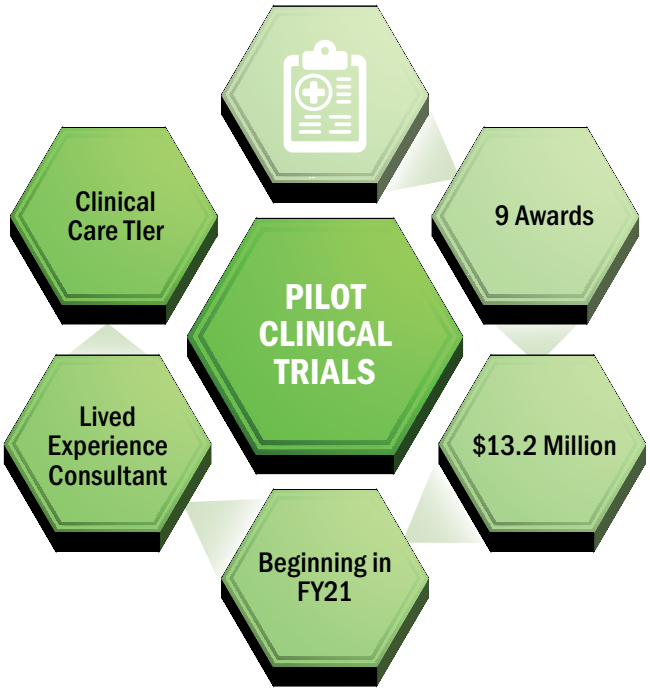
Carol Taylor-Burds, Ph.D.
Program Director, Division of Translational Research National Institute of Neurological Disorders & Stroke

PILOT CLINI

The earliest tests of treatments in humans, known as pilot clinical trials, can provi

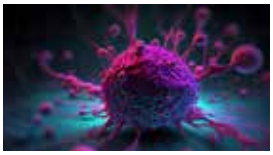


In FY21, the ALSRP began supporting early-phase clinical trials to de-risk and inform the design of later trials. From FY21-FY22, five new clinical trials are just getting underway.



Massachusetts General Hospital, *"Pilot Trial of Baricitinib for ALS Patients and Asymptomatic Mutant C9ORF72 Carriers Including Novel Peripheral Immune Cell Profiling and CSF Biomarkers"*

This study will assess the safety and tolerability of baricitinib in ALS patients and identify candidate biomarkers for response to baricitinib through analyzing unbiased proteomics data from the cerebral spinal fluid, CSF, and immune cell profiling of peripheral white blood cells patients before and after treatment of baricitinib.



Columbia University Medical Center, *"REGALS: Regulatory T Cells in Amyotrophic Lateral Sclerosis"*

Leveraging cutting-edge technologies, the team will test the safety and efficacy of cord-blood-derived Treg therapy in ALS and identify the type of toxic immune cells circulating in the blood and found in the brain and the spinal cord of sporadic ALS patients.

University of Florida, *"Safety of Metformin in C9orf72 ALS: Effects on RAN Proteins, Breathing, Imaging, and Metabolomic Outcome Measures"*

This study aims to to rapidly move a well-tolerated FDA-approved drug, Metformin, into the clinic as a safe, low-cost treatment for the most common genetic cause of both ALS and frontotemporal dementia, C9orf72.

University of California, Davis, *"A Brain-Computer Interface for Voice Synthesis in People with ALS"*

This study will develop a brain-computer interface to provide instantaneous voice synthesis for people with ALS. Through this research, the team plans to develop a neuro-prosthetic device for people living with the disease to fluently perform activities such as talking or singing.

Nova Southeastern University,*"Combined Respiratory Training to Improve Pulmonary and Cough Function in Persons with ALS"*

This study aims to provide an opportunity to intervene proactively and empowers persons with ALS with a tool to combat the loss of function early in the disease process. If successful, this combined training has the potential to improve the trajectory of decline in breathing and cough functions, ultimately prolonging survival in persons with ALS.

(Figure Legend Left to Right) Emily Plowman, Ph.D., Professor of Speech, Language, and Hearing Sciences; Laura Ranum, Ph.D., Kitzman Family Professor of Molecular Genetics and Microbiology; Director, Center for NeuroGenetics, College of Medicine, University of Florida and, James Wymer, Ph.D., Professor and Division Chief of Neuromuscular Neurology

The Therapeutic Potential of Metformin in ALS; Moving Through the ALSRP Pipeline from TDA to PCTA

Laura Ranum, Ph.D., University of Florida

In 2011, the Ranum lab identified the expansion of short sequences of genetic code located in the C9ORF72 gene as the most common cause of both familial and sporadic ALS. Toxic repeat associated non-AUG proteins, called RAN proteins, accumulate in the patient brain and spinal cord through the process of RAN translation. The accumulation of these RAN proteins as aggregates contributes to ALS disease pathology. However, no known drugs currently exist to reduce the production of these harmful RAN protein aggregates.

Metformin is an FDA-approved, widely used, and well-tolerated type-2 diabetes drug that researchers recently showed can block the formation of toxic RAN protein aggregates in the brain. In FY18, Ranum received a TDA to investigate the therapeutic potential of metformin to treat ALS. Using Metformin as a treatment method for ALS patients who express C9ORF72 could be helpful. Metformin has a long history of safe usage in the general population, so this approach may provide a fast, inexpensive, and effective treatment for ALS.

The team hypothesizes that metformin reduces RAN protein levels by preventing the activity of protein kinase R, PKR, which drives processes facilitating protein aggregation. They demonstrated that patient-derived neuronal cells from ALS patients with C9ORF72 mutations, C9-ALS, have elevated levels of phosphorylated PKR compared to controls. The team also confirmed that metformin treatment reduced RAN protein levels in patient-derived cells and a mouse model of ALS. These results indicate that RAN proteins are major drivers of disease for C9-ALS and that targeting RAN proteins for reduction, via metformin, is a viable therapeutic approach.

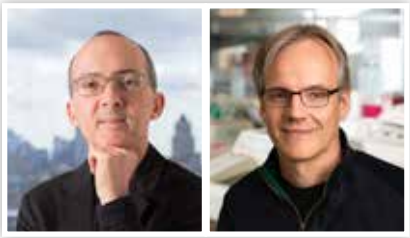
The team then realized that the levels of RAN proteins in patient-derived cells and organoids could act as potential biomarkers, or physiological measures that can help to determine whether someone had ALS. Upon further investigation, the data indicate that the RAN proteins may be relevant not just for patients with C9-ALS, but also those patients with genetically unknown forms of sporadic ALS. In FY21, Dr. Ranum received an ALSRP TIA with a Biomarker Option for additional work to identify and target novel RAN proteins in sporadic ALS.

Overall, the identification of an inexpensive FDA-approved drug and characterization of its mechanism of action in a preclinical animal model that recapitulates disease is a major step forward in the search for viable ALS therapeutics and has led directly to an initial clinical trial in C9-ALS patients (NCT04220021). If this clinical trial is successful or if other drugs identified by this study are successful in future clinical trials, these drugs could provide an urgently needed, relatively inexpensive, and long-term treatment option for patients with C9-ALS.

In FY22, the Ranum lab received further support from the ALSRP for the next stages of this investigation in the form of a PCTA to complete a small-scale human phase 2 clinical trial to assess the safety and potential efficacy of metformin for the treatment of C9-ALS, to continue to identify additional relevant biomarkers, and to prepare for a large multi-site placebo-controlled follow-up trial.

SUCCESS THROUGH THE ALSRP PIPELINE

TIA to TDA to Clinical Trial



A New Compound to Prevent Motor Neuron Toxicity in ALS Enters Clinical Trial

Brent Stockwell, Ph.D., and Hynek Wichterle, Ph.D., Columbia University

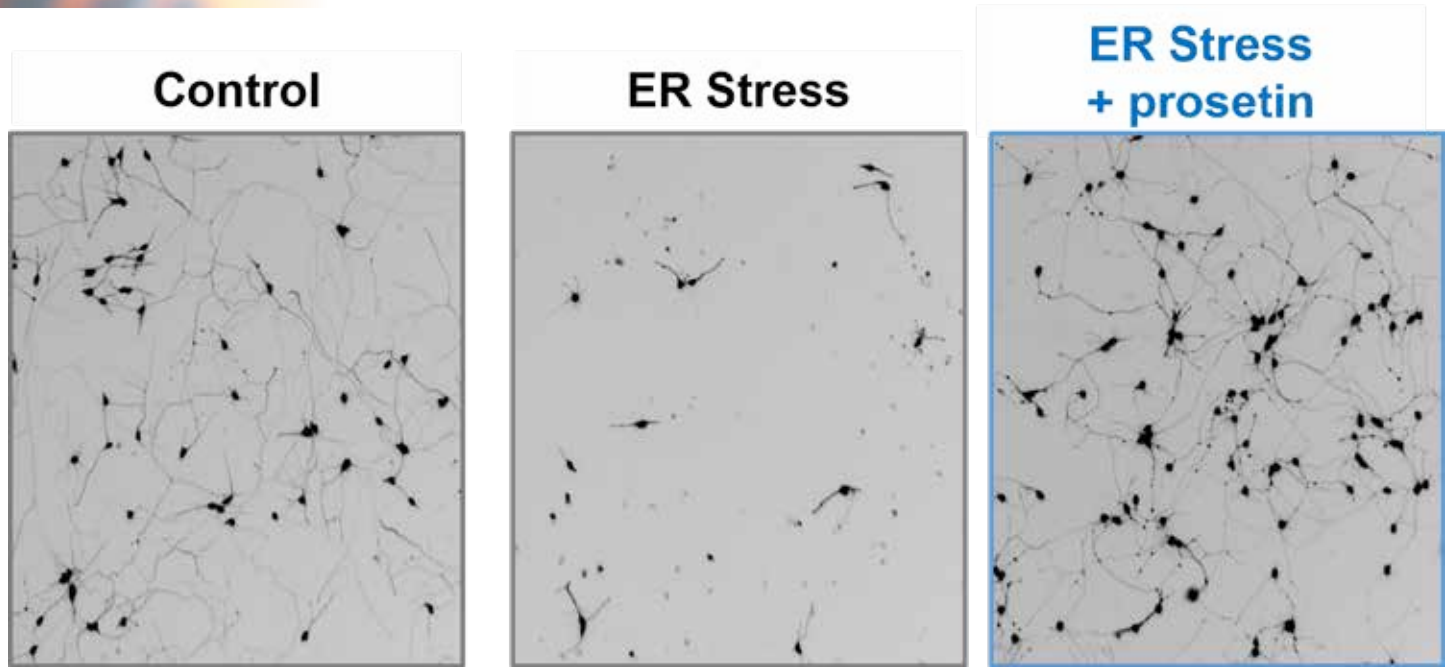
In ALS, motor neurons initially engage cellular endoplasmic reticulum, ER, stress pathways to purge misfolded proteins. If these efforts are unsuccessful, self-sacrificing branches of the ER stress pathway are initiated. ER stress activation has been observed across many models of ALS and in human patient tissues. This process may contribute to the widespread motor neuron death observed in ALS.

2015 TIA

In FY15, the ALSRP funded a TIA to Brent Stockwell, professor of biological sciences and chemistry at Columbia University, titled, "Motor Neuron-Protecting Agents as Therapeutics for Treating ALS." Stockwell and his team, in collaboration with another ALSRP-funded investigator at Columbia University, Hynek Wichterle, developed potent and selective inhibitors of ER stress in a cellular model of ALS and created prosetin, a brain-penetrant kinase inhibitor, as a promising therapeautic candidate. This initial TIA laid the groundwork for additional development efforts that continue through the ALS funding pipeline.

2020 TDA

In FY20, Stockwell and Wichterle received an ALSRP TDA to evaluate the pharmacology, safety, and efficacy profiles of prosetin, the potent kinase inhibitor that the team found to be efficacious across multiple models of ALS. As part of this new award, Stockwell and his team will further validate their hypothesis and more confidently determine the appropriate patient population for future clinical applications. Because ER-stress-related pathologies are observed familial as well as sproadic forms of ALS, prosetin's mechanism of action may be broadly applicable to ALS. Prosetin is an orally bioavailable, metabolically stable, central nervous system penetrant, and is well-tolerated in long-term administration paradigms, making it a prime candidate for the treatment of ALS.



The drug prosetin helps preserve the number of motor neurons lost to cellular stress; for that reason, researchers believe prosetin may act similarly in slowing disease progression in patients newly diagnosed with ALS.

Project ALS and the Therapeutics Core at Columbia University, collectively called The Core, started in 2018 to bring together preclinical and clinical ALS research with funding and strategic direction from the non-profit organization. Project ALS pursued orphan drug designation for prosetin, and the FDA granted the therapeutic orphan-drug status for the treatment of ALS in 2020. This positioned these ALSRP-funded investigators to initiate scientifically rigorous clinical trials of prosetin at an accelerated pace. Erin Fleming, who was director of external operations for The Core and director of research operations at Project ALS, served as project manager of this effort, coordinating contactor selection and managing workflow among our collaborators.

In early 2022, Project ALS partnered with a new startup company 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. This study will begin to determine the safety, tolerability, and pharmacokinetics of single and ascending doses of prosetin versus a placebo in the healthy volunteers. The overall goal of the trial is to determine the optimal dose of prosetin and acquire biomarker data to inform the design of future late-stage trials.

Ms. Fleming writes, **"The Core aims to bring more rational therapeutic candidates to ALS clinical trials, and as the first investigational drug developed through this collaboration with Columbia, this project was a top priority for Project ALS. ALSRP support has been critical in moving prosetin from concept to clinical trial on an accelerated timescale."**

Dr. Stockwell writes, **"To our knowledge, our commitment to advance prosetin through early clinical development independently, as a non-profit academic effort, was the first of its kind in ALS. Our ultimate aim is to deliver a meaningful therapy to people with ALS, and because our primary responsibility is to the ALS community, we will conduct this research of prosetin with the urgency and rigor that this disease demands."**

INCORPORATING THE EXPERIENCE OF THOSE LIVING WITH ALS

The ALSRP Pilot Clinical Trial Award aims to respond to the needs of people with ALS, their families, and/or their care partners. Beginning in FY24, the ALSRP requires research teams to establish and utilize effective and equitable collaborations and partnerships with community members to maximize impact potential of the proposed research.

In order to advance treatments successfully through clinical trials, those trials must be thoughtfully designed. The ALS community could play a role in de-risking and optimizing those trials. Dr. Robinson remarks, **"The better a company understands the lived patient experience, and the better patients' understand the research process, the better the research will be; the more patients understand [the research] the better they can advocate for the right processes. And, the deeper a company understands the lived patient experience with ALS, the better they can design trials with truly meaningful outcomes."**

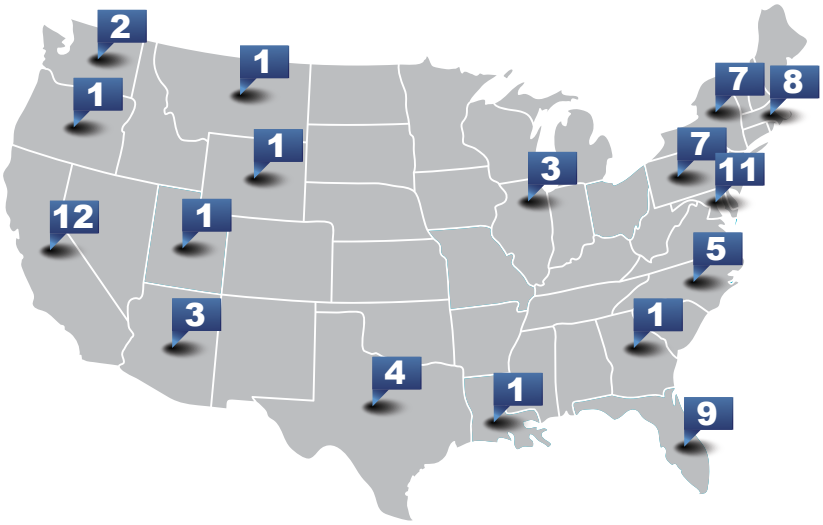
"As a patient with ALS, as well as being a retired physician and pharmaceutical executive, it gives me tremendous hope see what is being accomplished by the ALSRP. The ALSRP has made unprecedented contributions to the field by funding high-risk research that speeds up the development of potential new treatments. This includes research from bench science to pilot clinical trials. This program makes possible innovative drug discovery and feeding the pipeline of new potential therapies."

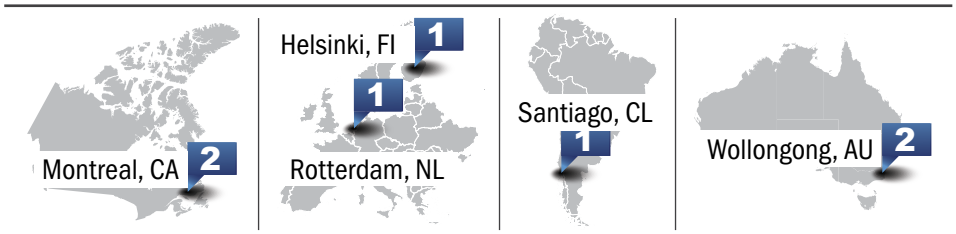
Michael Robinson, M.D.
Healey Platform Trial Patient Advisor
Programmatic Panel Consumer

ALSRP FACTS/STATS

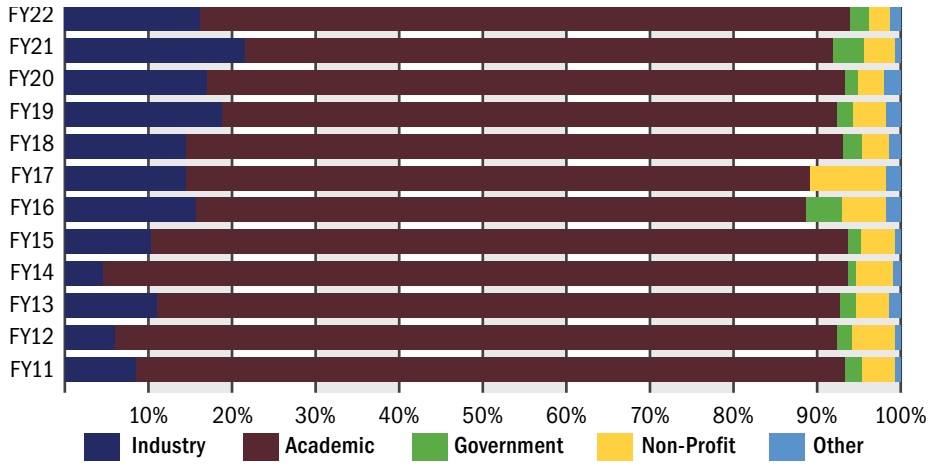
AWARDS TO DATE BY LOCATION

- Since FY07, ALSRP funded research across five countries
- The majority of awards are granted to academic research institutions





TYPES OF FUNDED INSTITUTIONS, FY11-FY22



WHO IS BEING FUNDED, FY15-FY22

167 to U.S. Institutions

23 to International Institutions

163 to Academic Institutions

27 to Industry

FY24 PROGRAMMATIC PANEL MEMBERS

The Programmatic Panel guides the program's investment strategy to address the mission and vision of the ALSRP.

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Lewis Katz School of Medicine at Temple University

Katja Brose, Ph.D.
Chan Zuckerberg Initiative

Kuldip Dave, Ph.D.
ALS Association

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Emory University

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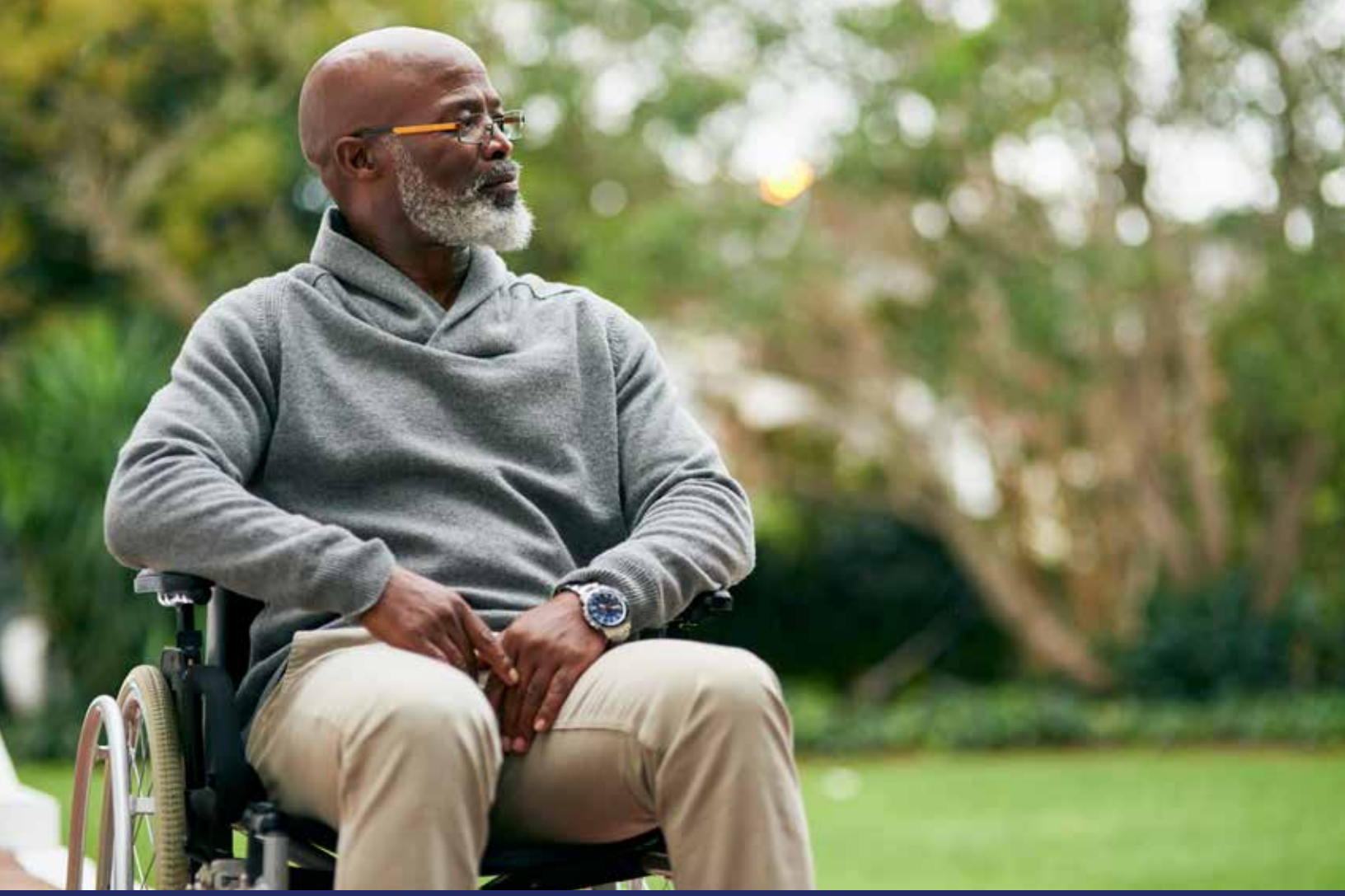

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3/2024
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