CDMRP HISTORY
The Office of the Congressionally Directed Medical Research Programs (CDMRP) was born in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since then, the CDMRP has grown to encompass multiple targeted programs and has received over $14.4 billion in appropriations from its inception through fiscal year 2019 (FY19). Funds for the CDMRP are added to the Department of Defense (DOD) budget, in which support for individual programs such as the Amyotrophic Lateral Sclerosis Research Program (ALSRP) is allocated via specific guidance from Congress.

CDMRP VISION: Transform healthcare for Service Members and the American public through innovative and impactful research.

CDMRP MISSION: Responsibly manage collaborative research that discovers, develops, and delivers health care solutions for Service Members, Veterans, and the American public.

Congressionally Directed Medical Research Programs

TWO-TIERED 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 both the most meritorious science and 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 scientific merit. The second tier is a programmatic review conducted by a Programmatic Panel composed of leading scientists, clinicians, and ALS consumers. In this tier of review, the Programmatic Panel compares the applications and makes recommendations for funding based on scientific merit as determined by peer review, potential impact, relevance to program goals, and portfolio composition.

CDMRP FUNDING AND AWARD MANAGEMENT PROCESS

PROGRAMMATIC PANELS
Each of the programs within the CDMRP is supported by a Programmatic Panel. The Programmatic Panel is a balanced, multidisciplinary group of research scientists, clinicians, military representatives, and consumers, and the panel members are all leaders in their respective communities. Ad hoc reviewers may be recruited to supplement the Programmatic Panel members’ expertise depending on the program.

The ALSRP Programmatic Panel includes program directors from other federal funding agencies such as the National Institutes of Health and the U.S. Department of Veterans Affairs (VA), as well as representatives from major non-profit research foundations, collaborative consortia, and – for the first time in FY20 - pharmaceutical industry scientist representation to contribute the perspective of the private sector. These panel members provide information regarding the research being funded by their organizations in related areas to ensure collaboration and prioritization of the most promising approaches.

Consumers have participated on CDMRP panels since their inception in 1993. Consumer reviewers are nominated by advocacy organizations, outreach/support organizations, or the Armed Forces and are selected on the basis of their leadership skills, commitment to advocacy, and interest in science. A firsthand experience with the target disease, disorder, or injury adds perspective, passion, and a sense of urgency, ensuring that the patient and caregiver perspective are incorporated into program objectives, investment
Amyotrophic Lateral Sclerosis Research Program

**ALSRP HISTORY**
The CDMRP ALSRP is guided by a vision to improve treatment and find a cure for ALS. The ALSRP was created in FY07 when the DOD redirected $5 million (M) of Army Research, Development, Test and Evaluation funding for the CDMRP to initiate the ALSRP as a broadly competed, peer-reviewed research program. The ALSRP was not funded in FY08; however, in FY09, Congress specifically appropriated funding for the ALSRP and has continuously provided funding since then, with a total appropriation of more than $109M, including $20M in FY20.

**ALSRP FOCUS**
From the inception of the program, the portfolio has been focused on therapeutic discovery and preclinical validation aimed at identifying new ALS drug candidates and moving them into advanced drug development. Recent increases in the ALSRP Congressional appropriation, from $20M in FY20 to $40M in FY21, have enabled the program to increase investments in innovative and unconventional preclinical therapeutic approaches. In FY20, the ALSRP expanded its mission by offering a mechanism in clinical research and in, FY21, the ALSRP further expanded by offering a biomarker pilot trial award.

Through FY20 there have been:

- $129.4M in Congressional appropriations
- 708 Applications received
- 108 Awards totaling $81.43M

**ALSRP VISION:** Improve treatment and find a cure for ALS

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

“...I first became acutely aware of ALS in October 2008 when I was diagnosed with ALS. I was a competitive long distance runner at the time and began tripping and falling in every race. Since that time, I have participated in several clinical trials at Johns Hopkins and The Robert Packard Center for ALS Research. I have also participated in the Baltimore Fiesta 5k race by creating a team (running for cArLSon) and raising over $100K for ALS research. I have served in the US Army as an Infantry and Special Forces officer for over 30 years both active and reserve and retired at the rank of Colonel. It has been an honor and a privilege to serve on the DOD ALSRP panels for the last 8 years and to represent my military brothers who are twice as likely to have ALS as those who have not served.”

COL Fred Carlson, USA, Retired
The Robert Packard Center for ALS Research

**FY21 PROGRAMMATIC PANEL**

- Lyle Ostrow, M.D., Ph.D. (Chair)
  Johns Hopkins University School of Medicine
- Katja Brose, Ph.D.
  Chan Zuckerberg Initiative
- COL Fred Carlson, USA, Retired
  The Robert Packard Center for ALS Research
- Kuldip Dave, Ph.D.
  ALS Association
- Amelie Gubitz, Ph.D.
  National Institute of Neurological Disorders and Stroke, National Institutes of Health
- Matt Harms, M.D.
  Columbia University
- Terry Heiman-Patterson, M.D.
  Lewis Katz School of Medicine at Temple University
- Neil Kowall, M.D.
  U.S. Department of Veterans Affairs
- Joseph Lewcock, Ph.D.
  Denali Therapeutics
- Mary Lou Pisone
  Les Turner ALS Foundation
ALSRP Supports the Therapeutic Pipeline and Beyond

ALSRP PRECLINICAL STRATEGY
Areas of emphasis have included development and validation of high-throughput screens to exploit novel drug targets and advancement of candidate therapeutics through the many steps required before Food and Drug Administration (FDA) approval. This has included drug production, purity, stability, toxicology, pharmacokinetics/dynamics, and efficacy in cell and animal models. The pie chart below provides examples of ALSRP-funded research topics.

**Drug Discovery Proof-of-Concept**
- Anti-oxidants
- Inhibitors of ER stress
- HSF1 modulators
- Blocking inflammation
- Kv2 channel blockers
- Treg modulators
- Autophagy regulators
- CNTF receptor agonists
- Targeting the NMJ

**High-Throughput Screens**
- Targeting Aggregated SOD1
- c9RAN translation inhibitors
- TDP-43 modifiers
- Multiplexed technologies
- Targeting FUS aggregates

**Drug Delivery**
- Nanoparticles
- Stem cell transplantation

**Drug Pharmacology**
- Targeting Aggregated SOD1
- c9RAN translation inhibitors
- TDP-43 modifiers
- Multiplexed technologies
- Targeting FUS aggregates

**Resource Development**
- Cell lines
- Animal models
- Imaging techniques

**Other Therapeutic Approaches**
- Cell therapy
- ER stress inhibitors
- Blocking inflammation

ALSRP FUNDING MECHANISMS

**Therapeutic Idea Award (TIA)**
- Ideas in early stage of development
- High-risk/high-reward research
- Strong rationale
- No preliminary data

**Therapeutic Development Award (TDA)**
- Post-discovery
- Strong preliminary data required
- Empirical/product-driven
- Target validation
- IND-enabling

**Search for Candidate Therapeutics for ALS**
- New in FY10, introduced “idea-type” award for undeveloped but promising approaches

**EVOLUTION OF ALSRP FUNDING MECHANISMS**

**FY07**
- No cost limit
- Required preliminary data
- Clinical trials allowed

**Funded:**
- 3 TDAs

**FY09**
- Total direct cost limited
- Clinical trials no longer allowed

**Funded:**
- 3 TDAs

**FY10**
- New in FY10, introduced “idea-type” award for undeveloped but promising approaches

**Funded:**
- 2 TDAs
- 6 TIAs

**FY11-FY14**
- Overall satisfaction with TIA and TDA
- No changes

**Funded:**
- 2 TDAs (avg)
- 3 TIAs (avg)

**FY15**
- Specified preliminary data requirements for lead molecules under the TDA

**Funded:**
- 1 TDA
- 8 TIAs
NYTHE NEW CLINICAL DEVELOPMENT AWARD (CDA)?

When the level of ALSRP funding was doubled for FY20, the ALSRP conducted a survey of ALS research stakeholders asking for suggestions for new, unexplored research approaches that the ALSRP might support with these additional funds.

- **88%** of respondents thought a clinical mechanism should incorporate patient biological samples and data to better define subtypes, predict therapeutic response, or assess prognosis.
- **76%** of respondents thought biosample collection and depositing in existing publicly available curated ALS biorepositories should be strongly encouraged.
- **91%** of respondents endorsed supporting studies that would leverage ongoing/planned clinical trials by adding a secondary aim/goal to foster biosample collection and data analysis.

THE CDA EXPLAINED:

The CDA supports correlative studies leveraging human-based ALS resources to enrich clinical trials or optimize components of current ALS clinical care. Leveraging can refer to the use of existing well-characterized and highly curated resources or collaboration with ongoing clinical research to amplify potential gains in knowledge. Analysis of results and/or biosamples collected under these projects will be made broadly available through deposition in existing publicly available curated repositories and data platforms. In FY20, the ALSRP funded six CDAs, which are listed on page 11.

A summary of the Mechanisms and Priorities Survey results is available on the ALSRP webpage. Click or scan the code:
NEW FOR FY21!

THERAPEUTIC/BIOMARKER PILOT TRIAL AWARD

STUDIES WITH THE POTENTIAL TO MAKE A TRANSFORMATIVE IMPACT ON THE LIVES OF INDIVIDUALS WITH ALS

With a growing portfolio of promising and innovative preclinical therapeutic candidates supported by biomarkers and IND-enabling studies, the ALSRP is uniquely positioned to support this next logical step in the therapeutic research pipeline. In FY21, in response to an increased appropriation totaling $40M and directives from Congress, the ALSRP is offering the Therapeutic/Biomarker Pilot Trial Award (TBPTA) for the first time. The TBPTA will support early-phase and exploratory clinical trials that aim to demonstrate the feasibility or inform the design of more advanced trials for the treatment or management of ALS. The ultimate goal of projects funded under the TBPTA mechanism is to de-risk and inform the design of anticipated later-phase trials.

ALSRP Congressional Language

“Peer-reviewed Amyotrophic Lateral Sclerosis - 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.”

TBPTA Key Features:

Funding: $2,000,000 over 4 years

Supports phase 1 and small phase 2 trials that will de-risk, improve, and accelerate later stage trials of promising ALS therapeutics

All projects must incorporate biomarker development and characterization

Projects will have significant impact, de-risking future trials and improving ALS interventions and/or standards of care

Biomarker Research Encourages Efficiency and Innovation in Drug Development:

Biomarkers help clinicians to differentiate subgroups within the patient population. Subgroup identification assists with clinical trial design and allows clinicians to provide better guidance to their patients in terms of their disease progression.

Biomarker research deepens disease understanding through exploration of pathophysiological mechanisms that can generate targets for novel therapies.

Biomarkers help determine which therapeutics are likely to have clinical benefit.

Biomarkers provide monitoring metrics during clinical trials to ensure target engagement and inform go/no-go decisions.

A database of publicly-available ALS research resources has been made available on the ALSRP web page. Click or scan the code:
Awards to Date by Location

- Since FY07, the ALSRP has funded research in five different countries
- The majority of awards have been granted to academic research institutions

Awards by Organization Type

ALSRP-funded research spans for-profit, nonprofit, public, and private organizations establishing partnerships and facilitating translation of promising research.

- Academia, $55M, 64%
- Research Institute, $13M, 15%
- Medical, $11M, 13%
- Biotech/Pharma, $6.8M, 7.8%
- Government/Military, $0.8M, 0.9%

ALS RP PANEL MEMBER DIRECTS DEPARTMENT OF VETERANS AFFAIRS (VA) ALS BIOREPOSITORY EFFORT

The VA Biorepository Brain Bank (VABB) is a human tissue bank that collects, processes, and stores research specimens for future scientific studies. The VABB is among the largest national collections of research-grade ALS patient tissue. The VABB collection includes a unique cohort of long-duration (10 to 40+ year) ALS cases. Extensive prospective serial clinical phenotype data from these patients are enhanced by data in the VA Electronic Health Record. Neuropathological characterization, including deep digital phenotyping, has also been performed on cases. Co-morbidities identified in this cohort allows examination of other diseases in the context of ALS, such as Traumatic Brain Injuries and Chronic Traumatic Encephalopathy. Analysis of known ALS-associated genes and whole genome sequencing data on all cases is expected to be completed by 2021.

“The VABB contains ALS tissue from almost 250 post-mortem donors. Researchers from any country can obtain ALS patient tissue and data from the VABB’s collections, and the ALSRP continues to encourage applicants to collaborate with VA investigators and utilize the resources within the VABB.”

Since FY07, the ALSRP has funded research in five different countries.

- Montreal, CA
- Helsinki, FI
- Rotterdam, NL
- Santiago, CL
- Wollongong, AU

The majority of awards have been granted to academic research institutions.
ALS RP Accomplishments

THREE NEW TREATMENTS NOW IN CLINICAL TRIALS

**Humanized Anti-CD40LG IgG Antibody:** Blocks damaging inflammation in motor neurons

https://clinicaltrials.gov/ct2/show/NCT04322149

**GDNF-Expressing Neural Progenitor Cells:** Transplanted cells secrete GDNF which protects and stimulates neurons

https://www.clinicaltrials.gov/ct2/show/NCT01348451

**Pimozide:** Strengthens electrical connections between nerves and muscles

https://clinicaltrials.gov/ct2/show/NCT03272503

FOUR NEW TREATMENTS IN PRECLINICAL ADVANCED DEVELOPMENT

**Riluzole + Elacridar** combination enhances the effectiveness of Riluzole treatments

**CuATSM** helps prevent misfolding in mutant Superoxide Dismutase enzymes in ALS

**MicroRNA Mir-155 Antagonists** reduce Mir-155 production reducing inflammation

**Apilimod** clearing toxic protein aggregates in ALS

ALS RP HAS FUNDED THROUGH FY20

59 DRUG DISCOVERY AWARDS

25 DRUG DEVELOPMENT AWARDS

RESOURCES DEVELOPED AND METRICS REPORTED

**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 screening and testing

**Nearly 100 Scientific Publications**

**16 New Treatment Patent Applications**

**6 New Treatment Patents**

**Cell Lines**
Cell lines as research models
Stem cells as regenerative therapeutics

**Drug Delivery Concepts**
Nanoparticles
Viral delivery of gene therapy

**Research Models of ALS**
Yeast
Cell Lines
C. Elegans
Drosophilia
Mouse
Dr. Karen Ho, Clene Nanomedicine, Inc.

A recent ALSRP TDA funded in FY19 is supporting the pioneering work of Dr. Karen Ho and the scientific team at Clene Nanomedicine, Inc. As Head of Translational Medicine at Clene, Dr. Ho is working to demonstrate the preclinical efficacy of a gold nanocrystal, CNM-Au8 (pictured below), as a disease-modifying, neuroprotective drug candidate for ALS. CNM-Au8 works through a novel nanocatalytic mechanism to protect both neuron and glial populations from oxidative, inflammatory, hypoxic, and excitotoxic insults. Oral administration of CNM-Au8 significantly extended the lifespan and the healthspan of the ALS mouse model SOD1G93A. Dr. Ho, along with her collaborators, Prof. Nicholas Maragakis at Johns Hopkins University and Profs. Giovanni Manfredi and Steven Gross at Weill Cornell Medicine, aims to identify the sub-population of patients who may respond optimally to CNM-Au8 by developing a bioenergetic clinical screening tool.

Kathleen Rodgers and Kevin Gaffney, University of Arizona

Researchers at the University of Arizona Health Sciences Center for Innovation in Brain Science are seeking to repurpose an investigational oral drug previously shown to reduce inflammation and oxidative stress, improve cognitive function, and stimulate muscle regeneration in Duchenne muscular dystrophy. In work funded by an FY18 ALSRP TIA, Drs. Rodgers and Gaffney are investigating the therapeutic Mas agonist RASRx1902. They hope that the drug will decrease neurological deficits and neuronal death and increase the lifespan of ALS mouse models, including SOD1G93A and C9-500, and in patient-derived iPSC. In 2017, the FDA granted orphan drug designation to RASRx1902, clearing its path to potential therapeutic use and bringing it another step closer to having a meaningful impact on patients’ lives.
Dr. Justin Ichida, University of Southern California Keck School of Medicine

Groundbreaking data generated by an FY14 ALSRP Therapeutic Development Award led to the discovery of a new therapeutic target and preclinical validation of the anticancer therapeutic, Apilimod, in an ALS models. Pluripotent stem cells (pictured below) were induced into ALS patient neurons for the chemical screen and Apilimod, an inhibitor of a protein called PIKFYVE, was one of the most potent and broadly efficacious drugs identified during the screening of over 4000 molecules. Furthermore, Apilimod had been tested previously in Phase 2 clinical trials for other indications including psoriasis and Crohn’s disease. In discovering PIKFYVE inhibition as a new target for ALS, Dr. Justin Ichida at the University of Southern California, Keck School of Medicine, found that blocking PIKFYVE activity triggered a new, extremely effective way for nerve cells to eliminate toxic proteins that cause neurodegeneration in ALS. In conjunction with AcuraStem, Inc, Dr. Ichida is now advancing a novel, improved PIKFYVE inhibitor into ALS clinical trials. The work funded by this grant has been so successful that it has yielded multiple outcomes in the form of viable therapeutic candidates to benefit the research community and, ultimately ALS patients. Dr. Ichida and associates additionally developed the analysis software with DRVision Technologies, enabling automated detection of neuron number, rate of neurodegeneration, and rate of neurite retraction in patient-derived neuronal cultures in vitro, which will increase the throughput of experiments in the field and enable others to perform large-scale screens. This novel software, which would greatly speed the analysis of experimental samples is now moving toward commercialization.

Dr. Matt Saarma and Dr. Merja Voutilainen at the University of Helsinki in Finland

The idea that a potential Parkinson’s disease (PD) treatment could be repurposed for use in ALS patients stems from the observation that both diseases share common pathogenic mechanisms and that the novel protein Cerebral dopamine neurotrophic factor (CDNF) acts only on injured neurons. This work, funded through an FY16 ALSRP TIA, is being conducted at the University of Helsinki, Finland, and led by Dr. Mart Saarma. CDNF is a trophic factor with a mechanism of action different from conventional neurotrophic factors. CDNF treatment has been shown to protect and restore damaged neurons in rodent models of PD more effectively than any other protein previously tested, and it has demonstrated promising topline results in the ongoing phase 1-2 clinical trial in patients with PD. In order to investigate and enhance the therapeutic potential of CDNF in ALS, Drs. Saarma, Voutilainen, Sendtner, and Harvey have optimized the dose and delivery system of the protein in ALS animal models. They have now been able to show that a single dose of a CDNF can increase survival and improve motor coordination in multiple ALS murine models. These treatments, or chronic infusion of this protein over time, also delayed symptom onset and protected motor neurons in the spinal cord. Importantly, these findings were observed even in the most severely diseased animal model tested. This work was recently published in bioRxivs (De Lorenzo et al., 2020) and is currently under review for peer-reviewed publication. CDNF has been granted orphan drug status, thus clearing the pathway for its development into a therapeutic agent for ALS. The research team is hopeful that CDNF holds great promise as a future therapeutic for ALS.
# Clinical Development on the Horizon

## NEW CLINICAL DEVELOPMENT AWARD MECHANISM – FY20 AWARDS

<table>
<thead>
<tr>
<th>Institution Principal Investigator</th>
<th>Project Description</th>
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<tbody>
<tr>
<td>Annexon, Inc. Enchi Liu</td>
<td>Multi-center, open-label, proof-of-biology study of intravenous ANX005. Assessing the safety, tolerability, and pharmacokinetics of ANX005 administered in patients with ALS.</td>
</tr>
<tr>
<td>Columbia University Medical Center Wassim Elyaman</td>
<td>Examining the FUS-ASO clinical trial to perform longitudinal deep dissection of the immune response in symptomatic and asymptomatic ALSFUS individuals to identify novel molecular targets that can be engaged for ALS therapy.</td>
</tr>
<tr>
<td>Pennsylvania State University, Milton S. Hershey Medical Center Andrew Geronimo</td>
<td>A longitudinal home study of ALS patients to assess bulbar progression via a smartphone-based, self-administered remote speech and swallow assessment.</td>
</tr>
<tr>
<td>Massachusetts Institute of Technology Ernest Fraenkel</td>
<td>Identifying biological pathways that define subtypes of ALS by leveraging the AnswerALS biorepository.</td>
</tr>
<tr>
<td>Emory University Christina Fournier</td>
<td>Building 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.</td>
</tr>
<tr>
<td>ALS Therapy Development Institute Fernando Vieira</td>
<td>Using the SomaScan proteomics platform to assess 5,000 potential proteins in blood samples to discover prognostic biomarkers of ALS disease progression.</td>
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For more information, please visit
http://cdmrp.army.mil/alsrp
or contact us at:
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(301) 619-7071

02/2021
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