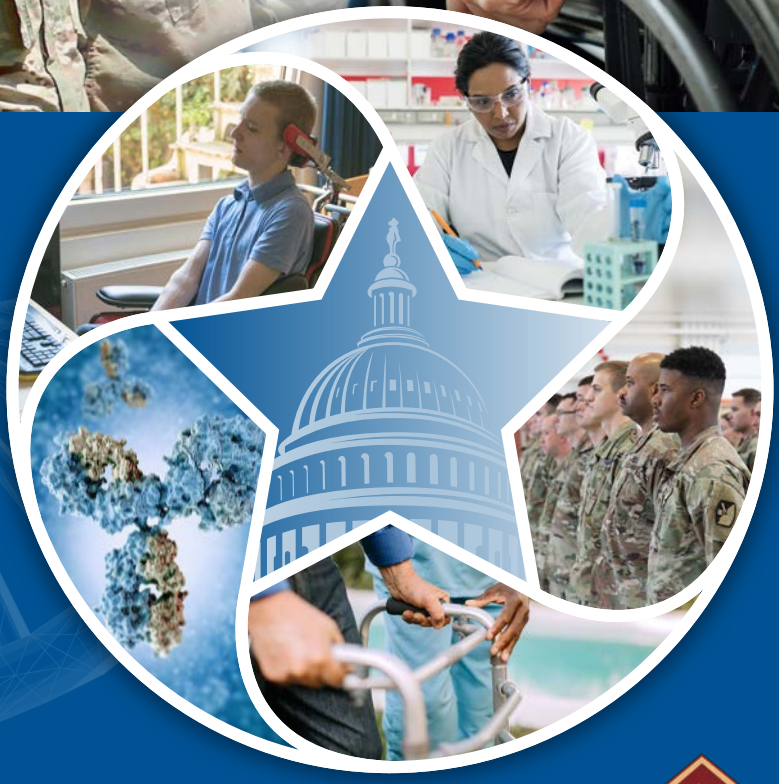
Amyotrophic Lateral Sclerosis Research Program



Congressionally Directed Medical Research Programs

CDMRP

Department of Defense

U.S. Army Medical Research and Development Command

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.

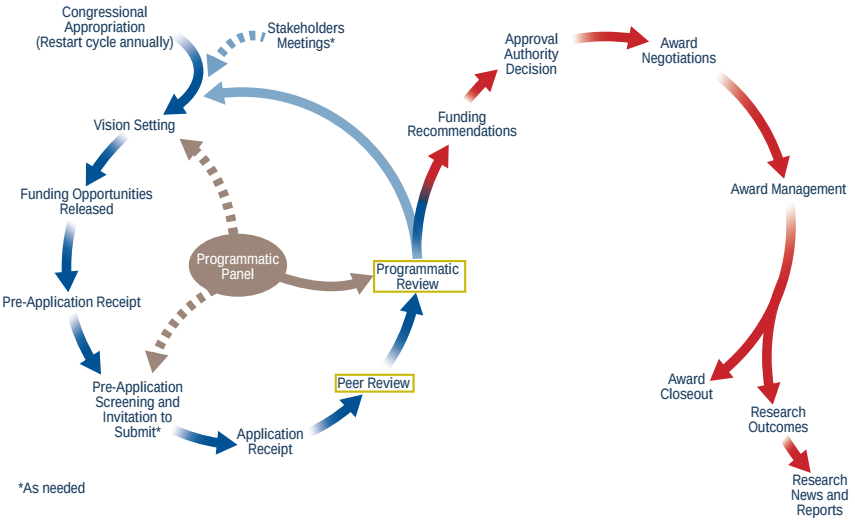
CDMRP MISSION: Responsibly manage collaborative research that discovers, develops, and delivers health care solutions for Service Members, Veterans, and the American public

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

ALSRP

VISION: Improve treatment and find a cure for ALS

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

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

ALSRP

Through FY20 there have been:

$129.4M in Congressional appropriations

708 Applications received

108 Awards totaling $81.43M

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.

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

strategy, and research focus. Input from consumers bears equal weight to subject matter experts in the field and military representatives. This is consistent with the unique research agenda of the CDMRP, which emphasizes a patient-centered focus and outcome for all programs.

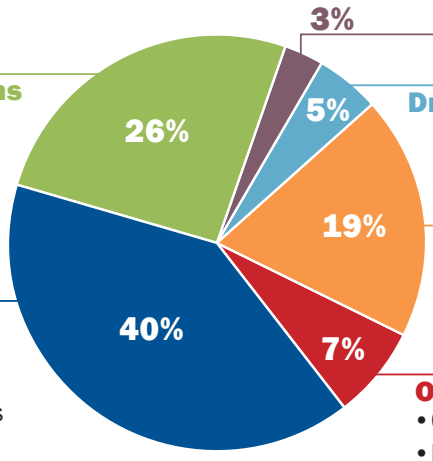
COL Fred Carlson, USA, Retired
The Robert Packard Center for ALS Research

"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."

ALSRP Supports the Thera

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.



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

Resource Development
- Cell lines
- Animal models
- Imaging techniques

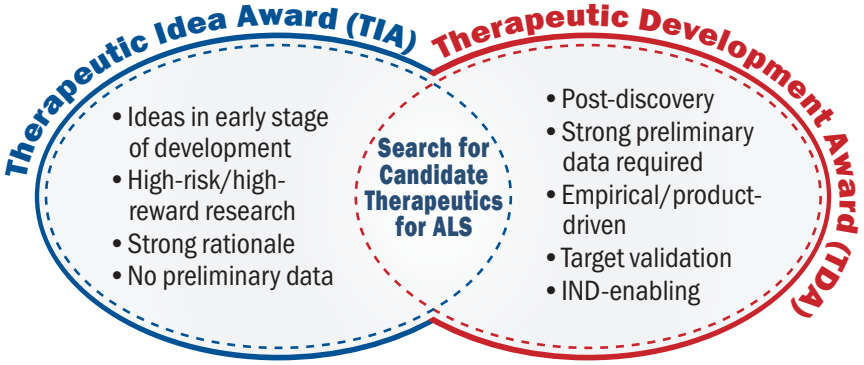
Drug Delivery
- Nanoparticles
- Stem cell transplantation

Drug Pharmacology
- Oral TW001 formulation
- CuATSM and derivatives
- Oral IZ10023 with riluzole
- AT-1501
- GLP-1R agonists
- RASRx1902

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

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

ALSRP FUNDING MECHANISMS



EVOLUTION OF ALSRP FUNDING MECHANISMS

FY07 $5M TDA ONLY	FY09 $5M TDA ONLY	FY10 $7.5M TDA/TIA	FY11-FY14 $6.8M-$8M TDA/TIA	FY $7 TDA
• No cost limit • Required preliminary data • Clinical trials allowed **Funded:** • 3 TDAs	• Total direct cost limited • Clinical trials no longer allowed **Funded:** • 3 TDAs	• New in FY10, introduced "idea-type" award for undeveloped but promising approaches **Funded:** • 2 TDAs • 6 TIAs	• Overall satisfaction with TIA and TDA • No changes **Funded:** • 2 TDAs (avg) • 3 TIAs (avg)	• Specified p requiremen molecules **Funded:** • 1 TDAs • 8 TIAs

peutic Pipeline and Beyond

Lyle Ostrow, M.D., Ph.D., ALSRP Programmatic Panel Chair

"ALS patients, caregivers, and advocates are involved in all aspects of ALSRP peer review, program policy, investment strategy, and research focus discussions. In this spirit, we distributed a Mechanisms & Priorities Survey to crowd-source the collective wisdom of the entire ALS community. Based on the survey responses, in FY20 we prioritized funding of novel innovative ideas through the TIA mechanism, provided greater emphasis on biomarker development to improve and de-risk eventual clinical trials, added the new CDA mechanism, and emphasized open data and resource sharing so that advances can be rapidly leveraged by the ALS research community."

WHY THE 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 be 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 web page. Click or scan the code:

Y15
.5M
/ TIA

reliminary data
ts for lead
under the TDA

FY16-FY17
$7.5M
TDA/TIA

- Clarified TIA-supported research must describe a path to a therapeutic
- Required transition plan
- Added animal model guidelines

Funded:
- 1-2 TDAs
- 7 TIAs

FY18-FY19
$10M
TDA/TIA

- Introduced option for development of biomarkers in parallel to the main therapeutic effort

Funded:
- 2 TDAs
- 7 TIAs

FY20
$20M
TDA/TIA/CDA

- New in FY20, introduced CDA
- Greater emphasis on biomarkers in parallel to therapeutic development
- Prioritized funding of TIAs

Funded:
- 16 TIAs
- 2 TDAs
- 6 CDAs

FY21
$40M
TDA/TIA/CDA/TBPTA

- New in FY21, introduced an early-phase clinical trial mechanism
- Increased direct cost limit of CDAs
- Continued to prioritize TIAs

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."

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

Bringing Therapeutics to the Clinic

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.

TBPTA Key Features:

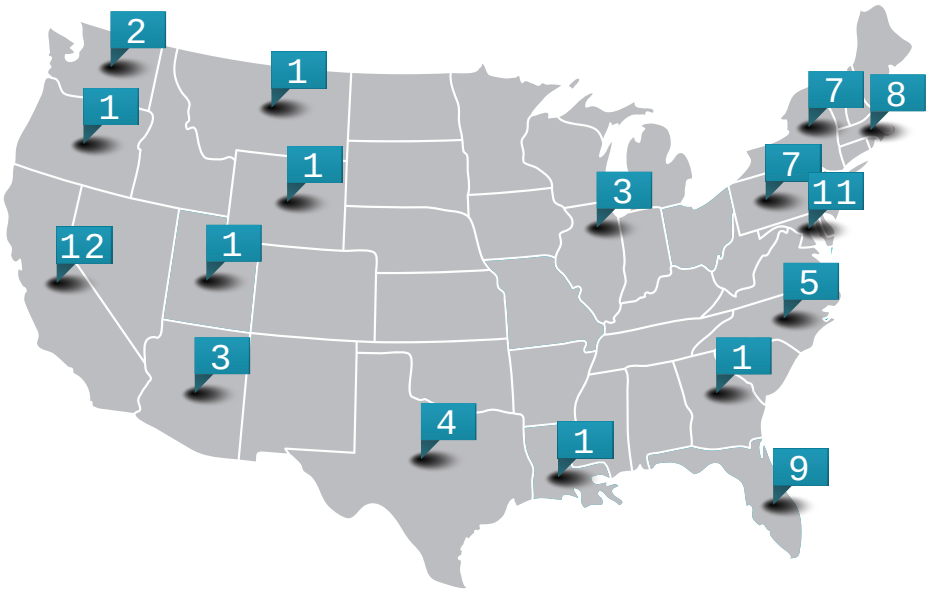
- Funding: **$2,000,000** over **4** years
- Supports phase 1 and small phase 2 trials that will **de-risk, improve, and accelerate** later stage trials of promising ALS therapeutics
- All projects must incorporate **biomarker development and characterization**
- Projects will have significant impact, **de-risking future trials and improving ALS interventions and/or standards of care**

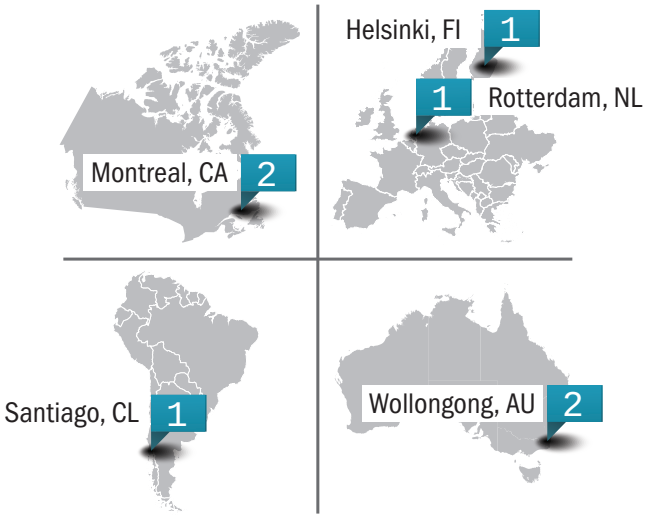
Biomarker Research Encourages Efficiency and Innovation in Drug Development:

- 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.

Awards to Date by Location

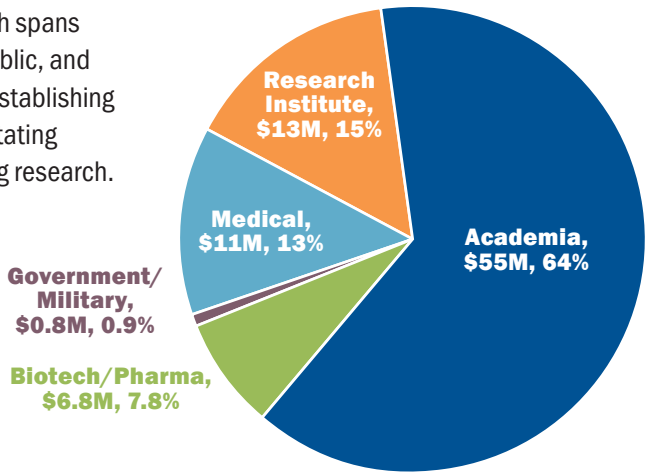
- Since FY07, the ALSRP has funded research in five different countries
- The majority of awards have been granted to academic research institutions





Awards by Organization Type

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



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

The VA Biorepository Brain Bank (VABBB) is a human tissue bank that collects, processes, and stores research specimens for future scientific studies. The VABBB is among the largest national collections of research-grade ALS patient tissue. The VABBB 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.

Neil Kowall, ALSRP Programmatic Panel Member

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

ALSRP 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

ALSRP 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

Yeast, Cell Lines, C. Elegans, Drosophila, Mouse

Research Models of ALS

Cell Lines
Cell lines as research models
Stem cells as regenerative theraputics

Drug Delivery Concepts
Nanoparticles
Viral delivery of gene therapy

6 New Treatment Patents

Kathleen Rodgers and **Kevin Gaffney,** University of Arizona

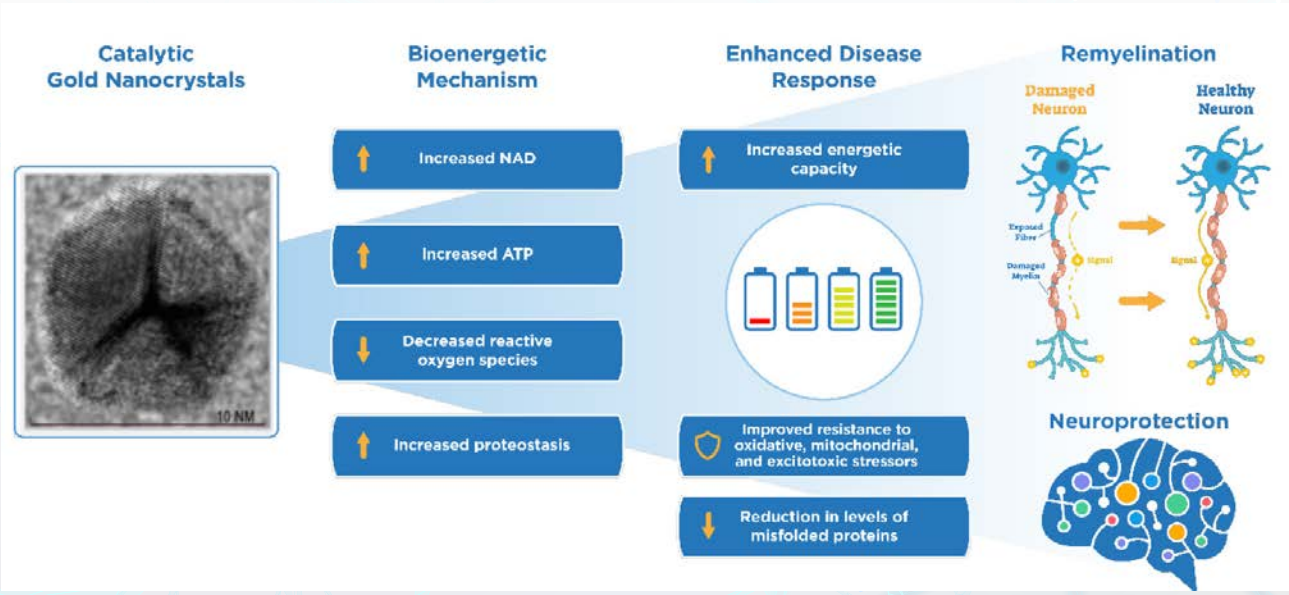
Researchers at the University of Arizona Health Sciences Center for Innovation in Brain Science are seeking to repurpose an investigational oral drug previously shown to reduce inflammation and oxidative stress, improve cognitive function, and stimulate muscle regeneration in Duchenne muscular dystrophy. 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. 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.

CNM-Au8 was competitively selected by a panel of ALS experts to be one of the first treatments tested in the HEALEY ALS platform trial. This platform is a leading-edge approach to clinical trials with the goal of dramatically increasing the pace from drug target discovery to therapeutic intervention.

SCHEMATIC OF THE GOLD NANOCRYSTAL, CNM-AU8, PROPOSED MECHANISM OF ACTION



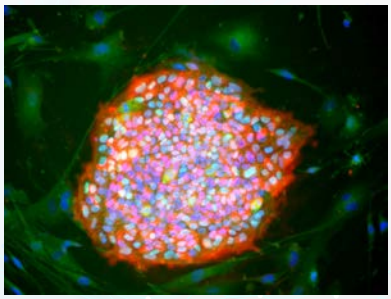
Making an Impact

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.

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.



Induced pluripotent stem cells, from ALS patients, labeled with immunofluorescence and used for chemical drug screening.

Clinical Development on the Horizon

NEW CLINICAL DEVELOPMENT AWARD MECHANISM – FY20 AWARDS

Institution Principal Investigator	Project Description
Annexon, Inc. Enchi Liu	Multi-center, open-label, proof-of-biology study of intravenous ANX005. Assessing the safety, tolerability,and pharmacokinetics of ANX005 administered in patients with ALS.
Columbia University Medical Center Wassim Elyaman	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.
Pennsylvania State University, Milton S. Hershey Medical Center Andrew Geronimo	A longitudinal home study of ALS patients to assess bulbar progression via a smartphone-based, self-administered remote speech and swallow assessment.
Massachusetts Institute of Technology Ernest Fraenkel	Identifing biological pathways that define subtypes of ALS by leveraging the AnswerALS biorepository.
Emory University Christina Fournier	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.
ALS Therapy Development Institute Fernando Vieira	Using the SomaScan proteomics platform to assess 5,000 potential proteins in blood samples to discover prognostic biomarkers of ALS disease progression.

For more information, please visit
http://cdmrp.army.mil/alsrp
or contact us at:
usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil
(301) 619-7071

02/2021
DoD visual images are for illustrative purposes only.
Some images were cropped to emphasize subject matter.