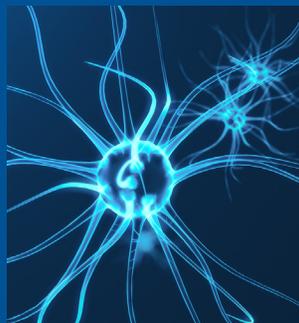


# Amyotrophic Lateral Sclerosis Research Program





# Amyotrophic Lateral Sclerosis Research Program

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

**MISSION:** Fund innovative pre-clinical research to develop new treatments for ALS for the benefit of Service members, Veterans, and the general public

## ALSRP History

Amyotrophic Lateral Sclerosis (ALS), also known as “Lou Gehrig’s disease,” is an incurable, degenerative neurological disorder. 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, but in FY09, Congress specifically appropriated funding for the ALSRP and has continuously provided funding since then, with a total appropriation of more than \$79M, including \$10M in FY18. Through its award mechanisms and funding recommendations, the ALSRP supports innovative preclinical research to develop new treatments for ALS.

## Research Priorities

### Preclinical Treatment Discovery

- Animal and cell models
- High-throughput screens
- Identify candidate drug leads
- Measure drug-target engagement

### Preclinical Treatment Validation

- Secondary validation and drug delivery
- Optimization of drug properties
- Collect data for FDA submission
- Develop Good Manufacturing Practice (GMP) methods

## ALSRP Portfolio

The ALSRP has focused on awards that support preclinical development of therapeutics for ALS. Areas of emphasis include development and/or validation of high-throughput screens to exploit novel targets with therapeutic potential and development of candidate therapeutics agents through the many steps required before U.S. Food and Drug Administration (FDA) approval as an investigational new drug. This includes studies on drug production, purity, stability, toxicology, pharmacokinetics, pharmacodynamics, and efficacy in cell and animal models.

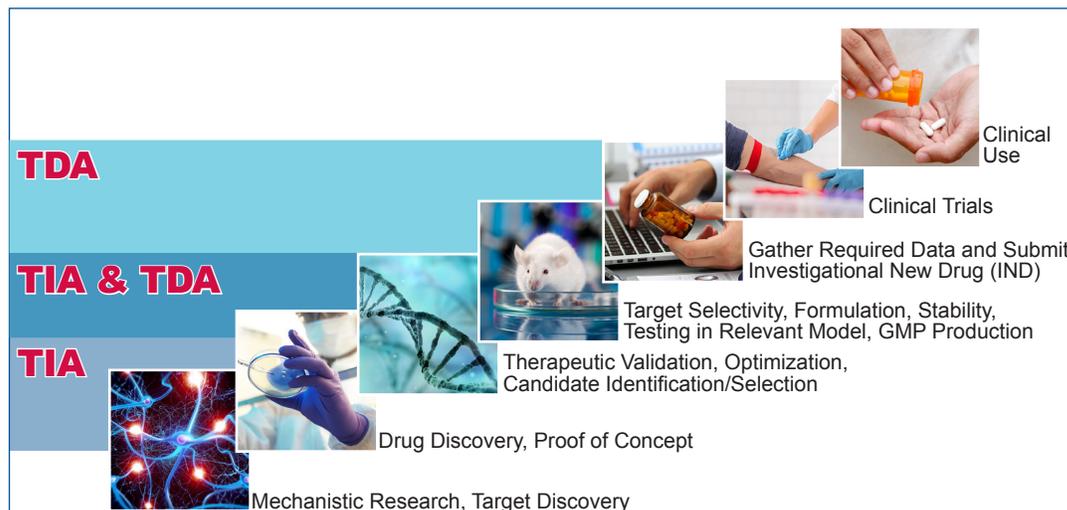
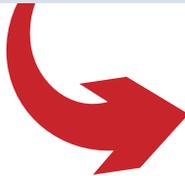
## Research Mechanisms

### Therapeutic Idea Award (TIA)

- FY10-present
- Identify candidate drugs in high-throughput screens, validate resulting drug candidates and assess pharmacological properties, and demonstrate effect on intended molecular targets

### Therapeutic Development Award (TDA)

- FY07-present
- Ready candidate drugs for clinical trials by secondary validation, optimization of pharmacological properties, development of manufacturing processes, and compilation of data for FDA submissions
- Develop markers to demonstrate drug actions on intended molecular targets.



## Interagency Collaboration



“This is a particularly exciting time for drug discovery for ALS, with an increasing number of small and large biotech companies dedicating programs to the disease. Investment through the ALSRP is critical to provide the necessary support for academia and small biotech to drive their novel treatment approaches toward the clinic. In just a few years, with the support from this program, six very different treatment approaches progressed from early pre-clinical development into advanced development and/or clinical trials.”

— **Lucie Bruijn**  
**Programmatic Panel Member**  
**Chief Scientist,**  
**ALS Association**

The ALSRP Programmatic Panel is composed of prominent members of the ALS research community, including scientists and consumers (i.e., ALS patients and/or their family members) from academia, the military, government, and non-profit organizations. The panel brings together stakeholders that typically might not collaborate. The collective wisdom of the talented and dedicated members of the panel results in a portfolio of cutting-edge research focused on benefiting those suffering from ALS.

The National Institutes of Health (NIH) and ALS Association are major funders of ALS research, and representatives from these organizations play a key role in the ALSRP as members of the Programmatic Panel. During the annual ALSRP Vision Setting meeting, the Programmatic Panel advises the ALSRP on programmatic focus and areas of scientific interest that should be addressed and the best type of award mechanisms for funding specific avenues of research. During Programmatic Review, the second tier of the application review process, the Programmatic Panel meets to recommend which applications best fulfill the ALSRP vision and mission, while addressing the program focus and research interests defined at Vision Setting. Programmatic Panel members from the NIH and ALS Association are called upon to help identify those proposed projects which might be redundant with ongoing efforts funded at their organizations, or alternatively, to identify those that may benefit from synergy with ongoing NIH or ALS Association efforts. The representatives from the ALS Association and the NIH help maximize the impact of the ALSRP by ensuring ALSRP priorities complement the research goals of each of their respective organizations. By filling underfunded research niches and incorporating best guidelines and practices developed by the NIH and ALS Association into funded research, the ALSRP ensures a synergistic approach to ALS research funding.



“The NIH and ALSRP share a strong commitment to finding effective treatments for ALS. To reach this goal, NIH supports a broad range of activities from basic ALS research to clinical studies in people with ALS. ALSRP’s focus on preclinical therapy development complements the ALS programs of NIH, and both funders work synergistically to move ALS research forward.”

— **Amelie Gubitza**  
**Programmatic Panel Member**  
**Program Director for Neurodegenerative Cluster,**  
**NIH National Institute of Neurological Disorders and Stroke**



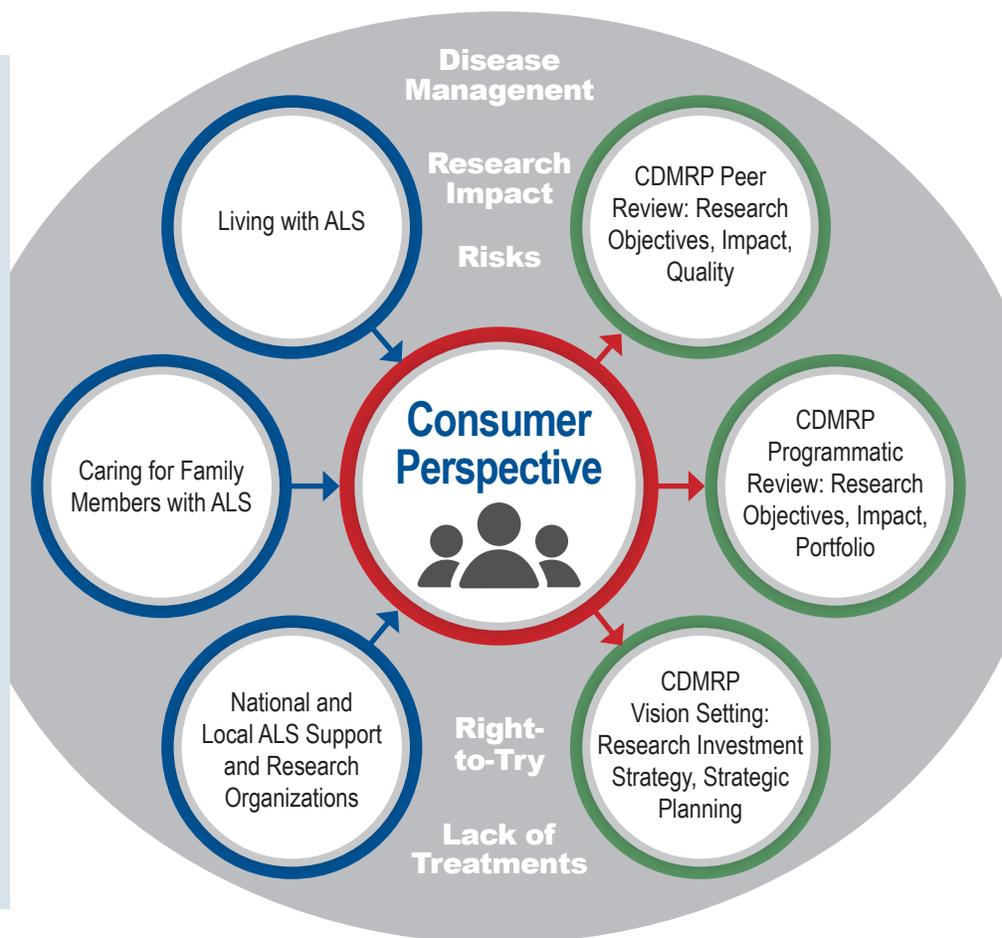
# Partnerships

## Peer Review Consumers



“Participating as a consumer advocate is an honor, a privilege, and a give/get in the most positive sense of the term. When I give my time to the ALSRP, I get the opportunity to be on the cutting edge of science, offering a unique perspective, as a caregiver/spouse, of how the research proposals, if successful, would affect the ALS community. When I spend a few days discussing the pros and cons of research proposals with a group of the finest minds in ALS research, I am always impressed by their indefatigable energy and commitment to their work. It is their work that gives me hope that successful treatments and a cure will be found.”

— **Mary Louise Pisone**  
**Peer Review Panel Consumer**  
**Les Turner ALS Foundation**



“When I first came to the CDMRP as a consumer reviewer 2 years ago, I felt my role was strictly to offer the patient perspective, providing the scientists with end-user input for the ALS research grant process. My participation on the panel has been very rewarding; I feel my input was listened to carefully by the scientists I have interacted with, and I appreciate the education they provided me. What I have also gained through participating in CDMRP is an expansion of my knowledge of ALS research.”

— **John Russo**  
**Peer Review Panel Consumer, ALS Association of Greater Philadelphia**

“My passion for ALS began in the late 70s when Les Turner, from Chicago, was diagnosed. As the Executive Director of the Foundation that bears his name, I also experienced personal loss, as both my aunt and significant other were diagnosed. Experiencing ALS from both sides has been both rewarding and painful. To serve as a consumer reviewer with world-class scientists, patients, and family members, to review and question new research ideas, was truly an honor. The dedication and determination of researchers and their passion to find answers gives us hope that we will see effective treatments for ALS very soon.”



— **Wendy Abrams**  
**Peer Review Panel Consumer, Les Turner ALS Foundation**

# Treatment Spotlight:

## Q&A with ALSRP Investigator Dr. Sytske Moolenaar

In 2016, Dr. Sytske Moolenaar, a scientist at the pharmaceutical company Treeway, received a TDA from the ALSRP to develop a new formulation of the drug Edaravone for the treatment of ALS. We caught up with Dr. Moolenaar recently and asked her a few questions.

**Q: Tell us about drugs used to treat ALS today. Why is Edaravone important?**

*A: Aside medications to treat symptoms like cramps, spasms, and fatigue, there are only two drugs approved by the FDA for treating ALS. For a long time, riluzole (sold as Rilutek® and Teglutik®) was the only drug approved for treating ALS. Riluzole is given orally, but only prolongs the life of people with ALS by a few months and does not prevent progression of debilitating symptoms. Edaravone (sold as Radicava®) was approved for treating ALS in 2017. It has been shown to delay the decline in functioning in people with ALS in a Japanese clinical trial.*

**Q: How does Edaravone work? Can it cure ALS?**

*A: Unfortunately there is no cure for ALS yet. Edaravone can only delay and reduce ALS symptoms. Edaravone readily crosses the blood-brain barrier and is thought to be a free-radical scavenger, but the exact mechanism by which it exerts its therapeutic effect in patients with ALS is unknown. Studies have shown that Edaravone delays the progression of debilitating symptoms of ALS. In one Japanese study, the decline in physical function in people with ALS was slowed down by 33% after 6 months of treatment.*

**Q: How is Edaravone administered in clinical practice?**

*Edaravone is currently available only as an intravenous medicine called Radicava and marketed by Mitsubishi Tanabe. It is administered through a needle in a vein under the supervision of a doctor at a*

*medical facility. Treatment roughly follows a cycle of 2 weeks of daily IV infusions at the facility followed by 2 weeks of no treatment, and the cycle continues indefinitely.*

**Q: Can you describe Treeway's development of an oral formulation of Edaravone?**

*A: As Treeway was founded by two ALS patients, we always have been in close contact with patient organizations and neurologists in the field of ALS. They have indicated that an oral version of Edaravone would be beneficial for ALS patients. Therefore, we are developing Edaravone as an oral formulation, which has been given the codename "TW001." We aim to give patients this formulation on a daily basis, which they can take at home.*

**Q: Can you tell us how your ALSRP-funded project to develop TW001 is going?**

*A: We have done studies using our prototype oral TW001 formulation and have shown that oral Edaravone is safe and well tolerated by healthy volunteers and ALS patients. We have shown that this oral formulation gives rise to effective levels of the drug in the bloodstream. Currently, we are performing development activities on the TW001 product needed to start larger clinical trials, which are funded by the TDA. Once these activities are finalized, Treeway can start additional ALS trials.*

**Q: What are your next steps?**

*We are determined to make TW001 available to the patients as quickly as possible so ALS patients all over the world can take this drug, and thereby delay the disease's progress.*



Treeway Research Team:  
Dr. Moolenaar seated,  
middle row on the left

# Approaches Investigated by the ALSRP

## Block or Reverse Aggregation

- SOD1, TDP-43, FUS, other
- Induce heat shock protein disaggregation activities
- Agents that reduce protein aggregation
- Agents that release RNA from aggregates

## High-Throughput Screening

- Patient-derived induced pluripotent stem cells
- Neuronal co-cultures
- Zebrafish
- Caenorhabditis elegans (roundworm)
- Automated phenotyping
- Phenotype rescue screens
- Aggregate reduction screens
- Pathway-targeted screens

## Reduce Toxicity of Mutants/Aggregates

- Prevent mitochondrial dimer exchange
- Inhibit transcription and translation of mutant DNA-repeat genes
- Mask aberrant structural features of RNA in aggregates
- Enhance degradation of aggregates/mutants

## Immune Response & Glial Activation

- Inhibitors of miRNA-155
- Reprogramming glial cells or astrocytes
- Blockade of immune signaling

## Other Approaches

- Reduce oxidative stress (ROS)
- Counteract glutamate toxicity
- Improve drug retention
- Boost the unfolded protein response (UPR) and protein degradation
- Alter fat/lipid metabolism
- Inhibit c-Jun N-terminal kinase (JNK) pathway
- Alteration of nucleocytoplasmic transport
- Replenish copper
- Sequester iron
- Restore miRNA-218 function
- Engraftment of engineered neuronal cells
- Enhance membrane repair
- Dopamine receptor antagonism
- Enhance neurofilament expression

# Therapeutic Idea Award



**Leonard Petrucelli,**  
Mayo Clinic and  
Foundation,  
Jacksonville  
**AL130125:**  
Inhibitors of

## c9RAN Translated Peptides and Toxicity in c9FTD/ALS

Dr. Petrucelli and colleagues studied DNA hexanucleotide -G4C2- repeat mutations, which are the most common mutation associated with C6ORF72-associated ALS (c9ALS). As potential therapeutics for ALS, they identified families of small molecules that can bind the RNAs transcribed from these repeats and prevent their translation into repeat proteins that are nonfunctional and toxic to nerve cells. Dr. Petrucelli has also investigated using the presence of the toxic repeat proteins as a marker for c9ALS and found that stable levels of these proteins were detectable in fluids and cells of c9ALS patients and from asymptomatic carriers of the C9ORF72 mutation.



**Jacob Robinson,**  
Rice University  
**AL150160:**  
High-Throughput,  
High-Dimensional  
(HT-HD)  
Phenotyping of

## C. elegans for ALS Drug Discovery

Microscopic worms expressing human G85R-mutated SOD develop ALS-like behaviors and characteristics. Dr. Robinson is using such worms in the development of a novel high-throughput screening system that can assess behavioral, anatomical, and electrophysiological characteristics of one worm per second. Using this system Dr. Robinson hopes to screen an initial bank of nearly 2,000 compounds for their ability to slow or reverse ALS-like signs.



**Gong Chen,**  
The Pennsylvania  
State University  
**AL150079:**  
Reprogramming  
Reactive  
Astrocytes

## Directly into Functional Motor Neurons in the Spinal Cord of ALS Model

Using genetically engineered viruses, Dr. Chen is endeavoring to reprogram spinal cord astrocytes into functional motor neurons. He hopes that this process will replenish motor neurons in the ALS spinal cord, thereby reducing inflammation and restoring normal motor neuron behavior. Dr. Chen states that employing viruses to assist in the conversion process has many benefits over stem cell transplantation, which often fails to generate a sufficient number of functional motor neurons necessary to initiate and sustain neural repair. Thus far, Dr. Chen's lab has been able to generate new neurons in SOD1 mutant mice, and he is currently conducting experiments to test if motor function has been restored in the mice.

## Milestones in the ALS Research Field

French neurologist Jean-Martin Charcot identifies ALS

1860



1995

FDA approves Riluzole

DoD/U.S. Department of Veterans Affairs (VA) studies link ALS to 1990-1991 Persian Gulf War

Early 2000's

# (TIA) Research Highlights

## ALSRP Products in Advanced Development



### Riluzole + Elacridar

Under an ALSRP TIA, treatment of ALS mice with Elacridar (efflux pump inhibitor) + riluzole was found to increase retention of riluzole in the central nervous system, improve behavioral measures including muscle function, and significantly extend survival of the mice. Under a follow-on ALSRP TDA, Izumi Biosciences is developing their own Elacridar formulation and continuing detailed pharmacokinetics, toxicology of the combination, and large-scale compound manufacturing. Izumi plans to submit an IND application for human clinical trials.



### Targeting Mir-155

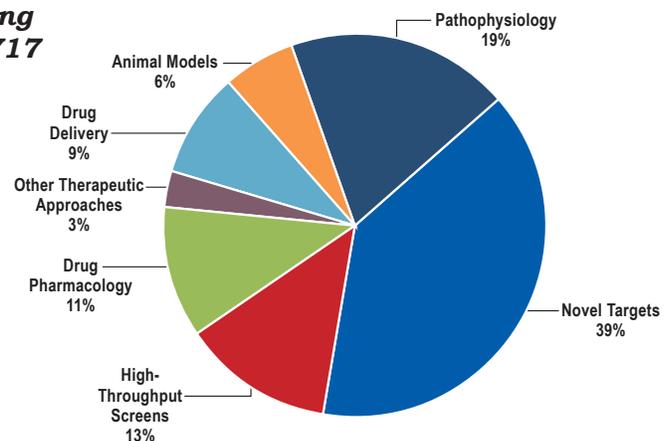
Mir-155 is a microRNA associated with ALS. Under an ALSRP TIA, genetic manipulation was shown to delay disease onset and extend survival in ALS mice. MiRagen Therapeutics is now developing a strategy to target miR-155 as a treatment for ALS.



### Apo-H-Ferritin

The ALSRP funded a TIA for the use of apo-ferritin, specifically the development of apo-H-ferritin encapsulated by liposomes for delivery in ALS mouse models, to study the effects of removal and redistribution of iron. Infusion at the time of disease onset was shown to be associated with an extension of lifespan. Development of this strategy is being continued through the ALS Association and a device company has been engaged for development of a delivery method involving surgical implantation of a pump that would deliver a trophic solution into the lumbar spinal space.

### TIA funding FY07 – FY17



2003

VA establishes a registry to identify cases of ALS in military veterans

National Institute of Environmental Health Sciences initiates the Genes and Environmental Exposures in Veterans with ALS (GENEVA) study in collaboration with the VA registry

2005



2006

Institute of Medicine releases report concluding that military service in general is related to the development of ALS

# Therapeutic Development Award



**Ole Isacson,**  
McLean Hospital  
**AL073054:**  
Development of  
Lead Agents for  
ALS Treatment in  
Preclinical Model

## Systems Based on Differential Gene Expression of IGF-II

Dr. Isacson used a high-throughput drug screening system to identify a subset of drugs that can elevate insulin-like growth factor 2 (IGF-II). Further down-selection based on IGF-II elevation and other ALS-relevant drug properties and activities identified the FDA-approved vardenafil hydrochloride (VDFL) as the strongest candidate. VDFL was subsequently shown to delay onset of symptoms and prolong survival in a mutant SOD1 ALS mouse model and to improve survival of cultured human motor neurons derived from ALS patients. Taken together, Dr. Isacson's data strongly suggest that modulation of the IGF-II pathway is beneficial in the treatment of motor neuron disease and that further studies of VDFL for the treatment of ALS symptoms are warranted.



**Steven Finkbeiner,**  
Gladstone Institutes  
**AL140088:**  
Development of  
Novel Neuronal

## Autophagy Inducers to Block Neurodegeneration and Treat ALS

Dr. Finkbeiner has previously identified FDA-approved small-molecule drugs that stimulate autophagy in neurons. Autophagy is a pathway cells employ to degrade and recycle damaged proteins and organelles; it does not generally remove normal proteins or healthy organelles from cells. Dr. Finkbeiner is using medicinal chemistry methods to improve the potency of these previously identified compounds and to remove unwanted neuroleptic side effects. Several of the improved compounds further increase autophagy in murine and human iPSC-motor neurons as well as offer increased protection from degeneration in ALS patient-derived iPSC-neurons. Dr. Finkbeiner hopes that one of the improved autophagy-inducing drugs may one day have an immediate impact on the treatment of ALS patients by rapidly slowing the progression of their disease.



**Justin Ichida,**  
University of Southern California  
**AL140122:** A  
High-Throughput  
Phenotypic

## Screen for C9ORF72 ALS Therapeutics Using Patient-Specific Motor Neurons

Dr. Ichida has developed a way to recreate ALS motor neurons from ALS patients' own blood cells. Specifically, he has developed a stem cell technology that successfully convert the blood cells of C9ORF72 ALS patients into a model of C9ORF72 ALS motor neurons. Dr. Ichida has shown that these patient motor neurons die faster than normal motor neurons and that they recapitulate the "disease in a dish." Dr. Ichida is currently treating these motor neurons with 40,000 different compounds to see if any increase their survival. By the end of the study, Dr. Ichida hopes to have generated the first therapeutic lead that targets the C9ORF72 mutation in ALS patients.

## Milestones in the ALS Research Field

The DoD redirected \$5M to FY07 Army Research, Development, Test, and Evaluation (RDT&E) funding to establish the ALSRP

2007



2008

VA establishes a "Presumption of Service Connection" for ALS

Centers for Disease Control and Prevention (CDC) launches a National ALS Registry (replaces the 2003 to 2007 VA registry)

2010

# (TDA) Research Highlights

## TDA supported Products Advancing to Clinical Trial



### Pimozide

The ALSRP funded large-scale screens of thousands of FDA-approved drugs to identify chemical modifiers of TDP-43 in preclinical models of ALS. A class of neuroleptics was identified and pimozide was the most potent compound, as confirmed in all models tested. Because pimozide is already FDA approved, it was able to move quickly into a small Stage IIb randomized clinical trial (NCT02463825) to look at the effects of a brief treatment of patients with sporadic ALS. Patients in ALS clinics in Canada were enrolled (Sponsors: University of Calgary and Alberta Health Services). The treated patients showed stabilization of motor activity, whereas untreated patients declined as expected. A national Phase IIb trial has started in Canada (funded by ALS Canada and Brain Canada) to determine the potential for pimozide as a therapeutic; 100 patients will be recruited and treated over a 6-month period (NCT03272503).



### CuATSM

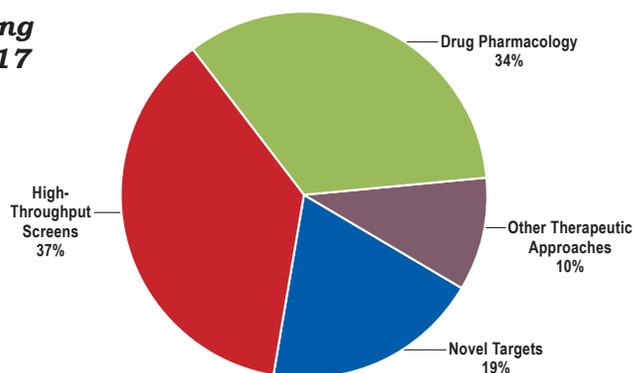
CuATSM is a copper chaperone that transfers copper from a carrier molecule to misfolded SOD1 and accelerates its maturation and function. Under an ALSRP TDA, ALS mice treated with CuATSM were found to live longer than controls. Procypra Therapeutics filed the paperwork required to initiate a clinical trial of their derivative form of CuATSM in Australia. The ALSRP is continuing to fund development of three novel classes of copper carriers with reduced toxicity, easy synthesis, and those that are effective at low dosages. The ALSRP-funded investigator has collaborative funding through The ALS Association and is moving forward with submission of an IND application to the FDA and plans to open a trial in the U.S.



### hNPCs Secreting GDNF

The ALSRP funded preclinical studies to move the use of growth factors, specifically glial cell-derived neurotrophic factor (GDNF), delivered to motor neurons as a therapeutic approach. Under a TDA, delivery of human neural cells (hNPCs) generated from post-mortem brain tissue, secreting GDNF, were injected into the spinal cord or directly into the cortex of ALS models. Using this method, enhanced motor neuron function and extended survival was found. The California Institute of Regenerative Medicine expressed interest in these preliminary results, and Dr. Svendsen has initiated an \$18M grant moving this into clinical trials in patients (NCT02943850).

### TDA funding FY07 – FY17



2014

ALS Association begins the Ice Bucket Challenge

FDA published detailed guidelines for development of therapeutics for ALS



2017

FDA approves Radicava (edaravone)

## FY18 Programmatic Panel:

**Bryan Traynor M.D., Ph.D. (Chair)**  
National Institute on Aging, National Institutes of Health

**Lucie Bruijn Ph.D., M.B.A. (Chair Emeritus)**  
ALS Association

**Pierre Drapeau Ph.D.**  
University of Montreal

**Amelie Gubitz Ph.D.**  
National Institute of Neurological Diseases and Stroke, National Institutes of Health

**COL Sidney Hinds M.D.**  
United States Army Medical Research and Materiel Command

**Jim Humay**  
Les Turner ALS Foundation

**Neil Kowall M.D.**  
U.S. Department of Veterans Affairs

**Larry Mink Ph.D.**  
ALS Association, Greater Philadelphia Chapter

**Lyle Ostrow M.D., Ph.D.**  
Johns Hopkins University

**John Ravits M.D.**  
University of California, San Diego

# Research on the Horizon

## Therapeutic Development Award

### *A GLP-1 Analog for the Treatment of ALS*

Nicholas Maragakis, Johns Hopkins University

## Therapeutic Idea Awards

### *Generation of a Mouse Model to Investigate IL-6 Trans-Signaling in ALS*

Gregory Hawkins, Wake Forest University Health Sciences

### *Identifying Drugs That Restore Neurofilament Level In ALS*

Zhong-Wei Du, BrainXell, Inc.

### *microRNA Replacement Therapy for ALS Treatment*

Samuel Pfaff, Salk Institute

### *Restoring Neuromuscular Junction Integrity to Alleviate ALS Progression*

Jingsong Zhou, Kansas City University of Medicine and Biosciences

### *Small Molecules Targeting TDP-43-RNA Interactions in ALS*

Daniela Zarnescu, University of Arizona, Tucson

### *Targeting Pathologic TDP-43 as a Therapeutic Approach in C9orf72 Disease*

Clotilde Lagier-Tourenne, Massachusetts General Hospital

### *Validating UBC9 as a Molecular Target to Develop a Therapy for All Forms of ALS*

Steven Finkbeiner, J. David Gladstone Institutes

For more information, visit

<http://cdmrp.army.mil>

or contact us at:

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