CDMRP

Department of Defense

Amyotrophic Lateral Sclerosis Research Program

U.S. Army Medical Research and Materiel Command

Congressionally Directed Medical Research Programs

CDMRP

VISION

Find and fund the best research to eradicate diseases and support the warfighter for the benefit of the American public.

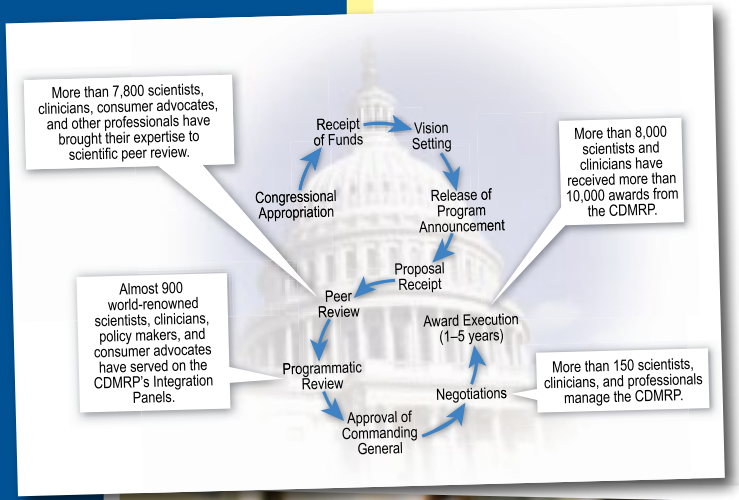
MISSION

Provide hope by promoting innovative research, recognizing untapped opportunities, creating partnerships, and guarding the public trust.

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 $7.5 billion in appropriations from its inception through fiscal year 2013 (FY13). 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.

Application Review Process



The CDMRP uses a two-tier review process to evaluate applications, with both tiers involving dynamic interaction among scientists and consumer advocates. The first tier of evaluation is a scientific peer review of applications measured against established criteria for determining scientific merit. The second tier is a programmatic review, conducted by the Integration Panel (IP), composed of leading scientists, clinicians, and consumer advocates, which compares applications to each other and makes recommendations for funding based on scientific merit, portfolio balance, and relevance to program goals.

Amyotrophic Lateral Sclerosis Research Program

ALSRP

VISION

Improve treatment and find a cure for ALS.

MISSION

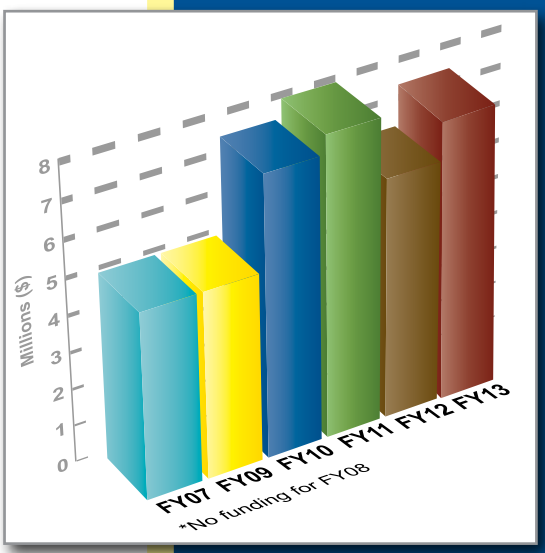
Fund innovative preclinical research to develop new treatments for ALS.

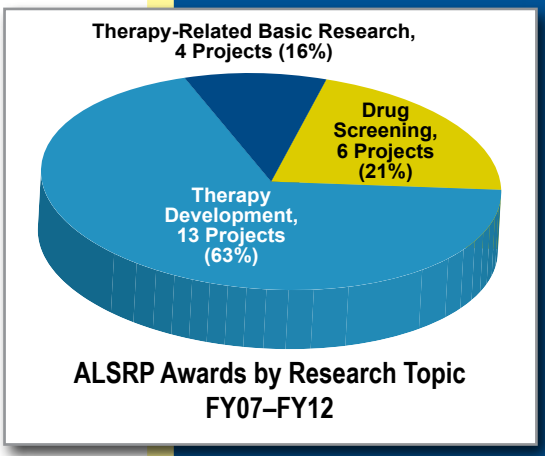
History

Amyotrophic lateral sclerosis (ALS), also known as "Lou Gehrig's disease," is a progressive neurodegenerative disorder in which the motor neurons of the brain and spinal cord controlling voluntary muscle movement gradually deteriorate. This leads to muscle weakness and atrophy and, ultimately, impacts swallowing and respiration. ALS usually strikes individuals between the ages of 40 and 70, although there are patients diagnosed in their 20s and 30s. Men are affected about 20% more than women. Average life expectancy after diagnosis ranges from 2 to 5 years,[1] and about 10% of ALS patients live more than 10 years after diagnosis.[2] Sporadic ALS comprises 90% to 95% of ALS cases and has no known risk factors, while 5% to 10% of cases are referred to as familial ALS and are associated with genetic inheritance.

It is estimated that approximately 30,000 people in the United States have ALS, and approximately 5,600 new cases of ALS are diagnosed annually.[1] Men and women who have served in the U.S. military are 60% more likely than civilians to develop a fatal muscle-wasting disease such as ALS.[3] In addition, 1990–91 Gulf War veterans have been shown to be twice as likely to develop ALS as the general population.[4] ALS can prove difficult to diagnose because the initial symptoms are both subtle and vague, and can be attributed to a number of known conditions.

There are currently no known therapies to effectively halt the progression of ALS, although one U.S. Food and Drug Administration (FDA)-approved drug, riluzole, modestly slows ALS progression. Several drug candidates are in clinical trials, and some show early promise.[5] A new focus area that currently has great potential for a therapeutic breakthrough surrounds the development and use of patient-derived induced pluripotent stem cells (iPSCs) for ALS disease modeling and drug screening.[6-8] A main advantage provided by iPSCs is the opportunity to study mechanisms and pathogenesis of neurodegeneration in human neurons.[9] In June 2007, the DOD redirected $5M to FY07 Army Research, Development, Test and Evaluation funding for the CDMRP to initiate the ALS Research Program as a broadly competed, peer-reviewed research program. Though not funded in FY08, Congress subsequently appropriated funding in FY09 and has continuously funded the program since then with a total appropriation of more than $46 million.





ALSRP Awards by Research Topic FY07–FY12

[1] ALS Association.
[2] Robert Packard Research Center at the Johns Hopkins Hospital.
[3] Weisskopf M, et al. 2004. Annual Meeting of the American Academy of Neurology, San Francisco, California.
[4] U.S. Department of Veterans Affairs, Research Advisory Committee on Gulf War Veterans' Illnesses. 2008. Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations.
[5] Northeast Amyotrophic Lateral Sclerosis Consortium (www.alsconsortium.org; Clinical Trial News).
[6] Burkhardt MF, Martinez FJ, Wright S, et al. 2013. Mol Cell Neurosci 56:355-64.
[7] Egawa N and Inoue H. 2013. Rinsho Shinkeigaku 53(11):1020-2.
[8] Egawa N, Kitaoka S, Tsukita K, et al. 2012. Sci Transl Med 4(145):145ra104.
[9] Hargus G, Ehrlich M, Hallmann AL, et al. 2014. Acta Neuropathol 127(2):151-73.

Consumer advocates and scientists working together

The two-tier review process established by the CDMRP brings together the expertise of scientists with the perspective and experience of "consumers," the ALS patients themselves and supportive family members. This innovative approach, recommended by the National Academy of Sciences' Institute of Medicine and adopted by other funding organizations, has proven to be a highly effective way to evaluate research applications for their potential to meet the program's goals for those we seek to serve.

"Working with the ALSRP program is a pleasure. The staff is dedicated to moving the program forward and the reviewers are committed to a thorough and fair process. The results from the funded projects have already led us to reevaluate our thinking of the progression of the disease and how best to tackle it."

-- Mahendra Rao, M.D., Ph.D., Director of National Institutes of Health Intramural Center for Regenerative Medicine, FY13 Therapeutic Development Award Peer Review Chair

"Fighting ALS is a team endeavor involving family, friends, clinicians, scientists, policy makers, and, at the center, people with ALS. I am privileged to be part of this fight while teaching students about the disease, making new discoveries in the lab, and caring for ALS patients. In addition, I have been honored to serve on and chair the ALS Therapeutic Idea Award peer review panel together with other committed scientists and lay people. Together, we have carefully reviewed, critiqued, and recommended the most compelling, innovative, and impactful scientific projects to move discoveries forward quickly for new therapeutics to treat and cure ALS."

-- Brent Harris, M.D., Ph.D., FCAP, Associate Professor and Director of Neuropathology at Georgetown University Medical Center, FY13 Therapeutic Idea Award Peer Review Chair

"I was diagnosed with ALS in October 2008 at the age of 65. Up until that time, my health was excellent. I was a competitive long-distance runner having competed in 25 full marathons and hundreds of shorter races.

After my diagnosis, I was determined to be an advocate for ALS research and awareness. With the help and support of my family and friends, we formed a team for The Fiesta 5K Race for ALS Research that is held in Baltimore the first Saturday of May. With over 90 members on our team, we have raised over $58,000 for ALS research.

I attended and spoke at an FDA hearing about the concerns of the ALS community in regards to the lengthy process of getting new drugs to market.

I was honored to be nominated and selected in the Fall of 2013 to serve on the DoD ALSRP as a consumer reviewer."

-- Fred Carlson, Packard Center for ALS Research at Johns Hopkins, FY13 Consumer Peer Reviewer

Scientists and consumers serve critical roles in the ALSRP

As peer reviewers, they evaluate applications for scientific and technical merit as well as the potential successful impact of the research.

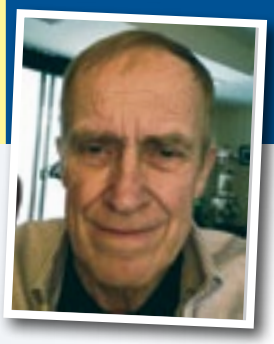
As IP members, they make programmatic recommendations for the ALSRP's vision, investment strategies, and funding selections intended to reflect the needs of the consumer and research communities.

"The ALSRP supports innovative research that explores novel therapeutic strategies for ALS and advances such therapies towards clinical testing. I have served as a member of the ALSRP Integration Panel for about two years and have been impressed by the quality and scientific breadth of the grant applications, the rigorous and fair review process, and the research progress attained by the funded projects. Overall, the ALSRP is speeding the development of promising treatments for ALS patients, and the program complements and enhances the investments of other funders of ALS research, including the NIH and patient advocacy groups."

-- Amelie Gubitz, Ph.D., Extramural Research Program Director for the National Institute of Neurological Disorders and Stroke

"There is growing excitement in the ALS field, a sense that we are on the cusp of really understanding what causes this form of neurodegeneration. The next challenge will be to translate these findings to help people with this devastating disease. The DoD ALS Research Program provides invaluable leadership and support to research efforts that may one day lead to effective treatments."

-- Bryan Traynor, M.B., M.D., Ph.D., MMSc, MRCPI, Investigator and Chief of the Neuromuscular Diseases Research Unit, Laboratory of Neurogenetics, National Institute on Aging



"Having personally experienced the heart of your family being torn from you, there's a realization how vulnerable we are to forces we don't understand. ALS takes parents from sons, daughters, grandchildren so they are denied the loving guidance and compassion only a mom, dad, or grandparent can provide. Currently, with ALS, no cause has been identified, no therapeutic developed, and no cure brought forth. Serving in the ALS Research Program, as a consumer reviewer, with Peer Review and currently with the Integration Panel, I have had the opportunity to witness the worldwide scientific commitment and dedication, focused by the CDMRP, to give us answers to this devastating neuromuscular disease. All things in life may be temporary and only for now, but the ALSRP is a symbol for those of us impacted by ALS, of hope and direction for our future answers in this war against ALS."

-- Jim Humay, Les Turner ALS Foundation

FY13 Integration Panel:

Dr. Lucie Bruijn (Chair)
ALS Association

Dr. Brenda Cuccherini
U.S. Department of Veterans Affairs

Dr. Amelie Gubitz
National Institute of Neurological Diseases and Stroke, National Institutes of Health

Mr. Jim Humay
Les Turner ALS Foundation

Dr. Edward Kasarskis
University of Kentucky

Major Carlos Maldonado
U.S. Air Force

Dr. Nicholas Maragakis
Johns Hopkins University

Ms. Ellyn Phillips
ALS Association

Dr. Bryan Traynor
National Institute on Aging, National Institutes of Health

ALSRP Award Mechanisms

In its short history, the ALSRP has offered two award mechanisms, the Therapeutic Development Award (TDA) and the Therapeutic Idea Award (TIA), to support scientists developing new treatments or studying neuroscience to improve ALS therapy in the future.

The TDA mechanism is designed to support preclinical testing and development of therapeutics for ALS. Scientists have used TDA awards to screen thousands of compounds, or refine a smaller sample, in nerve cell cultures and animal models to find candidate drugs that might be effective against ALS. Others have used TDAs to create new screening methods with nerve cell cultures. Since 2007, 12 TDAs have been awarded, totaling more than $21 million.

The TIA is designed to promote innovative, early-stage ideas with the potential to uncover new avenues of investigation for novel therapeutics in ALS. TIAs can help turn innovative ideas into new treatments for ALS. Since its inception in 2010, 11 TIAs have been awarded, totaling more than $6 million.

These award mechanisms have received a robust response from the ALS research community, which continues to respond with exciting research applications aimed at finding new ways to treat ALS.

The table below and the information on the following pages highlight a few of the TDAs funded by the ALSRP.

FY12 ALSRP Awards

The ALSRP recently finalized 3 awards from a $7.5 million FY12 congressional appropriation:

Therapeutic Development Award

Dr. Serge Przedborski Columbia University	A Cell-Based Assay To Identify Neuroprotective Molecules for the Treatment of Amyotrophic Lateral Sclerosis
Dr. Howard Weiner Brigham and Women's Hospital	Targeting miR-155 in Peripheral Monocytes for the Treatment of ALS

Therapeutic Idea Award

Dr. Michael Benatar University of Miami, School of Medicine	Therapeutic Targeting of Expanded C9ORF72 Transcripts in ALS

Preclinical Development of Therapeutics for Amyotrophic Lateral Sclerosis

Barrie Carter, Ph.D., University of Iowa, Iowa City, Iowa

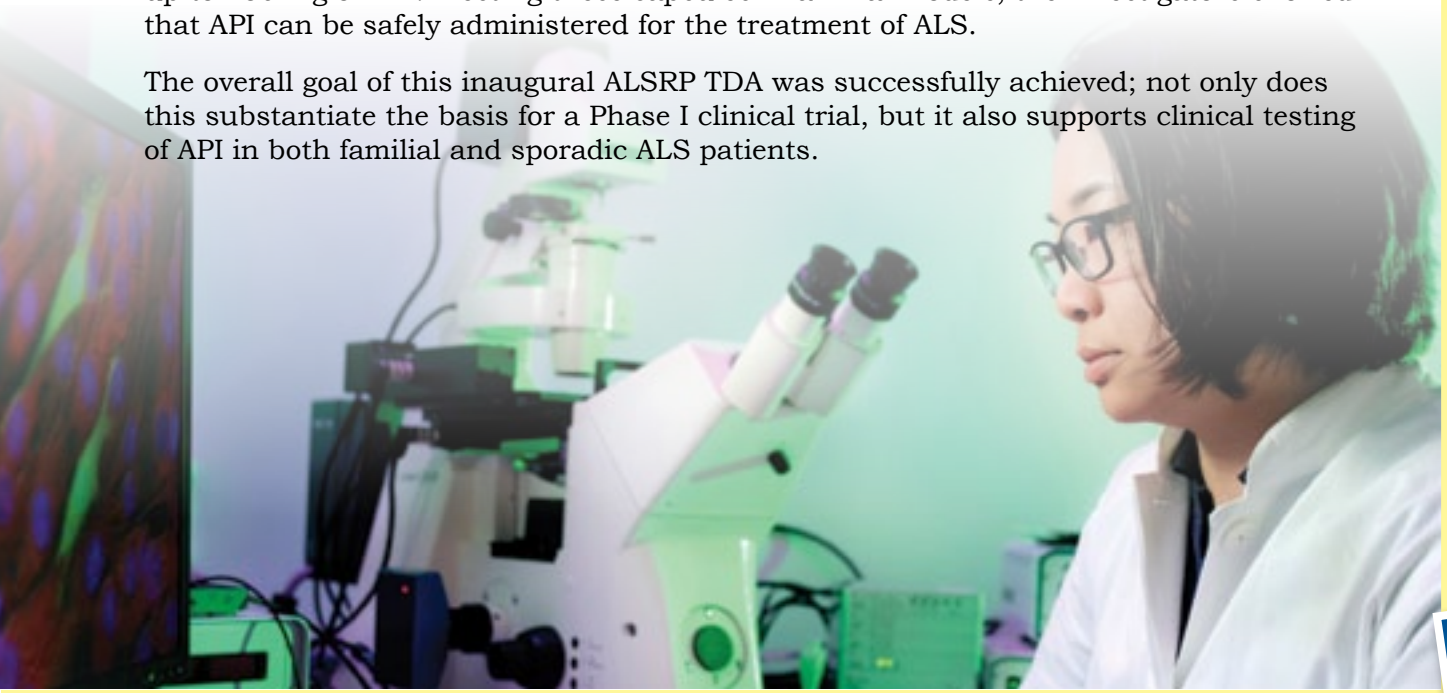
ALS is a devastating neurodegenerative disease characterized by the breakdown of motor neurons in the central nervous system (CNS) resulting in death, typically in 2 to 5 years after diagnosis. At present, ALS is incurable, with only one approved treatment, riluzole, which extends survival by a mere matter of months. Drs. Barrie Carter and John Englehardt at the University of Iowa, with the help of Dr. Pervin Anklesaria, used an FY07 TDA to perform preclinical studies and formulate drugs for clinical development of apocynin, a natural organic compound, in hopes of using it to treat ALS.

Mutations in the gene for superoxide dismutase 1 (SOD1) are a primary component of familial ALS pathology. Mutant SOD1 interacts with Rac1, which results in upregulation of the NADPH oxidase complex (Nox), leading to an overproduction of reactive oxygen species (ROS) from microglial cells in the CNS. ROS contributes to the deterioration of neurons in the CNS, which typifies ALS. Apocynin acts as an inhibitor of Nox to reduce microglial-activated motor neuron degeneration.

To prepare for eventual Phase I clinical trials, Dr. Carter and his team conducted studies in two animal species to support an FDA Investigational New Drug (IND) application. The IND application requires an established set of studies to examine a drug's safety and toxicity in animals before it can be used in humans. Included in these sets of studies are 7- and 28-day toxicity tests. In addition, the maximum tolerated dose, the rate at which the drug is absorbed into the body, and how long it takes the drug to be excreted from the body all must be determined for an IND application. Furthermore, studies of the safety of apocynin relative to cardiovascular, respiratory, and neurological systems were conducted. The team also conducted supplementary studies of apocynin in ALS mice to further understand its mechanism of action and to provide insight into the mechanism of ALS and the role of potential modifier genes.

The investigators developed an effective formulation for active pharmaceutical apocynin (API). Tablets were initially pursued for the formulation as their potentially high drug load suited the expected high daily dose regimen. However, due to solubility issues, the investigators ultimately opted for a dry powder capsule formulation, which is able to hold up to 150 mg of API. Testing these capsules in animal models, the investigators showed that API can be safely administered for the treatment of ALS.

The overall goal of this inaugural ALSRP TDA was successfully achieved; not only does this substantiate the basis for a Phase I clinical trial, but it also supports clinical testing of API in both familial and sporadic ALS patients.

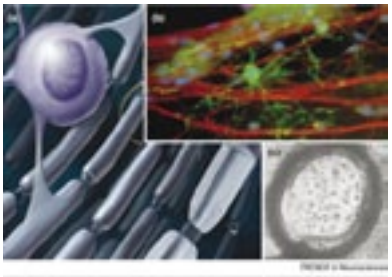


The Role of NG2 Glial Cells in ALS Pathogenesis

Jeffrey Rothstein, M.D., Ph.D., The Johns Hopkins University, Baltimore, Maryland

A subpopulation of glial precursor cells called NG2+ cells are a relatively newly described population of progenitor cells. During development these cells differentiate into oligodendrocytes and, possibly, astrocytes. In an ALS mouse model with mutant SOD1, these cells dramatically upregulate NG2 and show enhanced proliferation into ventral horn gray matter, which is where motor neuron death associated with ALS takes place. Dr. Jeffrey Rothstein is using an FY11 ALSRP Therapeutic Idea Award to further investigate the impact of NG2+ cells in ALS pathogenesis. Dr. Rothstein's preliminary work with NG2+ cells demonstrated that removal of mutant SOD1 from these cells in transgenic mice leads to a significant delay in ALS disease onset and an increase in survival of the animals. These results suggest that NG2+ cells and oligodendrocytes play an important role in ALS pathogenesis.

Using the FY11 award, Dr. Rothstein will differentiate human-induced pluripotent stem (iPS) cells from ALS patients into NG2+ cells and oligodendrocytes. Dr. Rothstein will then, for the first time, co-culture human-derived ALS NG2+ glial cells with human motor neurons, including those from ALS patients, to determine whether they will induce motor neuron cell death. A similar strategy will be carried out by co-culturing iPS-differentiated oligodendrocytes (both myelinating and non-myelinating) at different developmental stages with human motor neurons to study their impact on normal neuron function and survival. The potential results from this study represent a significant step forward in determining what role NG2+ cells and oligodendrocytes play in ALS pathogenesis and may provide novel targets for ALS therapeutic development.



Rethinking Drug Treatment Approaches in ALS by Targeting ABC Efflux Transporters

Piera Pasinelli, Ph.D., Thomas Jefferson University, Philadelphia, Pennsylvania

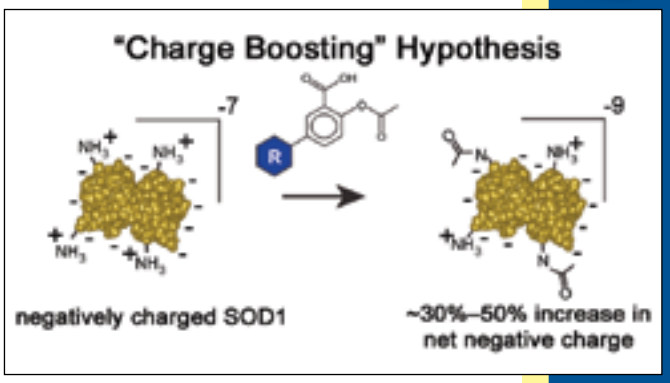
Despite numerous efforts at pharmacological approaches to treat ALS, only one drug, Riluzole, is currently available, and its impact on the disease is limited. One of the roadblocks in finding highly efficacious treatments in ALS may derive from the underestimated issue of disease-driven pharmacoresistance mediated by cells with ABC drug efflux transporters. These transporters protect the brain by actively pumping "foreign" substances out of the central nervous system (CNS), including Riluzole. Dr. Piera Pasinelli is using an FY10 ALSRP Therapeutic Development Award to investigate this aspect of pharmacoresistance and possibly develop a method to improve the effects of Riluzole. Dr. Pasinelli proposes to counter the ABC transporter's activity with an inhibitor, Elacridar, that could be co-administered with Riluzole to "open the door" to improve its effectiveness. Initially, Dr. Pasinelli planned to confirm an effective, non-toxic dose and delivery route for Elacridar and develop a reliable method for Riluzole administration. Preliminary testing confirmed the ability of Riluzole to improve survival in SOD1-G93A animals. Methods are now being optimized to measure Riluzole bioavailability in the blood and CNS of the test animals using mass spectrometry.

Initial results of the project have been positive, and it is hoped that this new approach will enhance the effectiveness of Riluzole as well as provide a mechanism to improve the action of other potential pharmacotherapies. Dr. Pasinelli is optimistic that if proven effective, this treatment should quickly move into the clinic to help those suffering with ALS.

Designing Pharmacological Agents that Inhibit the Aggregation of SOD1 by Increasing the Net Negative Charge

Bryan Shaw, Ph.D., Baylor University, Waco, Texas

Scientific evidence is mounting to show that the progressive neurodegeneration of ALS is associated with the incorrect folding of proteins or malfunctions in the disposal of proteins within nerves. The hereditary form of ALS (familial, or fALS) involves mutations in SOD1 that lead to its misfolding. It is not entirely clear why misfolding of this particular protein causes ALS, but there is evidence that aggregation of misfolded proteins accompanies nerve damage.



Using an FY10 ALSRP Therapeutic Idea Award, Dr. Bryan Shaw has been exploring his hypothesis that if the aggregates of misfolded proteins could be prevented, neurodegeneration would be stalled long enough to allow the cells to dispose of misfolded proteins properly. As most proteins possess a net negative charge, Dr. Shaw reasoned that if the net charge of SOD1 could be increased, the tendency to aggregate would decrease, since like-charged molecules repel each other. Knowing that normal SOD1 proteins bear a net negative charge, Dr. Shaw neutralized the positive charges of surface lysine sidechains, rendering the proteins more negative. He found that neutralizing even two lysines in the SOD1 A4V mutant (known to be associated with ALS) significantly reduced aggregation. For this finding to develop into a practical therapy, a drug based on this principle must specifically neutralize SOD1 and avoid the myriad of other proteins bearing surface lysine residues. Therefore, Dr. Shaw's group is designing molecules for this purpose using computer modeling programs to design easily synthesizable molecules that should bind exclusively to SOD1. The next steps will be to synthesize then test these molecules to identify those that will optimally prevent SOD1 aggregation.

Apoferritin as a Therapeutic Treatment

James Connor, Ph.D., Pennsylvania State University Milton S. Hershey Medical Center, Hershey, Pennsylvania

Numerous factors – iron in particular – are thought to contribute to the loss of motor control that characterizes ALS. Balancing the amount of iron in the body, especially in the brain, is vital since a lack of iron hinders effective cell functions, while an excess of iron results in oxidative damage to DNA, lipids, and proteins. Iron accumulation and deposition, which may worsen ALS pathology and symptoms, have been reported in ALS patients.

Supported by an FY10 ALSRP Therapeutic Idea Award, Dr. James Connor set out to investigate whether administration of a protein that binds and removes excess iron from the body could limit the oxidative damage that plays a key role in ALS-related nerve cell death. To do this, Dr. Connor infused apoferritin – ferritin that is not iron-loaded – into a solution containing nutrients and other components normally found in cerebrospinal fluid (CSF). The infused solution was administered to mice with ALS, where it was found to delay disease onset and extend lifespan. In contrast, Dr. Connor demonstrated that a mere "rinsing" solution was unable to improve disease progression, highlighting that dilution of the toxic factors in the CSF is not enough to achieve an equivalent effect. This approach is unique in its use of ferritin, a naturally occurring substance that sequesters iron, setting it apart from other pharmacological interventions that utilize synthetic components. Dr. Connor is actively pursuing the necessary studies to support a Phase I clinical trial in hopes of bringing this research closer to helping ALS patients.

Attacking ALS from All Sides

Apoptosis Signal regulating Kinase 1 (ASK1)

Involved in the ER stress response and associated with motor neuron death.

Developing ASK1 inhibitors.

NADPH oxidases (Nox) (neurotoxic)

Drug development to block Nox-2 production of ROS implicated in neuro-inflammation and degeneration.

SOD1 mutations (neurotoxic)

Associated with familial ALS.

Developing compounds to inhibit aggregation of SOD-1.

TAR DNA Binding Protein-43 (TDP-43, neurotoxic)

Associated with neurodegeneration.

Developing chemical screens for agents that suppress or augment TDP-43 mutations.

Levuglandins (LGs)

Increased lipid peroxidation is common in ALS, and LGs are toxic products from this reaction.

Studying compounds that can remove LGs.

IGF-II (neuroprotective)

May protect motor neurons from glutatmate-induced toxicity and promote axon regeneration.

C9orf72

Approximately 30 GGGGCC hexanucleotide repeat expansions in this gene are normal, but mutations in this gene, where there are hundreds or thousands of repeats, are a known cause of ALS.

Investigating ways to reduce C9orf72.

P-glycoprotein (multi-drug resistant protein)

Therapeutic target in spinal cord for increasing ALS drug efficacy.

c-Jun N-terminal kinases (JNKs)

Contribute to cell death.

Developing brain-penetrant JNK inhibitors.

Heat Shock Factor protein 1 (HSF-1)

Reduction in HSF-1 activity accelerates neuronal toxicity.

Peripherin

Overexpression of protein aggregates of the neuronal intermediate filament peripherin has been linked to neuronal injury and may actually play a therapeutic role in reversing neuronal degeneration.

Studying Per-28, peripherin isoform, to see if it may serve as a mechanism for attenuating motor neuron toxicity.

The ALSRP's 23 awards given from FY07-FY12 focus on a variety of molecular targets that either protect neurons from neurotoxicity or contribute to disease progression.

Looking Forward: THE ALSRP IN FY14

For FY14, the ALSRP will use a $7.5 million congressional appropriation to continue its mission to support preclinical therapeutic development for ALS using the previously offered mechanisms (TDA and TIA).

FY14 Program Announcements are expected to be released March 2014.

For more information, visit
http://cdmrp.army.mil
or contact us at:
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