

# Amyotrophic Lateral Sclerosis Research Program



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"I am privileged to represent the ALS community as the consumer member on the ALSRP Integration Panel. I have seen firsthand the dedicated work of these prominent researchers and clinicians. The projects selected are of the highest quality and designed to conduct innovative preclinical research to develop new treatments for ALS."

**Ms. Ellyn Phillips**  
ALS Consumer

# Congressionally Directed Medical Research Programs

## History

The Congressionally Directed Medical Research Programs (CDMRP) was born from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. The CDMRP was created as an office within the U.S. Army Medical Research and Materiel Command (USAMRMC) in fiscal year 1993 (FY93) to manage these funds, initiating a unique partnership among the public, Congress, and the military. Having grown to encompass multiple targeted research programs, the CDMRP has received almost \$5.9 billion in appropriations since its inception in FY93 through FY10. Funds for the CDMRP are added by Congress to the Department of Defense (DOD) budget annually, where support for individual research programs such as the Amyotrophic Lateral Sclerosis Research Program (ALSRP) is allocated via specific guidance from Congress.

## Proposal Review Process

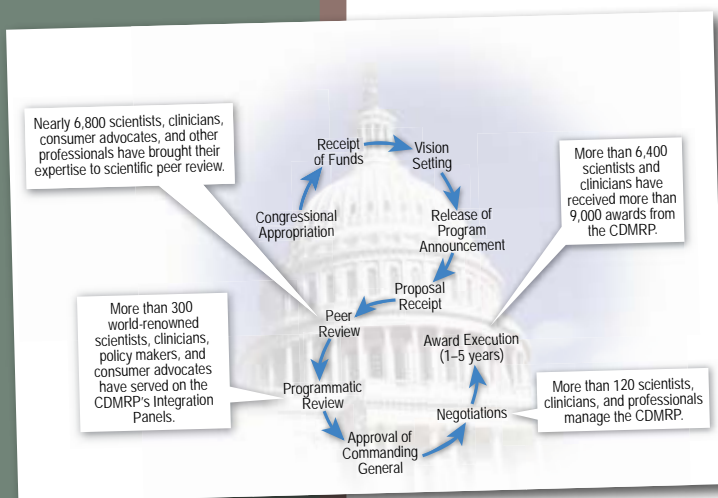
The CDMRP program management cycle includes a two-tier review process recommended by the National Academy of Sciences' Institute of Medicine. Each level of review is conducted by panels composed of scientists and clinicians—subject matter experts—and consumers.

The first tier of evaluation is an external scientific peer review of applications against established criteria for determining scientific merit. The second tier is a programmatic review conducted by members of the Integration Panel, who compare submissions and make funding recommendations based on relative scientific merit, portfolio balance, and relevance to program goals.

## Consumer Advocacy Participation

A unique aspect of the CDMRP is the active participation of consumer representatives throughout the program's annual cycle.

Consumers work collaboratively with leading scientists and clinicians in setting program priorities, reviewing proposals, and making funding recommendations. From a unique perspective gained through personal experience—as someone affected by ALS—the consumer brings a sense of urgency and focus to all levels of decision making. Consumers evaluate proposals based on the potential impact and benefit to the patient population, encouraging funding recommendations that reflect the concerns of patients, their families, and the clinicians who treat them.





# Amyotrophic Lateral Sclerosis Research Program

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 between the ages of 40–70 although there are patients diagnosed in their 20s and 30s. Men are affected about 20% more than women. Sporadic ALS (SALS) 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 (FALS) 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.<sup>1</sup> 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.<sup>2</sup> In addition, 1990–91 Gulf War veterans have been shown to be twice as likely to develop ALS as the general population.<sup>3</sup>

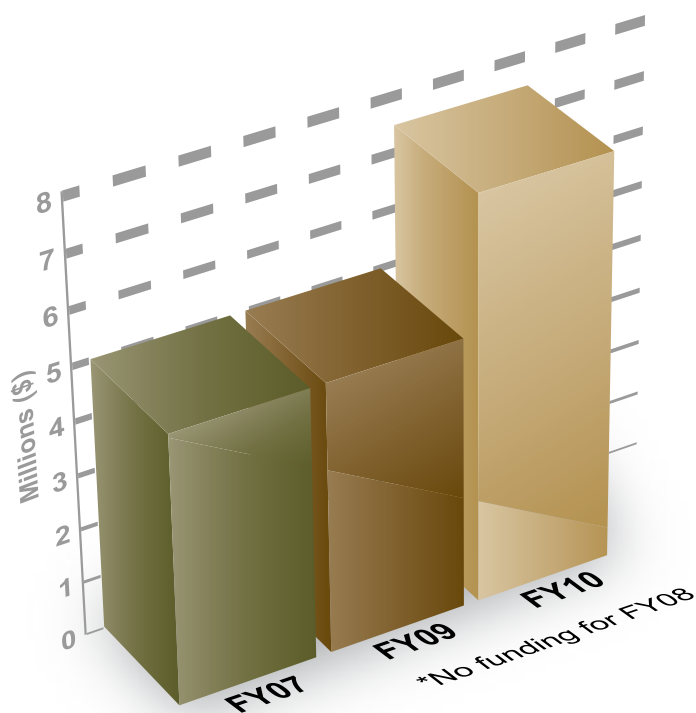
ALS can prove difficult to diagnose because the initial symptoms are both subtle and vague and can be attributed to a number of known conditions. Average life expectancy after diagnosis ranges from 2 to 5 years,<sup>1</sup> and about 10% of ALS patients live more than 10 years after diagnosis.<sup>4</sup> There are currently no known therapies to effectively halt the progression of ALS though one FDA-approved drug, riluzole, modestly slows ALS progression. Several drug candidates are in clinical trials, and some show early promise.<sup>5</sup> New focus areas, including transcript profiling and immune system modulation, are being investigated as novel approaches for ALS therapeutic interventions.<sup>6</sup>

## VISION

Improve treatment and find a cure for ALS

## MISSION

Fund innovative preclinical research to develop new treatments for ALS



<sup>1</sup> ALS Association

<sup>2</sup> Weisskopf M, et al. 2004. Annual Meeting of the American Academy of Neurology, San Francisco, California

<sup>3</sup> Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations, U.S. Department of Veterans Affairs, Research Advisory Committee on Gulf War Veterans' Illnesses. 2008

<sup>4</sup> Robert Packard Research Center at Johns Hopkins Hospital

<sup>5</sup> quest.mda.org

<sup>6</sup> Nature Genetics (28 March 2010) doi:10.1038/ng.557 Article



"There is an urgent need for treatments for ALS, a devastating disease with no cure and only one FDA-approved treatment that slows progression of the disease by a few months.

The ALSRP is a very exciting program providing the opportunity for investigators from academia and industry to develop new treatment approaches for ALS. This important program funding translational research fills an enormous gap in the research pipeline to enable new treatments to move from the laboratory to the clinic."

-- *Lucie Bruijn, Ph.D., Chief Scientist for The ALS Association and FY10 ALSRP Integration Panel Chair*

In June 2007, the DOD redirected \$5 million (M) of FY07 Army research, development, test, and evaluation funding for the CDMRP to initiate the ALSRP as a broadly competed, peer-reviewed research program. The ALSRP has focused on supporting preclinical development of therapeutics for ALS, offering a Therapeutic Development Award in FY07 and FY09. Six awards have been made using these funds, holding the promise of improved therapies for ALS patients. For FY10, the ALSRP has received a \$7.5M appropriation from Congress and will add a Therapeutic Idea Award to its portfolio to promote novel basic research related to therapeutics for ALS.

*Therapeutic Idea Awards (new for FY10) promote new, early-stage ideas with the potential for high impact and novel therapeutics for ALS. Evaluation Criteria for these awards include:*

- Innovation and impact
- High risk/high reward
- Strong scientific rationale



# Neuroprotective Small Molecules for the Treatment of Amyotrophic Lateral Sclerosis

Serge Przedborski, Ph.D., Columbia University, New York

Mutations in the gene encoding superoxide dismutase (SOD1), a potent antioxidant enzyme, are reportedly associated with about 20% of familial ALS cases. Dr. Serge Przedborski from Columbia University previously reported in vitro studies indicating that rodent astrocytes (non-neuronal cells surrounding neurons) expressing mutant SOD1 contribute to a more severe form of neurodegenerative process by killing spinal primary motor neurons and embryonic stem cell-derived motor neurons (ES-MNs). The death of motor neurons is accomplished through soluble neurotoxic factors mimicking the ALS phenotype compared to mutated SOD1 expression in primary motor neurons alone.

Dr. Przedborski received a 2007 ALSRP Therapeutic Development Award to identify small-molecule neuroprotective agents for the treatment of ALS. Dr. Przedborski along with collaborators Drs. Stockwell and Henderson at Columbia and Dr. Rubin at Harvard is performing high-throughput screening of libraries of small compounds (about 30,000 small molecules at Columbia and 50,000 molecules at Harvard) to examine the individual effect at 10  $\mu$ M concentration on the survival of mutant mouse ES-MNs cultured with rodent astrocytes expressing mutant SOD1. Promising compounds with high rates of ES-MN survival will be validated at both institutions and further tested at 10 different concentrations from 1 nM to 30  $\mu$ M. After a comprehensive primary screening, 100 confirmed protective compounds will be selected for secondary screening in the Przedborski laboratory using a model of ES-MNs exposed to rat or mouse SOD1 mutant astrocyte-conditioned culture media. In this secondary screening, neuronal survival and axonal length will be assessed to identify the molecules most protective of neurons and their processes.

Translational potential for this research project is high. It should yield approximately 20 promising compounds with the highest potential potency and efficacy, resulting from a screen with the most relevant in vitro models of ALS. These compounds will move forward for preclinical in vivo studies and may result in viable drug candidates for people living with ALS.



*Therapeutic Development Awards support preclinical assessment of therapeutics for ALS through:*

- Identification of lead compounds
- High-throughput screens
- Development through ADMET phase
- Development to FDA IND application
- FY07: 3 awards
- FY09: 3 awards





## Development of Lead Agents for ALS Treatment in Preclinical Model Systems Based on Differential Gene Expression of IGF-2

Ole Isacson, M.D., McLean Hospital,  
Harvard Medical School

Studies in ALS mouse models have indicated that the initiation of neurodegeneration may be due to intrinsic factors associated with somatic motor neurons (MNs) while astrocytes and microglia can also play an important role in the progression of neurodegeneration. Motor neuron subpopulations are prone to differential vulnerability to neurodegeneration with similar pathology and pattern in both forms of ALS, whether sporadic or familial.

Dr. Ole Isacson has taken a novel approach to targeting ALS drug development by examining differential gene expression in subpopulations of MNs. He has previously applied this approach successfully in determining neuroprotection biomarkers in Parkinson's disease. His preliminary data from a rat model of ALS highlighted by cranial nerves oculomotor/trochlear (CN 3/4) complex, hypoglossal nerve (CN 12), and lateral motor column (LMC) MNs in symptomatic SOD1G93A rats versus wild-type rats indicated a slight decline of CN 12 MNs and a larger decline in LMC MNs in symptomatic SOD1G93A rats while CN3/4 MNs seemed to be unaffected. Dr. Isacson then studied global gene and protein expression of CN3/4, CN12, and LMC of the cervical spinal cord in the normal rat. Analysis of in vitro functional assays demonstrated neuroprotective properties of insulin-like growth factor II (IGF-2) when used as a pretreatment for MNs. The image on page 7 from Dr. Isaacson's preliminary data demonstrates this neuroprotective effect against glutamate toxicity, an in vitro surrogate for the in vivo condition. In the top row, primary cultures of spinal MNs are shown with expression of proteins indicative of viable MNs (MNR2/HB9, islet-1, and neurofilament [NF]), and Hoechst staining of DNA in all cells in the control panel. The middle row shows MN toxicity following the glutamate insult, and the bottom row shows protection of the MNs resulting from pretreatment with IGF-2 prior to the glutamate insult.

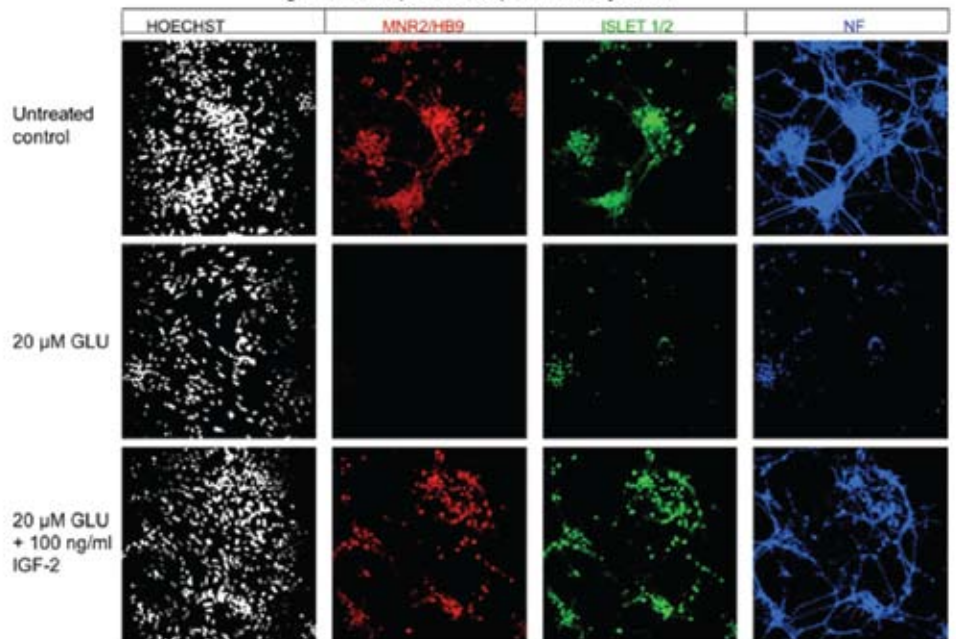
Building on these findings, Dr. Isacson, who received an ALSRP FY07 Therapeutic Development Award, has been developing a screening method for identifying compounds that can upregulate expression of IGF-2 and that may have neuroprotective properties. High-throughput screening and polymerase chain reaction (PCR) are used to screen drug-like compounds from selected compound libraries (150,000 compounds) featuring many different drug categories. An initial screen of 1,040 generally FDA-approved drugs using quantitative PCR from MN cultures demonstrated 10% of these drugs have a twofold to sixfold upregulation of IGF-2. Notable drug candidates were found in anti-inflammatory, analgesic, and sex hormone-related drug categories. The high-hit compounds were further evaluated and selected by enhancement of IGF-2-related pathway phenotypes and by an in vitro glutamate toxicity assay, a validated bioassay for

vulnerability to excitotoxic neuronal degeneration or MN death common in ALS.

Preliminary analysis of pharmacological and toxicological profiles of the selected candidate drugs are in progress both in vitro and in vivo. Additionally, selected candidate drugs with previously known brain permeability are being examined in both normal and presymptomatic SOD1G93A rats and mice for disease progression by behavioral and histopathological analysis.

A larger screen of drug compounds with structural analysis and pharmacological and toxicological profiles in animal models will follow. The result of the large study will be an optimized candidate drug with high-translational potential to be used as a first-line drug for ALS treatment.

Validation of protective effect of exogenous recombinant IGF-2 in modified glutamate protocol: preliminary data







For more information, visit

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