

A photograph of an older man with grey hair, wearing a brown jacket, looking out at the ocean under a cloudy sky. The text is overlaid on the right side of the image.

XI. Amyotrophic Lateral Sclerosis Research Program



A close-up photograph of a person's back being treated. A hand is holding a white, handheld medical device with a needle-like tip against the skin. Another hand is resting on the upper back. The person is lying on a white towel on a table. The text "Developing New Therapies" is overlaid in white on the right side of the image.

Developing New Therapies



Mission

Promote the development of ALS therapeutics.

“A November 2006 Institute of Medicine report concluded that Gulf War veterans and other combat veterans may be at an increased risk for ALS [Amyotrophic Lateral Sclerosis] when compared with the civilian population. The Veterans Health Administration’s Office of Research and Development has expanded its research efforts related to ALS and supports cooperative efforts to advance discoveries related to early diagnosis, therapeutic interventions, and mechanisms to improve the quality of life. CDMRP’s [Congressionally Directed Medical Research Programs’] Amyotrophic Lateral Sclerosis Research Program represents a very valuable resource that will allow current scientists with expertise in ALS to pursue their research efforts to both develop novel therapeutics and advance medical knowledge about ALS.”

Brenda Cuccherini, Ph.D.
Department of Veterans Affairs
FY07 Alternate Chair

The Disease

ALS, also known as “Lou Gehrig’s disease,” is an incurable, degenerative neurological disorder. For reasons that are not understood, the nerve cells of the brain and spinal cord that control voluntary muscle movement gradually deteriorate. Average life expectancy after diagnosis ranges from 2 to 5 years.¹ There are no known therapies to effectively halt the progression of ALS. Men and women who have served in the U.S. military are 60 percent more likely than civilians to develop a fatal muscle-wasting disease such as ALS.²

Signs and Symptoms

The early onset of ALS is often so subtle that signs and symptoms are overlooked. However, emerging physical symptoms of the disease include:

- ❖ Twitching, cramping, or stiffness of muscles
- ❖ Muscle fatigue and weakness affecting an arm or leg
- ❖ Slurred and nasal speech
- ❖ Difficulty chewing or swallowing

These general symptoms then develop into more obvious signs of muscle weakness or atrophy. As the disease progresses, patients experience difficulties moving, swallowing, and speaking. Eventually, patients afflicted with ALS are unable to stand, walk, swallow, or chew, and they experience difficulty breathing. The disease does not usually affect cognitive abilities.



¹ ALS Association, <http://www.alsa.org/als/facts.cfm?CFID=4240363&CFTOKEN=81327833>

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

Program Background

In June 2007, the DOD redirected \$5 million (M) of fiscal year 2007 (FY07) Army Research, Development, Test, and Evaluation funding for the CDMRP to initiate the Amyotrophic Lateral Sclerosis Research Program (ALSRP) as a broadly competed, peer-reviewed research program. Similar to other programs within the CDMRP, the ALSRP was conducted according to the two-tier review model recommended by the National Academy of Sciences Institute of Medicine. An Integration Panel (IP) was assembled to identify gaps in the field of ALS and make recommendations on how to address them.

“The ALS Association and the ALS community are delighted to partner with CDMRP through an ALSRP. Since the 1860s when ALS was first identified, the need for more research has been apparent. With the knowledge that those in the military have a higher incidence of ALS, we are optimistic that this research program will advance the efforts for more effective treatments and a cure.”

Ellyn Phillips
ALS Association
FY07 Integration Panel Member



The Program Today

FY07 Summary

One award mechanism, the Therapeutic Development Award, was offered in FY07 to promote the introduction of improved therapies for ALS by encouraging ALS investigators to undertake preclinical studies of novel and existing agents. A total of 21 proposals were received and 3 awards were made. The funding summary for the FY07 ALSRP is shown in Table XI-1.

Table XI-1. Funding Summary for the FY07 ALSRP

| Categories and Award Mechanisms | Proposals Received | Awards | Investment |
|---------------------------------|--------------------|----------|---------------|
| <i>Clinical Research</i> | | | |
| Therapeutic Development | 21 | 3 | \$4.5M |
| TOTAL | 21 | 3 | \$4.5M |

21
Proposals
Received

3
Awards

\$4.5M
Investment

The ALSRP Team

Melissa Forsythe, Ph.D., R.N.
Colonel (Retired), Program Manager

Jennifer Fallas, Ph.D.
Grants Manager

David Galey, Ph.D.
Program Coordinator, SAIC

Detrick Stith, Ph.D.
Peer Review Coordinator
SRA International

Extraordinary People

The ALSRP-supported studies would not have been made possible without the active participation of consumer advocates, peer review panel members, and IP members. The program recognizes that their collective knowledge, participation, and recommendations may lead to the development of novel therapies for those afflicted with ALS.

Consumer Advocates

Consumer advocates have made a meaningful difference in the ALSRP. Consumer advocates are individuals living with or family members of individuals living with ALS who are active participants in ALS-related support, outreach, or advocacy organizations. Similar to other CDMRP programs, consumer advocates are active participants in all aspects of program execution, including proposing program priorities, reviewing proposals, and recommending proposals for funding. Consumer advocates contribute their distinct viewpoint and bring a sense of urgency to the deliberations. Consumer advocates also serve as liaisons between their constituencies and the scientific community and are able to increase awareness about the program. Additional details about consumer advocate participation can be found in Section I, Overview.

Peer Review Panel Members

The ALSRP scientific peer review panel was composed of distinguished investigators from scientific and clinical disciplines as well as consumer advocates. The primary responsibility of scientific peer review is to provide unbiased, expert advice on the scientific and technical merit of proposals submitted to the program. Scientific peer reviewers are selected for their subject matter expertise and experience with scientific peer review. Consumer reviewers are nominated by a support or advocacy organization and are selected on the basis of their leadership skills, commitment to advocacy, and interest in science. The peer review process is described in further detail in Section I, Overview.

Integration Panel Members

The FY07 ALSRP IP is composed of eminent scientists, clinicians, and consumer advocates. The panel helped shape the focus of the program and facilitate progress in the field of ALS. Individual panel members recommended program priorities, a focused investment strategy, and a top-notch research portfolio (for more information about the functions of the IP, see Section I, Overview).

“Amyotrophic Lateral Sclerosis, commonly known in the United States as Lou Gehrig’s disease, is a devastating disease affecting nerve cells, leading to paralysis and death. The ALS Association is very excited about the recent commitment by the Department of Defense to fund researchers to find treatments for the disease.”

Lucie Bruijn, Ph.D.

ALS Association

FY07 Integration Panel Member



FY07 ALSRP IP Members

Air Force

Hendrick Ruck, Ph.D.

Chair

Air Force Research Laboratory

David Watson, Ph.D.

Major, U.S. Air Force

Air Force Laboratory Services

Department of Veterans Affairs

Brenda Cuccherini, Ph.D.

Alternate Chair

Office of Research and Development

Navy

Richard Haberberger, Ph.D.

Captain, U.S. Navy

Naval Medical Research Center

Army

Cornelius Maher, M.D., Ph.D.

Colonel, Europe Regional

Medical Command

ALS Association

Ellyn Phillips

Chair

Greater Philadelphia Chapter

Lucie Bruijn, Ph.D.

Scientific Director

Ad Hoc Representative

Walter Bradley, Ph.D.

University of Miami

Developing New Therapies

The FY07 ALSRP supported three Therapeutic Development Awards that hold the promise of bringing improved therapies to patients. A closer examination of these projects reveals that new frontiers are being explored.



In a project entitled “Preclinical Development of Therapeutics for Amyotrophic Lateral Sclerosis,” **Dr. Barrie Carter** of **Targeted Genetics Corporation** plans to further develop the small molecule apocynin for an investigational new drug submission. Evidence has suggested that oxidative stress and increased levels of reactive oxygen species (ROS) may damage neurons and play an important role in ALS. One route by which ROS is generated is through a multi-subunit enzyme complex known as NOX. The choice of apocynin, an inhibitor of NOX, is based on the observation that overactivation of NOX is associated with pathogenesis in the G93A mouse model of ALS.

Dr. Serge Przedborski of **Columbia University** proposed to identify small molecules with potential therapeutic benefit in ALS in the project entitled “Neuroprotective Small Molecules for the Treatment of Amyotrophic Lateral Sclerosis.” Though others have attempted to identify protective small molecules previously, many of those efforts were hampered due to the lack of an appropriate model. Dr. Przedborski, in collaboration with Dr. Lee Rubin of Harvard University, plans to make use of a high-throughput screen based on the recent observation that when primary or embryonic stem cell-derived motor neurons are grown on astrocytes expressing mutant superoxide dismutase (SOD1), as is seen in familial ALS, the motor neurons die. Due to the relevance of this observation, it is hoped that protective molecules identified will transition well to clinical use.

Recent laboratory findings indicate that enhancing the insulin-like growth factor II (IGF-II) pathway or inhibiting the peripherin pathway may be therapeutic for ALS, and **Dr. Ole Isacson** of **McLean Hospital** intends to expand this observation to the clinic in the project entitled “Development of Lead Agents for ALS Treatment in Preclinical Model Systems Based on Differential Gene Expression of Peripherin and IGF-II.” Dr. Isacson plans to perform high-throughput screens to identify compounds that will modulate expression of IGF-II and/or peripherin in a favorable manner.