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

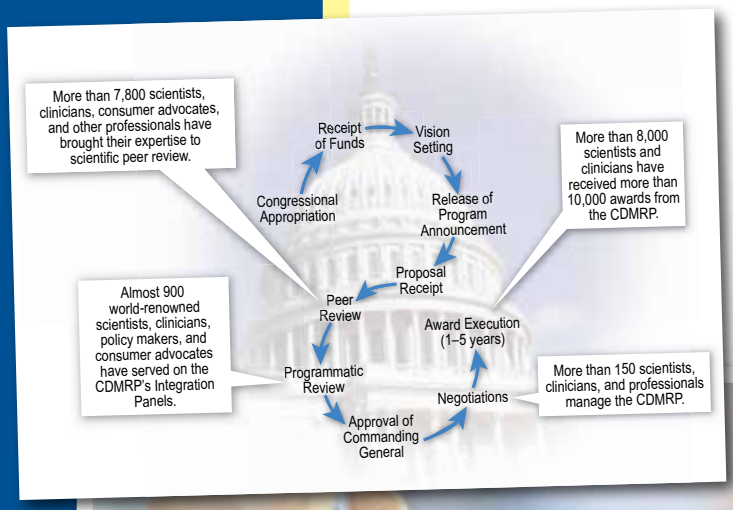
Provide hope by promoting innovative research, recognizing untapped opportunities, creating partnerships, and guarding the public trust.

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 that continues today. Since 1992, the CDMRP has grown to encompass multiple targeted research programs and has received $6.97 billion in appropriations from its inception through fiscal year 2012 (FY12). 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 or 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

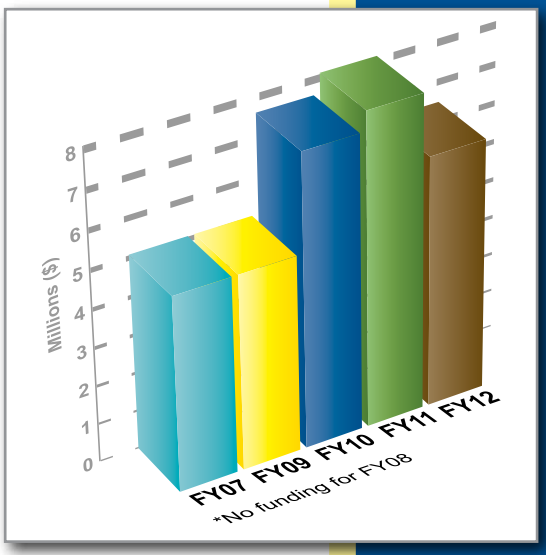
VISION

Improve treatment and find a cure for ALS.

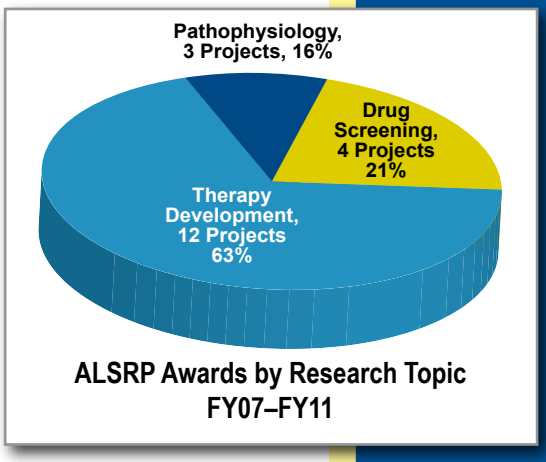
MISSION

Fund innovative preclinical research to develop new treatments for ALS.

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. 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 (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.[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 FDA-approved drug, riluzole, modestly slows ALS progression. Several drug candidates are in clinical trials, and some show early promise.[5] New focus areas, including transcript profiling and immune system modulation, are being investigated as novel approaches for ALS therapeutic interventions.[6]



ALSRP Awards by Research Topic FY07–FY11

The ALSRP was established by Congress in FY07 with a $5 million appropriation and a mission to support preclinical therapy development for ALS. Though not funded in FY08, the program has consistently been funded since FY09, with a total appropriation of more than $30 million.

[1] *ALS Association*
[2] *Robert Packard Research Center at Johns Hopkins Hospital*
[3] *Weisskopf M, et al. 2004. Annual Meeting of the American Academy of Neurology, San Francisco, California*
[4] *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*
[5] *quest.mda.org*
[6] Nature Genetics *(28 March 2010) doi:10.1038/ng.557 Article*

Strategic Partnerships

Consumer advocates and scientists working together

The two-tiered review process established by the CDMRP brings together the expertise of scientists with the perspectives and experiences of ALS patients and supportive family members (who we call consumers). This innovative approach, which was recommended by the National Academy of Sciences, Institute of Medicine and has been 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.

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.

Upon hearing of her father's ALS diagnosis, Tina says "I was determined to educate myself and my family about everything we could about this disease. That would be my contribution, my way of supporting his fight. I found the local ALS Chapter, attended some meetings, and got as involved as I could. My father, mother, and I have been to Washington DC multiple times for National ALS Advocacy Day on Capitol Hill and additional advocacy effort with the National ALS Association. I have also been fortunate enough to serve on the DOD review panel as a consumer reviewer. This opportunity came after an advocacy day which we participated in, so receiving these [appropriated] funds was proof that we'd made a difference."

-- Tina M. Forshey, National ALS Foundation, FY10 Consumer Peer Reviewer

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.

"There is an urgent need for treatments for ALS, a devasting 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 FY12 ALSRP Integration Panel Chair

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, 10 TDAs have been issued, totaling more than $17 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. Just introduced in 2010, 9 TIAs have been awarded, totaling more than $5 million.

These award mechanisms have received a robust response with the ALS research community, which continues to respond with exciting research proposals 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.

FY11 ALSRP Awards

The ALSRP recently granted 5 awards from an $8 million FY11 congressional appropriation:

Therapeutic Development Awards

Dr. Philip LoGrasso Scripps Research Institute, Florida	c-jun-N-Terminal Kinase (JNK) for the Treatment of Amyotrophic Lateral Sclerosis
Dr. Nicholas Cosford Sanford-Burnham Medical Research Institute, La Jolla	Developing ER Stress Inhibitors for Treating ALS

Therapeutic Idea Awards

Dr. Jiou Wang Johns Hopkins University	Developing Wide-Spectrum Antiproteotoxicity Agents to Treat ALS
Dr. Jeffrey Rothstein Johns Hopkins University	The Role of NG2 Glial Cells in ALS Pathogenesis
Dr. Raymond Grill University of Texas, Health Science Center at Houston	Targeted Riluzole Delivery by Antioxidant Nano-vectors for Treating Amyotrophic Lateral Sclerosis

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

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

ALS is a progressive neurodegenerative disease that can be sporadic (the most common form approximately 90% of cases) and familial (hereditary form approximately 10% of cases). The neurodegeneration affects only somatic motor neurons (MNs) and not autonomic MNs. Studies in ALS mouse models have indicated that the initiation of neurodegeneration might be due to intrinsic factors associated with MNs while astrocytes and microglia can also play an important role in the progression of neurodegeneration. Motor neuron subpopulations are prone to relatively 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-II) when used as a pretreatment for CN 3/4 MNs. IGF-II protected MNs from glutamate toxicity in a validated in vitro bioassay.

Building on these findings, Dr. Isacson, who received an FY07 ALSRP Therapeutic Development Award, has been developing a screening method for identifying compounds that can upregulate expression of IGF-II and that may have neuroprotective properties. High-throughput screening and polymerase chain reactions (PCRs) 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-II. 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-II-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 pre-symptomatic SOD1G93A rats and mice for disease progression and 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 that can be tested in a clinical trial as a first-line drug for ALS treatment.

This project will produce one or more optimized candidate drugs that can ultimately move forward into clinical trials.

"Cell Therapy for ALS: Re-Purposed to Help"

Preclinical Studies of Induced Pluripotent Stem Cell-Derived Astrocyte Transplantation in ALS

Nicholas Maragakis, M.D., Johns Hopkins University, Baltimore, Maryland

ALS is a degenerative disease affecting the upper and lower motor neurons in the brainstem and spinal cord. Neural degeneration from ALS leads to progressive loss of voluntary muscle function, then to paralysis, and ultimately to death. A recent development in stem cell technology called induced pluripotent stem cells, iPSCs, is helping scientists understand the abnormalities in the cell biology behind ALS. iPSCs start as skin cells harvested from an ALS patient that are reprogrammed in culture (through exposure to certain transcription factors), first into stem cells that have the capacity to become any type of cell, and then differentiated into glial-restricted precursor cells (iPSC-GRPs). These iPSC-GRPs act like neural developmental stem cells and can become motor neurons, astrocytes, or oligodendrocytes in culture. These cells may ultimately be transplanted into patients to treat ALS. Evidence exists suggesting that astrocytes and other non-neuronal cell types play a role in the neurodegeneration of ALS. Replacement of astrocytes derived from iPSC-GRPs may offer a technically and biologically more feasible treatment modality for ALS patients compared with motor neuron transplantation.

Using funding from an FY09 ALSRP Therapeutic Development Award, Dr. Nicholas Maragakis of Johns Hopkins University is initiating preclinical studies of iPSC-GRPs to assess their therapeutic potential. Dr. Maragakis will examine whether human iPSC-GRPs derived from either sporadic ALS (sALS), familial superoxide dismutase 1 (SOD1)-mediated ALS (fALS), or normal control subjects have the same capacity for engraftment, survival, and neuroprotective qualities following transplantation. It is not known whether iPSC-GRPs from ALS patients will be normal (and thus possibly neuroprotective) or whether these cells may harbor ALS-specific abnormalities that may lack benefit, or possibly even exacerbate disease. By comparing normal iPSC-GRPs with sALS iPSC-GRPs and fALS iPSC-GRPs, Dr. Maragakis will attempt to reveal inherent differences in astrocyte biology related to ALS, providing potential insight into ALS disease mechanisms. This initial assessment of the therapeutic potential of these cells will help determine whether continued investigation of this concept is warranted. Being able to use a patient's own cells to treat ALS (autologous cell transplantation) could preclude the need for significant immunosuppression, as well as decrease the probability of cell rejection.

In another phase of the study, Dr. Maragakis will build on previous studies in rats where mutant SOD1-GRPs transplanted into the cervical spinal cord of normal rats demonstrated initial feasibility for the proposed methodology. In vivo studies in this project will examine the activity of the different types of iPSC-GRPs (sALS, fALS, and normal) following transplantation into the spinal cords of normal rats. Survival, differentiation, migration, and other properties will be examined across the different cell types. These same cells will also be transplanted into the SOD1G93A rat model of ALS, where they will be compared for survivability and effects on motor neuron survival and muscular function.

Dr. Maragakis' study lays the framework to answer initial questions about properties of iPSCs from ALS patients through in vitro and in vivo comparative studies. It also offers an initial assessment of potential neuroprotection in an SOD1 animal model of ALS.

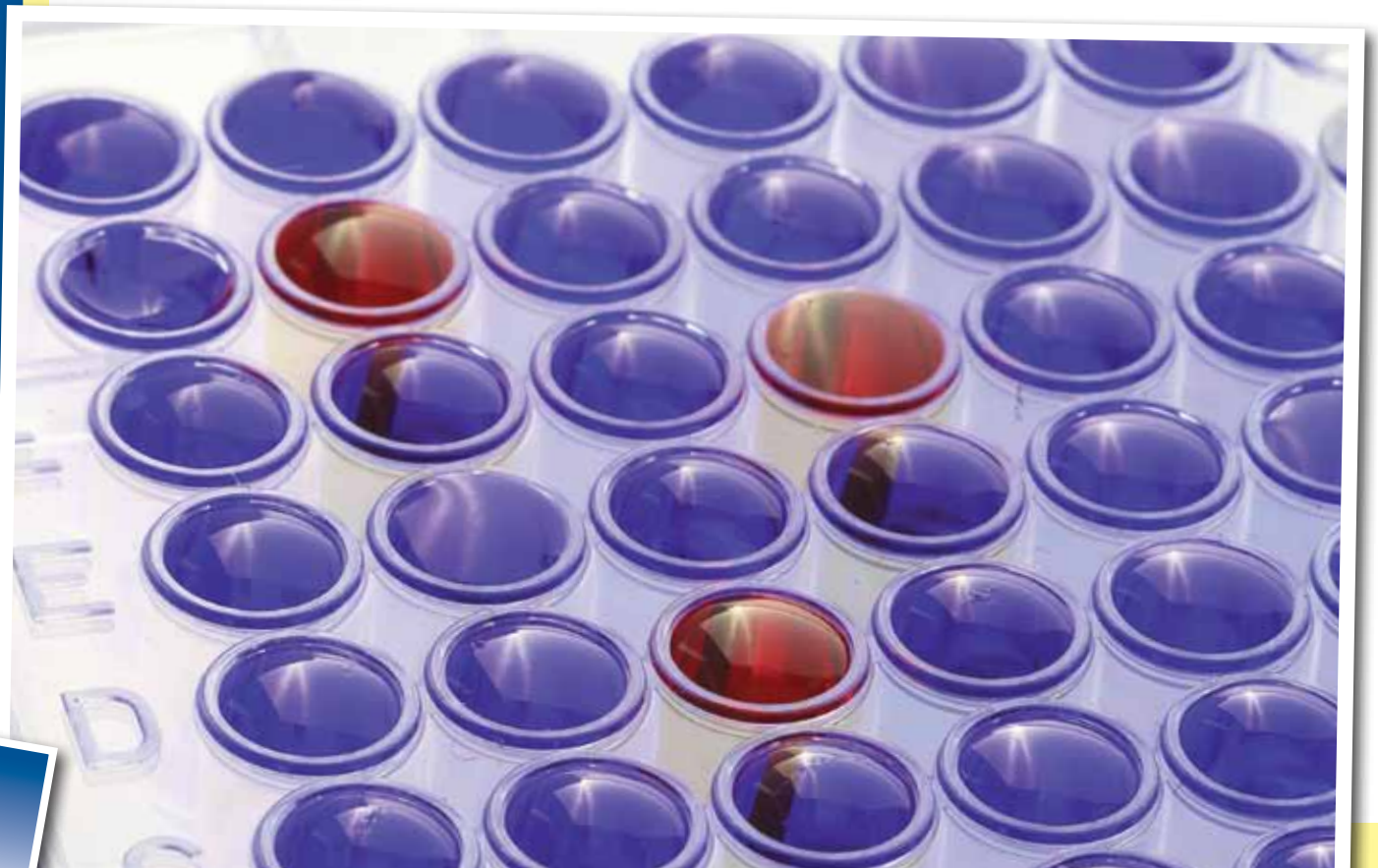
These studies could represent the original development of a viable autologous cell therapy for ALS patients.

Inhibitors of TDP-43 Aggregation and Toxicity

Leonard Petrucelli, Ph.D., Mayo Clinic and Foundation, Jacksonville, Florida

Dr. Leonard Petrucelli's laboratory has pioneered neuroscience research aiming to understand the underlying mechanisms of amyotrophic lateral sclerosis (ALS) and identify potential drug targets for its treatment. TAR DNA-binding protein-43 (TDP-43) is a protein that has been found to go awry in approximately 90% of all ALS patients. Studies in yeast have revealed that C-terminal TDP-43 fragments are prone to aggregate and only TDP-43 species that form inclusions, which result from continued protein aggregation, are toxic to neurons. Dr. Petrucelli is using an ALSRP FY09 Therapeutic Development Award to identify compounds that prevent TDP-43 aggregation as potential neuroprotective agents for ALS. Using a previously developed human neuroblastoma cell line (M17D3) that overexpresses green fluorescent protein (GFP)-tagged C-terminal TDP-43 truncation product, GFP-TDP220-414, Dr. Petrucelli has begun screening compounds that reduce TDP220-414 aggregation, which is expressed as an attenuation of the GFP fluorescence. To increase the overall efficiency of the screening process, Dr. Petrucelli was able to effectively expand the assay from 24 to 384 wells. Over half of the 58,000 compounds from a select, proprietary small-molecule library have been screened on the M17D3 cells, and to date, 2,141 compounds were found to attenuate GFP fluorescence (i.e., TDP fragment aggregation) by at least 30%. Expression of another relevant truncation product, GFP-TDP208-414, which can be exploited in M17D3 and also causes neurotoxicity in primary cortical neuronal cultures, is also being examined.

Future experiments will include further screening of the most promising compounds on primary cortical neuronal cultures. Expression of lactate dehydrogenase released into culture media will be measured as an indicator of cytotoxicity to further validate the compounds as potential therapeutic agents.



Screening Compounds That Protect Against SOD1 Aggregation

Richard Silverman, M.D., Northwestern University, Evanston, Illinois

ALS is a clinically severe, fatal neurodegenerative disorder characterized by a progressive and irreversible loss of upper and lower motor neurons, muscle atrophy, and paralysis, with a life expectancy of 2–5 years after diagnosis. The incidence of ALS is 1–2/100,000/year and may be rising. Although relatively rare, ALS has provided important insights into genetic disease that have become broadly relevant to other forms of neurodegeneration, including Alzheimer's disease, Parkinson's disease, and Huntington's disease. With very few treatment options available, understanding the molecular mechanisms that lead to ALS is an extremely urgent need. Dr. Richard B. Silverman (Northwestern University) and his collaborators, Dr. Donald R. Kirsch (Cambria Pharmaceuticals), Dr. Robert J. Ferrante (University of Pittsburgh), and Dr. Richard I. Morimoto (Northwestern University), were awarded an ALS Research Program Therapeutic Development Award in 2010 to investigate protein aggregation inhibition as a potential therapeutic strategy for ameliorating disease progression in ALS. Dr. Silverman and collaborators performed high-throughput screens to identify compounds that protect cells against the toxic effects of SOD1 aggregation.

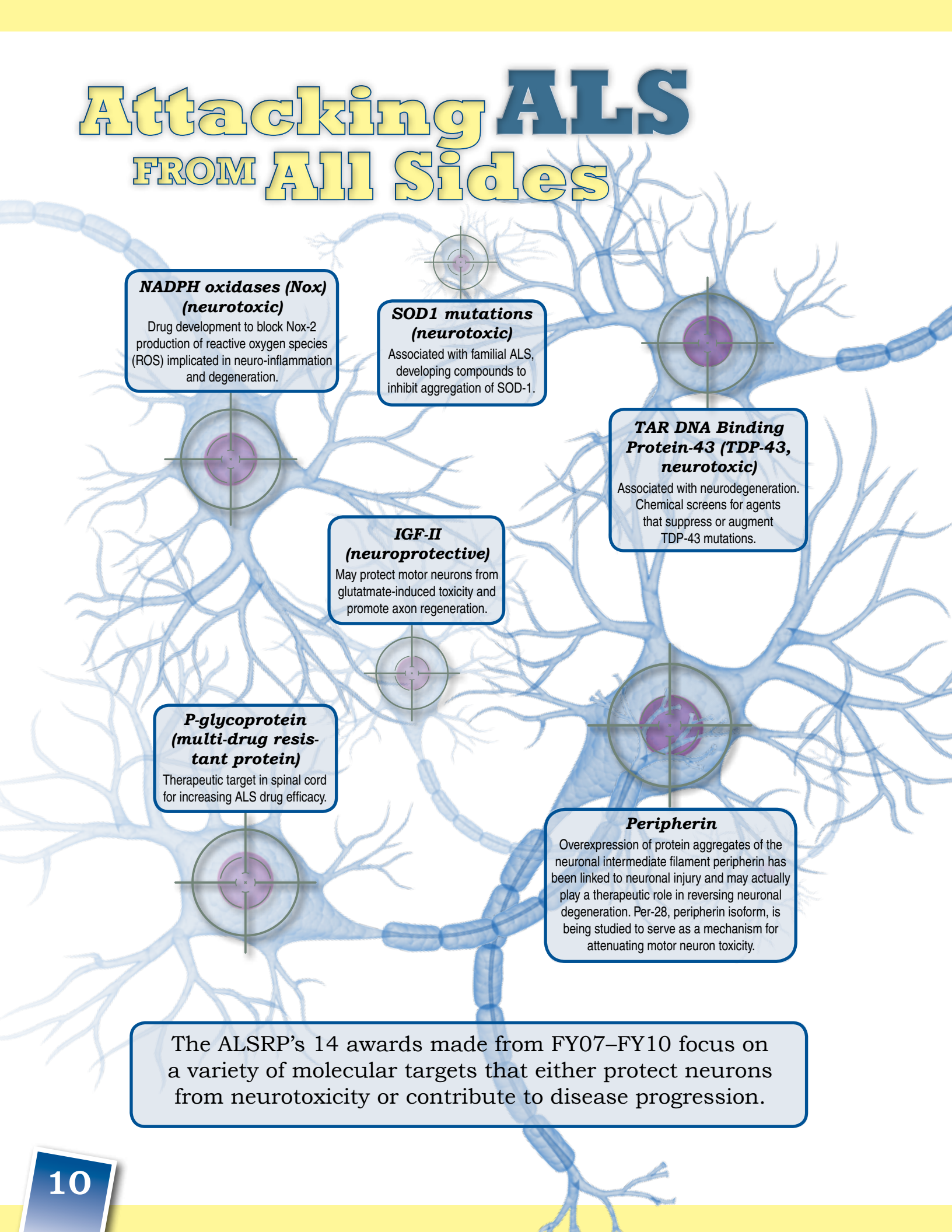
Dr. Silverman previously identified three lead chemotypes that protect cells from aggregated mutant SOD1: arylsulfanylpyrazolones (ASP), pyrimidine-2,4,6-triones (PYT), and cyclohexane-1,3-diones (CHD). The team found that CMB-021805, a PYT analog, when administered at a dose of 20 mg/kg to G93A ALS mice (transgenic mice with mutant SOD1 gene at codon 93), improved survival and extended the life of the mice by 26%. Pathological findings in untreated G93A mice, including gross spinal cord atrophy and neuronal loss in the ventral horns from the lumbar spinal cord, were significantly reduced by CMB-021805 as compared to untreated ALS mice. In addition, when mice were treated with CMB-021805 at 10 mg/kg twice daily (BID), survival was extended by approximately 31% in the G93A mice, as compared to untreated ALS mice. The 10 mg/kg BID-treated mice also displayed a significant improvement in the gross loss of white and grey matter at 126 days by 26% and 28%, respectively, and a reduction of the loss of ventral horn neurons by 36% compared to untreated mice.

To better understand the mechanism of action of CMB-021805, the investigators compared gene expression between ALS transgenic mice (G93A and G85R) and wild types in a neurotoxicity array. Genes found to be significantly upregulated included SOD2, angiopoietin-like 4 (Angpt14), Fas ligand tumor necrosis factor superfamily (FasL), brain-derived neurotrophic factor (BDNF), and IL10.

Further studies showed that CMB-021805 reversed the effects of 3-nitropropionic acid, which inhibits the mitochondrial electron transport chain, suggesting that it may improve mitochondrial function. SOD2 and BDNF expressions were increased in G93A mouse brains after 2 weeks of CMB-021085 treatment.

Findings from this study will identify potential drug candidates that will be more effective in managing ALS symptoms than the drugs currently available.

Attacking ALS FROM All Sides



NADPH oxidases (Nox) (neurotoxic)
Drug development to block Nox-2 production of reactive oxygen species (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. Chemical screens for agents that suppress or augment TDP-43 mutations.

IGF-II (neuroprotective)
May protect motor neurons from glutatmate-induced toxicity and promote axon regeneration.

P-glycoprotein (multi-drug resistant protein)
Therapeutic target in spinal cord for increasing ALS drug efficacy.

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. Per-28, peripherin isoform, is being studied to serve as a mechanism for attenuating motor neuron toxicity.

The ALSRP's 14 awards made from FY07–FY10 focus on a variety of molecular targets that either protect neurons from neurotoxicity or contribute to disease progression.

Looking Forward: THE ALSRP IN FY12

For FY12 the ALSRP will use a $6.4 million congressional appropriation to continue its mission to support preclinical therapeutic development for ALS. The program's two award mechanisms offered in the past, the TDA and the TIA, will again provide scientists an opportunity to investigate and develop new therapeutic agents and new ideas behind future therapies for ALS.

FY12 Program Announcements were released in March 2012.

For more information, visit
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