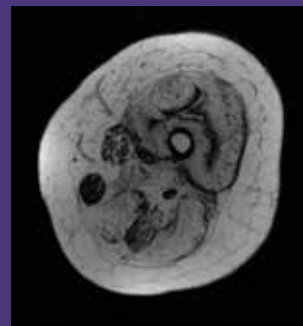


Duchenne Muscular Dystrophy Research Program



Congressionally Directed Medical Research Programs

History

The Office of the Congressionally Directed Medical Research Programs (CDMRP) was created 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 approximately \$11.2 billion in appropriations from its inception through fiscal year 2016 (FY16). Funds for the CDMRP are added to the Department of Defense (DoD) budget, in which support for individual programs, such as the Duchenne Muscular Dystrophy Research Program (DMDRP), is allocated via specific guidance from Congress.

Duchenne Muscular Dystrophy Research Program

VISION

To preserve and improve the function and quality of life, and to extend the life span of all individuals with Duchenne.

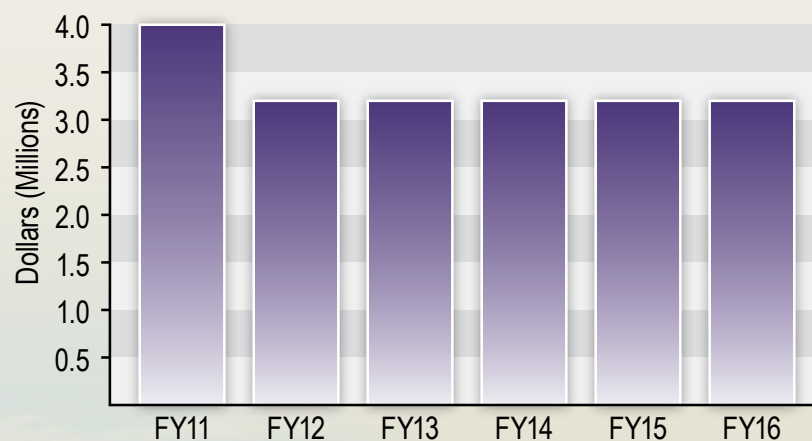
MISSION

To better support the discovery and development of therapeutics, devices, and other inventions, and to promote their effective clinical testing.

About the Program

Duchenne affects approximately 1 out of every 3,500 male infants (about 20,000 new cases a year). This form of muscular dystrophy results from mutations in the dystrophin gene that lead to an absence of dystrophin in muscle cells, allowing these cells to be easily damaged. Boys living with Duchenne experience devastating muscle weakness that affects the skeletal muscles, heart, and respiratory muscles. Symptoms of Duchenne typically develop prior to age 5, and by age 12, most patients are confined to a wheelchair. Currently, there is no cure for Duchenne, and young men with this disease rarely live beyond their early 30s. The DMDRP was established in FY11, the result of passionate and tireless advocacy efforts. The initial congressional appropriation was \$4 million (M), and since that time, \$20M has been appropriated to the program, including \$3.2M in FY16. Currently, no treatment can stop or reverse the progression of Duchenne; however, during the past several years, research has identified many new potential therapeutic targets and significantly expanded the number of potential therapeutics in the pipeline for Duchenne. In order to assist in the development of treatments for Duchenne, the DMDRP has focused on accelerating promising therapeutic ideas into clinical applications and supporting the training of new physician researchers to facilitate their pursuit of careers in Duchenne research.

DMDRP Congressional Appropriations



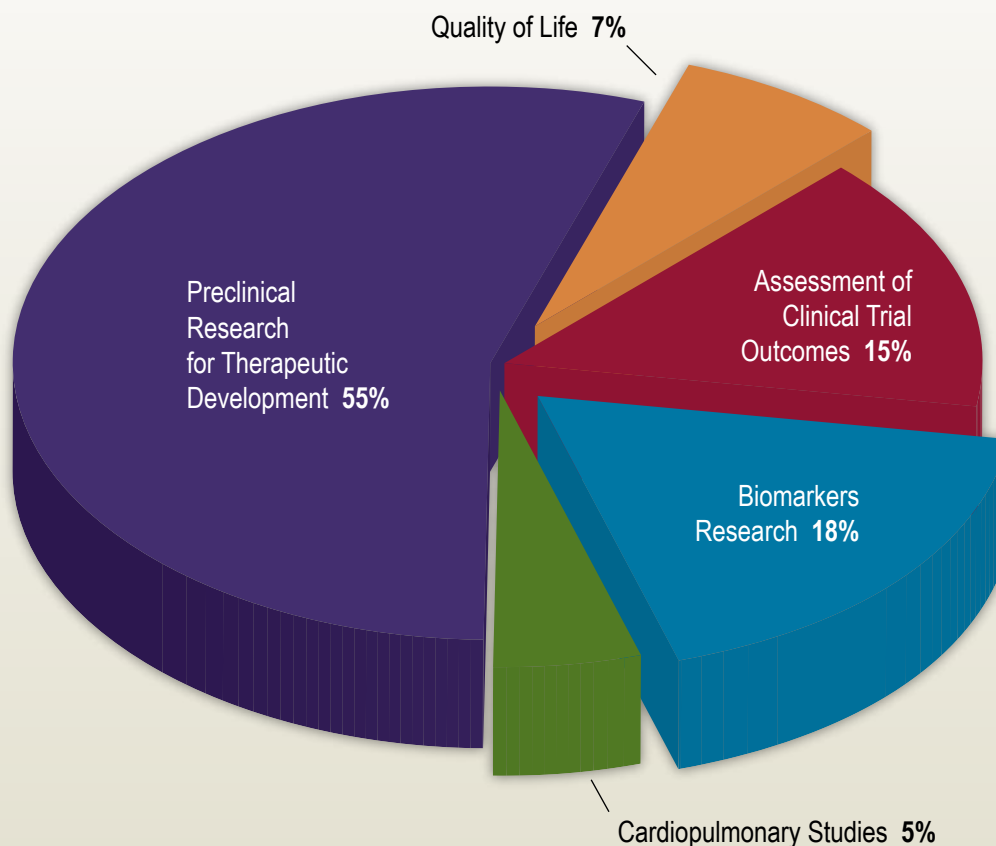
Investing in Duchenne Research Gaps

In order to address the needs of Duchenne patients, the FY16 Programmatic Panel has developed the following Focus Areas and required that any application submitted for funding must address at least one of these:

- Cardiac studies, including identifying mechanisms of pathology and therapeutic interventions
- Clinical studies and novel interventions that could improve clinical care and quality of life in areas such as:
 - ◆ Comorbidities
 - ◆ Endocrinology
 - ◆ Orthopedics
 - ◆ Gastrointestinal issues
 - ◆ Psychosocial issues
 - ◆ Cognitive function
 - ◆ Respiratory studies (including sleep-focused studies)
- Assessment of clinical trial tools and outcome measures, such as:
 - ◆ Discovery and qualification of pharmacodynamic, prognostic, and predictive biomarkers
 - ◆ Evaluating surrogate markers
 - ◆ Evaluating potential composite scores for outcomes assessment
 - ◆ Patient-centered outcomes, e.g., quality of life, activities of daily living
- Extension or expansion of existing preclinical translational data in support of a specific therapeutic development path (including independent replication and comparative studies)

FY11–FY15 DMDRP Portfolio by Focus Area

Portfolio analysis is by research dollars



Application Review Process

FY16 DMDRP PROGRAMMATIC PANEL MEMBERS

Valerie Cwik, M.D.
(Chair)
Muscular Dystrophy Association

C. Frank Bennett, Ph.D.
Ionis Pharmaceuticals, Inc.

Kristin Burns, M.D.
National Heart, Lung, and Blood Institute

Justin Fallon, Ph.D.
(Chair Emeritus)
Brown University

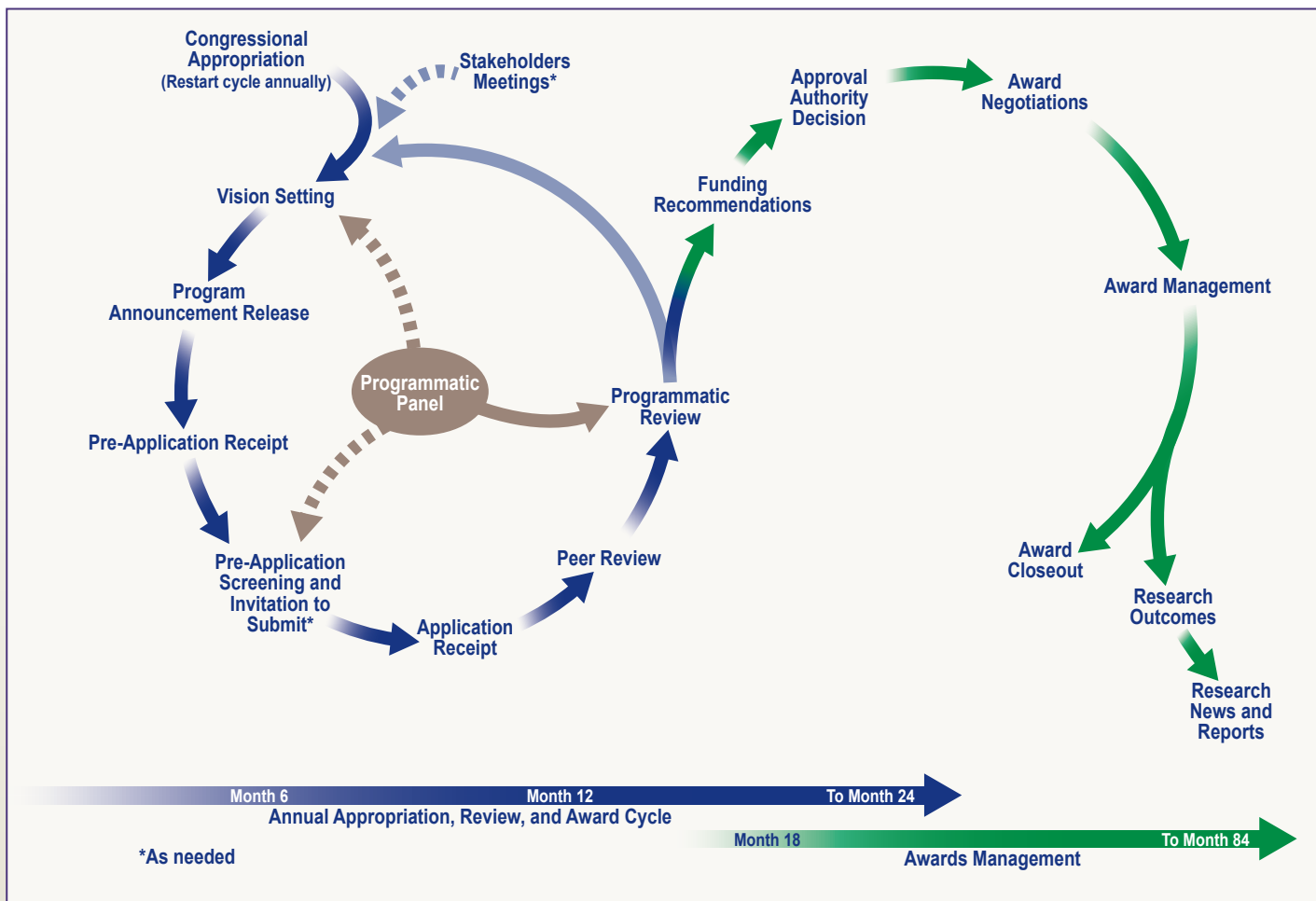
Patricia Furlong
Parent Project Muscular Dystrophy

Debra Miller
Cure Duchenne

Glen Nuckolls, Ph.D.
National Institute of Neurological Disorders and Stroke

John Porter, Ph.D.
Myotonic Dystrophy Foundation

The CDMRP uses a two-tier review process for application evaluation, which is critical to ensuring that each of the research program portfolios reflects not only the most meritorious science, but also the research that best meets the program goals. Both tiers involve dynamic interaction among scientists and consumers (family members of individuals with Duchenne muscular dystrophy). The first tier of evaluation is a scientific peer review of applications measured against established criteria determining scientific merit. The second tier is a programmatic review, conducted by a Programmatic Panel composed of leading scientists, clinicians, and consumers. In this tier of review, the Programmatic Panel compares the applications to each other and makes recommendations for funding based on scientific merit, as determined by peer reviews, potential impact, adherence to the intent of the award mechanism, relevance to program goals, and portfolio composition.



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 family members of a person living with Duchenne. This innovative approach, recommended by the National Academy of Sciences’ Institute of Medicine and adopted by other funding organizations, has proven to be an effective way to evaluate research applications for their potential to meet the program’s goals for those we seek to serve. As peer reviewers, consumers evaluate applications for scientific and technical merit, as well as the potential successful impact of the research. As Programmatic Panel members, consumers make programmatic recommendations for the DMDRP’s vision, investment strategies, and funding selections intended to reflect the needs of the consumer and research communities.



“I have completed two stints as a consumer reviewer for Duchenne research grants seeking funding from DMDRP. Because my son Noah had experienced all phases of the disease when I was participating in the review process, I was able to communicate to the panel the importance of considering the entire Duchenne community, regardless of age and/or the location of their gene mutation, when awarding funding. There were several occasions during the discussions of the proposals when a scientific reviewer would acknowledge the value of the consumer reviewer input. In several instances, this understanding of the value of the research to the patient community triggered a change in the scientific reviewers’ scoring of the proposals. This demonstrated to me the value of my input to the review process.”

Jeff Watkins, Consumer Peer Reviewer



“The Department of Defense’s (DoD’s) commitment to this program and the stringent review process were extremely gratifying and imparted to me the knowledge that many people are working very hard to help give those diagnosed with Duchenne a chance at longer and healthier lives. The consumer voice is vital when considering therapies in diseases like Duchenne, and my voice was heard and respected throughout the DMDRP grant review process. A Duchenne diagnosis comes with a lot of fear and uncertainty and, for me, participating in clinical trials, advocacy, and programs like the DMDRP are constructive ways to fight against the disease that threatens my son’s life. I am very proud to participate in this program.”

Mindy Cameron, Consumer Peer Reviewer



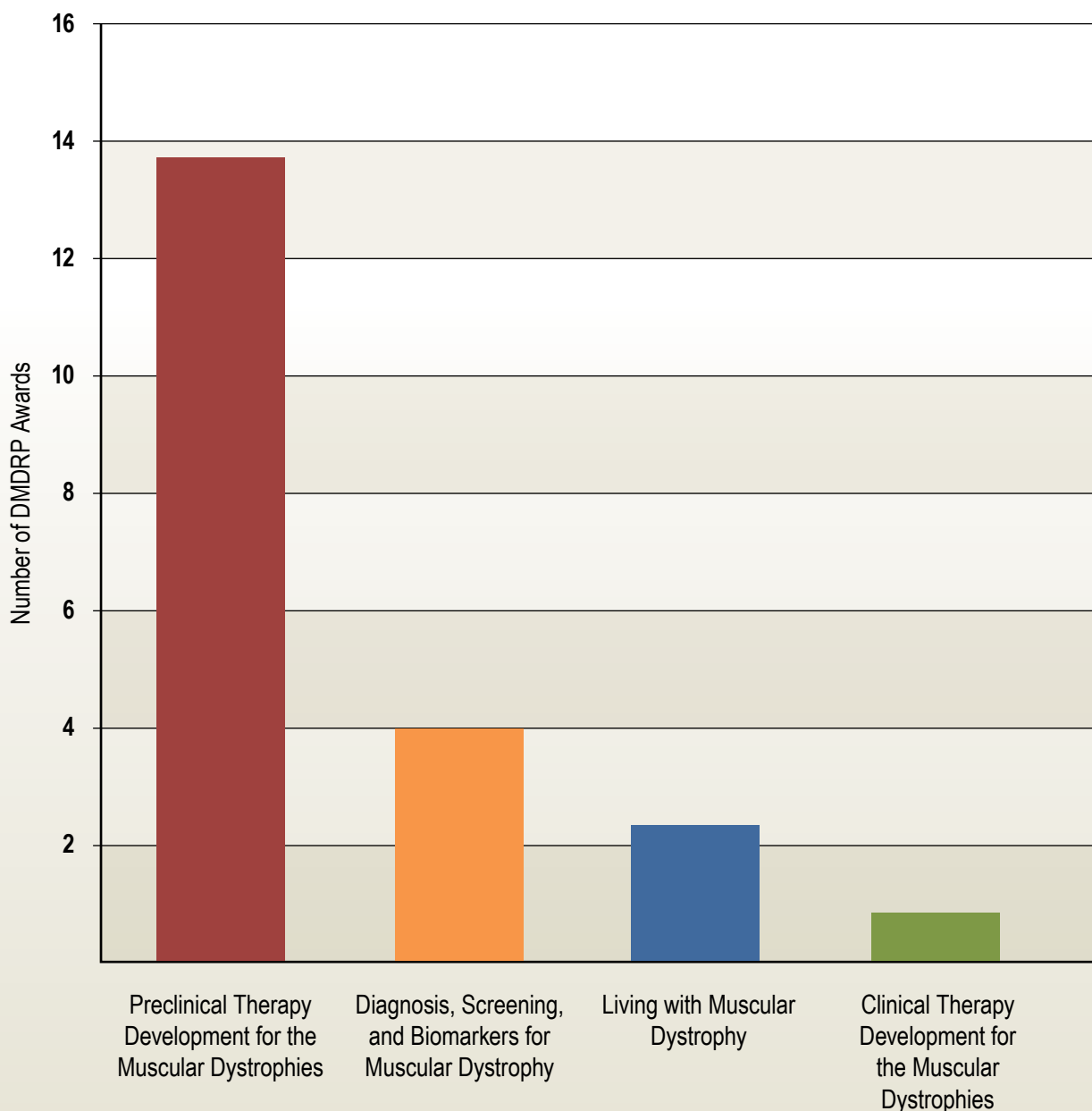
“Over the last many years, I have been honored to serve on the DMDRP review committee. The DMDRP is an essential program for the Duchenne community that vets a large number of the most compelling research projects in Duchenne. The review process is thorough and, as a committee member and a mother of a son with Duchenne, I appreciate the dedication of experts who are so successful in prioritizing the most impactful research.”

Debra Miller, Programmatic Panel Reviewer

MDCC Involvement and Objectives

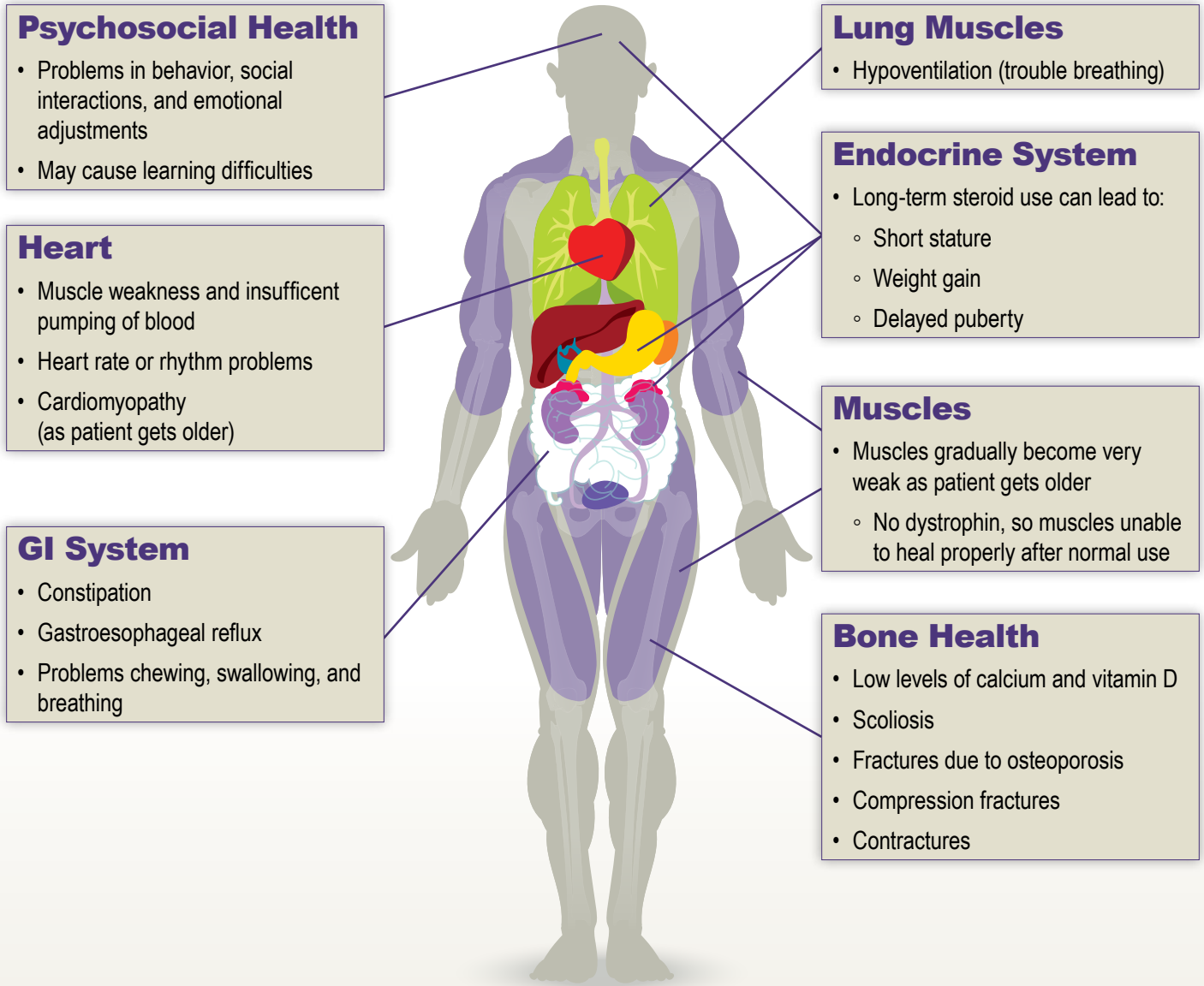
The Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 (MD-CARE Act; P.L. 107-84) authorized the establishment of the Muscular Dystrophy Coordinating Committee (MDCC) to coordinate research activities across the National Institutes of Health and with other Federal agencies and muscular dystrophy patient organizations. The MDCC was subsequently re-authorized in the Paul D. Wellstone Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2008 and 2014 (MD-CARE Acts of 2008, P.L. 110-361, and 2014, P.L. 113-166). In support of the MD-CARE Act, the MDCC developed an Action Plan for the Muscular Dystrophies in 2005 and updated this plan in 2015 to outline priority areas for improving treatments and reducing the personal and societal impacts of most types of muscular dystrophy. As a stakeholder and member of the MDCC, the DMDRP has funded projects in most of the major priority areas to help achieve the plan's objectives, with a focus on moving promising ideas in Duchenne into clinical applications.

FY11–FY15 DMDRP Portfolio by MDCC Priority Areas*

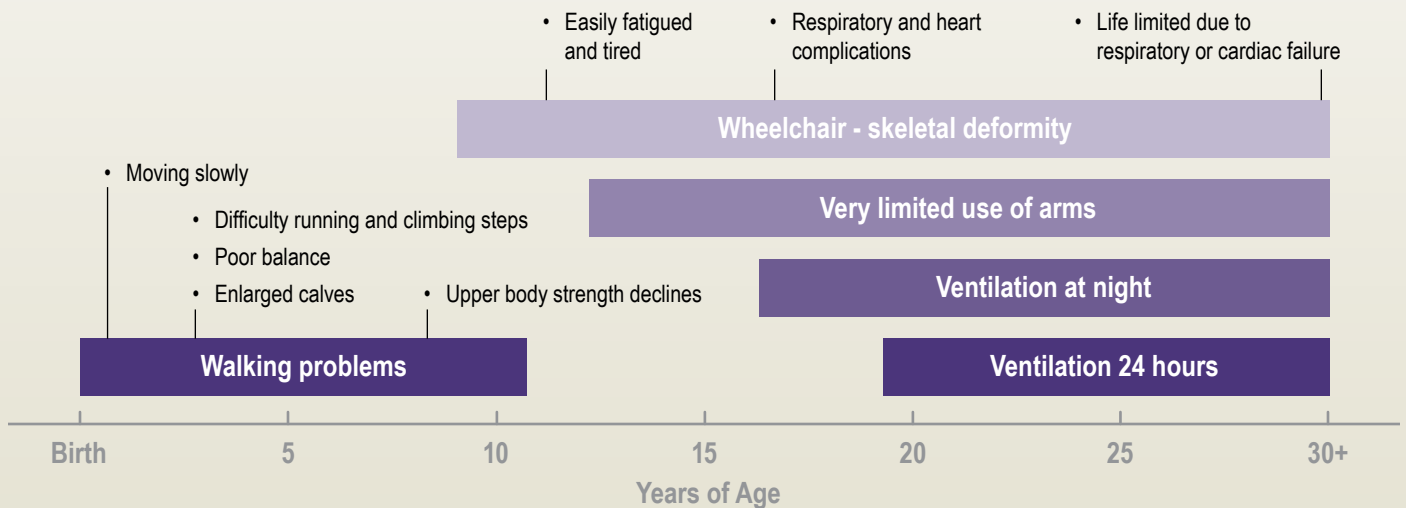


*Currently, DMDRP has not funded any awards in the priority areas "Mechanisms of Muscular Dystrophy" and "Infrastructure for the Muscular Dystrophies."

Duchenne Clinical Manifestations



Duchenne Clinical Timeline





New Advanced Technologies in Stem Cell Therapy

Johnny Huard, Ph.D., University of Texas Health Science Center at Houston

Adult skeletal muscles possess a remarkable regenerative ability that depends on muscle progenitor cells (MPCs). Despite the presence of this muscle regenerative cell population, skeletal muscle integrity can be debilitated by depletion of these cells and the deposition of adipose and fibrotic tissues in a variety of pathological conditions, including Duchenne. Duchenne is a genetic disease and one of the most common childhood muscular dystrophies, with approximately 1 in every 3,500 male infants

affected. The inherited disease is caused by a lack of functional dystrophin, an essential transmembrane muscle protein in both skeletal and cardiac muscle. Dystrophic muscle is continually damaged during typical muscle contraction due to membrane instability, resulting in significant inflammation. These damaged fibers degenerate, undergo necrosis, and lose their ability to regenerate. MPCs are recruited to form new muscle, but this process is often inefficient in Duchenne muscle due to depletion of the MPC population from repeated cycles of degeneration and regeneration.

Funded through a DoD award managed by the CDMRP, studies were conducted wherein Dr. Huard and his team of researchers at Children's Hospital of Pittsburgh optimized the isolation of a distinct population of muscle-derived stem cells (MDSCs), which are MPCs with high myogenic potential. They demonstrated a large increase in the number of regenerated muscle fibers following transplantation of MDSCs into the mdx mouse model of Duchenne. They observed differences in the regenerative capabilities of MDSC populations when isolated from mice of differing age and gender. MDSC populations from younger and female mice showed increased efficiency in muscle regeneration following transplantation into mdx model mice, compared to cells from male and/or older mice, a difference that was not apparent in the cell culture model. It is suspected that female hormones play a role in this difference, but studies are ongoing to further clarify the differences for therapeutic optimization and development.

While muscle wasting is a significant issue for patients with Duchenne, they often also suffer from fatty infiltration and intramyocardial lipid accumulation (IMCL), which lead to adipose accumulation within muscles and heterotopic ossification (HO) that results in bone formation within soft tissue. Dr. Huard's research has focused on determining the mechanisms underlying these processes. He has identified RhoA as a signaling protein involved in HO and IMCL. He demonstrated inhibition of RhoA-reduced inflammation, HO, and IMCL, in addition to improvement of muscle regeneration in a severe mouse model of Duchenne. These findings suggest RhoA may serve as a potential target for repressing the development of HO and IMCL that contribute to muscle weakness and degeneration in Duchenne. Reducing IMCL could prevent development of obesity and reduce inflammation and metabolic abnormalities in patients with Duchenne.



Dr. Huard continues to investigate the therapeutic potential of MDSCs, the underlying differences in regenerative capabilities between male and female cell sources, and the role of RhoA in adipose accumulation within the muscles of Duchenne patients. Elucidation of this information could lead to targeted development of a treatment to prevent muscle wasting in patients with Duchenne.

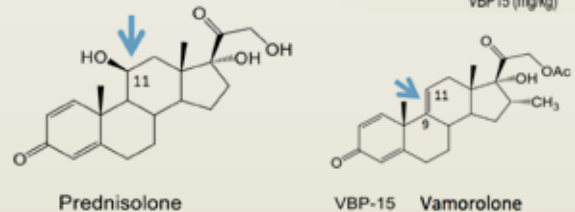
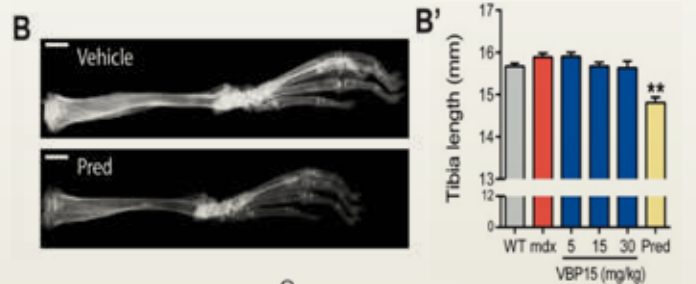
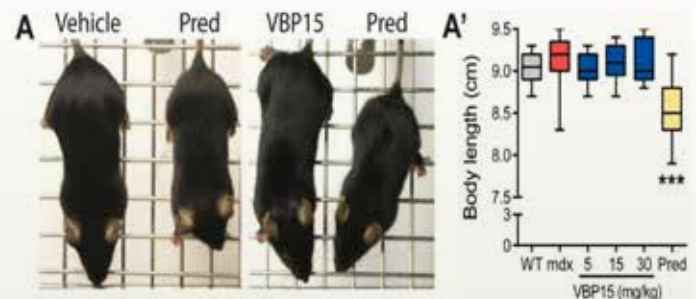
Advancement in Duchenne Therapeutics

Eric Hoffman, Ph.D., John McCall, Ph.D., Kanneboyina Nagaraju, D.V.M., Ph.D., Children's National Medical Center

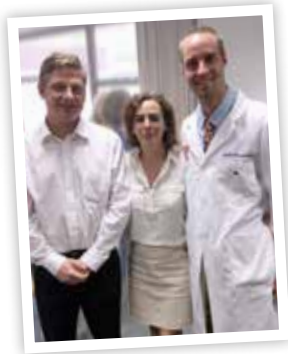
Duchenne is a rare disease caused by a genetic mutation resulting in the lack of production of a structural protein called dystrophin. Patients with Duchenne suffer from progressive muscle damage, weakness, and disability. Glucocorticoids, such as prednisone (Pred) and deflazacort, are the current standard of care for patients with Duchenne to reduce muscle damage and increase patient strength. While glucocorticoids provide a reduction in the inflammation caused by contraction-induced muscle damage in patients with Duchenne, they induce harsh side effects, particularly in children. These side effects include stunted growth, diabetes, mood swings, and weight gain, which reduce patient adherence and limit the therapeutic window.

Research indicates the harmful side effects induced by glucocorticoids are a result of transcriptional gene activation, termed "transactivation," whereas the beneficial anti-inflammatory effects occur through inhibition of inflammatory transcription factors, such as Nuclear Factor kappa B (NFκB), termed "transrepression." Drs. Hoffman, McCall, and Nagaraju sought to develop a novel therapeutic that could dissociate the beneficial transrepressive and anti-inflammatory effects of glucocorticoids from the harmful transactivation-induced side effects. They hypothesized a compound with these properties would continue to provide improvements in muscle inflammation and increase strength for patients with Duchenne without the harmful side effects of traditional glucocorticoids. Beginning with several DoD awards managed by the CDMRP, the research team screened compounds for inhibition of NFκB, a key signaling protein in inflammation, and binding to the glucocorticoid receptor of a signaling protein that is central to glucocorticoid functioning. They determined the compound vamorolone (previously VBP15) had the cellular signaling characteristics that were promising for therapeutic efficacy for inflammatory diseases with a reduced side effect profile. They used this compound for preclinical testing in murine models of Duchenne.

Vamorolone showed efficacy equal to prednisone in the treatment of muscular dystrophy, both in vitro and in vivo in the mdx mouse model of Duchenne, but lacked the associated side effects. These studies led to funding support by Therapeutics for Rare and Neglected Diseases to conduct the necessary toxicology studies in preparation for submission of an Investigational New Drug (IND) application to the Food and Drug Administration to enable in-human clinical trials for Duchenne. The IND enabling studies were successful, and an IND was filed in December 2014, followed by Phase I safety trials for vamorolone in healthy individuals. These trials were successful, and Phase II trials are set to begin in steroid-naïve Duchenne boys 4-7 years of age in the near future. Vamorolone represents an exciting opportunity for improving the lives of patients with Duchenne, and it is being explored as a potential therapeutic in other inflammatory disorders where the side effects of glucocorticoids outweigh benefits, such as in asthma, inflammatory bowel disease, and multiple sclerosis.



Mice exposed to increasing concentrations of VBP15 show dramatic decreases in prednisone-associated side effects, as indicated above by (A/A'), Body length, and (B/B'), Tibia length.



Optical Imaging of Damaged and Dystrophic Muscle

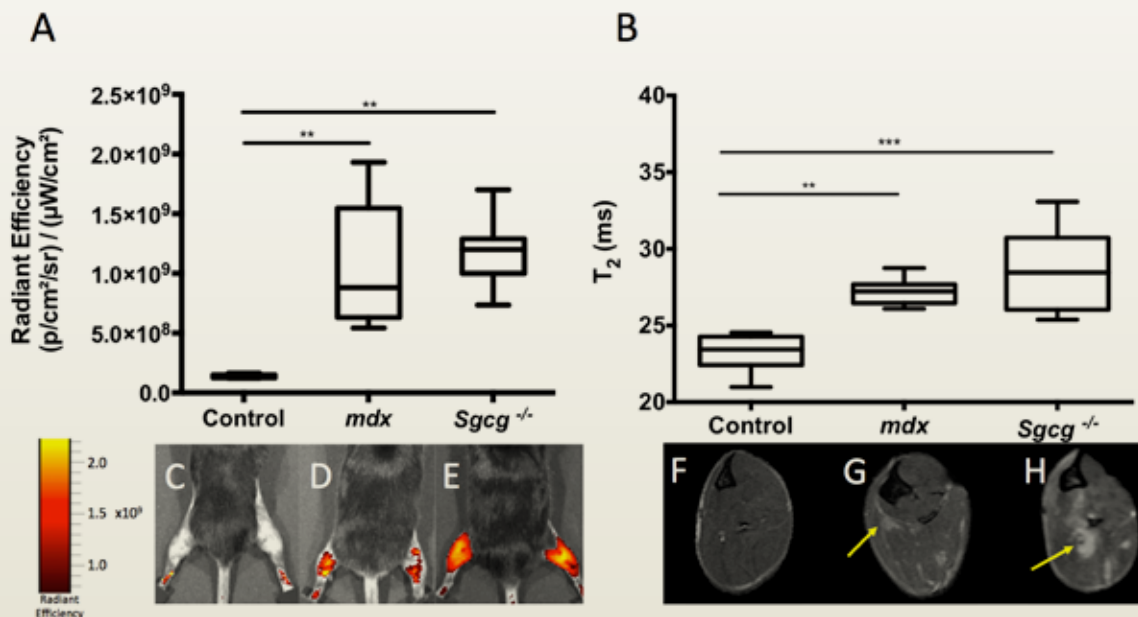
Glenn Walter, Ph.D., University of Florida

Duchenne is an inherited disease that is caused by defects in the production of the structural muscle protein, dystrophin, which provides support and repair in normal muscle cells. The absence of dystrophin results in progressive skeletal muscle damage that limits mobility and eventually leads to cardiac and respiratory complications. While novel therapeutics within the Duchenne research community are showing promising results in animal and human studies, a major limitation is the lack of effective methods to measure changes in muscle integrity noninvasively, in real time, at low cost, without harmful radiation, and with minimal patient discomfort. Dr. Glenn Walter, using an FY11 DMDRP Investigator-Initiated Research Award, sought to develop a novel optical tool using a near infrared (NIR) imaging technique to differentiate damaged muscle cells from rescued and normal muscle tissue.

Dr. Walter's work has demonstrated that NIR light, combined with magnetic resonance imaging (MRI), can be used to quantitatively image and assess muscle damage and noninvasively follow therapeutic interventions. Dr. Walter's studies have utilized murine models to optimize the use of NIR optical imaging (NIR-OI) and MRI to visualize damaged muscle using the contrast agent indocyanine green (ICG). These imaging techniques have shown improvements in muscle integrity resulting from gene therapy. Their work has explored the use of polylactide-coglycolide acid (PLA) polymer nanoparticles that contain ICG for enhanced imaging. These nanoparticles also have the potential to transport therapeutics, such as antisense oligonucleotides (AONs), for targeted drug delivery. Initial studies indicate the PLA-ICG nanoparticles have sustained in vivo imaging capabilities (up to four weeks) and show promise for prolonged release and delivery of therapeutic AONs. Dr. Walter's studies have indicated that NIR-OI is more sensitive than MRI for detection of muscle damage in vivo. In addition, Dr. Walter's group is currently evaluating the translation of NIR-OI using ICG in patients in a clinical trial with Duchenne and healthy pediatric subjects. The goal of this study is to validate the potential of these optical imaging techniques to detect and quantify muscle damage both in a population affected by Duchenne and in a healthy population that has undergone acute muscle damage due to an exercise intervention.

The success of this work is integral to being able to develop and track the progress of targeted therapeutics in neuromuscular disorders, such as Duchenne. This imaging shows promise in assessing individuals for muscle damage in a noninvasive, safe, repeatable, objective, and quantifiable manner for closer disease monitoring and management.

Optical^A and Magnetic Resonance^B Imaging of Healthy and Damaged Muscle in Dystrophic and Control Mice



FY15 Investigator-Initiated Research Awards

Treating Duchenne Cardiomyopathy in the Mouse Model by Gene Repair

Dongsheng Duan, Ph.D., University of Missouri

This research aims to test the restoration of dystrophin expression targeting cardiomyopathy symptoms using gene editing technology (CRISPR/Cas9) that was previously proven effective in restoration of dystrophin expression in the skeletal muscle of a muscular dystrophy mouse model. These studies aim to transform the field of Duchenne cardiomyopathy gene therapy and complete the necessary studies to move to canine-based validation studies for application in an Investigational New Drug for clinical trials.

Clinical Utility of Serum Protein Biomarkers in Very Young Duchenne Muscular Dystrophy Boys

Yetrib Hathout, Ph.D., Children's Research Institute at Children's National Medical Center

The goal of this study is to define serum biomarkers and evaluate their clinical utility as outcome measures in very young Duchenne boys (0-4 years of age). Dr. Hathout hypothesizes that molecular biomarkers accessible via blood analysis can be used to assess disease severity and progression in very young Duchenne boys. These studies will be extending current proteomic studies in older Duchenne boys to a younger population for comprehensive biomarker discovery.

New Therapies for Fibrofatty Infiltration

Fabio Rossi, M.D., Ph.D., University of British Columbia

Fibrofatty infiltration is the replacement of muscle tissue with hard fibrous tissue and fat that is thought to be one of the main causes of loss of muscle function in Duchenne. Dr. Rossi hypothesizes that inhibitors of the NFκB pathway, which is involved in the inflammatory response, will prevent fibrofatty infiltration in mouse models of muscular dystrophy. These drugs have been shown to prevent this fibrofatty cellular transformation in in vitro studies and, if successful, would offer novel treatment options for Duchenne patients.

FY15 Translational Leverage Awards

Generating the Evidentiary Data Package for Dystrophin Biomarker Qualification

Yetrib Hathout, Ph.D., Children's Research Institute at Children's National Medical Center

Dr. Hathout hypothesizes that dystrophin levels correlate with clinical phenotype and that accurate quantification of dystrophin combined with well-documented clinical phenotypes will resolve this correlation. This study will gather information from established resources of patient muscle biopsies to determine the relationship of dystrophin protein amount and the patient's overall health. The objective is to apply this correlation for qualification of dystrophin as a pharmacodynamic biomarker using the FDA Biomarker Qualification Program.

Validation of Functional Reaching Volume as an Outcome Measure across the Spectrum of Abilities in Muscular Dystrophy

Linda Lowes, P.T., Ph.D., Research Institute at Nationwide Children's Hospital

Previous efforts by Dr. Lowes have resulted in development of a custom-designed video game, ACTIVE, to quantify the ability of patients with Duchenne to interact with the environment, also known as functional reaching volume. Recent advancements in ACTIVE include Solitons, which tracks very small movements previously not identified by the game. The goal of this study is to produce a distributable, clinical trial-ready outcome measure that will improve the reliability and validity of functional assessments and increase the potential enrollment pool for clinical trials.



For more information, visit

<http://cdmrp.army.mil>

or contact us at:

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