CDMRP
Department of Defense

Duchenne Muscular Dystrophy Research Program

Strategic Plan

INTRODUCTION

The Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas. Programs managed by the CDMRP have formalized strategic plans that identify program-specific research priorities, how to best address these urgencies, short- and long-term goals, investment strategies, and ways to identify and evaluate program successes with respect to the priorities.

The Duchenne Muscular Dystrophy Research Program (DMDRP) Strategic Plan identifies the high-impact research goals most important to its stakeholders while providing a framework that is adaptable to changes in the medical research environment to address those goals. This plan has been formulated to clarify the program's goals over time for the public and other stakeholders. Funding for the DMDRP is congressionally appropriated on an annual basis; therefore, there is no guarantee of future funding. The DMDRP Strategic Plan will be reviewed during the program's annual Vision Setting meeting and updated as necessary.

DMDRP BACKGROUND AND OVERVIEW

Duchenne muscular dystrophy is an X-linked recessive disease and is the most common childhood form of muscular dystrophy, affecting approximately 1 out of every 5,000 male infants and about 20,000 babies worldwide each year. Duchenne mostly affects boys and reaches across all races and cultures. Duchenne is a severe, progressive disease that causes muscles to become weaker over time. Initially, Duchenne presents between ages 2 to 6, with loss of ambulation by age 12. Loss of upper arm use quickly follows in the teenage years, and muscle weaknesses progress to heart and respiratory failure, eventually leading to death before or during an individual's 30s. Improvements in care for Duchenne over the last 10+ years have resulted in delayed progression of the disease.

Duchenne is caused by nonsense or frameshift mutations in the dystrophin gene, resulting in loss of functional dystrophin protein. Dystrophin is an essential membrane-associated muscle protein in both skeletal and cardiac muscles. Dystrophin deficiency in the muscle cells of patients with Duchenne predisposes the muscles to contraction-induced damage due to membrane instability. Successive cycles of injury and repair lead to chronic inflammation, oxidative stress, and fibrosis, reducing the regenerative capacity of muscle and causing progressive muscle wasting and weakness.

There is no cure for Duchenne. Currently, treatment is limited to managing the symptoms of the disease. Glucocorticosteroids are used to slow disease progression by facilitating the maintenance of muscle strength longer; however, they have serious side effects. Recently, the glucocorticosteriod, deflazacort, received marketing approval in the United States, with data supporting a potentially improved side-effect profile over prednisone.

Cardiomyopathy is addressed with the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and/or beta blockers. Unfortunately, these treatments are only temporarily effective and, as previously noted, patients with Duchenne succumb to their disease due to heart and respiratory failure before or during their 30s.

VISION AND MISSION

The DMDRP was established in fiscal year 2011 (FY11), with a congressional appropriation of $4 million (M) to promote the understanding, diagnosis, and treatment of Duchenne. To address this guidance, the DMDRP has developed the following Vision and Mission statements:

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

DMDRP MISSION: To better characterize Duchenne pathophysiology, support discovery and development of therapeutics, related devices and tools, as well as to promote their rigorous preclinical and clinical testing for the benefit of military beneficiaries and the general public

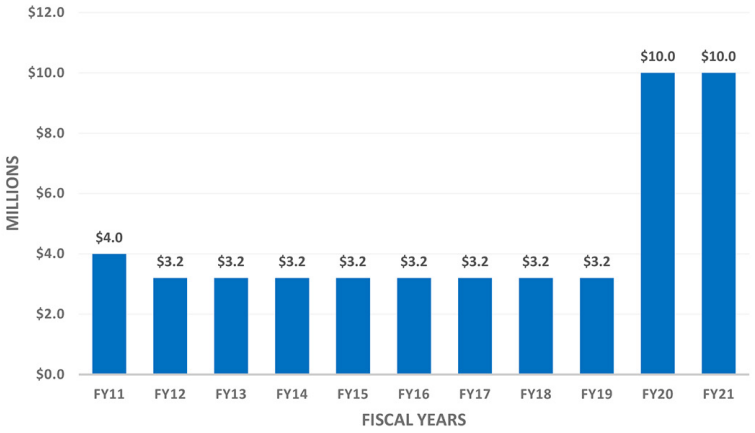
Since the program's inception, the DMDRP has followed the recommendations[1] made by the Institute of Medicine* (IOM) to the U.S. Army Medical Research and Development Command on the peer review procedures for evaluating an application's scientific merit and the preferred programmatic investment strategy for funds. In the two-tier peer review system, applications are first evaluated for scientific merit (first tier – peer review) using criteria outlined in the funding opportunity announcement. The ratings and evaluations of the peer reviewers and programmatic relevance are the primary criteria considered for selecting applications for funding (second tier – programmatic review), to ensure that awards are made to meritorious proposals that best meet the programmatic goals.

The IOM also recommended that consumers (disease survivors, people living with or family members of a person living with Duchenne) should be included as members of the panel (termed the Programmatic Panel) conducting programmatic review. The DMDRP adheres to this guidance, and consumers participate on the Programmatic Panel, as well as on peer review panels, as full voting members.

FUNDING HISTORY

Over its 11-year history, the DMDRP has received congressional appropriations annually. **Figure 1** shows the program's funding from FY11 to FY21, totaling $49.6M since its inception. During this time, the program funded 51 awards through the competitive two-tier review process targeted toward the program's vision.

Figure 1. DMDRP Funding per Fiscal Year



RESEARCH PORTFOLIO

Since the DMDRP was first established in FY11, the program has identified Focus Areas to assist researchers in concentrating their projects around the program's priorities.

DMDRP FOCUS AREAS

- Bone, cardiac, central nervous system (CNS), and/or gastrointestinal tract studies, including identifying mechanisms of pathology and therapeutic interventions
- Translational and clinical studies, novel interventions, and drug and biologic delivery technologies designed to improve clinical care and quality of life in areas such as:
  - Cognitive function
  - Endocrinology
  - Gastrointestinal issues
  - Immunology
  - Orthopaedics
  - Psychosocial issues
  - Pulmonary (including sleep-focused studies)
  - Skeletal muscle
- Assessment of clinical trial tools and outcome measures, such as:
  - Discovery and qualification of pharmacodynamic, prognostic, and predictive biomarkers, including potential surrogate markers
  - Novel clinical outcome assessment
  - Patient-centered outcomes (e.g., quality of life activities of daily living)
  - Secondary data analysis that helps to address clinical research tool validation and/or to understand natural history

**The National Academy of Sciences changed the Institute of Medicine (IOM) name to National Academy of Medicine in 2015.*

- Extension or expansion of existing preclinical translational data in support of a specific therapeutic development path (such as optimizing delivery to target tissues, including drug exposure, independent replication, and comparative studies)

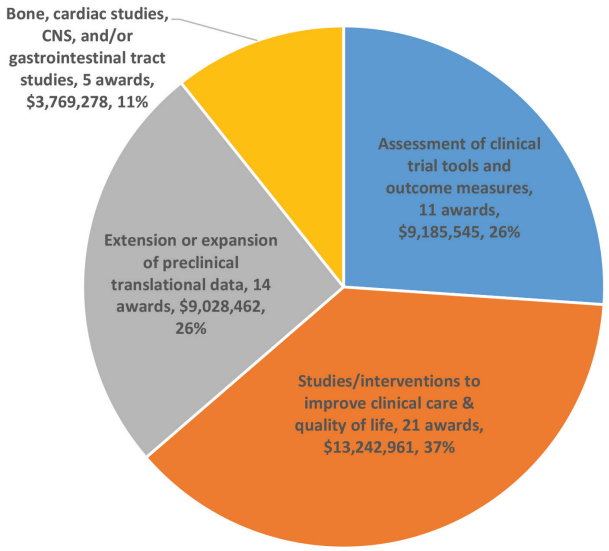
RESEARCH ACCOMPLISHMENTS

Over the years, the DMDRP has focused much of its research support on advanced preclinical stage projects in an effort to advance potential therapeutics to the clinic for testing in human subjects. The following DMDRP-funded projects have been successful, with results that translated to clinical trials or Food and Drug Administration (FDA) drug approval:

- Supported preclinical work that led to FDA approval of two therapeutics, Exondys® 51 and Viltepso®. These therapeutics are currently available as potential treatments for over 20% of patients with Duchenne who have mutations in exon 51 or exon 53.
- Support of preclinical studies developing Vamorolone led to a recently completed phase 2b clinical trial that showed promising results of Vamorolone as a potential replacement for glucocorticoid treatment in boys with Duchenne.
- Preclinical studies supporting vector optimization for GALGT2 gene therapy led to approval of an investigational new drug application and a phase 1/2 gene therapy clinical trial in patients with Duchenne (ClinicalTrials.gov identification number NCT03333590).
- Preclinical studies on the combination of an angiotensin-converting enzyme (ACE) inhibitor and mineralocorticoid receptor antagonist resulted in significant improvement in the function of dystrophic limb skeletal muscles, respiratory muscles, and the heart. An additional study arm was added to a phase 3 clinical trial based on these results (NCT02354352).
- Preclinical studies on adeno-associated virus (AAV) vector optimization, production, and delivery methods for gene therapy demonstrated improved cardiorespiratory function and persistent micro-dystrophin expression in large animal models for 2 years. These studies provided the foundation for a phase 1/2 clinical trial evaluating the safety, tolerability, and efficacy of micro-dystrophin gene transfer in adolescents and children with Duchenne (NCT03368742).

Figure 2 displays the DMDRP portfolio from FY11–FY20, based on the Focus Area the award is addressing, the percent investment, and the number of awards supported.

Figure 2. Dollars Invested per Focus Area (FY11-FY20) Total Investment: $35.2M



RESEARCH AND FUNDING ENVIRONMENT

The CDMRP is represented as a standing member of the Muscular Dystrophy Coordinating Committee (MDCC), as authorized by the Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 (MD-CARE Act, P.L. 107-84). The MDCC coordinates muscular dystrophy activities across the National Institutes of Health (NIH) and other federal agencies, as well as muscular dystrophy patient organizations. As part of the MDCC's mission, the committee is charged with developing an action plan for conducting and supporting research and education on muscular dystrophy through the national research institutes, which is periodically reviewed and revised. The first MDCC Action Plan was developed and approved in 2005. The MDCC Action Plan contains specific objectives that are appropriate to the missions of MDCC member agencies and organizations and has served as a central focus for coordination of efforts in muscular dystrophy. During the 10 years following the development of the 2005 MDCC Action Plan, significant progress has been made in several areas, but not all. Much of this progress came about through improved partnering among advocacy, academic, industry, and government stakeholders in the field. In 2015, the Action Plan was revisited and updated.

The recommendations put forth in the 2015 Action Plan for the Muscular Dystrophies (2015 MDCC Action Plan; https://mdcc.nih.gov/Action_Plan) built on what had been learned during the previous decade. This included a deeper understanding of disease mechanisms and more careful vetting of therapeutic targets; better aggregation of mutation/polymorphism, patient samples, and genotype-phenotype data to improve diagnostics, identify people with muscular dystrophy earlier and with more reliability, and develop biomarkers; improvement of the efficiency of preclinical and clinical vetting of candidate therapeutics in order to avoid failures in the late stages of clinical trials that can be catastrophic to the field; and increasing the efforts and urgency to address the quality of life, education, and employment of people living with muscular dystrophies. The DMDRP looks to the 2015 MDCC Action Plan as a resource when determining how it can best contribute and collaborate with other MDCC member organizations

to help advance the DMDRP vision of preserving and improving the function and quality of life and extending the life span of all individuals with Duchenne.

RESEARCH FUNDING LANDSCAPE

In order to maximize the DMDRP's ability to fill gaps and leverage the findings of investigators in the Duchenne research field, each year the DMDRP analyzes (1) the dollar investments and (2) the research portfolios of the major Duchenne research funding organizations. **Table 1** lists the Duchenne research funding investments from 2016–2020 for federal and several non-federal organizations.

The DMDRP is the second largest funder of Duchenne research after the NIH. However, it should be noted that the DMDRP invests only in new awards each year, whereas the NIH invests about 16% of its funds in new awards and the remaining 84% in support for the out-years of existing, continuing awards.

Following the release of the 2015 MDCC Action Plan, MDCC member agencies and organizations began collecting information about their research funding activities related to the priority areas established in the plan. Information about muscular dystrophy research projects supported by the MDCC member organizations is shared among MDCC members and is publically available. The 2015 MDCC Action Plan has 81 objectives that can be summarized in five priority areas:

- Understanding causes
- Screening and diagnosis
- Developing treatments
- Preparing for clinical trials
- Providing care, management, and access to services

Table 1 . Duchenne Research Funding Investments (2016–2020)

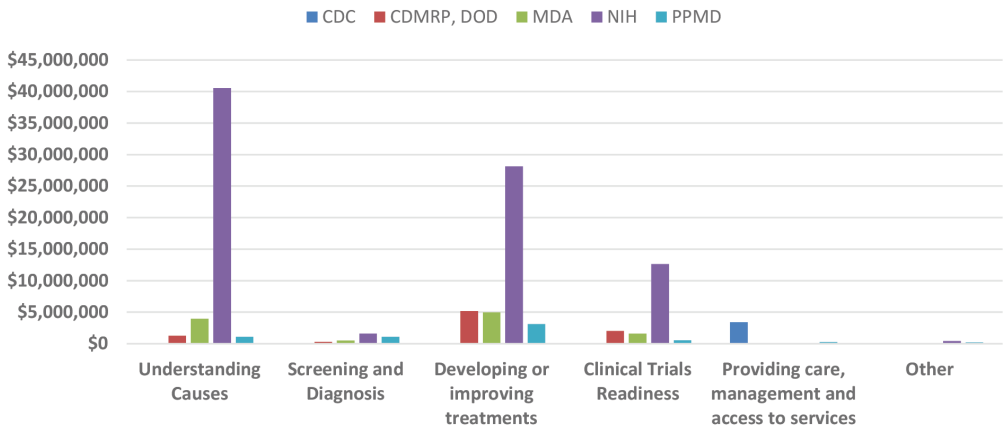
Funding Organization	Dollars Invested
Centers for Disease Control	$9,416,004
CDMRP DMDRP	$20,819,178
CureDuchenne	$15,158,231
FDA*	$8,077
Muscular Dystrophy Association±	$9,373,553
NIH (all awards)	$162,676,231
NIH (new awards)	$26,936,320
Parent Project Muscular Dystrophy	$13,220,207

**The FDA did not fund any Duchenne research from FY16–FY18. Amount presented is from FY19–FY20 awards.*

As the largest funder in Duchenne research, the NIH has invested in almost all priority areas, with Understanding Causes (49%) as the highest funding priority, followed by Developing or Improving Treatments (34%); Clinical Trial Readiness (15%); Screening and Diagnosis (2%); and Other (0.5%). The two major patient organizations, the Muscular Dystrophy Association (MDA) and Parent Project Muscular Dystrophy (PPMD), also have invested in almost all priority areas. The MDA's three largest investments were in Developing or Improving Treatments (45%); Understanding Causes (36%); and Clinical Trial Readiness (15%); less than 5% was invested in the remaining two priority areas. The PPMD's largest investment is in Developing or Improving Treatments (49%), followed by Understanding Causes (18%); Screening and Diagnosis (17%); and Clinical Trial Readiness (9%); less than 10% was invested in the remaining two priority areas.

Figure 3 compares the Duchenne project portfolios for funding organizations that are MDCC members based on five priority areas of the 2015 MDCC Action Plan.

Figure 3. Amounts Invested by MDCC Organizations per Research Priority Areas (Open Awards as of 2019)



CDC- Centers of Disease Control, MDA- Muscular Dystrophy Association, NIH- National Institute of Health, PPMD- Planned Parent Muscular Dystrophy

The DMDRP has invested a majority of its funding in Developing or Improving Treatments (59%) and Clinical Trial Readiness (23%). These are the two priority areas in which the DMDRP believes it can make its greatest impact for the Duchenne research field and patient communities, particularly considering the limited research funding available from government and non-government organizations across the entire muscular dystrophy field. The resources required to

produce a novel therapy/treatment are significant, and relying on only one organization to carry out this task is unrealistic; therefore, a considerable level of cooperation is required among all stakeholders in the field.

Today's medical research environment is dynamic. New research data sets are being created and made available to researchers at an ever-faster rate, and new technologies are emerging that will enable research that is impossible today. Funding for research comes from a variety of sources, through a variety of programs. Many are funded by the government through the NIH, Centers for Disease Control and Prevention, CDMRP and other DOD organizations, and various non-government organizations focused on disease-specific areas. The DMDRP must fit within this environment and effectively respond to changes in it to maximize the value and impact of DMDRP-funded research.

STRATEGIC DIRECTION

The DMDRP considered a broad range of unanswered research questions that are potentially critical to treating Duchenne patients, improving their quality of life, and developing a cure. Many of the research questions evaluated are covered by the 2015 MDCC Action Plan (https://mdcc.nih.gov/Action_Plan). The DMDRP recognizes that it plays a critical role in funding Duchenne research by strategically directing its efforts in the following areas:

- Support discovery and development of therapeutics, related devices, and tools
- Accelerate promising therapeutic ideas into clinical applications
- Advance basic research on the effect of Duchenne on the heart, bone, CNS, and gastrointestinal system
- Expand the Duchenne researcher community by supporting early career investigators

STRATEGIC GOALS/PRIORITIES

The DMDRP established four priorities/goals around which it will build its funding strategy; however, the program enables investigators to propose their best ideas and is interested in furthering high-impact, innovative Duchenne research. The DMDRP does not define which specific projects or products will be funded. The overarching strategic priorities for the DMDRP are listed below, and the program will focus on specific areas to help address each of these priorities:

- Support research on bone, cardiac, CNS, and/or gastrointestinal tract studies, including identifying mechanisms of pathology and therapeutic interventions
    - Prevent and treat cardiomyopathy
    - Understand the effects of restoring dystrophin on the heart, bone, endocrine, CNS, and/or gastrointestinal system
- Support research on translational and clinical studies, novel interventions, and drug and biologic delivery technologies designed to improve care and quality of life
    - Develop assistive devices (e.g., wearables, upper-arm robotics)
    - Immunology and understanding the role inflammation plays in the disease process, both in advancing or mitigating the pathology and how it may interfere with various types of therapeutic strategies
    - Develop alternative delivery systems of macromolecules and particles to muscle
    - Cognitive function
    - Endocrinology
    - Gastrointestinal issues
    - Orthopaedics
    - Psychosocial issues
    - Pulmonology (including sleep-focused studies)
- Support research on assessment of outcome measures and other clinical trial tools
    - Discover and validate pharmacodynamic, prognostic, and predictive biomarkers, including potential surrogate markers
    - Biomarkers essential for making go/no go decisions for therapeutic development
    - Develop novel clinical outcome assessment tools
    - Develop patient-centered outcome measures
    - Conduct secondary data analysis to assist in clinical research tool validation and/or understanding the natural history of the disease
- Extend or expand existing preclinical translational data in support of a specific therapeutic development path
    - Optimize delivery to target tissue
    - Drug exposure
    - Independent replication of preclinical data

INVESTMENT STRATEGY

Looking forward to the next 3 to 5 years, the DMDRP has developed a strategy to invest in research that will facilitate accomplishing the program's strategic goals. After each fiscal year, the program will evaluate whether the award mechanism supporting the strategic investment is working well or needs to be improved or discontinued. The following award mechanisms will be used:

- Researcher Development
  - Career Development Award
  - Optional Interdisciplinary Collaborator (offered with the Investigator-Initiated Research Award)
- Innovation and Impact
  - Idea Development Award
- Clinical and Translational
  - Investigator-Initiated Research Award
  - Translational Research Partnership Award
  - Translational Research Award

MEASURING PROGRESS

As shown below, the DMDRP will measure its near-term success based on its successful investments in those areas that are important to its investment strategy. Longer-term success may be evaluated based on how contributions have advanced the field of research by following the scientific findings and therapies linked to DMDRP-funded projects.

- Near-Term Progress (3–5 years)
  - Investments in each strategic priority/goal
  - Tracking investments to identify strategic priorities that are understudied and encourage more research in those areas
  - Contributions to advancing the research field, including publications, patent applications, patents, drug approvals, and clinical trials, which will vary based on the stage of the research project
- Medium- to Longer-Term Progress (6+ years)
  - Proportion of funded investigators receiving additional awards from other sources to continue successful research
  - Increase in the number of new investigators who establish their careers as Duchenne researchers and their contributions to the Duchenne research field (tracking criteria here will include faculty appointments, publications, and awards of new research grants)
  - Funded projects leading to clinical research studies or clinical trials
  - Cntributions to advancing the research field, including publications, patent applications, patents, drug approvals, clinical trials, commercialization of treatments, devices, and changes in standard of care

REFERENCES

1. Strategies for Managing the Breast Cancer Program: A Report to the U.S. Army Medical Research and Development Command. 1993. Institute of Medicine. *The National Academies Press*. Washington, DC.