DEPARTMENT OF HEALTH AND HUMAN SERVICES

Report to Congress on Implementation of the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001

July 2007

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Executive Summary

The Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (the MD-CARE Act, Public Law 107-84) specified a number of provisions for expanding and intensifying research on muscular dystrophy, including that the National Institutes of Health (NIH) establish centers of excellence for research on muscular dystrophy, that the Secretary of Health and Human Services (HHS) establish a Muscular Dystrophy Coordinating Committee (MDCC), that the MDCC develop a plan for conducting and supporting research and education on muscular dystrophy, and that the Centers for Disease Control and Prevention (CDC) expand epidemiological activities regarding muscular dystrophy. The MD-CARE Act also specified that the HHS Secretary must annually report to Congress on the implementation of the Act. This is the fifth annual report submitted on the implementation of the Act.

FY 2006 and FY 2007 Congressional Appropriations Committee Report language also requested certain information be included in this annual report. The Appropriations Committees requested that this report include the current research goals related to muscular dystrophy, funding toward these goals, and progress made toward these goals. In addition, it requested that the report contain information about NIH's translational research activities in muscular dystrophy.

To meet the reporting requirements in the MD-CARE Act and to respond to the Appropriations Committees' requests, we have organized this comprehensive report by section to include the requested information. The Background section describes the types of muscular dystrophies and available treatments. An Overview of NIH and CDC programs follows. Next, the report describes research activities at the six NIH-funded Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers and additional activities at the Centers to enhance collaborative activities, including a fellowship training program and support for workshops. The activities of the MDCC, including the MDCC's Action Plan for the Muscular Dystrophies is highlighted. The next section of the report is divided into the five sections of the Action Plan: Mechanisms of Muscular Dystrophy, Diagnosis and Screening of Muscular Dystrophy, Therapy of Muscular Dystrophy, Living with Muscular Dystrophy, and Research Infrastructure Needs for Muscular Dystrophy. The report presents an overview of the goals in each section and reports on NIH and CDC activities that represent progress toward these goals. Following the description of progress toward goals, NIH and CDC Funding Numbers in Muscular Dystrophy are also presented. Finally, the report describes NIH activities in translational research in muscular dystrophy, including a translational research initiative and plans for a workshop on translational research in the muscular dystrophies, which is scheduled for spring 2007.

Introduction

In December 2001, President George W. Bush signed into law the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (the MD-CARE Act, Public Law 107-84). According to the major provisions of the Act:

- The Director of the National Institutes of Health (NIH), working with the Directors of the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Institute of Child Health and Human Development (NICHD), shall *expand and intensify research* on the muscular dystrophies.
- The NIH shall *establish centers of excellence* for research on muscular dystrophy.
- The NIH shall *facilitate sharing of tissue and genetic samples* for muscular dystrophy research.
- The Secretary of Health and Human Services (HHS) shall *establish the Muscular Dystrophy Coordinating Committee* (MDCC) with two-thirds Government and one-third public members.
- The *Coordinating Committee shall develop a plan* for conducting and supporting research and education on muscular dystrophy through the national research institutes.
- The Secretary, acting through the Director of the Centers for Disease Control and Prevention (CDC), may award grants and provide technical assistance for collection, analysis, and reporting of data on muscular dystrophy and for the purpose of carrying out *epidemiological activities* regarding muscular dystrophy.
- The Secretary shall establish a program to *provide information and education* on muscular dystrophy to health professionals and the general public.
- The Secretary shall enter into a *contract with the Institute of Medicine to study and make recommendations regarding centers of excellence at the NIH.*
- The Secretary shall annually *report to Congress on the implementation* of the Act.

This report is presented as an annual report to Congress on the implementation of the Act. This is the fifth annual report, which highlights recent activities at NIH and CDC to advance our understanding and treatment of the muscular dystrophies.

FY 2006 and FY 2007 Congressional Appropriations Committee Report language requested that the Appropriations Committees be included in the distribution of this report, and that certain other information be included in the submission. Excerpts from the relevant report language are below.

"...The Committee understands that NIH also submits an annual report to Congress on implementation of the MD Care Act. The Committee requests that it be included in the Congressional distribution of [the] report. The Committee asks that the annual report state NIH's current research goals related to Duchenne muscular dystrophy, the progress made toward each goal, the total amount of money invested toward each goal as well as projected spending for the present and future fiscal year, and all opportunities for

translation research and external partnerships." (Report of the House Committee on Appropriations, FY 2006)

"The Committee requests that NIH's annual report to Congress, authorized in the MD Care Act, include information detailing the NIH's current DMD research goals, the progress made toward goals, the total amount of money invested toward the goals, and projected spending on DMD research for the present and future fiscal year." (Reports of the House and Senate Committees on Appropriations, FY 2007)

"...The Committee is advised that the NIH is working toward prioritizing opportunities for Duchenne and Becker Muscular Dystrophy translational research projects and plans to convene a workshop examining DBMD translational opportunities later this year. The Committee is pleased with this development and requests that NIH—through NINDS, the Muscular Dystrophy Coordinating Committee, and the other relevant Institutes—develop specific measurable milestones, including a timeline, needed to establish a DBMD Translational Research Initiative. The Committee also requests that this information be included in the annual report to Congress authorized by the MD Care Act...." (Reports of the House and Senate Committees on Appropriations, FY 2007)

Background

The muscular dystrophies are a group of diseases that cause weakness and progressive degeneration of skeletal muscles. There are many different forms of muscular dystrophy, which differ in their mode of inheritance, age of onset, severity, and pattern of muscles affected. Most types of muscular dystrophy are, in fact, multisystem disorders with manifestations in body systems including the heart, gastrointestinal and nervous systems, endocrine glands, skin, eyes, and other organs.

Types of Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is the most common childhood form of muscular dystrophy. DMD usually becomes clinically evident when a child begins walking. Patients typically require a wheelchair by age 10 to 12 and die in their late teens or early 20s. More than 15 years ago, researchers supported by the NIH and the Muscular Dystrophy Association (MDA) identified the gene for the protein dystrophin which, when absent, causes DMD. The dystrophin gene is the largest known gene in humans. Since the gene is on the X-chromosome, this disorder affects primarily males. Females who are carriers have milder symptoms. Sporadic mutations in this gene occur frequently, accounting for a third of cases. The remaining two-thirds of cases are inherited in a recessive pattern. **Becker muscular dystrophy (BMD)** is a less severe variant of the disease and is caused by the production of a truncated, but partially functional form of dystrophin. Dystrophin is part of a complex structure involving several other protein components. The "dystrophin-glycoprotein complex" helps anchor the structural skeleton within the muscle cells, through the outer membrane of each cell, to the tissue framework that surrounds each cell. Due to defects in this assembly, muscle

contraction leads to disruption of the outer membrane of the muscle cells and eventual weakening and wasting of the muscle.

Myotonic dystrophy is the most common adult form of muscular dystrophy. It is marked by myotonia (an inability to relax muscles following contraction) as well as muscle wasting and weakness. Myotonic dystrophy varies in severity and manifestations and affects many body systems in addition to skeletal muscles, including the heart, endocrine organs, eyes, and gastrointestinal tract. Myotonic dystrophy follows an autosomal dominant pattern of inheritance. This means that the disorder can occur in either sex when a person inherits a single defective gene from either parent. Myotonic dystrophy results from the expansion of a short repeat in the DNA sequence (CTG in one gene or CCTG in another gene). More simply put, the inherited gene defect is an abnormally long repetition of a three- or four-letter "word" in the genetic code—normally, this "word" is repeated a number of times, but in people with myotonic dystrophy, it is repeated many more times. While the exact mechanism of action is not known, this molecular change may interfere with the production of important muscle proteins.

Facioscapulohumeral muscular dystrophy (FSHD) initially affects muscles of the face (facio), shoulders (scapulo), and upper arms (humeral) with progressive weakness. Symptoms usually develop in the teenage years. Some affected individuals become severely disabled. The pattern of inheritance is, like myotonic dystrophy, autosomal dominant, but the underlying genetic defect is poorly understood. Most cases are associated with a deletion near the end of chromosome 4.

The **limb-girdle muscular dystrophies (LGMDs)** all show a similar distribution of muscle weakness, affecting both upper arms and legs. Many forms of LGMD have been identified, showing different patterns of inheritance (autosomal recessive vs. autosomal dominant). In an autosomal recessive pattern of inheritance, an individual receives two copies of the defective gene, one from each parent. The recessive LGMDs are more frequent than the dominant forms, and usually have childhood or teenage onset. The dominant LGMDs usually show adult onset. Some of the recessive forms have been associated with defects in proteins that make up the dystrophin-glycoprotein complex.

The **congenital muscular dystrophies**, another class of muscular dystrophies, also include several disorders with a range of symptoms. Muscle degeneration may be mild or severe. Problems may be restricted to skeletal muscle, or muscle degeneration may be paired with effects on the brain and other organ systems. A number of the forms of the congenital muscular dystrophies are caused by defects in proteins that are thought to have some relationship to the dystrophin-glycoprotein complex and to the connections between muscle cells and their surrounding cellular structure. Some forms of congenital muscular dystrophy show severe brain malformations, such as lissencephaly (a "smooth" appearance to the brain due to the absence of normal convolutions—or folds—in the brain) and hydrocephalus (an excessive accumulation of fluid in the brain).

Several other forms of muscular dystrophy also occur. **Oculopharyngeal muscular dystrophy**, which causes weakness in the eye, throat, and facial muscles, followed by pelvic and shoulder muscle weakness, has been attributed to a short repeat expansion in a gene which regulates the translation of the genetic code into functional proteins. **Emery-Dreifuss muscular dystrophy** is characterized by weakness in the shoulder girdle and lower legs, as well as the development of contractures (tightening or loss of motion) in regions of the body, particularly the elbows, Achilles tendons, and neck. Defects in proteins that make up the cell's nucleus are implicated in the disorder. **Miyoshi myopathy**, one of the distal muscular dystrophies, causes initial weakness in the calf muscles, and is caused by defects in the same gene responsible for one form of LGMD, suggesting that progress against one form of muscular dystrophy may lead to a better understanding of other forms as well.

Available Treatments

Currently, no treatment can stop or reverse the progression of any form of muscular dystrophy. Symptomatic treatments such as physical therapy, use of appliances for support, corrective orthopedic surgery and drugs may improve the quality of life for some individuals. However, even though some drugs such as steroids can slow the progression of DMD, there are side effects. Several therapeutic approaches, including gene therapy, cell-based strategies, and strategies to inhibit muscle degeneration have shown promise in cell-based systems and in animal models and some early clinical trials in humans have begun. Examples of these approaches include the use of drugs to reduce muscle membrane damage, cell-based replacement therapies, functional compensation for dystrophin by upregulation of certain proteins, increasing muscle mass via inhibition of other proteins that negatively regulate muscle growth, inhibiting muscle protein degradation, and strategies to bypass the mutations that cause disease.

Overview of Current NIH Program Activities

The following provides an overview of the program activities of the main NIH components currently supporting muscular dystrophy research. Although the intent of each section is to summarize the contributions of each individual Institute, it is important to recognize that many of these are collaborative activities. The NIH Institutes and Centers involved in muscular dystrophy are committed to working together to identify and support new initiatives to expand the NIH muscular dystrophy portfolio. NIH anticipates that a collaborative, multifaceted approach will yield the most significant advances in understanding and treating the muscular dystrophies.

National Institute of Neurological Disorders and Stroke (NINDS)

NINDS supports intramural and extramural research on many forms of muscular dystrophy ranging from basic studies of normal protein function through projects on gene, stem cell, and drug therapies at levels from the development of experimental therapeutics through clinical trials. The NINDS also continues to support a very active portfolio of basic research on the neuromuscular junction, the terminal between a nerve

cell and muscle fiber. Much of this basic research is critical to advancing our understanding of the mechanisms underlying the muscular dystrophies. In 1987, researchers supported by NINDS and the Muscular Dystrophy Association discovered that dystrophin mutations cause DMD and BMD. NINDS has continued to support subsequent work on understanding the role and function of the dystrophin-glycoprotein complex both in normal muscle and in muscular dystrophy-affected muscle tissue. The NINDS funds research relevant to understanding the molecular and genetic basis of FSHD, as well as research relevant to myotonic dystrophy, LGMD, and other forms of muscular dystrophy and neuromuscular disorders. Another area of focus is the improved diagnosis of the muscular dystrophies. For example, NINDS supports the United Dystrophinopathy Project at the University of Utah, which is developing enhanced diagnostic capabilities for DMD. This project serves as a major diagnostic resource and is helping facilitate clinical trials in DMD by identifying patients who may be candidates for trials based on their molecular diagnosis.

NINDS has a strong focus on translational and clinical research in muscular dystrophy. Translational research is the process of applying ideas, insights, and discoveries generated through basic scientific inquiry to the treatment and prevention of disease. Four therapy development projects in muscular dystrophy have been funded through the NINDS Cooperative Program in Translational Research, a program designed to support milestone-driven projects focused on the identification and preclinical development of drugs, biologics, and devices in cell and animal models. Among the currently funded projects, there is a focus on development of a class of compounds known as protease inhibitors to combat muscle degeneration, on gene modification strategies to bypass mutations in the dystrophin gene, on combined gene modification and cell therapy approaches, and on bringing gene therapy for DMD to readiness for clinical trials. An additional project has been funded through the specialized program for translational research in muscular dystrophy that NINDS developed in conjunction with NIAMS and NICHD. This project is exploring strategies of gene delivery to all muscles in an arm or leg, thereby starting to bridge the gap between ongoing single muscle injection clinical trials and the ultimate need for systemic gene therapy delivery in patients. This new specialized program for translational research in muscular dystrophy has generated a strong response from the muscular dystrophy research community and NIH anticipates that further applications will be submitted through this program.

NINDS also funds two clinical trials in muscular dystrophy. The aim of the trial at the Columbus Children's Research Institute is to test the potential of gentamicin as a therapy for DMD and LGMD by "skipping over" or "reading through" mutations in the causative genes. A second trial at the University of Rochester (one of the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, see page 12), is testing treatment with the growth factor complex IPlex in patients with myotonic dystrophy. NINDS is also funding a planning grant for a phase 3 trial to identify optimal treatment regimens for corticosteroids in DMD.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

NIAMS supports basic, translational and clinical studies on the muscular dystrophies and other muscle diseases and disorders. NIAMS funds considerable research to advance the understanding of the cellular and molecular mechanisms that underlie the muscle degeneration associated with the muscular dystrophies and to develop potential treatment strategies for these diseases. NIAMS supports basic research projects to study normal muscle development and pathophysiology of muscle disorders using animal models and cells from human subjects. Basic studies investigating the capacity of healthy muscle tissue to regenerate after injury have led to the identification and characterization of muscle stem cells and other cell types that can serve as precursors for muscle. NIAMS-supported investigators continue to advance the understanding of inflammatory components in several forms of muscular dystrophy and the role of the immune system in disease progression. Several groups of NIAMS-supported investigators have recently made significant advances in understanding the causes of myotonic dystrophy, which is an important step in developing treatments.

Discoveries from NIAMS-supported basic projects in muscle biology and disease have led to promising strategies for the treatment of muscular dystrophies including pharmacological, and gene- and cell-based therapies. NIAMS supports several translational research projects aimed at developing and testing recombinant viruses engineered to be vehicles for the delivery of therapeutic genes that may block or reverse muscle degeneration. For example, the Senator Paul D. Wellstone Cooperative Research Center at the University of Pittsburgh is exploring gene therapy and muscle derived stem cell therapies for the treatment of muscular dystrophies. Other areas of translational research include the identification and testing of potential drugs to block the enzymes that cause muscle degeneration and pharmacological methods to promote muscle growth. NIAMS supports studies of patients with LGMD, myotonic dystrophy, Emery-Dreifuss muscular dystrophy, and congenital muscular dystrophies, and facilitates clinical studies in myotonic dystrophy and FSHD through support of a registry of patient information, which is co-funded with NINDS (see pages 27-28). One of the NIAMS-supported Wellstone Centers, involving researchers at the University of Pennsylvania, Johns Hopkins University and the NINDS intramural research program is preparing to conduct a clinical trial on the efficacy of a class of compounds known as protease inhibitors for DMD. Additionally, the Institute supports extensive research in other areas of muscle biology, which may point to targeted interventions for the treatment of muscular dystrophies and other disorders.

National Institute of Child Health and Human Development (NICHD)

NICHD sponsors a portfolio of extramural research projects related to the muscular dystrophies and other neuromuscular disorders. Research topics related to muscular dystrophy are focused in two of the Institute's centers: the National Center for Medical Rehabilitation Research (NCMRR) and the Center for Developmental Biology and Perinatal Medicine (CDBPM).

The NCMRR is supporting several projects related to muscular dystrophy. Current research topics include development of non-invasive imaging to study loss and recovery of muscle strength and function, potential viral-mediated gene transfer to prevent disuse syndrome and accelerate restoration of function, and molecular characteristics of muscle remodeling in response to rehabilitation after immobilization. NCMRR is also interested in all aspects of exercise related to management of the muscular dystrophies.

Within CDBPM, the Mental Retardation and Developmental Disabilities Branch has supported research into cognitive disabilities in DMD and accepts applications for research on the nonskeletal manifestations of many of the muscular dystrophies. Areas of research interest also include nutrition and obesity in muscular dystrophy and family and psychosocial issues such as effects on other family members.

In addition, NICHD is addressing issues related to newborn screening that are expected to have relevance to the muscular dystrophies and other neuromuscular disorders in the near future. NICHD released two sets of initiatives relevant to newborn screening. The purpose of the first, "Innovative Therapies and Clinical Studies for Screenable Disorders," is to improve the understanding and/or stimulate the development of therapeutic interventions for currently screened conditions and "high priority" genetic conditions for which investigators could potentially develop screening tests in the near future, including DMD. The second, "Novel Technologies in Newborn Screening," seeks to develop a multiplexed screening technology prototype for newborn screening, particularly for disorders with current or promising therapeutic interventions, like DMD. NICHD is also currently planning to develop a translational newborn screening research network to create a system which can translate the outcomes from these initiatives into clinical practice. NICHD's activities in newborn screening are described in more detail on pages 17-18 of this report.

Finally, NICHD also sponsors several networks that are available to support muscular dystrophy research and research training. These include the Pediatric Pharmacology Research Network, which is available for the conduct of trials of new pharmacotherapeutic agents. Two current trials are: "An Open-Label Pilot Study of Pentoxifylline in Steroid-Naive Duchenne Muscular Dystrophy" which seeks to estimate the magnitude and variability of muscle strength change for patients with DMD treated with pentoxifylline, a potent anti-inflammatory compound, and "A Randomized Study of Daily vs. High-dose Weekly Prednisone Therapy in Duchenne Muscular Dystrophy," a prospective, randomized study to compare efficacy and safety of two dose schedules of prednisone in boys with DMD.

The other relevant program is the Pediatric Scientist Training Program, which can contribute to the training of new young investigators. Both of these programs are managed through the Center for Research for Mothers and Children, another component of NICHD.

National Heart, Lung, and Blood Institute (NHLBI)

The NHLBI supports a number of research grants focused on ultimately improving heart and lung health for children and adults with muscular dystrophy. The range of research support NHLBI provides in this area includes investigations of muscular dystrophy gene regulation and mutations, development of new treatments and diagnostic approaches, and access for investigators to patient data through a registry. A list of research highlights includes:

- Evaluation of the potential for diaphragm transplantation to improve respiratory mechanics in a mouse model of muscular dystrophy.
- Characterization of the roles of the cell nucleus and gene regulation in human and mouse cells with various genetic mutations, including the mutation underlying Emery-Dreifuss muscular dystrophy.
- Identification of the cellular and molecular effects of modifier genes that result in variations in muscular dystrophy severity.
- Cardiac imaging using state-of-the-art magnetic resonance imaging technology, and other studies of cardiac contraction, in mice with genetic mutations causing muscular dystrophy.
- Investigation in mice of a number of mutations in cardiac contractile and structural proteins that shed light on the different manifestations of muscular dystrophy.
- Assessment of the outcome of childhood heart problems through the Pediatric Cardiomyopathy Registry, which includes data on more than 125 children with heart muscle dysfunction due to neuromuscular diseases, primarily DMD, BMD, and Emery-Dreifuss muscular dystrophy.

In addition, NHLBI supports training and career development grants in the area of muscular dystrophy, which help to foster the next generation of researchers. NHLBI also supports an extensive extramural research portfolio that has relevance to understanding heart and lung involvement in the muscular dystrophies. Areas of investigation include numerous imaging studies that assess cardiac and pulmonary function in a variety of conditions (including muscular dystrophy), gene therapy development, and basic research on heart and lung cell function.

Overview of Centers for Disease Control and Prevention (CDC) Programs

The Duchenne-Becker Muscular Dystrophy program at CDC began in 2001. The DMD/BMD program is housed in the Single Gene Disorders and Disability Team in CDC's National Center on Birth Defects and Developmental Disabilities (NCBDDD) (www.cdc.gov/ncbddd), within the Division of Human Development and Disability (DHDD). The mission of the NCBDDD is to improve the health of children and adults by preventing birth defects and developmental disabilities and complications of hereditary blood disorders and to promote optimal child development and the health and wellness among children and adults living with disabilities. Activities include epidemiological studies, as well as research on appropriate disease interventions.

CDC is working with partners in State health departments and universities to answer a number of questions about DMD and BMD. Epidemiological activities include identifying how common these disorders are and if they are equally common in different racial and ethnic groups. CDC research also aims to identify early signs and symptoms of DMD and BMD, and whether the type of gene changes affect the severity or course of DMD and BMD. Access to medical and social services for patients and their families are other focuses of CDC's programs. These activities are investigating if the type of care received affects the severity or course of DMD and BMD, what types of medical and social services families affected by DMD or BMD are receiving, and if different groups of people receive different care.

Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers

The MD-CARE Act authorized NIH to establish centers of excellence for muscular dystrophy research, and NIH currently funds six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (referred to here as "Wellstone Centers"). NINDS, NIAMS, and NICHD each fund two of the Wellstone Centers. The award to each Wellstone Center provides up to $1 million in direct costs per Center per year for five years. The following six Wellstone Centers are currently funded by NIH:

- University of Pittsburgh (funded by NIAMS): This Wellstone Center focuses on development of gene therapy techniques as well as research to advance muscle stem cells as potential therapies for DMD. These approaches may be applicable to other muscular dystrophies in addition to DMD. The Center also includes a clinical trial of gene therapy for LGMD.
- University of Washington (funded by NICHD): Research at this Wellstone Center also focuses on gene therapy techniques, including the development of improved viral vectors. In addition, the Center is conducting research in animal models on the use of adult stem cell transplantation to treat DMD.
- University of Rochester (funded by NINDS): This Wellstone Center has a focus on myotonic dystrophy and FSHD; researchers are studying these disorders at the cellular and molecular levels to examine the factors that contribute to these forms of muscular dystrophy. Additionally, this Center has an active clinical trial to test the drug IPlex (a growth factor complex) in myotonic dystrophy patients. The dose escalation phase of this safety and feasibility trial is nearly completed with no serious adverse events. The next phase of the trial will test an optimal dose in myotonic dystrophy patients. Because IPlex is designed to help improve muscle regeneration, the drug may be useful in many types of muscular dystrophy.
- University of Iowa (funded by NINDS): This Wellstone Center focuses on gene and stem cell therapeutic strategies for DMD, LGMD, and other muscular dystrophies. The Center also serves as a national resource for clinical researchers by providing diagnostic services and maintaining a repository of relevant patient tissues.

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- University of Pennsylvania/Johns Hopkins University (funded by NIAMS): This Wellstone Center is investigating strategies to promote muscle growth or to inhibit muscle protein degradation. These approaches could be applicable to a wide range of muscular dystrophies and other muscle diseases and disorders.
- Children's National Medical Center (funded by NICHD): Research at this Wellstone Center is analyzing genetic and cellular factors that contribute to DMD progression and the response of patients to treatment.

Muscular Dystrophy Association (MDA) Partnership

In May 2003, NINDS, NIAMS, and NICHD signed a Memorandum of Understanding with the MDA in which the MDA agreed to commit up to $1.5 million to enhance research activities at each of the three Centers initially funded by NIH (Rochester, Washington, and Pittsburgh). The MDA provided supplements of up to $500,000 per Center per year for the initial three years for additional projects to each of these three Centers. The supplemental funding from the MDA ended in December 2006.

Collaborative Activities at the Wellstone Centers

The Wellstone Centers are designed to accelerate progress toward effective treatments for the muscular dystrophies through increased synergistic collaboration and coordination of research activities. The Wellstone Centers program has built-in set-aside funds to promote new collaborations. To date, four projects have been approved for funding using these collaborative funds, including two muscular dystrophy dog colonies led by the Washington and Pittsburgh Wellstone Centers, a collaboration between the Rochester and Washington Wellstone Centers to study target genes that may play a role in myotonic dystrophy, a collaborative project to evaluate a gene modification technique ("exon skipping") in the dystrophic dog model that is led by the Wellstone Center at Children's National Medical Center, and a project led by the Iowa Wellstone Center to develop more effective diagnostic techniques for LGMD and Miyoshi myopathy.

To further enhance ongoing and collaborative activities, the Wellstone Centers may apply for supplemental funds through two NIH-sponsored programs. The first, "NIH Administrative Supplements for Senator Paul D. Wellstone Muscular Dystrophy Research Fellowships at Wellstone Muscular Dystrophy Cooperative Research Centers," promotes collaborations by the Centers and maximizes opportunities for career development among junior investigators affiliated with the Wellstone Centers. Four fellowships are currently funded through this program (at the Rochester, Washington, Children's National Medical Center, and Iowa Wellstone Centers). The second, "Support for Muscular Dystrophy Workshops and Research Conferences," encourages the Directors of the Wellstone Centers, in collaboration with other muscular dystrophy researchers and/or representatives from voluntary health organizations, to apply for administrative supplements to support small workshops or conferences focused on specific topics in muscular dystrophy research. One workshop, "High Throughput Drug Screening for the Muscular Dystrophies," which took place at the Children's National Medical Center on April 17-18, 2006, was funded through this program. Participants

included industry, academic and government researchers as well as patient advocate representatives. The presentations and discussions highlighted the availability of resources for conducting high throughput screens and detailed the activities that are currently under way. The participants identified the need for additional, selective, robust assays relevant to the muscular dystrophies. More information about the outcomes of this workshop is included on page 29 of this report. Wellstone Center directors are currently considering new workshop proposal ideas for 2007.

Plans for Continuation of Funding of Wellstone Centers

NIH plans to reissue the Request for Applications for Wellstone Centers in 2007. NIH program staff are actively examining the program to ensure that the Wellstone Centers are as effective as possible in meeting the goal of developing better therapies for the muscular dystrophies. The existing Wellstone Centers will be competing with new applications for selection for the new funding period. NIH anticipates awarding these Wellstone Center grants in FY 2008.

Muscular Dystrophy Coordinating Committee

In accordance with the MD-CARE Act, the MDCC is composed of ten members from Government agencies and five members from the public. Government agencies include components of HHS, the Department of Education, and the Department of Defense (DOD). Public members include representatives from the MDA, Parent Project Muscular Dystrophy (PPMD), the Facioscapulohumeral (FSH) Society, and patient advocates for other forms of muscular dystrophy such as BMD and LGMD. Dr. Steve Katz, NIAMS Director, chairs the MDCC. The MDCC roster can be found on the MDCC's Web site: http://www.ninds.nih.gov/find_people/groups/mdcc/index.htm.

The most recent meeting of the MDCC was held on May 10, 2006. Participants discussed implementation of the MDCC's "Action Plan for the Muscular Dystrophies" (see below). Representatives from NIH, CDC, MDA, PPMD, DOD, and the Department of Education discussed how their current and planned activities applied to the goals of the Action Plan. In addition, there was a presentation on how the activities at the Wellstone Centers fit within the goals of the Action Plan. Minutes from this and all other MDCC meetings can be found on the MDCC's Web site.

The next meeting of the MDCC is scheduled for late spring in Washington, D.C. The agenda for this meeting will include updates on Action Plan-related activities at each agency and organization, and a discussion of the strategies for recruitment, training, and retention of basic and clinical researchers in the muscular dystrophies. The meeting will also provide an introduction for MDCC members to the NIH Workshop on Translational Research in Muscular Dystrophy, which is currently scheduled to immediately follow the MDCC meeting.

MDCC's Action Plan for the Muscular Dystrophies

As part of its charge in the MD-CARE Act, the MDCC, with input from scientific experts in the field, developed a Muscular Dystrophy Research and Education Plan for the NIH, which HHS submitted to Congress in August 2004. The plan contained broad research goals relevant to all forms of muscular dystrophy. The plan was further developed by an MDCC Scientific Working Group into the "Action Plan for the Muscular Dystrophies," which includes over 70 specific goals to accelerate progress toward the effective detection, diagnosis, treatment, and prevention of all types of muscular dystrophies. The Action Plan represents a consensus document for the entire muscular dystrophy community; therefore, implementation of the goals will require the efforts of all MDCC agencies and organizations. Following approval by the MDCC in November 2005, HHS sent the Action Plan to Congress and posted it on the public MDCC Web site (http://www.ninds.nih.gov/find_people/groups/mdcc/index.htm).

The five broad areas of the Action Plan are Mechanisms of Muscular Dystrophy, Diagnosis and Screening of Muscular Dystrophy, Therapy of Muscular Dystrophy, Living with Muscular Dystrophy, and Research Infrastructure Needs for Muscular Dystrophy. As requested in FY 2006 and FY 2007 House and Senate Appropriations Report language, these five broad areas and the progress toward the objectives in each section are described below. In addition, NIH has begun collecting funding numbers for each of the five areas of the Action Plan. Coding of grants based on these five areas is currently under way, and once FY 2006 numbers are finalized, they will be sent to Congress.

Mechanisms of Muscular Dystrophy

The muscular dystrophies comprise a group of diseases that are genetically, biochemically, and clinically diverse. Our current understanding of the mechanisms underlying the muscular dystrophies ranges from mutations in a single gene—in the case of DMD—to more complex genetic and cellular mechanisms for other forms of muscular dystrophy. Research goals in this section include identifying and understanding pathogenic mechanisms that contribute to different forms of muscular dystrophy, including DMD, FSHD, Emery-Dreifuss muscular dystrophy, and others. While some mechanisms of disease may be unique to certain forms of muscular dystrophy, there is increasing evidence that common mechanisms play a role as well. Therefore, some of the goals in this section support the identification of cellular and molecular mechanisms, such as membrane instability and repair, that may contribute to multiple forms of muscular dystrophy, including rare and understudied forms. Understanding common pathways in the dystrophies may help to identify important new targets for therapeutic intervention. Research objectives in this section also highlight the importance of understanding the specific cellular and genetic mechanisms underlying some of the less well understood forms of muscular dystrophy—for example, FSHD and Emery-Dreifuss muscular dystrophy—and elucidating the roles that certain cellular events may play in the pathogenesis of these diseases. Finally, understanding the mechanisms of muscular

dystrophy requires research infrastructure, and goals in this section identify infrastructure needs including the development of animal models of disease.

Progress toward goals:

- *Request for Applications (RFA): Nuclear Structure-Function Defects in the Pathogenesis of Muscular Dystrophy:* To address the goals in the Action Plan related to understanding disease-specific pathogenic mechanisms, NINDS and NIAMS, together with the MDA, released an RFA entitled, "Nuclear Structure-Function Defects in the Pathogenesis of Muscular Dystrophy." This RFA invites applications focused on determining the mechanisms underlying a subset of muscular dystrophies that may have their basis in defects in the structure/function of the cell's nucleus. Applications are specifically solicited for studies of Emery-Dreifuss, facioscapulohumeral, limb girdle muscular dystrophy 1B, and oculopharyngeal muscular dystrophies. Understanding the mechanisms of these disorders is a necessary step prior to launching a translational research effort targeted at developing therapies for these disorders. The partnership between the MDA and NIH on this initiative ensures that the widest possible audience of researchers is targeted and that the initiative has the greatest impact on research in these understudied muscular dystrophies. The NIH will review applications submitted for this RFA, considering meritorious applications for support. Applicants not funded by the NIH will be invited to submit their NIH applications and summary statements (critiques) to the MDA for a second level of consideration of funding.

- *Program Announcement (PA): Muscular Dystrophy: Pathogenesis and Therapies:* In January 2005, NIH reissued the PA, "Muscular Dystrophy: Pathogenesis and Therapies." While recent research has increased our knowledge about the molecular and cellular defects associated with a number of forms of muscular dystrophy, there has not been a corresponding improvement in treatment of these diseases. A principal goal of this initiative is to learn more about the pathogenesis of these diseases to improve early detection, diagnosis, treatment, and prevention for all muscular dystrophies. NIH has funded nine studies under the reissue of this initiative. These grants are described in more detail on page 32 of this report.

- *Studies at the Wellstone Centers:* There is considerable ongoing effort at the Wellstone Centers to help identify mechanisms of disease. At the Pittsburgh Wellstone Center, investigators are studying the basic genetic mechanisms underlying the differentiation of stem cells into muscle. This research is essential for understanding and supporting muscle regeneration and for supporting efforts to develop stem cell therapies. Studies directed toward similar goals, including understanding the muscle cell damage and remodeling pathways and deciphering mechanisms of muscle satellite cell (adult stem cells associated with muscle cells) development are being carried out at the Children's National Medical Center site. At the Rochester Wellstone Center, considerable progress is being made in understanding the molecular basis of myotonic dystrophy and the involvement of

vascular smooth muscle defects in the pathogenesis of FSHD. At the Washington Wellstone Center, investigators are also working to understand the molecular pathogenesis of myotonic dystrophy, partly in collaboration with the Rochester Wellstone Center. Researchers at the Iowa Wellstone Center are examining the mechanisms in fukutin-related protein muscular dystrophy; this form of muscular dystrophy may be caused by similar molecular mechanisms to specific types of congenital and LGMD.

- *Other NIH support for mechanistic studies:* NIAMS, NICHD, NINDS, and NHLBI also fund investigator-initiated research in the area of basic muscle biology and disease mechanisms. NIH-supported mechanistic research has identified and validated several targets for therapy development in DMD that are now being exploited by academic and corporate programs. In addition, there has been dramatic progress in understanding of disease mechanisms in myotonic dystrophy, such that rational drug design approaches are now plausible.

  Although the NIH-funded research grants and the resulting publications are too numerous to detail within the scope of this report, the basic mechanistic research supported by the NIH is essential to progress in diagnosis and treatment of patients in muscular dystrophy and is relied upon by academic and industry researchers engaged in treatment development.

Diagnosis and Screening of Muscular Dystrophy

Rapid and accurate diagnosis of the muscular dystrophies is an important goal of the muscular dystrophy patient community since it reduces unnecessary testing, decreases stress surrounding an uncertain diagnosis, allows for informed genetic counseling, enables specific disease treatments to be considered, and may allow for the initiation of treatment prior to the onset of symptoms. Characterization of the mutations in causative genes has led to relatively noninvasive, specific genetic tests for many types of muscular dystrophy, including DMD. However, for other forms of muscular dystrophy, accurate and specific diagnoses require more invasive tissue-based testing such as microscopic examination of muscle biopsies. Objectives in this section of the Action Plan include developing and expanding the use of minimally invasive techniques, such as blood tests or radiographic muscle imaging. Other goals focus on establishing mechanisms through which muscular dystrophy patients could obtain genetic counseling prior to or following genetic testing, and exploring the social and ethical issues as well as technological barriers involved in offering newborn screening for DMD.

Increased communication among molecular diagnostic laboratories and clinicians involved in the treatment and management of muscular dystrophy is important as diagnostic testing becomes more widespread. Support for public databases of mutation data, disease-specific registries, and collection and sharing of muscle biopsy materials are additional goals included in this section of the Action Plan.

Establishing current and accurate incidence and prevalence data for genetically confirmed forms of muscular dystrophy is another important goal because knowledge about the epidemiology of these diseases is valuable in developing reasonable approaches and novel treatments for specific diagnoses.

Progress toward goals:

- *NICHD Programs in Newborn Screening:* In April 2006, NICHD issued a funding announcement, "Innovative Therapies and Clinical Studies for Screenable Disorders," that specifically highlights the Institute's interest in newborn screening. This initiative will be active until November 2009. The initiative encourages research related to the understanding and/or development of therapeutic interventions for currently screened conditions and "high priority" genetic conditions for which investigators could potentially develop screening tests in the near future, including cystic fibrosis, severe combined immunodeficiency, DMD, and other disorders. The development of an efficacious therapy would make such conditions amenable to newborn screening. In addition to these efforts, NICHD also released a Request for Proposals (RFP) entitled "Novel Technologies in Newborn Screening," which seeks to develop a multiplexed screening technology prototype for newborn screening. As mentioned in the RFP, NICHD is particularly interested in "technologies that screen for "high priority" conditions with current or promising effective therapeutic interventions, which presently lack sensitive and specific tests." NIH hopes that the technology platforms that are developed will be expandable to include the muscular dystrophies.

  Beyond these funding activities, NICHD will be developing a translational newborn screening research network to create a system that can translate the outcomes from these initiatives into clinical practice. The research network will further facilitate and encourage collaborative research on screenable conditions, such as neuromuscular diseases, that will produce findings that are immediately relevant to newborn screening programs. NICHD plans to develop this network in conjunction with other agencies and NIH Institutes as well as nongovernmental organizations like the MDA and private industry organizations that have been active in developing clinical research programs for screenable disorders.

  NICHD is also active internationally, providing technical assistance in the development of newborn screening. For example, NICHD and the Ministry of Health of Morocco held a conference in 2006, titled "Strengthening Newborn Screening in North Africa and the Middle East."

- *Studies at the Wellstone Centers:* Efforts at the Rochester and Iowa Wellstone Centers are providing research resources that are essential to the development of diagnostic tools for muscular dystrophy. The repository of tissue samples and expression profiling data from myotonic dystrophy and FSHD patients at the Rochester Wellstone Center core facility complements the separate NIAMS/NINDS-funded registry of patients for these two disorders (see pages 27-28). In addition, the

Iowa Wellstone center has a repository of cells from patients with a wide variety of muscular dystrophies (DMD, BMD, LGMD and congenital muscular dystrophy) as well as a diagnostics core that will be invaluable for development of tools for early detection of muscular dystrophy. A new collaborative project at the Iowa Center is developing diagnostic tools for LGMD and Miyoshi myopathy due to mutations in the dysferlin gene.

- *The United Dystrophinopathy Project:* In 2006, the NINDS renewed grant support for the United Dystrophinopathy Project at the University of Utah, which serves as a major diagnostic resource for both academic and corporate clinical trials. This project has developed the methodology to rapidly, robustly, and economically perform direct sequence analysis of the entire dystrophin gene, greatly expediting the characterization of mutations in patients and facilitating their entry into clinical trials that require knowledge of the exact mutation present in each patient. The project will also identify cohorts of patients who may be candidates for any future trials either at the University of Utah or at other institutions.

- *Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet):* CDC is working with researchers in Arizona, Colorado, Iowa, western New York State, and Georgia to set up surveillance systems for DMD and BMD. The goal of the project is to find all DMD and BMD patients in the areas by using information from different sources, such as clinic medical records and hospital records. Information about each child's treatments and how he is doing medically will be collected from his medical records. Because many patients who have DMD or BMD are seen in MDA clinics, the researchers are working closely with the MDA clinics in their States. In addition, the researchers will be searching for DMD and BMD patients through other neuromuscular clinics, emergency rooms, pathology laboratories, orthopedists, and other muscular dystrophy associations to ensure that all patients with DMD or BMD are included in the project. The States have worked together to come up with a common system that can be used to find patients and collect information. Families who are identified in these areas will be asked to participate in interviews with public health workers to provide information related to DMD and BMD that might not be found in the medical records.

  The types of information that will be collected include basic demographic information (such as race and ethnicity), the descriptions of treatments that have been received, the types of clinics that the care was received in, and any medical problems associated with DMD and BMD. The researchers will collect information from medical records and interviews on a regular basis.

  In April 2004, researchers began collecting information from medical records. The group has now developed and begun using a computer system for saving and combining the information collected and is developing an interview questionnaire. In Arizona, Colorado, Iowa, and New York, researchers began to pool de-identified data in FY 2005. Later in FY 2005, the State of Georgia, in collaboration with CDC intramural researchers, was added to the system. An independent quality assurance

and quality control (QAQC) system contract was also awarded to the Titan Corporation in order to provide independent QAQC. Although the CDC plans to add one additional State or geographic area to the system in order to achieve a sample that better reflects the racial/ethnic makeup of the general U.S. population, FY 2006 obligations did not allow for the addition of a State to MD STARnet. For FY 2007, the participating States will begin analysis of pooled data sets and will focus on methodology, prevalence and the use of steroids for treatment of DMD patients.

The MD STARnet project is intended to serve as a model and framework for future surveillance of other forms of muscular dystrophy. Since MD STARnet has only been operational for a short period of time and other current financial obligations and constraints are currently in place, the project at this time has not expanded to other forms of muscular dystrophy; but CDC has every intention of doing so when funding permits.

Also in FY 2005, CDC awarded a contract to Booz Allen Hamilton Corporation to possibly transform the database of MD STARnet into a clinical tool that will be useful for physicians and that will allow collection and pooling of data into a national registry.

- *CDC Activities on Newborn Screening for DMD:*

- *Early Screening and Diagnosis of DMD:* To further research on the issues identified by the Newborn Screening for Duchenne Muscular Dystrophy Workgroup, the NCBDDD at CDC announced funding under a cooperative agreement for research in both infant and newborn screening for DMD in FY 2004. Two research groups were awarded cooperative agreements in September 2004, one to the Children's Research Institute in collaboration with the Ohio Department of Health and another to Emory University in Georgia. The Children's Research Institute in Ohio will pilot newborn screening for DMD and evaluate the informed consent process in the birth hospital. Emory University, in collaboration with local pediatric practices, will pilot infant screening for DMD, assess the access to screening through small clinics, and evaluate the informed consent process in a pediatric clinic setting. In addition, both programs will determine the number of false-positive and false-negative screening results, the types of problems false-positive screening results can cause, how families go through the screening process, and how pediatricians and other clinicians feel about the screening program. In FY 2005, both groups validated laboratory methodologies for bloodspot screening for DMD. Both groups have made significant progress toward the development of a screening protocol in their States, including informed consent procedures. In addition, Emory University conducted focus groups with parents of children with DMD and with parents of unaffected infant males. Both groups were asked to provide feedback on the type of information parents need when deciding on DMD screening and potential informational materials to be used in the informed consent process. Brochures on early screening for DMD were developed based on input from these groups. In collaboration with both groups and with the National Center for Environmental Health Newborn Screening Quality Assurance Program, CDC program staff has developed a quality assurance

protocol for screening in both States. Other countries that offer DMD screening will also be invited to participate in the quality assurance program. Currently the infant and newborn screenings are scheduled to take place in the winter of 2006 and extend into 2007, at which point data analysis will occur.

- *Newborn Screening Decision Analysis:* Newborn screening for DMD and BMD offers both advantages and disadvantages. Parents of children with DMD or BMD often express an interest in newborn screening; however, it is not known if families of newborn males will also be interested. In FY 2005, CDC awarded a contract to Research Triangle International (RTI) to conduct literature reviews and focus groups to identify factors that parents may consider in making decisions about newborn screening. RTI will use these data to develop a survey-based method for evaluating how parents weigh the various decision-making factors. This information will help public health departments and policy makers to understand to what extent parents value the information obtained from newborn screenings. RTI has performed its preliminary work groups and is in the process of developing the evaluation tool, which is expected to be delivered to CDC in late 2006.

Therapy of Muscular Dystrophy

With the development of new technologies, the ability to obtain precise molecular diagnoses of disease, along with the joint efforts of academic researchers, industry, Federal agencies and nonprofit organizations, considerable opportunity and promise exist for the emergence of new, more effective therapies for the muscular dystrophies. Goals in this section of the Action Plan include optimizing the use of corticosteroids for the treatment of DMD, developing strategies to use growth factors to treat various forms of muscular dystrophy, and pursuing gene therapy and gene repair approaches to treatment. Identifying strategies to implement translational research projects for muscular dystrophy and expanding small molecule screening efforts are also identified goals. In addition, treatment for cardiopulmonary complications of muscular dystrophy are identified as additional priorities in this area. Since much is known about the underlying mechanisms of DMD compared to other forms of dystrophy, many of the goals in this section of the Action Plan are specifically relevant to DMD.

Progress toward goals:

- *NINDS Cooperative Program in Translational Research.* The NINDS sponsors a broad Cooperative Program in Translational Research to support milestone-driven projects focused on the identification and preclinical development of drugs, biologics, and devices in cells and animals, leading to new and effective interventions for any neurological disorder. As part of this program, NINDS has issued a series of program announcements to encourage applications for translational research conferences, single-component or multicomponent translational research projects, translational research resource centers, exploratory/developmental grants in translational research, small business awards in translational research, and mentored research scientist development awards in translational research.

The NINDS has already funded four projects relevant to muscular dystrophy through this program. One recently funded project is a study that focuses on the development of compounds known as protease inhibitors that may be capable of delaying muscle degeneration in a variety of types of muscular dystrophy. Specifically, the study aims to evaluate the protease inhibitor, leupeptin, in the treatment of DMD. Two other grants funded through the program focus on gene modification strategies to bypass mutations in the dystrophin gene and on combined gene modification and cell therapy approaches to treat DMD. A fourth funded grant is a major project that brings together a team of basic and clinical scientists to carry out the steps necessary to move gene therapy for DMD to readiness for clinical trials.

- *NIH Translational Research Initiatives in Muscular Dystrophy:* As a result of an evaluation of the state-of-the science, as well as numerous discussions with representatives from patient advocacy groups who stressed an urgent need for translational research in DMD, NIH recognized the need for a more targeted initiative to encourage translational research in the muscular dystrophies. In response, within the past year, NIH developed and released two PAs, with set-aside funds and a special grant application review environment for (1) "Exploratory/Developmental Program for Translational Research in Muscular Dystrophy" and (2) "Translational Research in Muscular Dystrophy." The purpose of these initiatives is to implement a broad-based translational research program that may lead to new and more effective treatments for all forms of muscular dystrophy. The details of this program are described on page 33 of this report.

  To date, NIH has funded one grant through this program. The project is focused on testing gene therapy delivery techniques for treatment of DMD in a large animal model of the disease. The overall program has been successful in soliciting therapeutic development proposals and bringing new investigators and novel therapy ideas into the field. A number of other applications are currently in the review process.

- *Clinical trials:* NIH has a number of clinical research activities in muscular dystrophy. NINDS funds ongoing clinical trials in muscular dystrophy. The first is a phase 2 clinical trial at the Columbus Children's Research Institute testing the drug gentamicin in "skipping over" or "read through" of the mutations in causative genes. This treatment is applicable for 10-15 percent of patients with DMD. The second is a trial at the Rochester Wellstone Center to test the drug IPlex (an IGF growth factor complex) in myotonic dystrophy patients. The dose escalation phase of this safety and feasibility trial is nearly completed with no serious adverse events. The next phase of the trial will test an optimal dose in myotonic dystrophy patients. NINDS also has funded a planning grant for development of the clinical trial protocol for a definitive, phase 3 trial to compare different corticosteroid regimens in DMD patients.

- *Studies at the Wellstone Centers:* Ongoing therapeutic efforts at the Wellstone Centers focus on a number of different classes of therapeutics. In the area of corticosteroids and anti-inflammatory drugs, the Wellstone Center at Children's National Medical Center is conducting a study of genetic modifiers of DMD progression and responsiveness to steroid therapy. Several projects are focused on modulating muscle growth factors and thereby enhancing the regenerative response of dystrophic muscle. These include a study at the University of Pennsylvania/Johns Hopkins University Wellstone Center on mechanisms of myostatin (a negative regulator of muscle growth) activation and the interaction between positive and negative regulators of muscle growth and the trial at the Rochester Wellstone Center of the drug IPlex. The Center at the University of Pennsylvania and Johns Hopkins University, in collaboration with investigators in the NINDS intramural program, is preparing to conduct a clinical trial on the use of a compound that blocks muscle protein degradation in the treatment of Duchenne muscular dystrophy.

  In the area of cell-based therapies, the Pittsburgh Wellstone Center is using mouse and dog models to evaluate factors influencing the efficacy of muscle stem cell transplantation for muscle disease, while the Iowa Wellstone Center is looking at embryonic stem cell transplantation approaches. There are a number of ongoing studies optimizing viral vector ("vehicle") approaches for gene delivery, including packaging shorter versions of the dystrophin gene into vectors and testing these in a dystrophic dog model and mouse model (Pittsburgh and Washington). The Washington Wellstone Center is also working to optimize the viral vectors and their delivery to muscle and serves as a resource to other researchers. The Pittsburgh Wellstone Center is planning for a viral vector-based safety trial in LGMD. A variety of other candidate therapies also are being studied at the Wellstone Centers, including muscle membrane repair strategies (Iowa) and inhibition of proteins that degrade muscle components (Pennsylvania/Johns Hopkins).

Living with Muscular Dystrophy

The muscular dystrophies are multisystem disorders, meaning that they affect many body systems. Individuals with muscular dystrophy experience not only the principal effects of muscle degeneration but also many secondary conditions, some of which are quite serious on their own. Thus, the individual's quality of life is affected not only by muscle weakness and loss of mobility but also by joint contractures, breathing disorders, cardiomyopathy, cognitive decline, and other complications. The research objectives in this section apply, in large part, to all forms of muscular dystrophy and include assessing the prevalence and natural history of secondary conditions in muscular dystrophy using existing longitudinal data collection efforts and evaluating the effectiveness of clinical management approaches to prevent and treat secondary conditions. In addition, patient and family education, such as through annual conferences, strategies to integrate patients into their communities and reduce social isolation, and improved management of patients with muscular dystrophy by their physicians are additional objectives outlined in this section.

Progress toward goals:

- *National Center for Medical Rehabilitation Research (NCMRR) at NICHD:* The NCMRR aims to foster development of scientific knowledge needed to enhance the health, productivity, independence, and quality-of-life of people with disabilities. Currently, NCMRR is supporting several projects related to muscular dystrophy through a number of funding mechanisms. Research topics include molecular remodeling of muscle in response to rehabilitation after immobilization, viral-mediated gene transfer to prevent disuse syndrome and accelerate restoration of function, and development of imaging methods to study loss and recovery of muscle strength and function.

- *Center for Developmental Biology and Perinatal Medicine (CDBPM) at NICHD:* As described earlier in this report, the Mental Retardation and Developmental Disabilities Branch located within the CDBPM supports research into cognitive disabilities in DMD and is interested in the nonskeletal manifestations of many of the muscular dystrophies. Areas of research interest also include nutrition and obesity in muscular dystrophy, and family and psychosocial issues such as effects on other family members.

- *DMD/BMD Best Practices Conference:* CDC will sponsor a conference to present best practices for treating patients with DMD or BMD, identify gaps in evidence for evidence-based medical practices, and develop care consideration guidelines for diagnosis and treatment of children with DMD or BMD. In 2005, CDC awarded a contract to Booz Allen Hamilton Corporation to provide technical and administrative support for planning this conference. CDC has also involved other MDCC agencies and organizations in the planning effort, including representatives from CDC, MDA, PPMD, NIAMS, and NINDS.

- *CDC Family Needs Assessments:* CDC is sponsoring two projects to identify the service needs of families of patients with DMD or BMD. The results of these projects will help health departments and health care providers understand the needs of families with DMD or BMD so that necessary resources can be identified.

  - *National Initiative for Families with Duchenne (NIFD):* CDC is working with researchers at the Children's National Medical Center in Washington, D.C., on a survey of parents of children with DMD or BMD in the United States and Puerto Rico. The researchers on this project plan to ask parents of children with DMD or BMD their experiences having a child with DMD or BMD, what services they are able to receive, what services they need, what problems they have in getting needed services, and their feelings about newborn screening for these disorders. The survey will include a large number of families from many backgrounds, and the results will help State health departments improve services for families with DMD or BMD. In addition, because some of the families in this survey were first diagnosed through pilot newborn screening projects, the researchers will find out whether newborn screening had an impact on how families deal with the condition, use of services, and quality of life. In addition, clinic directors will be surveyed about the services that are provided in their

areas. This information will help State health departments that are considering the use of newborn screening for these disorders in the future. Survey mailing began in spring 2006.

- *Needs of Families and Patients with Muscular Dystrophy (NFPMD):* CDC is working with researchers at the University of Iowa on a project to identify the needs of families with DMD and childhood-onset BMD. The researchers are talking with families in Iowa who have a member with DMD or BMD. The goals of the project are to identify and rank the needs of patients and families with DMD and childhood-onset BMD at different stages in their lives, identify factors that can affect whether families can get needed services and resources, find out how a diagnosis of DMD or childhood-onset BMD affects the patient and his immediate family, and determine how the family feels about newborn screening.

- *CDC's Palliative Care and Hospice Needs of Families with Children with DMD:* Palliative care is comprehensive care offered to a person with a progressive illness and his or her family, with the goals of improving quality of life and the easing of symptoms. Palliative care also includes the end-of-life care that is more often found with hospice care. Unofficial reports indicate that males with DMD and their families are less likely to use palliative care and hospice services than families with children with other conditions that result in premature death. The two main goals of this CDC project are to identify the palliative care and hospice needs of males with DMD and their families and to identify the barriers that individuals and their families face in considering, seeking, or obtaining palliative and hospice care. This project has been awarded to the researchers within MD STARnet.

- *CDC Project on Health Care Issues for Hispanic Families with DMD:* Hispanic families of children with special health care needs face specific barriers to services and care. This study will help to gain insight into the need for and barriers to services faced by Hispanic families of children with DMD. One focus group with seven to nine individuals was conducted in Spanish in August 2004. A report is available on the CDC Web site. The information gathered from this initial project will be used to help develop future projects on this topic.

- *CDC's Project on Cardiac Health in Female Carriers of DMD:* Females can be carriers for DMD and BMD, which means they will have one copy of the gene associated with the disorder, but they do not usually develop muscular dystrophy. Females who are carriers sometimes have heart problems that leave them short of breath or unable to do moderate exercise later in adult life. The chance that a female carrier will develop heart problems is not known. However, such heart problems can be serious and life threatening. While there is no cure, there are a number of medications that might help reduce the effects of these heart problems. This project will use a large-scale, mailed, self-completed survey to collect information about what female DMD carriers know about cardiac health care and how they act based on this information. The survey will be mailed to about 7,000 women who are on MDA or PPMD mailing lists or are known by someone on one of the lists. Women will be

eligible to complete the survey if they are at least 19 years old and have given birth to a son with DMD/BMD or been told that they definitely or probably carry a genetic change that causes DMD/BMD. The objectives of this project are to find out what factors affect the use of preventive measures related to cardiac health in female carriers of DMD and to develop new and workable plans to increase preventive cardiac health care in this population.

Information from this survey will be used to develop public health messages about cardiac health specifically to DMD carrier females. It is likely that the results of this study can also be used to improve health messages to carriers of other X-linked conditions. The survey was instituted in the summer of 2006 and preliminary data analysis has been performed. The final report is expected to be delivered to CDC in the coming months.

- *Single Gene Resource Center:* On July 19, 2005, CDC issued a request for proposals for a cooperative agreement to develop a national resource network for single gene disorders. Initial funding will support projects related to DMD/BMD and Fragile X syndrome. The proposed national network will have the capacity to expand to other single gene disorders. The cooperative agreement was awarded to the Genetic Alliance in September 2005. CDC staff will work closely with both the Genetic Alliance and PPMD to ensure that education and outreach activities related to DMD/BMD are coordinated with each other and with other federally-funded projects. Genetic Alliance and its partners will continue their work on developing the resource center through FY 2007.

- *PPMD Outreach Project:* In accordance with congressional intent, CDC will award funding to PPMD in FY 2007 to develop and disseminate educational materials related to DMD and BMD to a diverse audience through multiple media. Target audiences may include the general population, primary care providers, teachers, and peers of boys with DMD or BMD.

- *Care Considerations and Single Gene Information Project:* CDC awarded a contract to Booz Allen Hamilton to support the agency's effort to develop clinical care considerations for the treatment of DMD. Using the RAND/UCLA appropriateness methodology, CDC will be working with experts from around the world to develop a comprehensive clinical care consideration for the treatment of DMD. CDC expects that the panel will convene in the spring of 2007. In addition, through the same contract, Booz Allen Hamilton is helping CDC work with key external stakeholders to develop new systems of data collection for DMD. The project is intended to receive data from multiple sources, including but not limited to electronic medical records and patient registries. The work is an effort to facilitate the gathering of a national sample of data for DMD patients in order to better describe the epidemiological features of DMD and the care of DMD patients.

Research Infrastructure Needs for Muscular Dystrophy

Research infrastructure transcends the other topics addressed in the Action Plan in that it includes those resources that would facilitate the accomplishment of many of the other research objectives identified throughout the Action Plan and enhance ongoing and future research efforts in all of the muscular dystrophies.

Objectives in this section focus on both preclinical and clinical research infrastructure, including the development of optimized models for therapeutic development screens and high throughput drug screens, the maintenance and rapid and easy distribution of mouse models of muscular dystrophy, and the development of standardized instruments to measure quality of life and cognitive function and rehabilitation assessment activities.

Research infrastructure needs apply not only to the actual research tools but also to other resource needs. For example, developing tools such as a Web site to list all available resources; organizing small, focused research meetings with a clear agenda and requirement for specific outcomes; and increasing the number and scientific breadth of basic scientists and clinicians involved in translational research in the muscular dystrophies through training activities are all identified objectives in this section.

Progress toward goals:

- *Wellstone Center Cores:* Each of the Wellstone Centers has core facilities that are available to other investigators as a national service. Access to some of these resources requires the establishment of collaborations, and some are available through a fee-for-service arrangement. The availability of these cores has been publicized at national meetings and through the Web sites that five of the Centers have established. Cores at the Washington Wellstone Center support viral vector development and optimization of gene-delivery strategies. The Pittsburgh Wellstone Center cores support imaging capabilities, development of gene therapy approaches, and a muscular dystrophy dog colony. The Rochester Wellstone Center core comprises the myotonic dystrophy/FSHD Registry (described below). A muscle biopsy and cell culture repository at the Iowa Wellstone Center serves as another resource to the muscular dystrophy community. This core is also developing important expertise on human embryonic stem cell transplantation. The Pennsylvania/Johns Hopkins Wellstone Center physiological assessment core is designed to aid therapeutic development using mouse models of muscular dystrophy through analysis of both isolated muscle mechanics and whole animal functional testing. The Wellstone Center at Children's National Medical Center houses a bioinformatics and computing core. It also serves as the coordinating center for the Cooperative International Neuromuscular Research Group (CINRG), which runs clinical trials in muscular dystrophy.

- *Myotonic Dystrophy and FSHD Registry:* Since September 2000, the NIAMS and NINDS have supported the National Registry of Myotonic Dystrophy and Facioscapulohumeral Dystrophy Patients and Family Members, a resource for the

collection and analysis of clinical information from patients and their families to accelerate the advance of research on these diseases. NIH recently renewed support for the registry for an additional five years. The long-term goal of the registry is to facilitate research in FSHD and myotonic dystrophy by serving as a liaison between families affected by these diseases who are eager to participate in research and investigators who are conducting specific projects relevant to these disorders. The registry, based at the University of Rochester, recruits and classifies patients and stores medical and family history data for individuals with clinically diagnosed FSHD and myotonic dystrophy. Genetic information is collected on individuals who provide their molecular diagnosis. The registry provides statistical analysis of the data, as well as access to the registry data for investigators with approved projects. The national registry serves as a resource for scientists seeking a treatment for these diseases, in addition to enhancing research to understand the mechanisms that cause muscular dystrophy. To date, ten research projects have utilized data from the registry.

- *Wellstone Fellowships:* As mentioned earlier (see page 13), NIH offers administrative supplements to the Wellstone Centers to support career development of junior investigators affiliated with the Centers. To date, NIH has awarded four fellowships to highly meritorious candidates to help advance their careers as basic and clinical scientists working in the muscular dystrophy field.

- *Program Announcements on Training in Muscle Disease Research*: The Action Plan highlights a need for training of basic and clinical researchers to facilitate the development of therapies for the muscular dystrophies. Two program announcements released by NIH encourage training of scientists in muscle disease research. The first, "Ruth L. Kirschstein National Research Service Awards for Postdoctoral Fellowships in Muscle Disease Research," encourages postdoctoral fellows with diverse scientific interests to apply their expertise to enhance our understanding of the pathogenesis and treatment of muscle diseases and disorders, including DMD and other dystrophies. Prior experience in muscle disease or muscle biology research is not necessary, provided that the mentor/sponsor has appropriate expertise. The NIH encourages applicants to develop innovative and novel approaches for studying and treating these diseases. The NIH issued the second, "Mentored Clinical Investigator Career Development Awards in Muscle Disease Research," in recognition of the urgent need for highly skilled, interactive researchers who are able to integrate various disciplines and levels of expertise to successfully address the increasing challenges in the current research environment of muscular dystrophy and other muscle diseases. This announcement calls for applications for mentored career development awards for clinical scientists engaged in laboratory or patient-oriented research. The NIH expects that these career development programs will increase the number of investigators in basic, translational, and clinical research on muscular dystrophy and other muscle diseases and will also increase the quality of their research and training.

- *Workshop*: *Muscle Study Group:* The NIH provided conference grant support for the Muscle Study Group, an organization centered out of the University of Rochester to promote clinical trials in neuromuscular disease, including the muscular dystrophies. The NINDS planning grant for a corticosteroid trial in DMD is being run under the auspices of the Muscle Study Group.

- *Workshop: Second New Directions in Biology and Disease of Skeletal Muscle:* NIH and the MDA, together with leading muscle researchers, organized a conference entitled "Second New Directions in Biology and Disease of Skeletal Muscle," which was held April 23-26, 2006, in Dallas. The purpose of this conference was to bring together researchers who focus on different aspects of muscle diseases since the lack of a centrally focused meeting was an impediment in understanding and treating important muscle diseases. This is only the second national meeting with a focus on the functions and disorders of skeletal muscle. The goal of the 2006 conference was to facilitate research progress and information exchange in the basic biology of muscle and therapeutics for muscular diseases. The conference attracted clinical and basic researchers and provided an excellent forum for them to interact and share ideas and advance the field of muscular dystrophy and other muscle disease research. NINDS, NIAMS, the NIH Office of Rare Diseases, and the MDA provided support for the conference. This conference is now planned to occur every two years, with the next meeting scheduled for April 2008. The conference will retain the focus on cellular and molecular aspects of skeletal muscle as they relate to health, disease and dysfunction.

- *Workshop: High-Throughput Drug Screening in Muscular Dystrophy*: In April 2006, NICHD, along with NIAMS, NINDS, and the NIH Office of Rare Diseases, co-funded a workshop at the Children's National Medical Center. This two-day workshop brought together leaders in the field of high-throughput screening from both academic and pharmaceutical laboratories to discuss the possible approaches to high-throughput screening of small molecules for therapy of muscular dystrophy. Both animal- and cell-based models and facilities, as well as the libraries and existing approaches for screening small molecules, were topics of discussion. This successful workshop was attended by an international and multi-agency group of experts. The workshop was the first in a new series of conferences that are supported by administrative supplements to the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers. Conclusions of the workshop included that substantial high-throughput screening resources are available, both in academia (supported by NIH and DOD) and industry, with opportunities for collaborations; that there are several screens under way focusing on a number of promising targets for therapy development in muscular dystrophy; and that additional novel, robust, and physiologically relevant assays are needed.

NIH and CDC Muscular Dystrophy Research Funding

Beginning with FY 2004, NIH began reporting spending broken down by three types of muscular dystrophy—DMD/BMD, FSHD, and myotonic dystrophy—as required by the MD-CARE Act. These categories are only part of the overall total of muscular dystrophy spending at NIH. The total muscular dystrophy number includes these three categories as well as projects focused on other forms of muscular dystrophy and projects applicable to the muscular dystrophies in general. The funding amounts for fiscal years 2005 through 2007 are listed below.

NIH Funding for Muscular Dystrophy			
Type	**Dollars in millions**		
	FY 2005 (actual)	FY 2006 (actual)	FY 2007 (estimate)
DMD/BMD	$ 17.1	$ 17.8	$ 16.0
FSHD	$ 2.0	$ 1.7	$ 1.7
Myotonic dystrophy	$ 6.4	$ 6.6	$ 6.1
Muscular dystrophy (total)	$ 39.5	$ 39.9	$ 39.9

CDC was appropriated $4.5 million (enacted amount) for muscular dystrophy research (all of which is devoted to Duchenne and Becker muscular dystrophy) in FY 2004. In FY 2005, CDC was appropriated $5.9 million (enacted amount), and the enacted funding for FY 2006 was $6.4 million. Current estimates project CDC appropriations of $6.4 million for FY 2007.

Translational Research in Muscular Dystrophy

Translational research is the process of applying ideas, insights, and discoveries generated through basic scientific inquiry to the treatment and prevention of human disease. Translational research includes preclinical studies to test potential therapies and bring them to readiness for clinical trials. Currently, no treatment can stop or reverse the progression of any form of muscular dystrophy. Although research has identified genetic and pathogenic mechanisms underlying DMD, as well as several of the other muscular dystrophies, the translation of basic research into effective therapies has been slow. Based on a better understanding of the disease mechanisms at play in the muscular dystrophies, there are now multiple potential pathways to therapeutic development. These include:

- *Developing drug-based therapies to maintain muscle mass.* Debilitating loss of muscle is characteristic of muscular dystrophy as well as other muscle disorders. Loss of muscle mass and function is primarily responsible for reduced quality and length of life. In the absence of a cure, drug treatment strategies may be able to inhibit the breakdown of muscle proteins.

- *Developing strategies to enhance the normal regenerative process of muscle.* Many muscular dystrophies share traits of progressive depletion of skeletal muscle regeneration and repair mechanisms. Applying knowledge of regeneration mechanisms may provide new therapeutic targets to offset muscle degeneration.

- *Developing cell-based muscle therapeutic strategies.* In muscular dystrophies due to inherited mutations in the dystrophin-glycoprotein complex, muscle degeneration results from the absence of key membrane-associated proteins. It may be possible to use stem cells to populate diseased skeletal and cardiac muscles with muscle fibers that express the absent proteins. These newly formed muscle fibers may be protected from the progressive degeneration characteristic of the disease and potentially restore muscle function in patients.

- *Developing, testing and improving strategies for gene replacement therapy.* Many of the dystrophies result from point mutations or deletions in identified genes or genetic regions. Gene or drug therapy strategies may replace the defective gene or increase expression of functionally equivalent genes that may compensate for the defective gene.

- *Developing and testing genetic modification therapies to bypass inherited mutations.* Some muscular dystrophy patients have mutations that cause gene product synthesis to terminate early, producing either no protein or defective protein. Several strategies including molecular drug and antisense exon skipping strategies can manipulate the steps leading to protein synthesis mechanisms in order to skip or "read-through" the defect in the gene. These strategies may allow diseased muscle to produce enough functional protein from the mutated gene to decrease or reverse the degeneration process.

- *Developing combination therapies that rely upon more than one of the strategies listed above to produce a more effective treatment than any single strategy provides.*

Overview of NIH Activities in Translational Research in Muscular Dystrophy

NIH currently supports many of the approaches to therapeutic development outlined above through investigator-initiated research projects, the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, and other programs, many of which have already been mentioned in this report. In addition, NIH has developed and issued two translational research initiatives targeted specifically at encouraging translational research in muscular dystrophy.

- *Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers.* As described earlier in this report (see page 12), the NIH funds six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, which have been designed to accelerate the translation of fundamental scientific advances to the clinic through close interaction between basic researchers and clinicians. Translational research projects at the Wellstone Centers are focused on optimizing gene therapy and stem-cell-based therapeutic approaches as well as identifying therapeutic strategies to enhance muscle regeneration mechanisms. The research cores at a number of the Wellstone Centers support translational research efforts as well.

- *Program Announcement: "Muscular Dystrophy: Pathogenesis and Therapies."* This PA is also described on page 16 of this report. Translational grants funded as a result of the 2001 issue of this announcement include a number of projects designed to advance treatment interventions for muscular dystrophy. For example, studies are aimed at improving gene therapy for DMD, including optimizing the delivery vector (vehicle) and improving vector delivery methods. Genetic rescue studies in animals funded under this program announcement include *in utero* gene therapy and *in utero* delivery of muscle progenitor cells containing an intact copy of the dystrophin gene. Another study focuses on developing gene modification technologies to promote exon skipping, or "read-through" of mutated genes. An additional grant studies the mechanisms for turning on a gene that represents an alternative to dystrophin, utrophin. Finally, this program announcement has facilitated development of the methodology to rapidly, robustly, and economically analyze mutations in the dystrophin gene, allowing the identification of patients that are best suited for specific gene therapy or repair strategies. As mentioned previously, NIH re-issued this initiative in January 2005 and has since funded nine additional studies. These include grants to explore the role of gene mutations in muscle structural proteins in muscle disease, to study immune tolerance to muscle cell therapy, to understand the molecular mechanisms of myotonic dystrophy, to screen for small molecules that may enhance muscle membrane repair, to evaluate the potential for glycosyltransferase (an enzyme involved in some forms of muscular dystrophy) therapy, to assess the role of the cell death pathway in muscular dystrophy, to examine dystrophin exon structure in the context of facilitating genetic modification strategies, to study the causes of dystrophy related cardiomyopathy, and to assess the role of the enzyme calpain in LGMD.

- *NINDS Cooperative Program in Translational Research.* The NINDS sponsors the broad Cooperative Program in Translational Research to support milestone-driven projects focused on the identification and preclinical development of drugs, biologics, and devices in cells and animals, leading to new and effective interventions for any neurological disorder. As part of this program, NINDS has issued a series of program announcements to encourage applications for translational research conferences, single-component or multicomponent translational research projects, translational research resource centers, exploratory/developmental grants in translational research, small business awards in translational research, and mentored research scientist development awards in translational research.

The NINDS has already funded four projects relevant to muscular dystrophy through this program. One recently funded project is a study that focuses on the development of compounds known as protease inhibitors that may be capable of delaying muscle degeneration in a variety of types of muscular dystrophy. Specifically, the study aims to evaluate the protease inhibitor, leupeptin, in the treatment of DMD. Two other grants funded through the program focus on gene modification strategies to bypass mutations in the dystrophin gene and on combined gene modification and cell therapy approaches to treat DMD. A fourth funded grant is a major project that brings together a team of basic and clinical scientists to carry out the steps necessary to bring gene therapy for DMD from the stage of the ongoing single muscle injection trial to clinical trials delivering gene therapy to all muscles in an arm or leg. Development of the isolated limb delivery approach not only represents an important, and necessary, intermediate step on the way to whole body gene therapy, but improving individual limb function, in and of itself, is an important goal to the patient community as it can aid walking or arm/hand functions, such as computer use by DMD patients.

NIH Translational Research Initiatives in Muscular Dystrophy

The activities described above have helped to significantly advance translational research in the muscular dystrophies, and ongoing efforts through these programs will continue to stimulate the translation of basic research into potential therapies. However, as a result of an evaluation of the state-of-the science, as well as numerous discussions with representatives from patient advocacy groups who stressed an urgent need for translational research in DMD, NIH recognized the need for a more targeted initiative to encourage translational research in the muscular dystrophies. In response, the NIH developed and released two PAs, with set-aside funds and a special grant application review environment, for (1) "Exploratory/Developmental Program for Translational Research in Muscular Dystrophy" and (2) "Translational Research in Muscular Dystrophy."

As mentioned earlier (see page 22), the purpose of these initiatives is to implement a broad-based translational research program that may lead to new and more effective treatments for muscular dystrophy. These initiatives encourage translational research in all forms of muscular dystrophy, since understanding and treating one form of muscular dystrophy will likely apply to other forms as well. This program has two components: exploratory/developmental research projects and cooperative agreements. Exploratory/ developmental projects will develop the tools and resources necessary for the subsequent conduct of a translational research program. Examples include the identification of targets for therapeutic intervention, the development of assays that permit preliminary screening of candidate therapeutics, and the development of tools and technologies that can be directly used for therapy development. Cooperative agreements are milestone-driven projects that focus on the identification and preclinical testing of therapies suitable for one or more of the muscular dystrophies. As part of the cooperative agreement, the NIH staff works closely with the applicant to help develop and guide the project. To ensure that grants are reviewed by individuals with the appropriate expertise, the NINDS

convenes a special review panel made up of scientists with the highly specific expertise necessary to review applications received through this program. Collectively, the milestone-driven design, preapplication consultation with NIH program staff and special review environment constitute a comprehensive program to facilitate translational research in the muscular dystrophies.

NIH has awarded the first grant through this program. The project focuses on testing gene therapy techniques for treatment of DMD in a large animal model of the disease. A number of other applications are currently in the review process.

Workshop on Translational Research

The muscular dystrophy community has held a number of recent workshops to discuss the different approaches to and issues surrounding translational research in the muscular dystrophies. For example, MDA has convened two recent meeting relevant to translational research: the Clinical Research Network Exploratory Meeting in the summer of 2004 and the meeting "Challenges in Drug Development for Muscle Disease" in the summer of 2005. Information on both of these meetings can be found at: http://www.mdausa.org/research/trac/trac_meetings.cfm. In addition, the meeting of the MDCC on November 9, 2005, served as a forum to discuss translational research in the muscular dystrophies. Representatives from MDCC member organizations, including the NIH, Parent Project Muscular Dystrophy, the MDA, and the DOD, described in detail the translational research programs in muscular dystrophy at these agencies and organizations. Discussions at the meeting focused on the progress and future opportunities related to various approaches to therapeutic development for muscular dystrophy. These meetings provided valuable information that helped to shape the initiatives and other programs recently launched by NIH.

Building on these recent activities, the NIH is planning the Workshop on Translational Research in Muscular Dystrophy for June 2007. This meeting will be held back-to-back with the spring MDCC meeting, thereby encouraging the active participation by MDCC member organizations in the workshop and fostering better coordination of efforts of the various agencies and organizations. The meeting will serve as a forum to discuss and evaluate progress toward identifying the best strategies for therapy development and promising areas in therapeutic development.

Conclusion

Since the MD-CARE Act became law in December 2001, NIH has been actively implementing the provisions of the Act and has engaged in many other activities to enhance muscular dystrophy research. NIH now funds six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, which serve as national centers for basic, translational, and clinical research in the muscular dystrophies. The MDCC's "Action Plan for the Muscular Dystrophies" is serving as a comprehensive plan for the entire muscular dystrophy community, and implementation of many of the goals in the Plan are under way by NIH and CDC and their partner agencies and organizations on the

MDCC. The need for translational research in the muscular dystrophies is stressed in several of objectives of the Action Plan and is also addressed by a number of current and planned activities at NIH including two recently released initiatives focused on translational research in muscular dystrophy and a workshop on translational research, which is being planned for June 2007.