

NIH Centers of Excellence

Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers

Overview

Why the Wellstone MDCRCs Were Established

The Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 (the MD-CARE Act, Pub. L. No. 107-84) included provisions for expanding and intensifying research on muscular dystrophy and mandated that NIH establish Centers of Excellence for muscular dystrophy research. Congress designated the centers as the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (Wellstone MDCRCs) in the Omnibus Appropriations for FY 2004 (Public Law 108-199) in honor of the former Minnesota senator who was a driving force behind the MD-CARE Act. The MD-CARE Act of 2008 officially renamed the centers.

How the Wellstone MDCRCs Function within the NIH Framework

NIAMS, NINDS, and NICHD fund the Wellstone MDCRCs through the U54 Specialized Centers Cooperative Agreement award mechanism (see Table 4-3). NHLBI also has co-sponsored the two most recent competitions for Wellstone MDCRCs and plans to support projects within future Wellstone MDCRCs if NIH receives fundable applications that address NHLBI's mission.

A Steering Committee, consisting of directors and co-directors of each center and NIH science officers, coordinates the Wellstone MDCRCs' scientific program. Through annual meetings and regular conference calls, the Steering Committee promotes collaborations among center investigators and makes strategic decisions about Wellstone MDCRC goals and activities, including standardization of operating procedures.

Description of Disease or Condition

The muscular dystrophies are a group of more than 30 genetic diseases characterized by progressive degeneration of skeletal muscles. Many dystrophies also affect other organ systems such as the heart, blood vessels, and gastrointestinal tract (stomach and intestines). Some forms occur in infancy or childhood, whereas others usually do not appear until middle age or later. The Wellstone MDCRCs address, but are not limited to, the following conditions.

- **Duchenne and Becker Muscular Dystrophies.** Duchenne muscular dystrophy (DMD) is the most common childhood form of muscular dystrophy. An X-linked recessive disease (related to genes carried on the X chromosome), it primarily affects males who inherit a genetic mutation from their mothers. Boys who have DMD lack the protein dystrophin, which muscle cells need to function properly. DMD usually becomes evident when a child begins walking. Patients typically require a wheelchair by age 10 to 12 and die in their late teens or 20s. Becker muscular dystrophy (BMD), a less severe disease, occurs when the body produces a form of dystrophin that does not work properly.

- **Myotonic Dystrophy.** Myotonic dystrophy is the most common adult form of muscular dystrophy, although forms of this disease can affect newborns and other children. It is marked by myotonia (an inability to relax muscles after they contract) and muscle wasting and weakness. Myotonic dystrophy varies in severity and symptoms. It can affect body systems in addition to skeletal muscles, including the heart, endocrine organs (organs that release hormones, or substances that affect cell function in another part of the body, into the bloodstream), eyes, and gastrointestinal tract.
- **Facioscapulohumeral Muscular Dystrophy (FSHD).** FSHD initially affects muscles of the face (facio), shoulders (scapulo), and upper arms (humeral). Symptoms usually develop in the teenage years. Some affected individuals become severely disabled. Wasting of muscles of the trunk can lead to life-threatening breathing complications.
- **Limb-Girdle Muscular Dystrophies (LGMDs).** All LGMDs show a similar distribution of muscle weakness, affecting both upper arms and legs. Scientists have identified many forms of LGMDs; some affect children, whereas others affect adults.
- **Miyoshi Myopathy.** Miyoshi myopathy causes initial weakness in the calf muscles. It is caused by defects in the same gene that is responsible for one form of LGMD, suggesting that research progress against one form of muscular dystrophy could lead to a better understanding of other forms as well.

Currently, no treatment can stop or reverse the progression of any form of muscular dystrophy. Treatments such as physical therapy, use of appliances for support, corrective orthopedic surgery, and drugs can reduce symptoms and improve quality of life for some individuals. Some drugs, such as corticosteroids, can slow the progression of DMD to some extent but have adverse effects. Several treatments, including gene therapy, cell-based treatments, and strategies to reduce muscle wasting have shown promise in experiments using cells and animals. Clinical trials of some therapies have begun, including the use of drugs to reduce muscle damage, approaches to increase muscle mass by stopping the activity of other proteins that inhibit muscle growth, and strategies to bypass mutations that cause disease.

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Burden of Illness

DMD and BMD affect 1 in 3,500 to 1 in 5,000 boys. With more than 4 million annual births in the United States, about 400 to 600 boys are born with DMD or BMD every year.¹⁶ Myotonic dystrophy affects approximately 1 in 8,000 people worldwide,¹⁷ whereas FSHD affects approximately 1 in 20,000 people and affects men and women equally.¹⁸

The MD-CARE Act called for the Centers for Disease Control and Prevention (CDC) to collect and analyze information on the number, incidence, correlates, and symptoms of individuals with muscular dystrophy. Recently published results from the project described the delay between the start of symptoms and definitive diagnosis of DMD.¹⁹

¹⁶ For more information, see www.cdc.gov/ncbddd/duchenne/who.htm.

¹⁷ For more information, see <http://ghr.nlm.nih.gov/condition=myotonicdystrophy>.

¹⁸ For more information, see www.nlm.nih.gov/medlineplus/ency/article/000707.htm.

¹⁹ [Ciafaloni E, et al. J Pediatr 2009;155\(3\):380-5. PMID: 19394035.](#)

Scope of NIH Activities: Research and Programmatic

As nationally recognized Centers of Excellence in muscular dystrophy, the Wellstone MDCRCs promote communication and collaboration, develop and share research resources, and help train new muscular dystrophy researchers. Each center can conduct a mixture of basic research to understand the diseases, translational research to turn basic research findings into interventions for patients, and clinical studies to test interventions in people. The overall focus of the Wellstone MDCRCs is to integrate activities to develop therapies for muscular dystrophies. In 2008, NIH funded two new Wellstone MDCRCs and renewed one that had received funds from the original competition in FY 2003.

Collectively, the Wellstone MDCRCs conduct research on various forms of muscular dystrophy, including some not listed above. Examples of research topics addressed by the Wellstone MDCRCs in FY 2008 and FY 2009 follow.

- The **University of Pittsburgh** center, for which funding ended in FY 2009, focused on developing gene therapy techniques, as well as research on muscle stem cells as potential therapies for DMD.
- At the **University of Rochester** center, researchers are examining cellular and molecular factors that contribute to myotonic dystrophy and testing potential treatments.
- The **University of Washington** center, for which funding ended in 2009, focused on developing gene therapy techniques for DMD and studying the processes that lead to FSHD.
- Ongoing research at the **Children's National Medical Center** focuses on genetic and cellular factors that contribute to DMD's progression and patient responses to treatment.
- Research at the **University of Iowa** center focuses on gene and stem cell treatments for DMD, LGMDs, and other muscular dystrophies.
- Ongoing research at the **University of Pennsylvania** and **Johns Hopkins University** center focuses on improving muscle growth or slowing muscle deterioration. In the future, researchers may be able to use these approaches to treat several kinds of muscular dystrophies and other disorders.
- Established in FY 2008, the **Boston Biomedical Research Institute** center seeks to identify biomarkers and is conducting a clinical trial of a potential FSHD therapy. In FY 2009, the center received funding through the American Recovery and Reinvestment Act of 2009 (ARRA) to accelerate collection and study of multiple biopsies.
- Established in FY 2008, the **University of North Carolina at Chapel Hill** center is developing and testing gene therapies for DMD and other muscle disorders.

Each Wellstone MDCRC has core facilities that provide unique resources or services for the muscular dystrophy research community. Cores include repositories of research data and biologic resources from patients with different types of muscular dystrophy, assistance with gene therapy development and production, and a data-coordinating site for clinical trials conducted by the Cooperative International Neuromuscular Research Group (CINRG). The Wellstone MDCRC program also contributes to therapy development by supporting the National Center for Canine Models of Duchenne Muscular Dystrophy and a facility at the University of Pennsylvania that tests mice for muscular dystrophy investigators.

NIH Funding for FY 2008 and FY 2009

Actual NIH funding for the Wellstone MDCRC program was \$9.9 million in FY 2008 and \$9.3 million in FY 2009, including \$406,000 from ARRA funds.

FY 2008 and FY 2009 Progress Report

Programmatic Activities and Outcomes

Programmatic accomplishments in FY 2008 and FY 2009 include establishing new Wellstone MDCRCs at the Boston Biomedical Research Institute and the University of North Carolina at Chapel Hill in FY 2008. In addition, the Wellstone MDCRC at the University of Rochester competed successfully for renewal through FY 2013. The two other centers funded under the first Wellstone competition (University of Pittsburgh and University of Washington) ended their formal center programs in FY 2009. However, many of these centers' investigators continue to conduct muscular dystrophy research with support from other grants. Moreover, these universities still are eligible to compete for future Wellstone MDCRC grants.

In 2005 and 2006, NIH invited junior investigators from the Wellstone MDCRCs to apply for Wellstone fellowships, which support salary and some research expenses.²⁰ In FY 2008 and FY 2009, fellowship recipients published articles in high-quality journals; one left the center to establish a muscular dystrophy research program at a new institution; and another received an independent NIH research grant. Because training and career development is an important component of the Wellstone MDCRC program, all centers funded under the Wellstone MDCRC FY 2008 or FY 2010 competition will have formal training and education core facilities. These facilities will provide stipends to predoctoral and postdoctoral researchers and enhance the programs' educational environments.

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The Wellstone MDCRC program has enhanced public-private partnerships in muscular dystrophy. Projects have involved collaborations with, and additional support from, companies such as PTC Therapeutics, Acceleron Pharma, and Insmed. The centers also have strong ties with patient advocacy groups, including the Muscular Dystrophy Association, Parent Project MD, the FSH Society, Inc., the Jain Foundation, and the Foundation to Eradicate Duchenne, Inc. These organizations provide additional support for center research projects. The synergy created by NIH resources and the involvement of industry and advocacy groups is accelerating progress toward muscular dystrophy treatments.

In FY 2008, the NIH Wellstone MDCRC program, the NIH Office of Rare Diseases, the Foundation to Eradicate Duchenne, Inc., and the European organization TREAT-NMD hosted two workshops.²¹ The goal of these workshops was to develop standard protocols for DMD treatment studies in mice and dogs. By adopting standardized protocols, investigators will be better able to compare results from different studies. Moreover, the outcomes will greatly accelerate treatment testing in animals.

The Wellstone MDCRC core facilities are national resources for the muscular dystrophy community. These facilities have been publicized at national meetings and through center websites and the [Wellstone MDCRC](#) website. These shared research tools foster collaborations across departments or schools within institutions and among investigators and health care providers nationwide. Examples of these facilities follow.

- The University of Rochester established the **Repository and National Registry of Myotonic Dystrophy Patients and Family Members** when NIH renewed the center's funding in FY 2008. The facility, a combination of the center's existing Tissue Repository Core and the NIH-funded Registry of Myotonic Dystrophy Patients and Family Members, provides researchers with cell or tissue samples and clinical information about the donors of these samples. This resource has facilitated two publications in 2008, advancing understanding of sleep disturbances²² and chronic pain²³ in these patients.
- The University of Iowa's **Muscle Tissue/Cell Culture/Diagnostics Core** maintains a muscle tissue repository of well-characterized samples from a spectrum of muscular dystrophy types. The core

continues to expand its repertoire of diagnostic services that are not readily available through clinical laboratories. Accomplishments in 2009 include contributions to a genetic test for a mutation associated with congenital muscular dystrophy in the Ashkenazi Jewish population.²⁴

- The MDCRC at the University of North Carolina at Chapel Hill launched the **National Vector Muscular Dystrophy Core** in FY 2008. The Core is producing and testing gene therapy materials for researchers.²⁵ As tests are completed successfully, the facility will supply investigators with materials that they can use for clinical research. The core also will help investigators submit documents to regulatory agencies (such as the U.S. Food and Drug Administration) and comply with all relevant regulations. In FY 2009, the center successfully competed for supplemental ARRA funding to purchase additional laboratory equipment.
- The **Physiological Assessment Core** at the University of Pennsylvania evaluates muscle integrity and function for center investigators and other academic and industrial researchers. The facility's experienced staff conduct measurements that now are the standard for showing whether a new treatment is effective in animals. Accomplishments in FY 2008 and 2009 include contributions to papers on muscle function in models of FSHD²⁶ and DMD.²⁷

²⁰ For more information, see <http://grants2.nih.gov/grants/guide/notice-files/NOT-AR-05-001.html>.

²¹ [Nagaraju K, et al. *Neuromuscul Disord* 2009;19\(7\):502-6. PMID: 19560356. PMCID: PMC2766092.](#)

²² [Ciafaloni E, et al. *Neurology* 2008;70\(3\):226-30. PMID: 18195268.](#)

²³ [Jensen MP, et al. *Arch Phys Med Rehabil* 2008;89\(2\):320-8. PMID: 18226657.](#)

²⁴ [Chung W, et al. *Prenat Diagn* 2009;29\(6\):560-9. PMID: 19266496. PMCID: PMC2735827.](#)

²⁵ [Li C, et al. *J Virol* 2009;83\(13\):6817-24. PMID: 19369348. PMCID: PMC2698563.](#)

²⁶ [Daniels DW, et al. *Arch Oral Biol* 2008;53\(2\):187-92. PMID: 18028868. PMCID: PMC2262833.](#)

²⁷ [Millay DP, et al. *Nat Med* 2008;14\(4\):442-7. PMID: 18345011. PMCID: PMC2655270.](#)

Research Activities and Outcomes

The Wellstone MDCRCs conduct basic, translational, and clinical studies related to a variety of muscular dystrophies. Examples of accomplishments in FYs 2008 and 2009 are provided below.

- Investigators at the Nationwide Children's Hospital (Columbus, Ohio), funded through a subcontract from the University of Pittsburgh Wellstone MDCRC, developed a gene-therapy technique for making alpha-sarcoglycan protein (which is essential for muscle function) without triggering a destructive response by the body's immune system. The three-person clinical trial builds on findings from the University of Iowa and elsewhere showing that restoring alpha-sarcoglycan gene expression can halt the advance of a type of limb-girdle muscular dystrophy in mice.²⁸ The Nationwide Children's Hospital study demonstrated that the gene-delivery strategy was safe and that a single injection produced gene expression for at least 12 weeks.²⁹ Although the study was designed to test safety (not improvements in muscle function), findings from one patient suggest that the delivered gene might be useful for restoring muscle function.
- Animal study findings from Wellstone MDCRCs have suggested strategies for people who have various muscular dystrophies. For example, mouse studies at the University of Pennsylvania and Johns Hopkins University Wellstone MDCRC showed that a drug being studied for hepatitis C treatment slowed progression of congenital muscular dystrophy, DMD, and LGMDs by blocking damage caused by calcium to mitochondria (the main energy sources of cells).³⁰ Although the drug might not be appropriate for people because of its potential side effects, the study shows that protecting cells from calcium damage could be beneficial.
- Researchers at the Children's National Medical Center increased the amounts of modified dystrophin protein in dogs with DMD, a disease caused by the body's inability to make dystrophin protein. They used artificial molecules (morpholino oligonucleotides) that cause the cell's protein-generating machinery to skip over the damaged segment of the dystrophin gene and produce shortened, but

functional, dystrophin. If researchers can refine this strategy so that it can safely be studied in people, this approach could benefit nearly 90 percent of patients with DMD.³¹

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- Wellstone MDCRC researchers are using animals to find treatments that could be effective for several different types of muscular dystrophies. Some researchers are exploring the role of neuronal nitric oxide synthase (nNOS) in controlling blood flow in skeletal muscle and thus in minimizing the fatigue associated with exercise that many people with a nerve or muscle disease experience.³² University of Iowa scientists used mice with DMD to show that a drug that allows blood vessels to dilate prevents the severe fatigue that the mice experienced after brief exercise periods. Other studies by researchers at the University of Missouri in collaboration with an investigator at the Seattle Wellstone Center restored functioning of diseased mice to nearly normal levels by using a gene therapy strategy involving nNOS.³³

²⁸ Pacak CA, et al. *Mol Ther* 2007;15(10):1775-81. PMID: 17653106.

²⁹ Mendell JR, et al. *Ann Neurol* 2009; 66(3):267-70. PMID: 19798725.

³⁰ Millay DP, et al. *Nat Med* 2008;14(4):442-7. PMID: 18345011. PMCID: PMC2655270.

³¹ Millay DP, et al. *Nat Med* 2008;14(4):442-7. PMID: 18345011. PMCID: PMC2655270.

³² Yokota T, et al. *Ann Neurol* 2008;456(7221):511-5. PMID: 18953332. PMCID: PMC2588643.

³³ Lai Y, et al. *Clin Invest* 2009;119(3):624-35. PMID: 19229108. PMCID: PMC2648692.

Recommendations for Improving the Effectiveness, Efficiency, and Outcomes of the Wellstone MDCRCs

In response to research advances and Steering Committee recommendations, NIH changed the requirements for FY 2008³⁴ applicants to improve the program's overall effectiveness, efficiency, and outcomes. The FY 2008 solicitation emphasized multidisciplinary teams and patient-oriented research. Details about the recommendations' rationale and implementation follow.

- NIH removed the requirement that all centers conduct basic research on disease mechanisms because the number of findings that are ready to be studied in animals or humans has increased dramatically since the last competitions.^{35,36} This change allows the Wellstone MDCRCs to focus more on translating basic findings to human studies and conducting studies in humans. Meanwhile, NIH continues to encourage basic muscular dystrophy research through other funding mechanisms, such as traditional research project grants.
- By reducing the required number of projects from three to one, NIH allowed FY 2008 applicants to propose collaborative studies involving animal models of disease or human subjects that were larger, more expensive, and more in-depth than were possible under the original structure.
- NIH urged FY 2008 applicants to propose collaborative studies that address at least one gap in muscular dystrophy treatment research and overcome obstacles in the development of therapies.
- In FY 2008, all applicants had to provide letters from other researchers to show how one of their proposed cores would fill a high-priority need beyond their individual institutions. This change was designed to increase the Wellstone MDCRC program's ability to serve the entire muscular dystrophy research community.
- NIH enhanced the program's training activities in FY 2008 by requiring all centers to create Research

Training and Education Cores that support predoctoral students and postdoctoral fellows. The addition of a formal career-development program at each site enhances the Wellstone MDCRCs' contributions to the pipeline of new muscular dystrophy researchers.

- Engaging patients throughout the research process can improve a program's impact by ensuring that researchers are developing and testing treatments that are acceptable to patients (and the parents of pediatric patients). To this end, the new Wellstone MDCRC at the Boston Biomedical Research Institute has been working closely with the FSH Society to jointly set and achieve research objectives with the patient community.
- NIH is organizing a broader collaborative network of muscular dystrophy researchers. To make communication more seamless among everyone who cares about people with muscular dystrophy and to increase the exchange of knowledge for treatment development, NIH invited major advocacy groups and grantees who have other center awards to participate in a 2009 meeting of the Wellstone MDCRCs. Investigators presented examples of collaborations among the centers and other researchers. New opportunities for interactions and multi-laboratory projects were identified.

³⁴ For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-08-002.html>.

³⁵ For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-03-001.html>.

³⁶ For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-04-008.html>.

Evaluation Plans

Major review criteria for the Wellstone MDCRCs include the degree to which an institution shows that it can foster substantive collaborations among its researchers and with scientists elsewhere that address key issues in muscular dystrophy and its potential to serve as a national infrastructure and training resource.

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NIH responded to the burgeoning number of basic research findings in muscular dystrophy by changing the focus of the FY 2008 Wellstone MDCRC competition to encourage research that translates basic findings about the disease to human studies and applications in the clinic. Informal comments about the change in focus from reviewers, grantees, and advocacy groups were positive. Discussions about the centers' structure among NIH program staff and IC directors led to a decision to retain the structure adopted for the FY 2008 competition. NIH will continue to monitor the program's coordination and productivity as staff review the progress of each center at the time of noncompeting renewal and through regular contact with Wellstone MDCRC leaders through the Steering Committee.

Future Directions

NIH is committed to supporting six outstanding Wellstone MDCRCs. The agency issued 3 5-year awards to the Wellstone MDCRC program in FY 2008. In FY 2010, NIH is holding an open competition and intends to fund up to three other center sites.³⁷ Grantees will join the network of Wellstone MDCRCs to translate scientific findings and technological developments into treatments for muscular dystrophies.

NIH supports multi-project grants and core centers for muscular dystrophy research at academic institutions in addition to the Wellstone Centers. The agency also is promoting interactions among investigators at the Wellstone Centers and these other institutions to expand the scope and strength of the Wellstone Network. For example, the Wellstone Center meeting in June 2009 included participants from two NIAMS-funded core centers, two NINDS-supported program project grants, the NINDS- and NIAMS-supported National Center for Canine Models of DMD, and representatives from patient advocacy groups.

³⁷ For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-09-027.html>.

Table 4-3. Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRCs)

Institution and Location	Year Established
University of Pittsburgh, Pittsburgh, PA	2003
University of Rochester, Rochester, NY	2003
University of Washington, Seattle, WA	2003
Children's National Medical Center, Washington, DC	2005
University of Iowa, Iowa City, IA	2005
University of Pennsylvania, Philadelphia, PA, and Johns Hopkins University, Baltimore, MD	2005
Boston Biomedical Research Institute, Boston, MA	2008
University of North Carolina, Chapel Hill, NC	2008