

# 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) specified provisions for expanding and intensifying research on muscular dystrophy and mandated that NIH establish Centers of Excellence for research on muscular dystrophy. Congress designated the centers as the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (Wellstone MDCRCs) in the Omnibus Appropriations for FY 2004 (Pub. L. No. 108-199). Former Minnesota Senator Paul D. Wellstone, who died on October 25, 2002, was a driving force behind the Muscular Dystrophy Community Assistance Research and Education (MD-CARE) Act (see Table 4-3).

#### How the Wellstone MDCRCs Function Within the NIH Framework

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NINDS, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) fund two Wellstone MDCRCs each, using the U54 Specialized Centers Cooperative Agreement award mechanism. A Steering Committee oversees scientific coordination of the Wellstone MDCRCs, sets goals, and makes strategic decisions about activities such as establishing collaborations. The committee consists of the directors and co-directors of each center, NIH science officers, and a public member. The External Advisory Committee, which is composed of experts in muscular dystrophy research and a patient advocate, helps inform NIH programmatic decisions regarding the Wellstone MDCRC program.

#### Description of Disease or Condition

The muscular dystrophies are a group of more than 30 genetic diseases characterized by progressive degeneration of the skeletal muscles, which control movement. Some forms occur in infancy or childhood, whereas others may not appear until middle age or later. Diseases addressed by the Wellstone MDCRCs include, but are not limited to, the following conditions.

- **Duchenne and Becker muscular dystrophies:** Duchenne muscular dystrophy is the most common childhood form of muscular dystrophy. It is an X-linked recessive disease, primarily affecting males who inherit a genetic mutation from their mothers. Boys with Duchenne muscular dystrophy lack the protein dystrophin, which is essential for keeping muscle cells intact. Duchenne muscular dystrophy 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 early twenties. Becker muscular dystrophy, a less severe disease, occurs when a partially functional form of dystrophin is produced.
- **Myotonic dystrophy:** Myotonic dystrophy is the most common adult form of muscular dystrophy, although it

can strike at any age. It is marked by myotonia (an inability to relax muscles after contraction) and muscle wasting and weakness. Myotonic dystrophy varies in its severity and manifestations. It can affect other body systems in addition to skeletal muscles, including the heart, endocrine organs, eyes, and gastrointestinal tract.

- **Facioscapulohumeral muscular dystrophy:** Facioscapulohumeral muscular dystrophy initially affects muscles of the face (*facio*), shoulders (*scapulo*), and upper arms (*humeral*). Symptoms usually develop in the teenage years, and some affected individuals become severely disabled.
- **Limb-girdle muscular dystrophies:** All limb-girdle muscular dystrophies show a similar distribution of muscle weakness, affecting both upper arms and legs. Many forms of limb-girdle muscular dystrophy have been identified; some affect children, whereas others manifest in adulthood.
- **Miyoshi myopathy:** Miyoshi myopathy, one of the distal muscular dystrophies, causes initial weakness in the calf muscles. It is caused by defects in the same gene that is responsible for one form of limb-girdle muscular dystrophy, suggesting that research progress against one form of muscular dystrophy may 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. Symptomatic treatments such as physical therapy, use of appliances for support, corrective orthopedic surgery, and drugs improve the quality of life for some individuals. However, even though some drugs, such as steroids, can slow the progression of Duchenne muscular dystrophy, there are side effects. Several therapeutic approaches, including gene therapy, cell-based treatments, and strategies to inhibit muscle degeneration, have shown promise in cell culture systems and animal models. Clinical trials of some therapies have begun, including the use of drugs to reduce muscle damage, cell-based replacement therapies, functional compensation for the lack of dystrophin by increasing the body's production of certain proteins, increasing muscle mass via inhibition of other proteins that negatively regulate muscle growth, and strategies to bypass the mutations that cause disease.

### Burden of Illness

Duchenne and Becker muscular dystrophies affect boys at a rate of 1 in 3,500 to 1 in 5,000. More than 4 million births occur annually in the United States, and about 400 to 600 boys are born with Duchenne or Becker muscular dystrophy every year<sup>11</sup>. Myotonic dystrophy affects approximately 1 in 8,000 people worldwide<sup>12</sup>, whereas facioscapulohumeral muscular dystrophy affects approximately 1 in 20,000 people and affects men and women equally<sup>13</sup>. 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. This surveillance system, once fully operational, will provide additional burden of illness data.

### Scope of NIH Activities: Research and Programmatic

As nationally recognized Centers of Excellence in muscular dystrophy, the Wellstone MDCRCs are expected to promote communication and collaboration, develop and share research resources, and contribute to the training of new muscular dystrophy researchers<sup>14</sup>. Each Wellstone MDCRC includes at least one basic research project and one clinical research project, with a minimum of three individual but interrelated research projects, an

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<sup>11</sup> For more information, see <http://www.cdc.gov/ncbddd/duchenne/who.htm>

<sup>12</sup> For more information, see <http://ghr.nlm.nih.gov/condition=myotonicdystrophy>

<sup>13</sup> For more information, see <http://www.nlm.nih.gov/medlineplus/ency/article/000707.htm>

<sup>14</sup> For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-03-001.html>; <http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-04-008.html>

administrative core, and at least one scientific resource core that serves as a resource for the national muscular dystrophy research effort.

Collectively, the Wellstone MDCRCs are engaged in research on various forms of muscular dystrophy, including some not listed above. Designed to accelerate progress toward effective treatments for muscular dystrophies through increased synergistic collaboration and coordination of research activities, they promote side-by-side basic, translational, and clinical research. Each center coordinates efforts to help bring together investigators at multiple sites.

Examples of research topics addressed at the various centers are as follows.

- The **University of Pittsburgh** center focuses on developing gene therapy techniques as well as research on muscle stem cells as potential therapies for Duchenne muscular dystrophy. The center is also preparing to conduct a clinical trial of gene therapy for limb-girdle muscular dystrophy.
- The **University of Rochester** center focuses on myotonic dystrophy and facioscapulohumeral muscular dystrophy. Researchers are examining cellular and molecular factors that contribute to these diseases and are conducting a clinical trial of the drug IPLEX (mecermin) for patients with myotonic dystrophy.
- The **University of Washington** center focuses on gene therapy techniques and has begun several new collaborative projects focused on the mechanisms underlying facioscapulohumeral muscular dystrophy
- Researchers at the **Children's National Medical Center** are analyzing genetic and cellular factors that contribute to the progression of Duchenne muscular dystrophy and the response of patients to treatment.
- The **University of Iowa** center focuses on gene and stem cell therapeutic strategies for Duchenne, limb-girdle, and other muscular dystrophies. It provides diagnostic services for physicians around the country and banks biopsy samples that can be used for research.
- The **University of Pennsylvania/Johns Hopkins University** center focuses on strategies to promote muscle growth or inhibit muscle protein degradation, approaches that could be applicable to a range of muscular dystrophies and other muscle disorders. It also provides state-of-the-art animal model physiological testing services as a resource for other researchers.

The Wellstone MDCRC program reserves funds to support new collaborative projects involving center investigators and pilot projects by non-center investigators. Center directors are also encouraged to collaborate with other muscular dystrophy researchers 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<sup>15</sup>.

Each of the Wellstone MDCRCs has core facilities that provide unique resources or services for the muscular dystrophy research community. Resources include repositories of research data and biologic resources from patients with various muscular dystrophies; imaging, diagnostic, bioinformatics, and computing capabilities; and viral vector development and production. The Wellstone MDCRC program also aids therapeutic development by maintaining a muscular dystrophy dog colony and providing sophisticated functional testing of mouse models.

### **NIH Funding for FY 2006 and FY 2007**

In FY 2006 and FY 2007, NIH invested a total of \$9.6 million and \$8.5 million, respectively, in the Wellstone MDCRC program. The three original Wellstone MDCRCs (Rochester, Washington, and Pittsburgh) also received up to

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<sup>15</sup>For more information, see <http://grants.nih.gov/grants/guide/notice-files/NOT-AR-05-008.html>

\$500,000 per year from the Muscular Dystrophy Association. This supplemental funding ended in December 2006.

## Outcomes: FY 2006 and FY 2007 Progress Report

### Programmatic Accomplishments

Programmatic accomplishments include awards of NIH Administrative Supplements for Senator Paul D. Wellstone Muscular Dystrophy Research Fellowships at Wellstone MDCRCs to advance the careers of four basic and clinical scientists who study muscular dystrophy.

New collaborative projects supported by the Wellstone MDCRC in FY 2006 and 2007 include the following:

- A collaborative effort between investigators at the Wellstone MDCRC at Children's National Medical Center and researchers in Japan to evaluate a gene modification technique (i.e., exon skipping) in a dystrophic dog model
- Collaboration between the Iowa Wellstone MDCRC and Ohio State University to develop more effective diagnostic techniques for limb-girdle muscular dystrophy and Miyoshi myopathy
- A partnership between University of Pittsburgh and University of Pennsylvania investigators to study myostatin inhibition using the dog colony supported by the Pittsburgh Center

In 2006, the Wellstone MDCRC Administrative Supplements program to support workshops and research conferences funded a workshop entitled "High Throughput Drug Screening for the Muscular Dystrophies" at the Children's National Medical Center. Industry, academic, and government researchers, as well as patient advocates, participated. The center is planning a second workshop, which will address the development of standard protocols for testing therapies in animal models.

The availability of Wellstone MDCRC core facilities has been publicized at national meetings, through Web sites that the centers have established, and through the [Wellstone MDCRC Web site](#). Sharing these research tools fosters collaborations across departments or schools at a single institution and among investigators and health care providers at several institutions. For example, the Muscle Tissue/Cell Culture/Diagnostics Core at the University of Iowa Wellstone MDCRC serves as both a local and a national resource for muscular dystrophy research. In addition to maintaining a muscle tissue repository of well-characterized tissues and cells representing the spectrum of muscular dystrophy diagnoses that are available for research, the center provides diagnostic services that are not readily available through clinical laboratories and is facilitating the development of new diagnostic tests.

### Research Accomplishments

The Wellstone MDCRCs conduct basic, translational, and clinical studies related to a variety of muscular dystrophies. Each center has at least three distinct but interrelated research projects. Examples of research accomplishments in FYs 2006 and 2007 are noted below.

- In the past 2 years, investigators at the University of Rochester MDCRC have begun a clinical trial to test the drug Iplex in patients with myotonic dystrophy. The dose escalation phase of this safety and feasibility trial suggests that the drug is well tolerated. The next phase of the trial will test an optimal dose in patients with myotonic dystrophy. Because Iplex improves muscle regeneration, it may be useful in many types of muscular dystrophy.

- Two other clinical trials, including one to test a gene therapy for limb-girdle muscular dystrophy, are preparing to begin recruiting patients.
- Wellstone MDCRC investigators have made numerous other advances with respect to gene therapies for other muscular dystrophies. Many strategies that 2 years ago were being tested in mice are now being evaluated in dogs. Wellstone MDCRC researchers are refining their technologies and are identifying how genes should be administered. They also are discovering interactions between gene therapy vectors and human immune responses and have developed an immunosuppression protocol that shows promise in dogs<sup>16</sup>.
- Researchers at the University of Pennsylvania/Johns Hopkins University Wellstone MDCRC have tested a class of compounds known as protease inhibitors (i.e., Bowman-Birk inhibitors) that show promise in animal models of Duchenne muscular dystrophy and are planning to begin a clinical trial.
- The Wellstone MDCRCs are also contributing basic research findings to the understanding of muscular dystrophy. For example, during a search for stem cell traits that predict effective muscle regeneration, University of Pittsburgh researchers determined that cell sex (i.e., whether the cells originated in a male or a female donor) has a profound influence on whether muscle stem cells can produce muscle fibers in a mouse model of Duchenne muscular dystrophy<sup>17</sup>. The results could influence future research on the use of cell transplants for treating muscular dystrophy and affect the overall field of stem cell biology and regenerative medicine by prompting other investigators to consider and report the sex of the cells used in their research.
- In other basic research, investigators at the University of Rochester conducted a comprehensive genome-wide scan of biopsies from patients with early-stage facioscapulohumeral muscular dystrophy. The scan results are dispelling a widely held belief that a deletion on chromosome 4 triggers the development of facioscapulohumeral muscular dystrophy by disrupting expression of neighboring genes<sup>18</sup>. Results from this study have connected vascular abnormalities commonly observed in the retinas of patients with facioscapulohumeral muscular dystrophy who have the skeletal muscle weakness and wasting characteristics of the disease and may eventually lead to new treatments of this disease.

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

Due to NIH efforts to improve the Wellstone MDCRCs' effectiveness, efficiency, and outcomes, centers funded in FY 2008<sup>19</sup> will differ somewhat from their established counterparts in the following ways:

- Whereas the Wellstone MDCRCs established in 2003 and 2005 have three research projects, an administrative core, and a scientific research core, institutions applying for the program in FY 2008 are required to have at least one research project and specific core activities.
- Because the number of basic findings that are ready for translation has increased dramatically since the last competition, NIH removed the basic research requirement to allow the Wellstone MDCRCs to focus more of their efforts on translational research.
- The need for a clinical or patient-oriented project remains unchanged in the new solicitation, but because the required number of projects has been reduced from three to one, center applicants are free to propose larger, more expensive clinical research activities.
- Whereas the existing centers could apply for a training supplement to support the career development of a

<sup>16</sup> [Wang Z, et al. \*Mol Ther\* 2007;15:1160-6](#), PMID: 17426713

<sup>17</sup> [Deasy BM, et al. \*J Cell Biol\* 2007;177:73-86](#), PMID: 17420291

<sup>18</sup> [Osborne RJ, et al. \*Neurology\* 2007;68:569-77](#), PMID: 17151338

<sup>19</sup> For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-08-002.html>

postdoctoral and nontenure track investigator, the training aspect of the next round of Wellstone MDCRCs will be formalized by Research Training and Education Cores that will support a predoctoral student and a postdoctoral fellow at each site. This addition was made in response to suggestions from the Steering Committee, combined with an analysis of existing training opportunities in the field of muscular dystrophy research.

- To better promote coordination of information and resources among the Wellstone Centers and throughout the muscular dystrophy research community, each applicant institution is required to provide letters documenting how one of its proposed core resources will fill a high-priority need in the muscular dystrophy research community.

As the Wellstone MDCRC program gains momentum, NIH plans to reexamine the role and composition of the External Advisory Committee to ensure that it continues to contribute to the growth and success of the program.

### **Evaluation Plans**

NIH reissued the RFA for the Wellstone MDCRCs in FY 2007. The competition was open to new applicants, and the three centers that were originally established in 2003 had to compete again for funding. Major review criteria for the Wellstone MDCRCs include the degree to which an institution demonstrates its ability to engage in substantive collaborations to address key issues in muscular dystrophy and its potential to serve as a national infrastructure and training resource.

### **Future Directions**

As noted above, the reissued RFA for Wellstone MDCRCs reflects several changes to further strengthen the program. NIAMS, NINDS, and NICHD intend to fund up to three Wellstone MDCRCs. NHLBI will participate by supporting meritorious cardiopulmonary research in successful applications. Grantees will join a network of existing Wellstone MDCRCs to foster the translation of new scientific findings and technological developments into novel treatments for the muscular dystrophies