



## Overview of 2010 Operations

### Research

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Despite the prolonged recession in the U.S. economy, MDA research continued at a rapid pace in 2010. The Association awarded 90 grants for research in the diseases in its program, for a total of more than \$33.1 million.

MDA researchers throughout the world continued to explore strategies they've been pursuing and set out in several new directions as well.

### Translational research a major focus for MDA

MDA's translational research program took center stage in 2010 in several disease categories. (Translational research seeks to "translate" promising basic science into actual therapies.) Highlights of MDA's translational research achievements in 2010 follow.

### DMD and BMD

In 2010, several studies got under way under the auspices of the MDA Duchenne Muscular Dystrophy (DMD) Clinical Research Network. The network consists of five U.S. centers that collaborate on clinical trials and studies designed to improve and standardize care for DMD and the related disease, Becker muscular dystrophy (BMD).

In the fall, the network began studying the natural history of heart function in DMD and BMD, and its correlation to skeletal-muscle function and to specific mutations in the dystrophin gene. Mutations in this gene underlie both DMD

and BMD. The network also began a study to compare the effectiveness of the cardiac drugs losartan and lisinopril in DMD.

Late in 2010, the network undertook two additional studies to develop outcome measures for DMD clinical trials in children younger than 3 years old and in boys and young men with DMD who are no longer walking. Most trials in DMD require participants to be old enough to cooperate with strength tests and to be still walking. Being able to measure the effects of experimental treatments in participants who are not in these categories will expand the reach of clinical trials in DMD.

In October, results of a small safety and feasibility trial of dystrophin gene therapy for DMD/BMD were announced and showed that an unwanted immune response to the therapy occurred in some of the participants. In this trial, miniaturized dystrophin genes, encased in viral shells, were injected into the biceps muscles of six participants. These results indicate that immune system rejection of DMD/BMD gene therapy is a factor that deserves major consideration as the field moves forward.

Also in October, New Jersey biotechnology company PTC Therapeutics announced that the low-dose regimen of its experimental drug ataluren increased walking distance in boys with Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy

***“MDA is important for a variety of reasons, not the least of which is it funds – strategically and knowledgeably – good research.”***

**John McCall**

*Drug discovery consultant  
Chair of the spinal muscular atrophy development team  
National Institutes of Health*

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(BMD) who had a certain type of mutation in the dystrophin gene. Ataluren, developed with MDA support to PTC, makes use of a strategy called *stop codon read-through*. It's designed to coax muscle cells to ignore, or “read through,” molecular stop signals in the dystrophin gene and produce a functional dystrophin protein.

In April, the multinational pharmaceutical company GlaxoSmithKline and the Dutch biotechnology company Prosenza announced encouraging results from an early-stage trial of their experimental drug PRO051/GSK2402968 in boys with DMD with specific types of dystrophin gene

mutations. Eleven of the 12 participants in this trial produced the needed dystrophin protein after treatment with this drug, which is designed to change the way cells read genetic instructions for dystrophin. The drug is a synthetic molecule and makes use of a strategy called *exon skipping*.

The same month, biotechnology company AVI BioPharma of Bothell, Wash., announced similarly encouraging results for its exon-skipping molecule, AVI-4658. MDA funded much of the basic science research that made development of exon-skipping drugs possible.

MDA has supported a strategy called *myostatin inhibition* for DMD, BMD and potentially other muscular dystrophies. Myostatin is a naturally occurring protein that limits muscle growth, and interfering with it could allow muscles to grow



larger and possibly stronger. In 2010, Acceleron Pharma of Cambridge, Mass., began testing the myostatin inhibitor ACE-031 in people with DMD.

Delaware biotechnology company Tivrosan Pharmaceuticals announced in September that it would develop an experimental drug for DMD or BMD based on a protein called biglycan, which had been the subject of MDA-supported research. The goal of biglycan treatment is to improve the structure and function of the muscle-fiber membrane, which is fragile in DMD and BMD because of a deficiency of dystrophin.

Also in 2010, BioMarin Pharmaceutical of Novato, Calif., began testing BMN195 in healthy volunteers. BMN195 is designed to increase production of utrophin, a protein that's very similar to dystrophin and can probably compensate at least partially for the absence of dystrophin. Utrophin research has been a major focus of MDA's basic science program for several years.

## ALS

MDA continued its partnership with the ALS Therapy Development Institute (ALS TDI) in Cambridge, Mass., giving the institution a new milestone-driven grant of \$2.5 million in January, in addition to the \$18 million previously awarded. ALS TDI is a nonprofit research center focused exclusively on developing treatments for ALS.

In 2010, ALS TDI's leading therapeutic candidate was ALS TDI 00846, an immune system modulator.

Also this year, MDA's ALS Clinical Research Network, a consortium of five MDA/ALS centers located throughout the United States, continued to forge ahead. Established by MDA in 2008, each of the five centers in the network receives support from the Association to build infrastructure and conduct clinical trials in ALS (amyotrophic lateral sclerosis). In 2010, a trial to

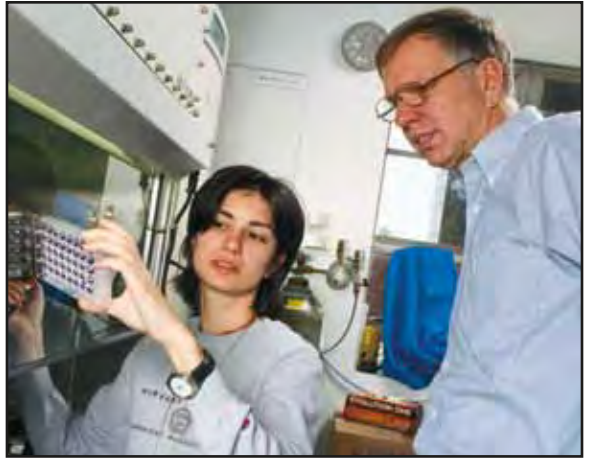


compare the effects of a regular diet, a high-calorie diet and a high-calorie, high-fat diet in people with ALS continued.

A clinical trial of an experimental drug called ISIS-SOD1-Rx, developed by Isis Pharmaceuticals of Carlsbad, Calif., with MDA support, began in 2010. This is a drug to test a molecular strategy called *antisense*, to see whether it can block genetic instructions for a toxic protein called SOD1 in people with ALS who have mutations in the SOD1 gene. The clinical trial is designed to establish the safety profile of this new compound.

Four other ALS clinical trials, while not directly funded by MDA, were made possible in large part by basic science research conducted by MDA-supported investigators. In 2010, Neuraltus Pharmaceuticals of Palo Alto, Calif., began testing its experimental drug NP001. This small-molecule drug, whose development is based on MDA research on the immune system in ALS, is designed to switch immune system cells from an active, inflammatory mode to a more normal, healing mode in ALS.

Sangamo BioSciences of Richmond, Calif., reported that its experimental compound SB509 was safe and showed hints of possible efficacy in people with ALS. The development of SB509, designed to increase production of a protein called vascular endothelial growth factor (VEGF), benefited from MDA research on this molecule.



## Pompe disease

May 2010 saw the approval by the U.S. Food and Drug Administration of Lumizyme, a drug specifically for late-onset Pompe disease (acid maltase enzyme deficiency). Biopharmaceutical company Genzyme of Cambridge, Mass., received approval from the FDA in 2006 to market the closely related drug Myozyme for infants and children with this metabolic muscle disorder. Myozyme and Lumizyme both replace the missing enzyme and were developed in part because of MDA-supported basic science research on acid maltase.

## SMA

In December 2010, MDA awarded \$1.4 million to the biopharmaceutical company Repligen of Waltham, Mass., for development of RG3039, an experimental drug to treat spinal muscular atrophy (SMA). RG3039 is designed to increase the amount of fully functional SMN protein, which is deficient in people with SMA, by causing cells to process the genetic instructions for SMN in a different way.