Recent Research Developments

Supported by the Muscular Dystrophy Association

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MDA Research Advances Rapidly

This pamphlet lists highlights from among hundreds of major research breakthroughs made in recent years by MDA-funded scientists around the world. MDA, the world’s largest private-sector supporter of research on neuromuscular diseases, annually funds grants to more than 330 physicians and scientists.

2011: Guidelines developed for CMD

An international panel of doctors and scientists, including many supported by MDA, produces the first-ever standard of care guidelines for the congenital muscular dystrophies (CMD). The guidelines are intended to improve and standardize the diagnosis, treatment and clinical care of people affected by this group of muscular dystrophies.

MDA awards additional $2 million to ALS TDI nonprofit biotech

MDA awards an additional $2 million to the ALS Therapy Development Institute of Cambridge, Mass., for development of treatments for amyotrophic lateral sclerosis. The new grant brings the total amount the Association has awarded to this nonprofit biotech institution to more than $23.7 million since 2007. ALS TDI plans to test four new compounds in the SOD1 ALS research mouse model and to begin working with the new TDP43 mouse model of ALS.

MDA awards grant to develop new stop codon read-through drug

MDA awards a translational research grant of about $500,000 for development of a new “stop codon read-through” drug called RTC13 to treat Duchenne or Becker muscular dystrophy caused by premature stop codon mutations. The grant is to a research group at the University of California, Los Angeles. It’s been estimated that up to 15 percent of boys with DMD or BMD have this type of mutation, which creates an erroneous “stop signal” in the dystrophin gene. It’s this type of mutation that RTC13 will target. Another stop codon read-through drug, called ataluren, is being developed for this type of DMD/BMD mutation by biotechnology company PTC Therapeutics. PTC also has received MDA support for drug development.

MDA makes translational research award to develop new MG treatment

MDA’s translational research program makes an award of more than $500,000 for development of a potential new treatment for myasthenia gravis, a disease in which the immune system attacks the neuromuscular junction (the place where nerve and muscle fibers meet). The grant is for development into a therapy of the protein GM-CSF, which may stimulate regulatory immune system cells, dampening the unwanted immunologic attack.
Exon-skipping drugs show promise in boys with DMD

Two experimental drugs to treat Duchenne muscular dystrophy, both of which make use of a strategy called “exon skipping,” show promise in human trials in this disease. One drug, PRO051/GSK2402968, results in increased production of the needed dystrophin protein and improved walking ability in boys with DMD. It’s being developed by the pharmaceutical companies Prosensa and GlaxoSmithKline. The other drug, known as eteplirsen, being developed by AVI BioPharma, also increases dystrophin production. Both are designed to cause cells to reinterpret genetic instructions for the dystrophin protein by telling the cells to “skip” a section of the instructions called exon 51. MDA-supported laboratory research on exon skipping provided much of the scientific data on which these trials are based.

ISIS-SOD1-Rx shows safety in familial ALS trial

An MDA-supported clinical trial of ISIS-SOD1-Rx demonstrates safety in people with a form of familial amyotrophic lateral sclerosis caused by a mutation in the SOD1 gene. ISIS-SOD1-Rx is an “antisense oligonucleotide” in development by Isis Pharmaceuticals with MDA support. It’s designed to block synthesis of toxic SOD1 protein molecules in this form of ALS. The trial moves to a higher dosage level.

MDA supports development of GLX1112 for ALS

MDA’s translational research program awards a grant of more than $250,000 to biotechnology company Glialogix to develop a new glutamate inhibitor for the potential treatment of amyotrophic lateral sclerosis. The grant will fund a study of the experimental compound GLX1112 in the SOD1 research mouse. Excessive glutamate, a central nervous system chemical, is believed to play a role in ALS. Riluzole, the only drug approved by the U.S. Food and Drug Administration to treat ALS, is a glutamate inhibitor with modest benefits in this disease.

Three drug candidates identified for DMD/BMD in zebrafish model

A screen of 1,120 chemicals in a recently developed zebrafish model of Duchenne muscular dystrophy leads MDA-supported scientists to three new drug candidates for this disease and the related Becker muscular dystrophy. The three candidates caused improved survival and muscle structure in the fish. All three have been used to treat other human diseases.

MDA supports development of HSP70 for ALS

MDA’s translational research program awards $250,000 to biotechnology company ALS Biopharma to develop a new strategy for the treatment of amyotrophic lateral sclerosis, with the goal of bringing it into human trials. The company will test different forms of HSP70, a “heat shock protein” that’s part of a class of chemicals known to help cells withstand stress. Preliminary studies have shown that HSP70 delays symptom onset and improves survival time in the SOD1 mouse model of ALS.
ALS Clinical Research Network studies nutrition, meaningful changes

MDA’s ALS Clinical Research Network is conducting a trial to compare the effects of a standard diet, a high-calorie diet or a high-fat diet in people with ALS (amyotrophic lateral sclerosis), as well as a study to determine what ALS-affected families consider to be meaningful changes in medical, psychosocial or quality-of-life status. The network, established in 2008, is made up of five research centers across the United States working to improve and standardize clinical trials and care recommendations for people with ALS.

Two DNA changes needed to cause FSHD symptoms

MDA-supported scientists uncover a previously missing piece of the puzzle posed by facioscapulohumeral muscular dystrophy. Not only does this disease require the presence of a contracted area of DNA on chromosome 4 (a previously recognized factor), but it also requires a “permissive” DNA signal on the same chromosome. The permissive DNA signal may allow potentially toxic proteins, including one called DUX4, to last long enough to cause muscle damage.

Encouraging results for gene therapy in LGMD

An MDA-supported trial of gene therapy in limb-girdle muscular dystrophy results in some encouraging news. The trial finds that five out of six people with type 2D LGMD produced a protein that’s deficient in the disease from newly transferred alpha-sarcoglycan genes. Investigators are moving ahead with the work necessary to start the next trial of this therapy.

FDA approves testing of RG3039 in people with SMA

The U.S. Food and Drug Administration (FDA) gives biotechnology company Repligen approval to begin a human trial of RG3039, an experimental treatment for spinal muscular atrophy. A $1.4 million grant from MDA supports this phase 1 trial and also supported earlier, laboratory development of RG3039. The drug is a small-molecule therapy designed to increase levels of the SMN protein, which is deficient in SMA. It’s the first medication specifically designed to treat SMA.

2010:
Tadalafil to be tested in men with Becker MD

MDA awards a grant of approximately $1 million for a clinical trial to study the effects of tadalafil on blood flow to exercising arm muscles in men with Becker muscular dystrophy. Tadalafil, which is approved by the U.S. Food and Drug Administration for other uses, relaxes blood vessels.

DMD Clinical Research Network studies disease progression, heart drugs

MDA’s Duchenne Muscular Dystrophy Clinical Research Network gets several studies under way, including one on how DMD progresses in the very young and in those no longer walking; the “natural history” of heart disease in DMD and in Becker muscular dystrophy (BMD); and a comparison of two drugs, losartan and lisinopril, for their effects on cardiac and skeletal muscle weakness. The network, established in 2008, consists of five U.S. research centers working together to improve patient care, as well as to streamline and standardize DMD studies and clinical trials.
Lower-dose ataluren slows decline of walking ability in DMD/BMD

A large trial of ataluren (formerly called PTC124), conducted by PTC Therapeutics of South Plainfield, N.J., finds that the lower of two tested doses of this drug may slow the decline of walking ability in boys with Duchenne or Becker muscular dystrophy who have a “premature stop codon” flaw in the dystrophin gene. Ataluren, developed by PTC with help from MDA, is designed to coax cells into ignoring premature stop signals (codons) in the dystrophin gene and synthesize the needed protein.

Gene therapy advances in DMD

An MDA-supported clinical trial of gene therapy in Duchenne muscular dystrophy finds that at least some of the trial participants mounted an unexpected immune response to the dystrophin protein newly synthesized from the transferred genes. Investigators say the trial taught them important lessons about the need for careful monitoring of the immune system during a gene therapy trial and the value of screening trial participants for possible immune responses prior to enrollment.

Research in this area continues.

DMD gene repair strategy takes a big step forward

An MDA-supported research group reports that a new generation of molecules can help cells permanently repair errors in the dystrophin gene, fixing the underlying cause of Duchenne muscular dystrophy. In experiments on cells and in mice, the new molecules stimulated more than 10 times the DNA repair levels of previous molecules, providing a “proof of concept” for gene repair as a therapy for DMD.

Synthetic enzyme approved for late-onset Pompe disease

Lumizyme, an enzyme manufactured by Genzyme Corp., becomes commercially available for the treatment of late-onset acid maltase deficiency (Pompe disease) in individuals ages 8 and older. MDA-supported basic research played a role in the development of both Lumizyme and Myozyme, Genzyme’s enzyme replacement drug for infants and very young children with Pompe.

Therapeutic strategy in MTM opens muscle fibers

MDA-supported researchers report a new molecular strategy designed to transport the needed myotubularin enzyme (a type of protein) into muscle fibers in myotubularin-deficient mice and perhaps eventually in humans with X-linked myotubular myopathy.

More evidence implicates immune system in ALS

MDA-funded investigators at the ALS Therapy Development Institute find that disrupting an immune system pathway called CD40L delays disease onset and extends survival in mice with a disease mimicking human amyotrophic lateral sclerosis. The experimental drug candidate, a blocking protein, or “antibody,” called ALSTDI-00846, prevents interaction between two key CD40L pathway components, blocking a signal to the body to launch an immune system attack.

Toxic clumps not the only molecular cause of OPMD

An MDA-supported study team finds that a loss of function of the PABPN1 protein likely is a contributing factor, along with the formation of potentially toxic protein...
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New ALS research mouse added to scientists’ toolkit

An MDA-supported research team develops a new research mouse with a mutation in the gene for the TDP43 protein, known to cause amyotrophic lateral sclerosis. The new mouse develops a disease resembling human ALS and is expected to broaden scientists’ ability to observe disease onset and progression, and the effects of experimental treatments.

New muscle stem cell found

MDA-supported scientists in France identify a previously unknown muscle stem cell in the spaces between muscle fibers in mice. Called “PICs,” the cells may play an important role in muscle regeneration and repair and could have implications for treatment of muscular dystrophies.

Gene therapy rescues mice with SMA

A research team reports “unprecedented” improvement in newborn SMA-affected mice that received gene therapy via intravenous injection. Newborn mice that received the treatment demonstrate near-normal motor function (movement) and brain-to-muscle signaling, as well as a dramatic increase in survival. The team utilized key findings derived from previous MDA-supported studies in their investigation.

2009: New drugs being developed for Friedreich’s ataxia

Repligen Corp. of Waltham, Mass., reports significant progress in developing a treatment for Friedreich’s ataxia. Repligen has MDA support to develop compounds called histone deacetylase (HDAC) inhibitors, which coax cells into manufacturing frataxin protein despite the presence of a mutation in the frataxin gene (the underlying cause of FA). The company submits an application to the U.S. Food and Drug Administration to begin clinical trials of its lead compound, RG-2833.

Small molecule drug disrupts the disease process in MMD1

A drug called pentamidine, already approved by the U.S. Food and Drug Administration to treat several conditions, counteracts some of the effects of abnormal genetic instructions in type 1 myotonic muscular dystrophy. MDA-supported researchers continue to refine the compound in pursuit of a safe, long-term treatment for the disease.

Three new possible ALS risk raisers identified

A large-scale study in which MDA-supported researchers participated identify two DNA sequences on chromosome 9 and one on chromosome 19 that differ significantly in people with and without sporadic (nonfamilial) amyotrophic lateral sclerosis. The identified DNA regions on both chromosomes contain genes for biological processes that could have an effect on the disease.

Obesity drug increases utrophin in DMD mice

An experimental drug being developed to treat obesity and high blood lipid (fat) levels also may have promise for the treatment of Duchenne muscular dystrophy and Becker muscular dystrophy.
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WNT7a protein boosts muscle repair

Researchers receiving MDA support find a protein called WNT7a causes specialized muscle-repair cells to proliferate, a finding that could have implications for treatment of muscular dystrophies. The protein acts on the so-called satellite cells, which can mature and form muscle tissue and can replicate themselves and form new stemlike repair cells. Understanding these processes has important implications for therapy development in diseases where muscles degenerate.

IGF1 genes rescue SBMA-affected muscles

A protein known as insulin-like growth factor 1 (IGF1) may provide a new lead in the treatment of spinal-bulbar muscular atrophy, MDA-supported researchers find. Mice with an SBMA-like disease that received extra IGF1 genes fared better than those without the extra IGF1 genes on measures of motor function, muscle mass and strength.

Immune system modifier identified as promising compound for ALS

Scientists at the MDA-supported ALS Therapy Development Institute in Cambridge, Mass., find that a molecule they call ALSTDI-00846, which modifies the immune system, has beneficial effects in mice with a disease resembling amyotrophic lateral sclerosis. The molecule will undergo further testing.

Injections of utrophin help mice missing dystrophin

MDA-supported researchers modify utrophin protein molecules to enter and benefit muscle fibers in mice with a disease similar to Duchenne muscular dystrophy. Utrophin can partially substitute for the missing muscle protein dystrophin, and may be less likely to cause an adverse immune response than dystrophin in boys with DMD. Previously, utrophin has been given to mice as a gene but not as a protein. Delivering utrophin as a protein may pose fewer safety concerns than utrophin gene injections.

Compound that frees trapped protein shows promise as MMD treatment

Researchers who have received MDA support find a compound called CAG25, an “antisense oligonucleotide,” frees the needed MBNL1 protein from entanglement in extra genetic material associated with myotonic dystrophy. The compound shows promise in mice with an MMD-like disease. It will receive further testing.

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Second DMD exon-skipping trial restores dystrophin

AVI BioPharma of Portland, Ore., announces its experimental compound AVI4658 injected into a foot muscle restored production of the muscle protein dystrophin in about 10 boys with Duchenne MD in the United Kingdom. Developed by an international team including two MDA-supported investigators, AVI4658 is a laboratory-engineered molecule that coaxes muscle cells to “skip” a flawed section (exon) of the
the nervous system likely play a larger role in amyotrophic lateral sclerosis than previously believed, opening new targets for therapy.

‘Read-through’ drug restores dystrophin in DMD-affected boys

The experimental medication PTC124, developed by PTC Therapeutics of South Plainfield, N.J., with MDA support, restores production of the needed protein dystrophin in six boys with Duchenne muscular dystrophy who took it at a high dose for a month. Earlier, about half of 26 boys with DMD who took PTC124 at a lower dose also began making dystrophin. The drug is designed to make muscle cells ignore an aberrant molecular “stop sign” in the dystrophin gene.

Exon-skipping compound restores dystrophin production in DMD

Four boys with DMD who received muscle injections of an exon-skipping compound called PRO051, developed by the Dutch company Prosensa and by an MDA-supported scientist at Leiden (Netherlands) University, begin making the needed protein dystrophin in a leg muscle.

New SMA gene identified

MDA-supported researchers identify an X-chromosome gene that causes a rare form of spinal muscular atrophy. The finding may yield additional information about all forms of this disease.

High-dose vitamin C to be tested in CMT

An MDA-supported trial will test the hypothesis that high-dose vitamin C may help patients with type 1A Charcot-Marie-Tooth disease, a disorder of peripheral
nerves, after studies in mice with a CMT-like disease appear promising.

2007:

300 ‘antisense’ compounds developed for possible use in DMD

An MDA-funded team in Australia develops some 300 “antisense” compounds that can coax muscle cells to skip over errors in the dystrophin gene and produce functional dystrophin protein molecules. Dystrophin is needed but missing in DMD. One such compound is already being tested in boys with the disease.

Researchers release molecular ‘brake’ on protein that could help treat DMD

MDA-supported researchers identify a molecule called ERF that keeps a potentially therapeutic protein, utrophin, confined to one small area of muscle fibers. Reducing ERF levels appears to release this “brake” on utrophin production, allowing it to be produced all over the fibers and opening up a possible new therapeutic pathway for DMD.

Toxic neighboring cells identified in ALS-affected nervous system

MDA-supported researchers find that nervous system cells called glia secrete an unknown toxic compound that kills neighboring motor neurons, the muscle-controlling nerve cells affected in amyotrophic lateral sclerosis. They say transplanting stem cells that become good glia into people with ALS might be beneficial.

Blocking inflammation pathway helps in DMD

MDA-backed researchers confirm that blocking inflammation has significant benefits in Duchenne muscular dystrophy. When they treated DMD-affected mice with an engineered molecule that blocks a specific part of the inflammatory pathway, the animals had more regeneration of muscle tissue and more effective breathing muscles than untreated mice did. The researchers believe these findings may help unravel some of the underlying mechanisms involved in DMD and improve understanding and use of anti-inflammatory drugs, such as prednisone.

Researchers identify new type of muscle stem cell

MDA-supported researchers in Italy announce they’ve identified a new type of muscle stem cell that they believe is highly promising for treatment of muscular dystrophies. These new stem cells, called “pericyte-derived,” are located around small blood vessels in muscle tissue. When injected into mice with Duchenne muscular dystrophy, they matured into muscle fibers and improved the animals’ ability to grip a rod and stay on a treadmill.

Two anti-scarring drugs show promise in mice with DMD

An MDA research grantee is among the scientists who announced that two drugs, losartan and pirfenidone, have shown promise in reducing scar formation (fibrosis) in mice affected by Duchenne muscular dystrophy. Scar formation resulting from excess deposits of connective tissue is a major factor in muscle damage in DMD and other muscle diseases.
Largest ever ALS drug search begins
MDA and the ALS Therapy Development Institute in Cambridge, Mass., launch the largest drug discovery project in amyotrophic lateral sclerosis in history. The three-year, $36 million endeavor will attempt to identify biochemical targets and find drugs that work on them.

2005:
Cardiac stem cells ID’d in lab
MDA research grantees find cardiac muscle stem cells in the hearts of rodents and humans. They say the cells, identified by the presence of the protein islet-1, are likely to help researchers understand human heart muscle disease and may even lead to treatment strategies.

Sodium phenylbutyrate trial begins in ALS
MDA researchers discover that sodium phenylbutyrate appears to interfere with a cell death program and extends the lives of mice with amyotrophic lateral sclerosis (Lou Gehrig’s disease). In conjunction with the Veterans Administration, they begin a trial of the drug in people with ALS.

Ceftriaxone helps mice with ALS
An MDA-supported research team reports that the drug ceftriaxone extends lives and prolongs strength in mice with ALS. A clinical trial of the drug, which experts believe improves recycling of the potentially toxic chemical glutamate, is approved by the U.S. Food and Drug Administration in 2006.

2006:
Lab-made enzyme approved by FDA
Myozyme, a laboratory-engineered enzyme patented by Genzyme and developed in part with basic research funded by MDA, is approved for use in children and adults with acid maltase deficiency (Pompe disease). It replaces the missing enzyme in this metabolic muscle disease.

Gene therapy trial for Duchenne dystrophy begins
Scientists and physicians launch the first U.S. human gene therapy trial directed at Duchenne muscular dystrophy, with the support of a $1.6 million grant from MDA. The first of six boys with DMD receives an injection of genes for dystrophin, the missing protein in DMD, in one arm and a placebo in the other. The scientists will later measure dystrophin production and monitor the effects of the gene transfer on the children.

Variants in ‘detox’ genes found to raise ALS risk
MDA-supported investigators identify variations in and around genes known as PONs, whose normal role is to detoxify poisons such as pesticides and nerve gas, as risk factors for developing amyotrophic lateral sclerosis. The finding may help explain why Gulf War veterans have a higher than normal rate of ALS development and why occupational clusters of ALS (Lou Gehrig’s disease) occasionally have been identified.

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2004:

Three MD Centers of Excellence result from MDA-NIH collaboration

Three new “centers of excellence” in muscular dystrophy research are established at the University of Washington in Seattle, the University of Pittsburgh and the University of Rochester (N.Y.), as a result of a collaborative funding arrangement between MDA and the National Institutes of Health.

Key mechanisms found in myotonic MD

MDA-funded groups discover that two types of proteins — transcription factors and muscleblind — are both interfered with in cells affected by myotonic muscular dystrophy. The findings lead to additional investigations at the newly established muscular dystrophy center of excellence at the University of Rochester (N.Y.), co-funded by MDA and the National Institutes of Health.

Gene found for rare form of ALS

MDA-backed researchers find the gene for a rare, juvenile-onset form of ALS. The gene, on chromosome 9, carries instructions for a protein called senataxin. The finding has clear implications for diagnosis of juvenile-onset ALS and may increase understanding of ALS in general.
Metabolic Diseases of Muscle
- Phosphorylase deficiency (McArdle disease)
- Acid maltase deficiency (Pompe disease)
- Phosphofructokinase deficiency (Tarui disease)
- Debrancher enzyme deficiency (Cori or Forbes disease)
- Mitochondrial myopathy
- Carnitine deficiency
- Carnitine palmityl transferase deficiency
- Phosphoglycerate kinase deficiency
- Myoadenylate deaminase deficiency
- Lactate dehydrogenase deficiency

Myopathies Due to Endocrine Abnormalities
- Hyperthyroid myopathy
- Hypothyroid myopathy

Other Myopathies
- Myotonia congenita
- Paramyotonia congenita
- Central core disease
- Nemaline myopathy
- Myotubular myopathy
- Periodic paralysis

Inflammatory Myopathies
- Polymyositis
- Dermatomyositis
- Inclusion-body myositis

Diseases of Neuromuscular Junction
- Myasthenia gravis
- Lambert-Eaton (myasthenic) syndrome
- Congenital myasthenic syndromes

Diseases of Peripheral Nerve
- Charcot-Marie-Tooth disease
- Friedreich’s ataxia
- Dejerine-Sottas disease