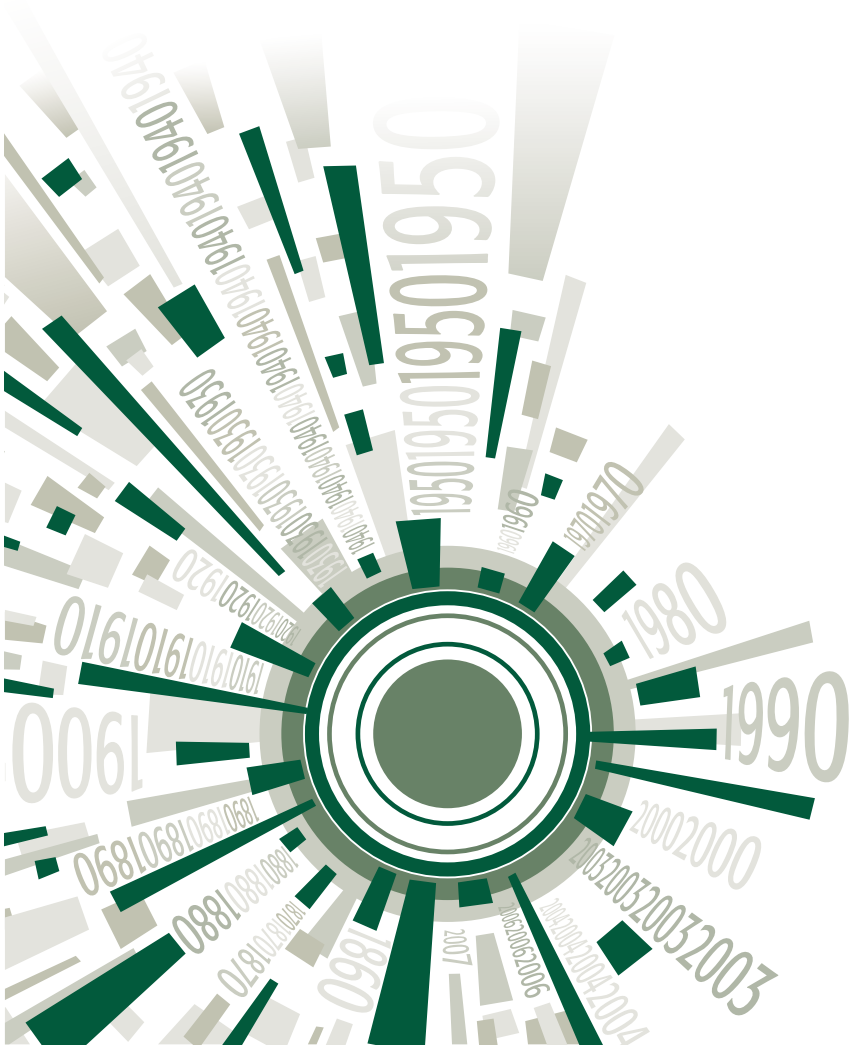


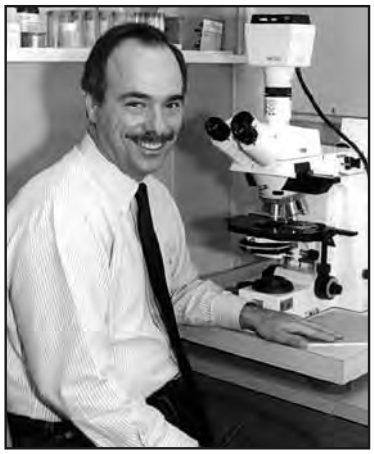
Milestones in Duchenne Muscular Dystrophy Research

MDA Muscular Dystrophy Association
Fighting Muscle Disease

Updated January 2009

Duchenne de Boulogne, after whom Duchenne muscular dystrophy is named. (From "The Founders of Neurology," courtesy Charles C. Thomas Publisher.)

Lou Kunkel, whose team identified the dystrophin gene in 1986.



Kevin Campbell

1860-1900:

French physician Guillaume Duchenne de Boulogne and British physician Edward Meryon describe what would later be called Duchenne muscular dystrophy (DMD)

Microscope used to study muscle in health and disease

1930-1960:

Different types of muscular dystrophies recognized

X-chromosome-linked inheritance pattern for DMD confirmed

German physician Peter Emil Becker describes a muscle disease similar to DMD and with same inheritance pattern but less severe and allowing longer survival (1950s); it later will be called Becker muscular dystrophy (BMD)

1960-1975:

Location of basic DMD defect (nervous system, muscles or blood flow) debated

Elevated serum creatine kinase (CK) levels begin to be used to detect DMD carriers

First studies report on the benefit of prednisone in DMD

1975-1980:

MDA conference on site of DMD defect establishes muscle-fiber membrane defect hypothesis as front-runner to explain DMD

Research attention shifts to muscle-fiber membrane

1980-1984:

Emerging techniques in molecular genetics localize gene underlying DMD to a specific region of the X chromosome and show BMD is likely due to a defect in the same gene

1984-1988:

Using different approaches, Louis Kunkel at Harvard Medical School in Boston and Ronald Worton at the Hospital for Sick Children in Toronto narrow the region of the X chromosome containing the gene that, when defective, causes DMD

Gene responsible for DMD is identified by Louis Kunkel's team

Protein made from DMD gene is described, named dystrophin and localized to muscle-fiber membrane

1988-1994:

Kevin Campbell at the University of Iowa shows that dystrophin protein is not directly inserted into the muscle-fiber membrane, but is attached via a cluster of proteins that would become known as the dystrophin-glycoprotein complex (DGC)

DGC is further described, and proteins in it are found to be significantly deficient in DMD and reduced to a lesser degree in BMD

Severity of DMD or BMD determined to be correlated with amount of dystrophin present at muscle-fiber membrane (the more dystrophin, the less severe the symptoms)

Location and type of flaw in dystrophin gene determined to be correlated with DMD or BMD severity in some cases

Cell transplantation technique called myoblast transfer helps DMD-affected mice

Myoblast transfer explored in several human trials but survival of transplanted cells and dystrophin production from them are minimal

Corticosteroid prednisone confirmed to slow the progression of DMD in several clinical trials

Transferring functional dystrophin genes into DMD-affected tissues (gene therapy) explored in cells and mice

MDA National Chariman Jerry Lewis, with former MDA Goodwill Ambassador Benjamin Cumbo, advocating for the MD-CARE Act before a U.S. Senate subcommittee on Feb. 27, 2001.

Scientists at PTC Therapeutics received MDA support to develop PTC124.

1995-2000:

Dystrophin gene miniaturized to facilitate gene therapy

Methods of delivering dystrophin gene, with or without viral transporters, explored

Dystrophin gene further miniaturized to fit inside adeno-associated viral shell, which becomes preferred delivery method

Stem cells to treat DMD come under consideration

Mice with DMD found to benefit from high levels of utrophin (a protein similar to dystrophin), whether bred to produce extra utrophin or given utrophin genes via gene therapy

2000-2005:

Corticosteroid prednisone found effective in slowing progression of DMD in more trials

American Academy of Neurology publishes guidelines for prednisone use in DMD

MD-CARE Act passed in U.S. Congress in 2001 with MDA's help; mandates establishment of centers of excellence in muscular dystrophy

MDA and National Institutes of Health co-fund MD centers of excellence at University of Washington-Seattle, University of Rochester (N.Y.) and University of Pittsburgh

Dystrophin-deficient mice given a compound to block myostatin protein show increased muscle mass and strength

L-arginine and molsidomine found to increase levels of utrophin (possible substitute for dystrophin) in mice

Constructs called antisense oligonucleotides found to block flawed parts of genes and allow nearly normal protein molecules to be produced in mice; technique dubbed "exon skipping"

Compound called PTC124 found to allow cells to ignore molecular stop signs and produce normal dystrophin protein molecules

MDA gives PTC Therapeutics $1.5 million to develop PTC124 for DMD

Trial of PTC124 opens to boys with DMD with "premature stop codon" mutations

2005-2009:

Follistatin protein found to turn off myostatin and increase muscle mass in mice

Plans begin for multinational trial to optimize corticosteroid use in DMD

PTC124 found to restore dystrophin in about half of boys with DMD in 28-day trial

PTC Therapeutics launches larger, longer trial of PTC124

Exon-skipping trial in Netherlands finds compound developed with MDA support allows dystrophin production in all four DMD-affected boys tested

Exon-skipping trial opens in United Kingdom using a second compound developed with MDA support

Some 300 exon-skipping compounds developed to target different parts of dystrophin gene

First U.S. clinical trial of gene therapy in DMD begins

Dystrophin gene injections into an arm muscle judged safe and well-tolerated in six boys with DMD; plans are made to test three additional boys at higher dose

Intravenous injection of highly miniaturized dystrophin genes restores muscle structure and function in mice

Method of delivering genes without viral transporters developed

Andrew Kilbarger, 8, receiving an injection of dystrophin genes in March 2006.

Giulio Cossu

Molecule identified that allows utrophin to be produced all around muscle fibers instead of in one small place

Dystrophin-deficient mice produce dystrophin after an arterial injection of muscle-derived stem cells

Dystrophin-deficient dogs produce dystrophin after receiving arterial injections of stem cells called mesoangioblasts that were taken from muscle tissue

Pericyte-derived stem cells are identified in human muscle tissue by Giulio Cossu of the Istituto Scientifico San Raffaele, Milan, Italy

Stem cells carrying an exon-skipping compound cause significant recovery of muscle form and function in dystrophin-deficient mice

MDA-associated physicians join pulmonologists in releasing recommendations for use of anesthesia in DMD

Transfer of utrophin gene via blood vessels found as effective as dystrophin gene transfer in mice with severe DMD-like disease

Chemical switch called zinc-finger protein 51 found to activate utrophin production in DMD mice

Raising level of sarcospan protein improves muscle health in DMD mice, probably by stabilizing utrophin

MDA commits $1 million to new, 10-center Clinical Research Network, designating five centers as DMD-specific

MDA has funded Duchenne muscular dystrophy research since 1950, and has paid for more research into this disease than any nongovernmental agency. It also provides the most comprehensive services program of any nonprofit organization in the country.

MDA's website is constantly updated with the latest research information. Go to www.mda.org.

Louis Kunkel and Jerry Lewis at a press conference announcing the identification of the dystrophin gene on Oct. 16, 1986.

MDA's Purpose and Program

The Muscular Dystrophy Association fights neuromuscular diseases through an unparalleled worldwide research effort. The following diseases are included in MDA's program:

Muscular Dystrophies

Myotonic dystrophy *(Steinert disease)*
Duchenne muscular dystrophy
Becker muscular dystrophy
Limb-girdle muscular dystrophy
Facioscapulohumeral muscular dystrophy
Congenital muscular dystrophy
Oculopharyngeal muscular dystrophy
Distal muscular dystrophy
Emery-Dreifuss muscular dystrophy

Motor Neuron Diseases

Amyotrophic lateral sclerosis *(ALS)*
Infantile progressive spinal muscular atrophy *(Type 1, Werdnig-Hoffmann disease)*
Intermediate spinal muscular atrophy *(Type 2)*
Juvenile spinal muscular atrophy *(Type 3, Kugelberg-Welander disease)*
Adult spinal muscular atrophy *(Type 4)*
Spinal-bulbar muscular atrophy (*Kennedy disease)*

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

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
Phosphoglycerate mutase deficiency
Lactate dehydrogenase deficiency
Myoadenylate deaminase 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

MDA Muscular Dystrophy Association
Fighting Muscle Disease

MDA's website, mda.org, is constantly updated with the latest research news and information about the diseases in its program. Follow MDA on Facebook, Twitter and YouTube.

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P-533W 6/11