Milestones
in ALS Research

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ALS DIVISION

Muscular Dystrophy Association • als.mda.org

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Lou Gehrig made all Americans aware of the devastating effects of ALS.

Eleanor Gehrig, Lou's widow, worked with MDA in its early years.

MDA's ALS Research Mission

ALS (amyotrophic lateral sclerosis, or Lou Gehrig's disease) is a multisystem neurodegenerative disorder that primarily affects motor neurons, the nerve cells that control voluntary muscle movement. The loss of motor neurons causes the muscles they control to become weak and then paralyzed. Death, which can occur as early as three to five years after diagnosis, usually is due to respiratory complications caused by paralysis of the muscles used in breathing.

MDA is the world leader in funding ALS research. Its worldwide program supports research efforts ranging from basic (early-stage) science, to preclinical testing and therapy development, to human clinical trials. Since its inception, MDA has dedicated $324 million to ALS research, services, education and advocacy programs.

Current MDA-supported ALS research is focusing on several areas, including:

- ALS-associated genes SOD1, TDP43, FUS, UBQLN2 and C9ORF72;
- potentially toxic protein clumps called aggregates;
- oxidative stress;
- factors that cause support cells to attack motor neurons instead of nourishing and protecting them;
- disruption of the cellular waste-disposal system;
- the role of the immune system in ALS;
- ways to nourish and protect motor neurons;
- mitochondrial energy production;
- "antisense" therapy designed to block toxic protein production;
- stem cell therapy; and
- drug discovery and development.

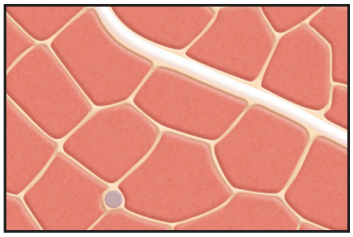
Other critical MDA-funded ALS research contributions include:

- maintenance of an MDA ALS Clinical Research Network to streamline and support tests of experimental treatments. The network is located at five centers: Methodist Neurological Institute (Houston), Massachusetts General Hospital (Boston), Columbia University (New York City), Emory University (Atlanta), and California Pacific Medical Center (San Francisco);
- sponsorship and hosting of national and international scientific meetings on ALS research;
- support of the MDA Neuromuscular Disease Registry, which aims to expedite clinical trials, and improve survival and quality of life in ALS and other diseases; and
- advocacy efforts focused on speeding up the regulatory pathway to approval for experimental ALS therapies.

As you will see in this report, ALS has so far resisted the best efforts of decades of dedicated researchers. But the disease is slowly giving up its secrets. MDA continues to be inspired by the words of the late Michael E. DeBakey, world-renowned heart surgeon and an MDA national vice president, who said, "There are no incurable diseases. There are only diseases for which no treatment has yet been developed."

1874:

French neurologist Jean Martin Charcot establishes amyotrophic lateral sclerosis as a distinct disease



By the 1960s, MDA-supported scientists were becoming highly knowledgeable about the microscopic structures of nerve and muscle tissues.

MDA research grantee W. King Engel at the University of Southern California in Los Angeles tested thyrotropin-releasing hormone in ALS.

1900s-1940s

Cluster of ALS cases identified on Western Pacific island of Guam

High incidence of ALS noted on Kii Peninsula off Japanese island of Honshu

New York Yankees first baseman Lou Gehrig retires because of ALS in 1939

Lou Gehrig dies of ALS in 1941

ALS becomes widely known as Lou Gehrig's disease

1950s

MDA is founded and begins funding ALS research, focusing mainly on basic nervous system physiology

Eleanor Gehrig, Lou Gehrig's widow, becomes MDA National Campaign Chairman

1960s

Studies of nerve-to-muscle signal transmission begin

Studies continue of microscopic structures of nerve and muscle cells

1970s

Studies of distribution of ALS cases on the island of Guam and the United States mainland raise questions about the possibility of environmental factors contributing to ALS

Attempts to isolate viruses from ALS-affected tissue are unrevealing

Studies continue of muscle and nerve structure and physiology in ALS

1980s

Clinical trials in people with ALS of thyrotropin-releasing hormone, a substance secreted by the hypothalamus that stimulates the pituitary gland (not effective)

Attempts to isolate viruses in ALS continue

Possible role of polio virus infection in ALS ruled out

Clinical trial of virus-fighting chemicals called interferons (not effective)

Studies begin of the possible role in ALS of autoimmunity (an immune response to the body's own tissues)

Clinical trial of irradiation of lymph nodes, part of the immune system (not effective)

Clinical trial of immunosuppressant cyclosporine (not effective)

Studies start of familial ALS (where there is a history of ALS in more than one family member)

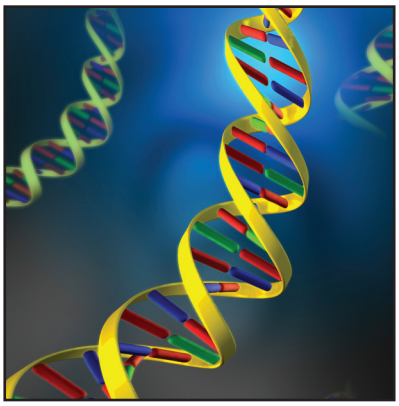
ALS genetics studied

Isolation of genes related to ALS attempted

Clinical trial of growth hormone (not effective)

Clinical trial of branched chain amino acids (not effective)

ALS clusters investigated



Attempts were made in the 1980s to isolate genes related to ALS, but the first ALS gene (SOD1) would not be identified until 1993.

MDA-supported researcher and clinician Stanley H. Appel was among the first to suspect a major role for the immune system in ALS.

The 1990s marked the first wave of human clinical trials in ALS.

1990s

Clinical trial of immunosuppressant cyclophosphamide (not effective)

Studies begin of the nervous system chemical glutamate

Building on glutamate data, riluzole (Rilutek), a glutamate inhibitor, is approved for use in ALS; the drug modestly extends life span

Clinical trial of gabapentin (Neurontin), a glutamate inhibitor (not effective)

Factors in nerve cells that make them susceptible to ALS-related damage investigated

Cellular waste disposal system studied

Neurotrophic (nerve-nourishing) natural chemicals and spinal motor neurons examined

Effect studied of immune system proteins taken from blood of those with ALS

Mutations in the superoxide dismutase 1 (SOD1) gene on chromosome 21 identified as the cause of some familial forms of ALS

Mouse with mutated SOD1 gene developed as a research model of ALS

Building on knowledge that SOD1 has antioxidant properties, many studies begin of free radical activity (which SOD1 combats)

Clinical trial of SOD1 delivered into spinal fluid (not effective)

Genetic regulation of programmed cell death, a potential cause of degeneration, investigated

Study begins to identify ALS risk genes

An imaging technique called magnetic resonance spectroscopy is used to study the ALS-affected brain

Scientists transfer neuroprotective genes into mice with an ALS-like disease

Investigations of the roles of insulin-like growth factor 1 (IGF1), ciliary neurotrophic factor (CNTF), glial-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) lead to industry-sponsored clinical trials of each of these; results from two IGF1 studies were conflicting; none of the other drugs were effective

Role of motor neurons (muscle-controlling nerve cells) versus glia (nervous system support cells) studied in ALS

2000s

Scientists find that the alsin gene, when flawed, can cause a childhood form of ALS

Clinical trial conducted of celecoxib (Celebrex), an anti-inflammatory drug (not effective)

Clinical trials conducted of coenzyme Q10, an antioxidant that acts in cellular energy centers called mitochondria (not effective)

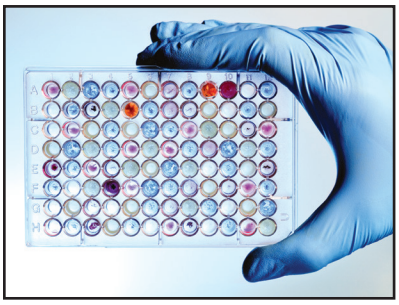
Findings suggest people with ALS make a variant form of glutamate transport protein

Flaws in VEGF gene implicated as ALS disease factor

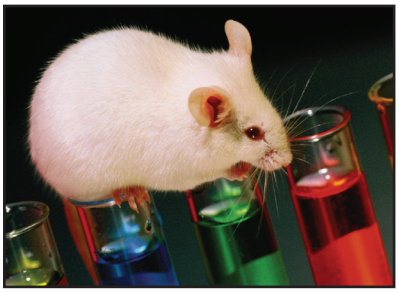
Flawed senataxin gene identified as a cause of juvenile ALS

MDA and the ALS Therapy Development Institute (ALS TDI) join forces to fund an ALS drug discovery effort

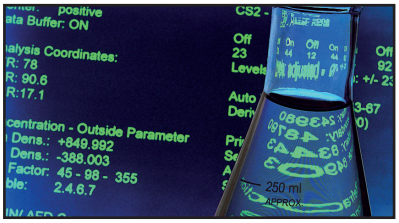
National Institutes of Health funds trial of ceftriaxone, a possible glutamate transport enhancer, based on MDA-funded basic science research (not effective)



Scientists continued to pinpoint alterations and distinct characteristics of immune system cells at the different stages of ALS.



The development of the TDP43 mouse model of ALS is expected to broaden scientists' ability to observe disease progression and the effects of experimental treatments.



In the second decade of the 21st century, commonalities in underlying mechanisms are increasingly noted between the sporadic and familial forms of ALS.

2000s *(continued)*

Variations in enzymes that help detoxify nerve gas and pesticides linked to ALS

Clinical trials of high-dose coenzyme Q10, Myotrophin (IGF1) and thalidomide, based on MDA-supported early-stage research, show these drugs are ineffective in human ALS

Clinical trial of minocycline, an antibiotic (not effective)

Trial of lithium carbonate conducted after a small Italian study suggests it may slow ALS progression (not effective)

An industry-sponsored trial of the glutamate-blocking drug talampanel begins, based on MDA research showing excess glutamate around nerve cells may contribute to ALS (not effective)

Researchers find evidence to support the presence of a leakier-than-normal barrier between spinal cord nerve cells and blood vessels in people with ALS

Scientists create nerve cells from the skin cells of an ALS patient as a way to study disease development on the cellular level

Investigators find immune system T cells are involved in protecting motor neurons in mice with an ALS-like disease

An industry-sponsored trial of arimoclomol in the SOD1 form of familial ALS opens at MDA/ALS centers in Atlanta and Boston; the drug is designed to increase levels of molecular "chaperones," which help cells that are under stress

Investigators find a variant version of the gene for a protein called KIFAP3 increases survival time in people with ALS by an average of 14 months

An industry-sponsored clinical trial of stem cells in people with ALS begins at the MDA/ALS Center at Emory University in Atlanta (ongoing)

Scientists develop mice with a mutation in the TAR DNA binding protein (TDP43) gene, which can cause ALS in humans, giving the field an additional research tool

Two DNA sequences on chromosome 9 and one on chromosome 19 are found to be significantly different in people with ALS compared to those without the disease

2010s

A study of the safety and possible benefits of a high-fat, high-calorie diet in people with ALS is launched by the MDA ALS Clinical Research Network (ongoing)

A clinical trial shows that the "antisense" therapy ISIS-SOD1-Rx, designed to block production of toxic SOD1 protein molecules in people with the SOD1-related form of familial ALS, is well-tolerated

A new avenue of therapeutic investigation is opened after findings show that blocking the immune system CD40L pathway delays disease onset and extends survival in mice with an ALS-like disease

Emphasis placed on identifying and developing clinical biological indicators ("biomarkers") of ALS as a way to more accurately diagnose the disease and measure the effects of therapies in ALS clinical trials

Abnormalities in immature "NG2+" nervous system cells in mice with an ALS-like disease appear to play a role in the ALS disease process

A large-scale study begins to examine the relationship between cell-damaging oxidative stress and the ALS disease process

Focus of ALS research expands from motor neurons to central nervous system support cells (glia), which include astrocytes, microglia and oligodendrocytes

Research into the normal and abnormal functions of TDP43 protein helps uncover possible disease mechanisms and targets at which to aim experimental therapies in sporadic and some familial forms of ALS ("sporadic ALS" refers to ALS in which there is no known family history of the disease)

Researchers identify mutations in the valosin-containing protein (VCP) gene as a cause of some cases of familial ALS

Scientists find that normally supportive nervous system cells called astrocytes are toxic to motor neurons when taken from people with SOD1-releated ALS or sporadic ALS, supporting the idea that SOD1-related familial ALS and sporadic ALS share disease mechanisms

In work built on earlier MDA-supported findings, mutations in the ubiquilin 2 gene on the X chromosome are found to cause ALS, and accumulations of the ubiquilin 2 protein, even without gene mutations, also are associated with the disease

An expanded section of repeated DNA elements on chromosome 9 in a gene called C9ORF72 is identified as the most common known genetic cause of familial and sporadic ALS, familial frontotemporal dementia (FTD) and ALS with FTD

Mutations in the profilin 1 (PFN1) gene are identified as the cause of familial ALS in 1 to 2 percent of people with the disease

A clinical trial is launched to determine whether the NeuRx Diaphragm Pacing System, an implanted device that stimulates the diaphragm muscle, can improve respiratory function and quality of life in people with ALS (ongoing)

Low levels of immune system cells known as regulatory T cells — T-regs for short — and reduced FOXP protein production are associated with faster disease progression

As the world leader in the fight against ALS, MDA has funded ALS research for more than six decades. MDA-supported scientists around the world have contributed to the advances listed in this publication.

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