

# PLAYING DEFENSE AGAINST LOU GEHRIG'S DISEASE

## KEY CONCEPTS

- Amyotrophic lateral sclerosis (ALS) is a disease that kills motor neurons. Patients become paralyzed and usually die within three to five years of onset. The most famous victim is legendary New York Yankees player Lou Gehrig (*below*).
- ALS was once considered nearly insurmountable to a scientific attack, but researchers have recently discovered treatments that can slow the progress of the disease in rodents by protecting the axons of motor neurons.
- Investigators are now preparing clinical trials to test the effectiveness of the proposed ALS treatments in humans.

## Researchers have proposed potential therapies for a paralyzing disorder once thought to be untreatable

By Patrick Aebischer and Ann C. Kato

The official name of the illness is amyotrophic lateral sclerosis (ALS), but in the U.S. it is better known as Lou Gehrig's disease. The great New York Yankees first baseman was diagnosed with ALS in 1939 and died two years later from the progressive neuromuscular disorder, which attacks nerve cells that lead from the brain and the spinal cord to muscles throughout the body. When these motor neurons die, the brain can no longer control muscle movements; in the later stages of the disease, patients become totally paralyzed.

First described in 1869 by French clinician Jean-Martin Charcot, ALS is a misunderstood illness. Doctors once thought it was rare but now consider it fairly common: about 5,000 people in the U.S. are diagnosed with ALS every year. In total there are about 30,000 ALS patients in the U.S. and approximately 5,000 in the U.K. ALS typically develops between the ages of 40 and 70, but the disease strikes younger and older patients as well. Other well-known people who suffered from ALS include British actor David Niven, Russian composer Dmitri Shostakovich and Chinese leader Mao Zedong. Researchers have found unusual clusters of patients with the disorder among Italian soccer players, veterans

of the Persian Gulf War and residents of the island of Guam, although no one knows why.

In his famous farewell address at Yankee Stadium, Gehrig called ALS "a bad break," which was a heartrending understatement. People usually succumb to the disease within three to five years after diagnosis. (A notable exception is Stephen Hawking, the renowned physicist of the University of Cambridge, who has lived with ALS for more than 40 years and is still making major contributions to the fields of cosmology and quantum gravity despite his physical handicap.) Until recently, investigators had few practical ideas for fighting the disorder, but in the past several years researchers have made great progress in determining how motor neurons die in ALS patients. In the near future, scientists may develop therapies that could retard the progress of ALS and perhaps even prevent its onset.

### A Devastating Disorder

You can glean a basic understanding of amyotrophic lateral sclerosis by parsing its name.

CREDIT

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“Amyotrophic” is an amalgam of Greek terms: “a” for negative, “myo” for muscle and “trophic” for nourishment. Putting it all together, the word conveys that the muscles in an ALS patient have no nourishment, so they atrophy or wither away. “Lateral” signifies the area of the spinal cord where portions of the dying nerve cells are located. As this area degenerates, it becomes hardened or scarred. (“Sclerosis” means hardening.) Perhaps the most devastating aspect of the illness is that the higher functions of the brain remain undamaged and patients are obliged to watch the demise of their own bodies.

The most common form of the disease is called sporadic ALS because it appears to strike randomly, targeting anyone in any given place. Familial ALS is a particular form of the disease that is inherited, but only about 5 to 10 percent of all patients fall into this category. Although the early symptoms of the disorder vary from one individual to another, they usually include dropping objects, tripping, unusual fatigue in the arms or legs, difficulty in speaking, muscle cramps and twitches. The weakness that affects ALS patients makes it hard for them to walk or use their hands for daily activities such as washing and dressing. The disease eventually hampers swallowing, chewing and breathing as the weakening and paralysis spread to the muscles in the trunk. Once the muscles responsible for breathing are attacked, the patient must be put on a mechanical ventilator to survive.

Because ALS harms only motor neurons, the senses of sight, touch, hearing, taste and smell

**DYING BACK:** One of the key breakthroughs in the fight against ALS is the finding that the degeneration of the motor neurons begins at the ends of the axon—the nerve cell’s main branch—and proceeds back to the cell body.

are not affected. For unknown reasons, the motor neurons responsible for movements of the eyes and bladder are spared for long periods. Hawking, for example, still has control of his eye muscles; at one time he communicated by raising an eyebrow as an assistant pointed to letters on a spelling card. (He can also move two fingers on his right hand and now uses a speech synthesizer controlled by a hand switch.) The U.S. Food and Drug Administration has so far approved only one treatment for ALS: riluzole, a molecule that can prolong survival by several months, most likely by curbing the release of harmful chemicals that damage motor neurons.

What do we know about the causes of this horrible disease? Investigators have put forward a vast number of theories to explain its origin, including infectious agents, a faulty immune system, hereditary sources, toxic substances, chemical imbalances in the body and poor nutrition. Although scientists have not yet determined what triggers the disorder in most patients, a breakthrough came in 1993, when a consortium of geneticists and clinicians discovered a gene that was responsible for one form of hereditary ALS that represents approximately 2 percent of all cases. This gene turned out to code for an enzyme called superoxide dismutase (SOD1) that protects cells from damage caused by free radicals (highly reactive molecules produced

## A CROWD OF PATIENTS

ALS was once thought to be rare, but about 30,000 Americans suffer from the disease—enough to fill more than half the seats in Yankee Stadium.

in the body by normal metabolic processes).

Researchers subsequently identified more than 100 different mutations in the SOD1 gene that cause ALS. It remains a mystery, though, how alterations in this ubiquitous enzyme can produce such specific damage to one type of cell in the nervous system. At first scientists thought that the toxicity was related to a loss of the cell's capacity to fight free radicals. Now, however, several lines of evidence suggest that the various mutations confer some destructive property to the mutated enzyme, a phenomenon that geneticists call a gain of function.

The identification of mutations in the SOD1 gene enabled scientists to insert the variant DNA into the genomes of laboratory animals, creating lines of rodents that would develop a motor neuron disorder that is very similar to ALS. Because investigators could now examine the course of the disorder in these animal models, there was a sudden explosion of research and publications on a disease that had previously been considered nearly insurmountable to a scientific attack. Other animal models became available after the discovery of unrelated genes that also caused the death of motor neurons. At last, it was possible to challenge the assortment of hypotheses that had been pro-

posed over the years to explain how ALS arises.

We are beginning to understand that the motor neuron may have a novel mechanism for degenerating. The motor neuron's axon—the main branch extending from the cell body—is unusually long, extending as much as one meter in a tall person [see box at left]. At its terminal, the axon splits into a series of branches whose tips sit glued onto the muscle like the tines of a rake. Each connection between the nerve and the muscle is called a synapse. By releasing small molecules called neurotransmitters, the nerve stimulates the muscle to contract.

For many years, researchers believed that the motor neuron and its various parts die simultaneously. Scientists have now learned, however, that the different compartments of the motor neuron can die by different mechanisms. The cell body, which contains the nucleus of the neuron, usually dies by a process called apoptosis in which cells self-destruct by cutting themselves into pieces and packaging the fragments into small membrane bags that are easily removed. The axon dies by another mechanism, and, most likely, the synapse by yet another. If the nerve cell dies starting from the terminal region of

the axon, the process is called “dying back.” If it dies starting from the cell body, the process is called “dying forward.” More and more evidence indicates that in ALS the nerve cells show their first signs of degeneration in the region of the synapse and the axon. As a result, researchers are concentrating their efforts on finding drugs that can protect the axons of motor neurons rather than simply the cell bodies.

### Paths of Destruction

As mentioned earlier, some motor neurons are more susceptible to ALS than others, but researchers are only beginning to understand why. Recently Pico Caroni and his colleagues at the Friedrich Miescher Institute in Basel, Switzerland, have addressed this issue by making a map that shows how nerve impulses travel from the motor neurons to the muscles of a mouse. The investigators genetically engineered the mice to have fluorescent markers in the axons of some of their

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motor neurons. The neurons that connect to muscles in the limbs are divided into three types. The first type innervates fast-twitch and fast-fatigable (FF) muscle fibers that enable rapid, high-energy movements in the arms and legs. The second class of neurons control fast-twitch and fatigue-resistant (FR) fibers that are common in the smaller muscles in the limbs, and the third group innervates slow-twitch (S) fibers that are in constant use, such as the ones in the torso that maintain posture.

When Caroni and his co-workers examined the fluorescent markers in the SOD1 mice that were genetically prone to ALS, they found that the neurons controlling FF fibers degenerated early in the course of the disease. The FR neu-

rons failed during the intermediate period, and the S neurons stayed intact until the latter stages. This pattern closely matches the progression of symptoms in people with ALS, confirming the similarity between the animal and human forms of the disease.

Joshua Sanes and Jeff Lichtman, both now at Harvard University, have taken a similar approach, studying fluorescent axons with time-lapse imaging in living SOD1 mice. In this way, they were able to distinguish degenerating motor neurons from closely related nerve cells that are making an attempt to regenerate. Sanes and Lichtman concluded that two types of neurons exist within the same motor pathways in ALS mice: “losers” that become so fragmented that

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their connection with the muscle is broken and “compensators” that grow new axonal branches. If scientists can determine what factors are keeping the compensator neurons alive, they may be able to apply the results in future therapies.

Studies have shown that it is necessary to protect both the axon and the cell body to extend the life span of animals with ALS; protection of the cell body alone has no effect. These experiments reinforce the idea that different parts of the motor neuron are dying by different molecular processes. In the axon, the most abundant proteins responsible for maintaining its rigid shape are the neurofilaments. For unknown reasons, the more of these proteins there are in the axon, the larger its diameter and the greater its vulnerability to ALS. A group led by Jean-Pierre Julien at Laval University in Quebec has shown that when abnormally high amounts of neurofilaments accumulate in axons, they can block the flow of nutrients from the cell body to the synapse. This interference in the transport of material through the axon essentially strangles the motor neuron’s cell body to death. About 1 percent of all ALS cases arise from mutations in the gene that codes for neurofilaments.

Because of the structural asymmetry of the motor neuron, the cell body has to furnish an enormous amount of energy to keep its long axon and synaptic terminal alive. Important cellular

## Researchers have made great progress in determining how motor neurons die in ALS patients.

components, such as energy-generating mitochondria, must be fabricated in the cell body and then transported down the axon to the terminal; conversely, certain critical substances such as growth factors (proteins that can stimulate cell maturation and proliferation) must be transported from the terminal back to the cell body. All this intracellular movement requires molecular motors that are hooked up in a cogwheel fashion to minuscule tracks composed of microtubules. A breakdown in any of these processes can lead to the development of a motor neuron disease. Several research groups have shown that mutations in the molecular motors can kill motor neurons.

Until recently, scientists had believed that the motor neurons in ALS patients caused their own destruction, but new evidence is beginning to reveal that neighboring glial cells, which normally provide physical support and nutrition for neurons, may also play a role in inflicting the damage. ALS does not develop in mice with one type of SOD1 mutation, for example, if the mutant enzyme is produced only in the motor neurons or neighboring glial cells. Furthermore, Don Cleveland’s group at the University of California, San Diego, has shown that healthy glial cells can protect sick motor neurons and that, conversely, sick glial cells can induce degeneration in healthy motor neurons. Thus, it appears that both motor neurons and adjacent glial cells collaborate in causing the disease.

### Hopes on the Horizon

Given all the recent advances in basic research on ALS, what are the prospects for discovering effective treatments for the disorder? Researchers have already identified certain molecules that can protect the axons of motor neurons. One of these is a protein called ciliary neurotrophic factor, which is crucial to the survival of both motor and sensory neurons. Other molecules, such as glial cell–derived neurotrophic factor, protect the neuron’s cell body from self-destruction but do nothing for the axon.

In one study to find molecules that can protect axons, a group led by Jeffrey Milbrandt at Washington University in St. Louis decided to use a mouse mutant called Wld<sup>S</sup> (which stands for slow Wallerian degeneration) that has a natural mechanism of axonal protection because the animal’s DNA has an unusual fusion of two different genes. This genetic sequence codes for a chimeric protein that includes a peptide, or protein fragment, that is essential to the cellular garbage-disposal system, as well as the enzyme

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**NEURODEGENERATION:** Whereas a healthy motor neuron in culture (*top left*) has distinct axonal branching, a dying motor neuron (*bottom left*) has a distorted shape and a withered axon. Furthermore, DNA in the neuron’s nucleus forms clumps (*inset*). Although most ALS patients die within a few years, renowned physicist Stephen Hawking (*right*) has lived with the disease for more than four decades.

# Reading the Ailing Brain

With effective treatments for ALS still years away, researchers are developing devices that can receive signals from paralyzed patients' minds, enabling such patients to communicate, perform basic computer functions and, in some cases, operate prosthetic devices. Some of these so-called brain-computer interfaces (BCIs) require surgically implanted electrodes, which read the output of small clusters of neurons inside the brain's motor cortex, the brain's movement-control center.

Noninvasive BCIs, on the other hand, pick up the wavelike electrical activity emanating from millions of neurons through electrodes affixed to a patient's scalp. Neuroscientists Jonathan Wolpaw, Theresa Vaughan and Eric Sellers of the Wadsworth Center, part of the New York State Department of Health in Albany, and their colleagues have developed such a BCI—essentially, a brain-wave keyboard for ALS patients—that works by tapping into a brain signal that turns up when something attracts a person's attention. In the Wadsworth system (*photograph at right*), 17 rows and columns in a grid of 72 letters, numbers, punctuation marks and keyboard controls flash rapidly in sequence on a

**BRAIN-COMPUTER interface in action.**

computer screen while an ALS patient watches for the symbol or function he wants. Each time the desired symbol or function flashes, the user's brain emits the characteristic wave, and a computer processes the wave's timing and other features to discern which character or function the individual is trying to select.

So far five ALS patients have used the Wadsworth BCI to write and converse. One ALS-afflicted scientist uses it to run his research laboratory. Another depends on the technology to convey simple but important requests and information such as "Do not put sweaters on me" and "The dog peed on the floor." —*Ingrid Wickelgren, staff editor*

## COMPARING NEURODEGENERATIVE DISEASES

Researchers hope that the study of ALS will yield insights for treating other neurological disorders as well. Below is a comparison of the characteristics of the diseases.

### ALS

Age of onset: typically between 40 and 60  
Disease course: usually three to five years  
Genetically linked: about 10 percent of cases  
Neurons affected: motor  
Patients in the U.S.: 30,000

### HUNTINGTON'S

Age of onset: about 40  
Disease course: about 14 years  
Genetically linked: 100 percent  
Neurons affected: striatum (located deep within each hemisphere of the brain)  
Patients in the U.S.: 30,000

### PARKINSON'S

Age of onset: typically between 60 and 70  
Disease course: about 10 to 20 years  
Genetically linked: about 10 percent  
Neurons affected: substantia nigra (part of the midbrain)  
Patients in the U.S.: 1 million

### ALZHEIMER'S

Age of onset: usually between 60 and 70  
Disease course: about five to 20 years  
Genetically linked: about five to 10 percent  
Neurons affected: in the brain's cortex and hippocampus  
Patients in the U.S.: 5 million

for synthesizing nicotinamide adenine dinucleotide (NAD), a small molecule that is required for many metabolic reactions. When a nerve cell is injured in a *Wld<sup>S</sup>* mouse, the axon will degenerate much more slowly than it would in an ordinary mouse.

By studying mouse neurons in culture, Milbrandt's team showed that the Wallerian mutation enhances the activity of the NAD-synthesizing enzyme and that the resulting increases in NAD somehow protect the axons. The researchers extended their findings to show that higher levels of NAD were stimulating a biochemical pathway in the cell that appears to be responsible for prolonging longevity in roundworms and fruit flies [see "Unlocking the Secrets of Longevity Genes," by David A. Sinclair and Lenny Guarente; *SCIENTIFIC AMERICAN*, March 2006]. What is more, other small molecules such as resveratrol, which is found in the skin of red grapes, are active on this pathway and may also safeguard injured neurons. Several pharmaceutical companies are now trying to develop drugs that could fight ALS and other neurodegenerative diseases by invigorating the NAD pathway.

Another promising possibility comes from a

group led by Peter Carmeliet at the Catholic University in Leuven, Belgium. In the course of studying a different research problem, the investigators created transgenic mice—carrying genes transferred from another species—that were defective in producing vascular endothelial growth factor (VEGF), a protein involved in controlling the growth and permeability of blood vessels. Unexpectedly, these mice developed motor neuron disease.

The scientists wanted to know whether they could slow the degeneration of the mice's neurons by delivering VEGF to the nerve cells. Administering therapeutic proteins to the brain and spinal cord is a formidable task, however, because the walls of blood vessels in the central nervous system are impermeable to large molecules. A team led by Mimoun Azzouz and Nicholas Mazarakis at Oxford Biomedica, a British pharmaceutical company, tackled this challenge with a gene therapy approach, using a virus that could manufacture VEGF after it entered a nerve cell. The researchers injected the virus into various muscles in the VEGF-deficient mice; the terminals of the motor neurons captured the virus, which was then transported to the cell bod-

## POTENTIAL THERAPIES

Scientists have identified several possible treatments that may be able to slow the progress of ALS.

### NEUROTROPHIC FACTORS

Proteins such as vascular endothelial growth factor (VEGF) and insulinlike growth factor 1 (IGF-1) appear to protect motor neurons. These large molecules, however, cannot pass from the bloodstream to the central nervous system, so clinicians would have to use direct injections or viral delivery to administer the therapy.

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### SMALL MOLECULES

Compounds such as resveratrol, which is found in the skin of red grapes, may be able to protect neurons by stimulating the production of nicotinamide adenine dinucleotide (NAD). One advantage of small molecules is that they can pass through the blood-brain barrier.

### STEM CELLS

Grafted stem cells can act as biological pumps for delivering vital growth factors to damaged neurons. Experiments in rodents have shown that the stem cells can actually migrate to the regions where the injured neurons are located.

### RNA INTERFERENCE

Synthetic strands of RNA can interfere with the production of toxic proteins in neurons and glial cells. The RNA strands bind to certain messenger RNAs (mobile carriers of genetic information), preventing them from manufacturing their corresponding proteins.

### PHYSICAL EXERCISE

Studies have shown that putting mice on a regimen of exercise on running wheels can slow the progress of ALS. Combining the exercise with IGF-1 therapy has a synergistic effect that is more pronounced than that of either treatment alone.

ies in the spinal cord [*see box above*]. Once inside the motor neurons, the virus produced VEGF in sufficient quantities to delay the onset, and slow the progression, of ALS in the mice.

Employing a different drug-delivery technique, Carmeliet's research group used a small pump to convey VEGF into the cerebrospinal fluid of the brains of rats with ALS. Again the degeneration of motor neurons was slowed, demonstrating that the direct administration of the growth factor could protect the nervous system from the disease. What is more, the team found that human subjects with ALS had significantly lower levels of VEGF in their blood. Carmeliet's group is now working with NeuroNova, a Swedish pharmaceutical company, to develop clinical trials for the VEGF therapy.

Another nerve-protecting protein that holds promise for the treatment of ALS is insulinlike growth factor 1 (IGF-1), which has shown pow-

erful effects on motor neurons both in cultured cells and in animal models. Fred Gage of the Salk Institute for Biological Studies in San Diego and his colleagues engineered a virus that produces IGF-1, then injected the infectious material into mice that had developed an ALS-like disease because they carried SOD1 mutations. From the injection sites in the muscles, the virus traveled to the motor neuron terminals and then to the cell bodies, where it began to produce IGF-1. The treatment resulted in a 30 percent increase in the life span of the mice, probably by acting directly on their motor neurons and the neighboring cells. Researchers are currently laying the groundwork for clinical trials that would test the effectiveness of viral delivery of IGF-1 in humans with ALS.

One of the most surprising discoveries in the past few years is that regular physical exercise can stimulate the growth of new neurons, improve learning and increase the level of growth

factors in the nervous system. Furthermore, animal studies have shown that physical exercise can protect neurons following trauma or disease. Gage and his co-workers, for example, found that putting their ALS-SOD1 mice on a regimen of exercise on running wheels boosted their average life span from 120 to 150 days. The researchers hypothesized that exercise may somehow stimulate the production of IGF-1 in the mice, improving their motor responses and even rescuing damaged neurons. In view of these results, Gage's team decided to examine the consequences of combining physical exercise with IGF-1 treatment. Remarkably, the combination had a synergistic effect that was much more pronounced than that of either treatment alone: the mice that exercised and received IGF-1 injections lived an average of 202 days.

Recent breakthroughs in stem cell research have also opened up new avenues for treating ALS and other neurological disorders. At first scientists focused on the idea of using stem cells—precursor cells that can differentiate into specialized cells such as neurons—to replace the nerve cells harmed by neurodegenerative diseases. Over the past few years, however, several studies have indicated that grafted stem cells can act as a biological pump that delivers vital growth factors to damaged neurons. In this way, it may be possible not only to protect the injured nerve cells but also to promote regeneration in the spinal cord. Surprisingly, experiments in rodent models of motor neuron disease have shown that grafted stem cells can actually migrate to the region where the damaged neurons are located. The tissue at the injury site apparently emits some molecular signal to tell the stem cells to move into that area. Because new evidence suggests that both motor neurons and neighboring cells are responsible for motor neuron disease, it may be necessary to graft stem cells that can produce a variety of cell types and not just motor neurons.

Yet another intriguing possibility for treatment has come from the revolutionary discovery of RNA interference (RNAi). This process occurs when short strands of RNA specifically bind to certain messenger RNAs (mobile carriers of genetic information that serve as templates for making proteins); the binding prevents the messenger RNAs from synthesizing their corresponding proteins. Investigators can take advantage of this phenomenon by infecting target cells with viruses that encode RNAi strands, which can then stop the cells from manufacturing toxic proteins. Research groups headed by one of us

**Turning any of these novel approaches into an effective therapy will be challenging.**

(Aebischer) and Oxford Biomedica's Azzouz have shown that this technique can slow disease progression in ALS-SOD1 mice by using RNAi to shut down the faulty SOD1 gene.

The success of these experiments has encouraged researchers and physicians to plan a clinical trial for the treatment of patients that have the familial form of ALS caused by a mutated SOD1 gene. (Cleveland of U.C.S.D. is spearheading this effort.) In the initial trials, a mechanical pump will deliver a synthetic segment of interfering RNA (called an oligonucleotide) directly into the cerebrospinal fluid of the patients. These molecules are designed to interact with messenger RNAs before they can assemble amino acids to manufacture the toxic SOD1 protein in neurons and glial cells. If this new technology produces promising results in ALS patients, it could possibly be used in other neurodegenerative diseases triggered by flawed genes.

Turning any of these novel approaches into an effective therapy will be challenging. Before doctors can deliver growth factors or RNAi strands by viruses, for example, they must ensure that the procedure can be performed safely. (Viral delivery of genes has had a checkered history in humans.) Furthermore, clinicians must calculate how many muscles in an ALS patient would need to be injected to cause a functional improvement. Ideally, researchers will be able to devise treatments incorporating combinations of proteins and RNAi strands that would confer much greater survival benefits than any one factor alone would. In the meantime, a nonprofit group called the ALS Association is already conducting clinical trials of a drug combination that has prolonged survival in animals: celecoxib (an anti-inflammatory drug that can curb the cellular destruction caused by overactive glial cells) plus creatine (an amino acid). Because these substances are small molecules, they can easily reach motor neurons in the central nervous system.

Of course, the best outcome would be for researchers to discover a way to prevent ALS from developing instead of just a method to treat the symptoms once they appear. The secret to this goal may well depend as much on lifestyle as it does on genes. Researchers know that regular exercise can offer some protection against neurodegenerative diseases, and they are beginning to explore the effects of eating habits as well. Once scientists determine which physical activities and foods provide the best defense against ALS, we may be able to combat this horrible disease before it has time to strike the nervous system. ■

## MORE TO EXPLORE

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**Axon Degeneration Mechanisms: Commonality amid Diversity.** Michael Coleman in *Nature Reviews Neuroscience*, Vol. 6, No. 11, pages 889–898; November 2005.

More information about ALS research can be found online at [www.alsa.org](http://www.alsa.org)