ALS researchers aim for the fences

Nobody likes bad news. Especially when it's a grim medical diagnosis like amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease.

ALS, a rapidly progressing, fatal neurodegenerative disease, usually strikes people between 40 and 60 years of age; those afflicted have an average survival of just two to five years. *Amyotrophic*, a word with Greek origins, means "no muscle nourishment." *Lateral* identifies the areas of the spinal cord where motor neurons—nerve cells that signal muscles—are found. And *sclerosis* refers to the scarring and hardening this region undergoes as it degenerates. But though the brain becomes increasingly unable to control the muscles, it maintains its cognitive abilities. So ALS patients are painfully aware of their progressive loss of function.

"It's a hard disease to treat, to tell patients that they have it," says Dartmouth neurologist Elijah Stommel, M.D., Ph.D. He sees patients at DHMC's nationally recognized ALS center and also conducts research exploring the underlying mechanisms of the disease. One of the most common neuromuscular diseases in the world, ALS entered the national lexicon when the career of Yankee slugger Lou Gehrig was cut short by the condition in the 1930s. In the U.S. today, about 20,000 people have it at any given time and about 5,000 new cases are diagnosed each year.

Role: It's not yet known what causes ALS, but there's increasing evidence that neuroinflammation is involved. Stommel and DMS neuropathologist Brent Harris, M.D., Ph.D., have looked at the role of tumor necrosis factor-alpha (TNF-a), a pro-inflammatory molecule present at elevated levels in ALS patients. Their study, published in the April issue of *Neuroscience*, showed that TNF-a induces the redistribution of mitochondria in motor neurons grown in the lab. Mitochondria generate energy as well as release substances that can cause cell death. In the experiment, TNF-a caused the mitochondria to cluster where the axon—the part of the nerve cell that carries signals to other cells—meets the cell body. Similar mitochondrial clustering has been noted in patients who died of ALS.

Test tube: But Stommel would extrapolate the finding to humans "with trepidation." He says that "it's very hard to be sure that what you're looking at under the microscope, or in the test tube, has very much in common with what's going on in a live human or a live animal." The team will continue to study the significance of neuroinflammation and mitochondrial dysfunction in ALS.

Stommel and Harris are also running a Phase II clinical trial to treat ALS using thalidomide, a TNF-a blocker. Phase II trials test whether a therapy, at a safe dose, works against a given disease (while Phase I assesses safe dosing, and Phase III compares new therapies to established therapies and/or placebos).

About 5,000 new cases of ALS are diagnosed each year.

About 20 patients are enrolled in the trial but the dropout rate has been high, says Stommel, mostly due to thalidomide's unpleasant side effects—including sedation, constipation, and blood clotting. Thalidomide was once used to treat morning sickness in pregnant women but was banned in the 1960s in the U.S. after it caused birth defects in thousands of babies. But it has since been approved to treat some cancers. The team hopes to also test lenalidomide, a related drug that is more potent but has fewer side effects.

The researchers believe that multiple risk factors are involved in the development of ALS, including genetic makeup and, as Stommel puts it, "walking into the wrong situation at the wrong time." Some scientists suspect that exposure to environmental toxins such as aluminum, which is neurotoxic in high doses, might play a role.

Clusters: Stommel and Harris have also undertaken an epidemiological study of several ALS clusters—areas with an unusually high incidence of the disease—in New Hampshire and Vermont. They plan to test the water in those areas to measure levels of a neurotoxin produced by cyanobacteria that live in some lakes in the region.

They agree that discovering a biomarker for ALS is key. "My guess is that to find successful treatments for ALS is going to require finding out about the disease very early, before the motor neurons are irreversibly damaged," Stommel says. "By the time you're diagnosed with ALS, probably the majority of your motor neurons are already dead or dying and not salvageable."

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Stommel, left, and Harris study Lou Gehrig's disease from several angles.