NEW HOPE FOR TREATING LOU GEHRIG'S DISEASE (ALS)

ALS, also known as Lou Gehrig's disease or motor neuron disease, is a devastating illness characterized by relentless progressive paralysis with death occurring typically after 1-5 years.

It has no cure. For years, researchers have been thwarted in finding new approaches to treat the disease. Now, through the work of Linus Pauling Institute Principal Investigator and Burgess and Elizabeth Jamieson Chair in Healthspan Research Joseph Beckman, Ph.D., a possible avenue has opened up, though it is still in the early stages.

Using a specific type of copper compound, Beckman's laboratory was able to essentially stop the progression of amyotrophic lateral sclerosis (ALS) for nearly two years in one type of mouse model used to study the disease – allowing the mice to approach their normal lifespan. His findings were recently published in the journal *Neurobiology of Disease*.

"We are shocked at how well this treatment can stop the progression of ALS," said Beckman. In decades of work, no treatment has been discovered for ALS that can do anything but prolong human survival less than a month. The transgenic mouse model used in this study is one that scientists believe may more closely resemble the human reaction to this treatment, which consists of a compound called copper-ATSM.

It's not yet known if humans will have the same response, but clinical collaborators are moving as quickly as possible toward human clinical trials, testing first for safety and then efficacy of the new approach. It appears likely that the Phase I trial for copper-ATSM will start recruiting in Australia and then in the U.S. in a few months (for more, please see **clinicaltrials.gov**).

ALS was identified as a progressive and fatal neurodegenerative disease in the late 1800s, and gained international recognition in 1939 when it was diagnosed in American baseball legend Lou Gehrig. It's known to be caused by the death and deterioration of motor neurons in the spinal cord, which in turn have been linked to mutations in the enzyme known as "copper, zinc superoxide dismutase."

After years of research, scientists have developed an approach to treating ALS that's based on bringing copper into specific cells in the spinal cord and mitochondria weakened by copper deficiency. Copper is a metal that helps to stabilize superoxide dismutase, and is important for its function as an antioxidant protein. But when it lacks its metal co-factors, the enzyme can partially "unfold" and become toxic, leading to the death of motor neurons.

Copper-ATSM is a known compound that has low toxicity, easily penetrates the blood-brain barrier, is already used in human medicine at much lower doses for some purposes, and is well tolerated in laboratory animals at far higher levels.

However, this approach is not as simple as taking a traditional dietary supplement of copper, which can be very harmful to the body. Such supplements would be of no value to people with ALS, researchers said. Although copper is an essential micronutrient, even a small excess of copper is toxic. The Linus Pauling Institute's online Micronutrient Information Center provides a good summary of the body's requirements for copper, dietary sources, and toxicity issues (**lpi.oregonstate.edu/mic/minerals/copper**).

"We have a solid understanding of why the treatment works in the mice, and we predict it should work in both familial and possibly sporadic human patients," Beckman said. "But we won't know until we try."

Familial ALS patients are those with more of a family history of the disease, while sporadic patients reflect the larger general population. Only 2-7% of ALS patients have mutations in the enzyme superoxide dismutase. There is evidence that this approach, which also works in part by improving mitochondrial function, may have value in Parkinson's disease and other conditions. Research is progressing on those topics as well.

The treatment is unlikely to allow significant recovery from neuronal loss already caused by ALS, the scientists said, but could slow further disease progression when started after diagnosis. It could also potentially treat carriers of mutant superoxide dismutase genes that will eventually cause ALS to develop.

For more information, please read this follow-up blog written by Professor Beckman: **tinyurl.com/BeckmanALS**.

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