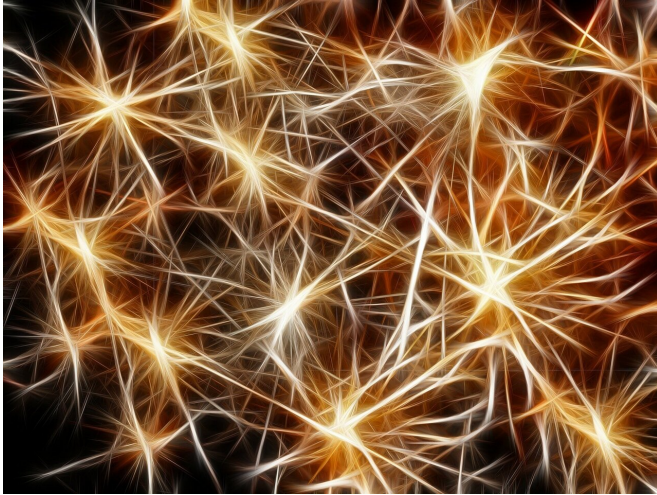


New insight into motor neuron death mechanisms could be a step toward ALS treatment

4 September 2019, by Steve Lundeberg



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Researchers at Oregon State University have made an important advance toward understanding why certain cells in the nervous system are prone to breaking down and dying, which is what happens in patients with ALS and other neurodegenerative disorders.

The study into the role a protein known as [heat shock protein](#) 90 plays in intracellular signaling is a key step on the way to figuring out the reason some motor [neurons](#) in the spinal cord die and some do not.

Findings, which could eventually lead to therapies to counter motor neuron death, were published in *Experimental Biology and Medicine*.

Neurons are [cells](#) in the [nervous system](#) that carry information to muscles, glands and other nerves. Motor neurons are large neurons in the spine and brain stem, with long axons extending outside the

nervous system to contact muscles and control their movements via contraction.

Researchers led by Alvaro Estevez and Maria Clara Franco of the OSU College of Science have shown that a ubiquitous "protein chaperone," heat shock protein 90, is particularly sensitive to inhibition in motor neurons that depend for survival on "trophic factors"—small proteins that serve as helper molecules.

Trophic factors attach to docking sites on the surface of nerve cells, setting in motion processes that help keep a cell alive. Research in animal models has shown trophic factors may have the ability to salvage dying neurons.

"It is well known that there are some motor neuron subpopulations resistant to degeneration in ALS, and other subpopulations that are highly susceptible to degeneration," said Estevez, associate professor of biochemistry and biophysics and the corresponding author on this research. "Understanding the mechanisms involved in these different predispositions could provide new insight into how ALS progresses and open new alternatives for the development of novel treatments for the disease."

In this study, a motor-neuron-specific pool of heat shock protein 90, also known as Hsp90, repressed activation of a key cellular receptor and thus was shown to be critical to neuron survival; when Hsp90 was inhibited, motor neuron death was triggered.

The Hsp90 inhibitor used in this research was geldanamycin, an antitumor antibiotic used in chemotherapy. Findings suggest the drug may have the unintended consequence of decreasing motor neurons' trophic pathways and thus putting those nerve cells at risk.

"The inhibition of Hsp90 as a therapeutic approach may require the development of inhibitors that are more selective so the cancer cells are targeted and healthy [motor](#) neurons are not," said Franco, assistant professor of biochemistry and biophysics.

ALS, short for [amyotrophic lateral sclerosis](#) and also known as Lou Gehrig's disease, is caused by the deterioration and death of [motor neurons](#) in the spinal cord. It is progressive, debilitating and fatal.

ALS was first identified in the late 1800s and gained international recognition in 1939 when it was diagnosed in a mysteriously declining Gehrig, ending the Hall of Fame baseball career of the New York Yankees first baseman. Known as the Iron Horse for his durability—he hadn't missed a game in 15 seasons—Gehrig died two years later at age 37.

More information: Amy L Strayer et al. Highlight article: Ligand-independent activation of the P2X7 receptor by Hsp90 inhibition stimulates motor neuron apoptosis, *Experimental Biology and Medicine* (2019). [DOI: 10.1177/1535370219853798](https://doi.org/10.1177/1535370219853798)

Provided by Oregon State University

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