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New therapy for amyotrophic lateral sclerosis successfully tested on mice

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A team from Université Laval and the CERVO Brain Research Centre has demonstrated the efficacy in mice of a new therapy that addresses the main manifestation of amyotrophic lateral sclerosis (ALS). The researchers developed an antibody that reduces the number of TDP-43 protein aggregates in the brains of mice with ALS, resulting in significant improvements in their cognitive and motor performance. Details of this breakthrough were recently published in the *Journal of Clinical Investigation*.

"ALS is characterized by a degeneration of the neurons that control muscle activity," explained Jean-Pierre Julien, principal investigator and professor at Université Laval' Faculty of Medicine. "It causes a progressive weakening of the arms and legs followed by paralysis and, two to five years later, respiratory problems that lead to death. There is no treatment for this disease, which affects 1 in 1,000 adults."

Dr. Julien and his team had already demonstrated in previous work that TDP-43 protein was overexpressed in the spinal cords of people with ALS. This overexpression leads to the formation of TDP-43 aggregates in nerve cells and an exaggerated inflammatory response that increases the neurons' vulnerability.

In their most recent study, Professor Julien and his colleagues produced an antibody that targets the TDP-43 protein. They inserted the genetic material encoding this antibody into viruses that were then injected into the nervous system of mice producing TDP-43 aggregates. "We

subsequently observed a reduction in the number of aggregates of this protein," explained Professor Julien. "We also found a decrease in the immune response and a significant improvement in the mice's cognitive and motor performance."

This breakthrough paves the way for the development of immunotherapies for ALS and frontotemporal dementias involving TDP-43 aggregates. "We are now trying to develop an approach that would not require the use of viruses," Professor Julien added. "Preliminary results suggest that injecting TDP-43 antibodies directly into the cerebrospinal fluid could effectively reduce protein aggregates in nerve cells."

The authors of the study are Silvia Pozzi, Sai Sampath Thammisetty, Philippe Codron, Reza Rahimian, Karine V. Plourde, Geneviève Soucy, Christine Bareil, Daniel Phaneuf, Jasna Kriz, Claude Gravel, and Jean-Pierre Julien.

More information: Silvia Pozzi et al, Viral-mediated delivery of antibody targeting TAR DNA–binding protein 43 mitigates associated neuropathology, *Journal of Clinical Investigation* (2019). DOI: 10.1172/JCI123931

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