# Studies point the way to broadly effective treatments for ALS

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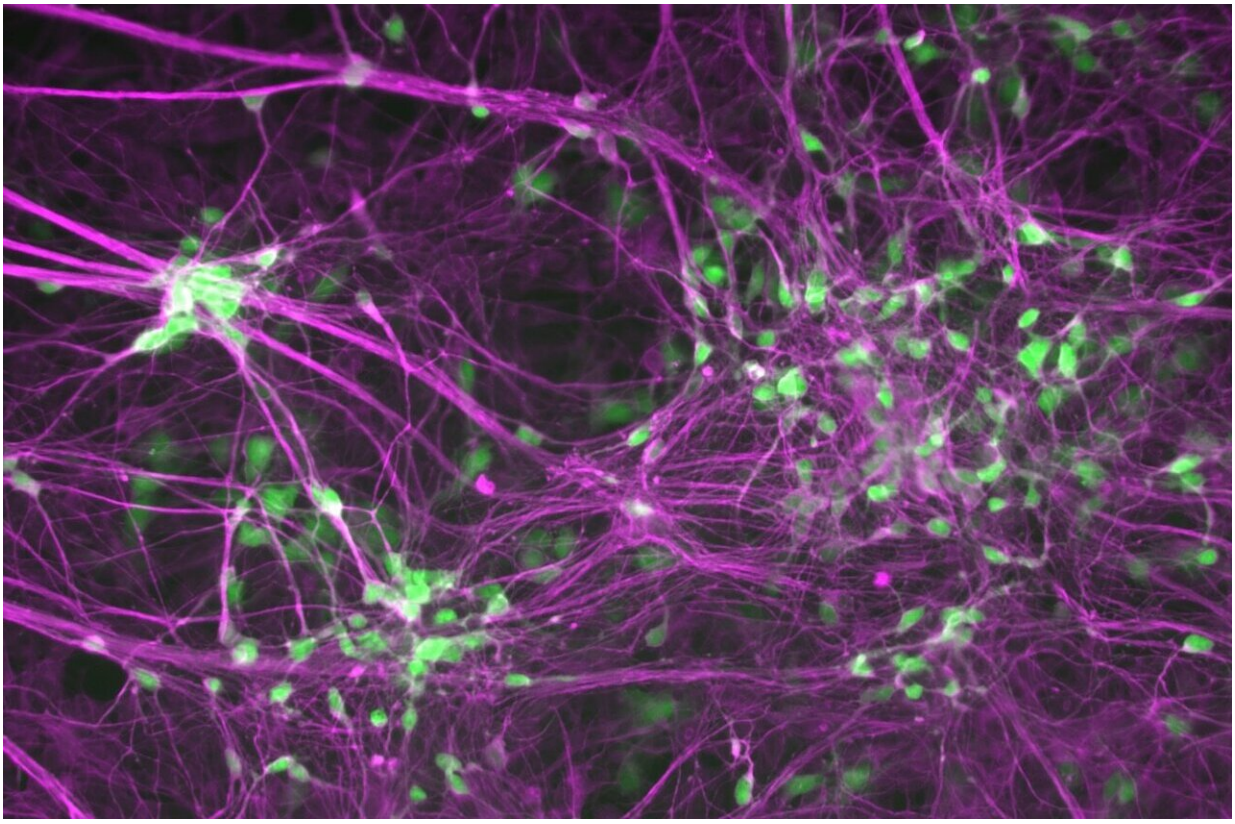

Human induced motor neurons that are labeled with a motor neuron marker HB9 in green and a neuron marker TUJ1 in purple. Credit: Ichida Lab

Each year in the U.S., 5,000 patients receive a diagnosis of ALS, an incurable neurodegenerative disease that will likely kill them within two

to five years. In the quest to find a cure for these patients, a team of researchers led by USC Stem Cell scientist Justin Ichida has identified two promising avenues for developing new treatments for diverse forms of this devastating disease, which is also known as amyotrophic lateral sclerosis or Lou Gehrig's disease. Their findings are published in a pair of studies: the first appearing in the journal Cell Stem Cell on February 2, and the second in the journal Cell on February 7.

"A minority of patients have a variety of genetic causes of ALS that can be inherited within families, and a majority have what is known as "sporadic" disease because its causes are unknown," said Gabriel Linares, a postdoc in the Ichida lab and a co-first author on both studies. "This makes it a difficult challenge to find one treatment that will work for all patients with ALS."

To meet this challenge, the researchers collected skin or blood samples from patients with both familial and sporadic ALS. The scientists reprogrammed the skin and blood cells into motor neurons, which are the nerve cells responsible for movement that degenerate in the disease. These patient-derived motor neurons provided an opportunity to screen thousands of FDA-approved drugs and drug-like molecules to find ones that might be effective against multiple forms of ALS.

In the *Cell Stem Cell* study, co-first authors Linares and Yichen Li found that several of the most effective drugs and drug-like molecules increased the activity of androgens, the well-known group of sex hormones that include testosterone. However, because androgen-boosting drugs could have undesirable or unsafe side effects for patients with ALS, the scientists aimed to identify a genetic change that might yield similar results.

To accomplish this, they leveraged a public bioinformatics database known as Connectivity Map, developed by the Broad Institute of

Harvard and MIT. By analyzing this vast database of information about how drugs affect the genetic landscape underpinning diseases, the scientists accurately predicted that suppressing the SYF2 gene would increase the survival of motor neurons derived from patients with diverse forms of ALS. In addition, suppressing this gene reduced neurodegeneration, motor dysfunction, and other symptoms in mice with ALS.

"What's really exciting is that SYF2 suppression improved symptoms and pathology related to a protein called TDP-43, which can become toxic and is implicated in close to 97 percent of cases of ALS," said Li, a postdoc in the Ichida Lab.

In the second study published in *Cell*, co-first authors Shu-Ting (Michelle) Hung and Linares detail how inhibiting a protein, the PIKFYVE kinase, could represent another effective strategy for treating many different forms of ALS.

In an extensive series of experiments, the researchers inhibited PIKFYVE using the drug apilimod, as well as through genetic and RNA-based approaches, in fruit flies, roundworms, mice, and motor neurons derived from patients with different forms of ALS.

They found that inhibiting PIKFYVE reduced neurodegeneration, improved motor function, and lengthened life by stimulating motor neurons to clear toxic proteins through a process of exocytosis, in which membrane-bound sacs envelop and actively transport waste to the exterior of the cell.

"We were able to pinpoint precisely how PIKFYVE inhibition mitigates neurodegeneration, which is important for informing the development of new targeted treatments," said Hung, a Ph.D. student in the Ichida Lab.

Ichida, who is the John Douglas French Alzheimer's Foundation Associate Professor of Stem Cell Biology and Regenerative Medicine at USC, and a New York Stem Cell Foundation–Robertson Investigator, added, "Our discoveries bring us closer to achieving our big picture goal: finding treatments that can be broadly effective for all patients who suffer from ALS."

Additional co-authors on both studies are: Yunsun Eoh, Manuel Santana, Jonathan Chang, and Joscany Perez from USC; and Wen-Hsuan Chang, Stacee Mendonca, Sarah Hong, and Samuel V. Alworth from AcuraStem, Inc.

For the *Cell Stem Cell* study, co-authors also include Hung, Jasper Rubin-Sigler, Wenxuan Guo, Yi-Hsuan Huang, Nomongo Dorjsuren, Michael Chickering, Hao-Jen Deng, Kieu-Tram Bach, and Kamden Gray from USC; Johnny Yu and Hani Goodarzi from the University of California, San Francisco; Tze-Yuan Cheng, Chi Chou Huang, and James Lee from Leica Microsystems; and Jeffrey Rosenfeld from Loma Linda University.

For the *Cell* study, additional co-authors include Li, Yingxiao Shi, Sarah Perry, Alexander Couto, Jesse Lai, Eric Hendricks, Yaoming Wang, Berislav V. Zlokovic, and Dion K. Dickman from USC; Gopinath Krishnan and Fen-Biao Gao from the University of Massachusetts; Chuol Kueth, Samantha Macklin-Isquierdo, and Daniela C. Zarnescu from Penn State University; and Sarah Duhaime, Claudia Maios, and J. Alex Parker from the Université de Montréal.

**More information:** Justin K. Ichida, PIKFYVE Inhibition Mitigates Disease in Models of Diverse Forms of ALS, *Cell* (2023). DOI: 10.1016/j.cell.2023.01.005.
www.cell.com/cell/fulltext/S0092-8674(23)00005-3

Gabriel R. Linares et al, SYF2 suppression mitigates neurodegeneration in models of diverse forms of ALS, *Cell Stem Cell* (2023). DOI: 10.1016/j.stem.2023.01.005