

# New insights into treating Parkinson's from yeast, stem cell experiments

By Carolyn Y. Johnson | GLOBE STAFF | OCTOBER 25, 2013

A team of scientists at the Cambridge-based Whitehead Institute for Biomedical Research have identified a compound that can reverse some of the toxicity that occurs in brain cells created from Parkinson's disease patients' stem cells.

The work, described in a pair of studies published Thursday in the journal Science, is still very early -- the researchers aren't even using the word "drug" when describing the small molecule that jumped out when they screened a chemical library of about 200,000 compounds. But the methods they used demonstrate the power of an approach that knits together multiple basic biology technologies, including the use of stem cells made from a patient's skin cells.

Similar experiments may now be used to aid drug development efforts in a wide variety of neurodegenerative diseases, including ALS (Lou Gehrig's disease) and Alzheimer's.

"It's a very nice piece of work -- an elegant demonstration of bridging basic yeast screens to cells that are directly relevant to the human condition," said Dr. Dennis Selkoe, professor of neurologic diseases at Brigham and Women's Hospital and Harvard Medical School, who was not involved in the studies. "The drug in question did interesting things, but is still a long way from being converted into a medicine that people can take."

The work in Susan Lindquist's laboratory at the Whitehead grew out of her ongoing efforts to utilize the humble Baker's yeast to model complex neurodegenerative diseases. Although the connection between single-celled yeast and the movement problems of Parkinson's disease may seem tenuous at best, the researchers engineered the yeast to overproduce alpha-synuclein, a protein that forms toxic clumps in the brains of Parkinson's patients.

Similar to human brain cells, yeast were sickened when the protein formed clusters. The researchers then looked for compounds that were able to reverse the problems when administered to the yeast. A number of compounds seemed promising, but one in particular appeared to affect the way the cells cleared out the alpha-synuclein clusters. They saw similar promising results when they tested the compound in a roundworm and eventually in rat brain

Dr. Vikram Khurana, a neurologist who sees patients with movement disorders at Massachusetts General Hospital and a scientist in the Lindquist laboratory, recruited patients with an aggressive genetic form of Parkinson's to provide skin samples. Researchers created stem cells from those patients' samples using a technique that won the Nobel prize in 2012. From the stem cells, they created the neurons that are afflicted in Parkinson's.

Those nerve cells provided an additional screen -- one that was more closely connected to the biology of Parkinson's -- to test whether the compound they had identified using yeast would have similar effects. They found that the compound reversed signs of pathology, and it worked the same way it did in the yeast cell, by targeting a particular cellular pathway that is now of greater interest.

"It was a real surprise," Khurana said. "We would have had no clue about this target if we hadn't had yeast genetics to show us the way."

Khurana said that the team will now focus on trying to tweak the compound, making chemical changes to it, so that it can be tested in animals.

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