# Scientists create neurons with symptoms of Parkinson's disease from patient's skin cells

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Neurons have been derived from the skin of a woman with a genetic form of Parkinson's disease and have been shown to replicate some key features of the condition in a dish, say researchers at the Stanford University School of Medicine. The scientists hope to use the neurons to learn more about the disorder and to test possible treatments. Such a tool is critical because there are no good animal models for Parkinson's disease. It also validates the use of induced pluripotent stem cells, or iPS cells, to model various diseases.

"Now that we can see that these neurons exhibit some of the earliest signs of the disorder, we can begin to develop methods to screen for factors that might protect them," said Renee Reijo Pera, PhD, director of Stanford's Center for Human Embryonic Stem Cell Research and Education and co-senior author of the research, which will appear in the March issue of *Cell Stem Cell*.

The iPS cells are created by transforming skin or other specialized cells to look and act like embryonic stem cells. Many scientists and policy-makers have hoped that these cells, which can be created without the use of human embryos, could stand in for their more ethically fraught counterparts.

Recent research from Stanford and elsewhere, however, has begun to identify significant differences between the two classes of stem cells that call into question the ability of iPS cells to completely replace embryonic stem cells. Instead many researchers feel that the true strength of iPS

cells may lie in their ability to create disease-specific cell lines for study from patients with a variety of disorders — something that would be difficult to do with embryonic stem cells.

Associate professor of neurosurgery Theo Palmer, PhD, is the other senior author of this new paper; the research was conducted in the labs of both Palmer and Reijo Pera, who is also a professor of obstetrics & gynecology. Ha Nam Nguyen, a former research associate now at John's Hopkins, along with graduate students Blake Byers and Branden Cord are joint first authors of the work.

"This is the first time that neurons from a Parkinson's disease patient have exhibited disease qualities in a petri dish," said Palmer. "And it provides hints of what to look for in patients who have different genetic mutations or where a cause has not been identified. By comparing neurons from patients with different forms of Parkinson's disease, we may find commonalities or differences that will help to optimize future treatments for each patient."

Parkinson's disease is a neurodegenerative disorder that causes the gradual loss of a certain type of neuron in the central nervous system. As the neurons are lost, the patient begins to experience the tremors, movement difficulties and rigidity that are the hallmarks of the condition. It affects about 1 percent of people over the age of 65, and about 5 percent of those over age 85. Currently there is no way to halt the progress of the disease, though some medications can help Parkinson's patients manage their symptoms for several years. Most cases of Parkinson's occur sporadically, but some (between 0.5 percent to about 8 percent) are caused by a genetic mutation.

Byers and his colleagues chose to collect skin cells from a 60-year-old woman with a genetic form of Parkinson's, reasoning that they would have better chance of replicating the signs of the disorder with her cells

rather than the cells of someone with the sporadic form.

Byers coaxed the iPS cells from the patient to develop into the type of neurons that die off in Parkinson's disease. At first, the neurons looked and acted normally: They were able to generate electrical signals, they produced and secreted a messaging molecule called dopamine, and their gene expression profiles over time mimicked those of neurons created from "normal" iPS cells.

However, after about 30 to 60 days of culture, the neurons from the Parkinson's patient began to exhibit some unusual characteristics. They expressed higher levels of genes for proteins needed to deal with oxidative stress — a condition in which destructive molecules wreak havoc on DNA and proteins within a cell — and churned out elevated levels of a protein involved in abnormal clumps of protein called Lewy bodies that are found in the neurons of people with Parkinson's and Alzheimer's disorders. Oxidative stress has been previously associated with Parkinson's disease.

"We needed to stress the cells with exogenous factors to elicit a disease-related phenotype," said Byers. The upshot, the researchers concluded, is that the neurons from the Parkinson's patient seem to be replicating many of the common features of the disorder, but in a much shorter timeframe.

"Parkinson's disease takes decades to manifest itself as clinical symptoms in patients, so we were concerned about how rapidly these cells would change in culture," said Byers. "We needed to be able to identify abnormal characteristics of the cells in a reasonable timeframe, so that we could identify what pushes a Parkinson's-disease-affected neuron to degrade. As it turns out, the culture dish is a pretty stressful place for a cell to be. That environment, combined with the addition of selectively toxic chemical agents, probably accelerates the visible signs

of the disorder. It's also likely that there are innate mechanisms within the body that protect against these changes and cause a more protracted disease course."

The researchers are now planning to begin testing various compounds to see if they can protect the neurons. They are also investigating whether they can see similar signs of disease in iPS-cell-derived neurons from patients with the non-genetic form of the disorder.

Provided by Stanford University Medical Center

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