# Scientists turn human skin cells directly into neurons, skipping IPS stage

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Human skin cells can be converted directly into functional neurons in a period of four to five weeks with the addition of just four proteins, according to a study by researchers at the Stanford University School of Medicine. The finding is significant because it bypasses the need to first create induced pluripotent stem cells, and may make it much easier to generate patient- or disease-specific neurons for study in a laboratory dish.

It may also circumvent a recently reported potential problem with iPS cells, in which laboratory mice rejected genetically identical iPS cells — seemingly on the basis of the proteins used to render them pluripotent.

The new research parallels that of the same Stanford group in 2010, which showed it was possible to change mouse skin cells directly into neurons with a similar combination of proteins. However, when done in human cells, the conversion of skin cells to neurons occurs less efficiently and more slowly.

"We are now much closer to being able to mimic brain or neurological diseases in the laboratory," said Marius Wernig, MD, assistant professor of pathology and a member of Stanford's Institute for Stem Cell Biology and Regenerative Medicine. "We may perhaps even be able to one day use these cells for human therapies."

Wernig is the senior author of the research, which will be published online May 26 in *Nature*. Postdoctoral scholars Zhiping Pang, PhD, Nan

Yang, PhD, and graduate student Thomas Vierbuchen share first authorship of the paper. Wernig's laboratory collaborated with that of neuroscientist Thomas Sudhof, MD, the Avram Goldstein Professor in the School of Medicine, on the work.

After their success in laboratory mice — the results of which were published last year in *Nature* — the researchers applied a similar technique to human cells. They first showed that they could convert human embryonic stem cells to neurons by infecting them with a virus expressing the same combination of proteins: transcription factors called Brn2, Ascl1 and Myt1l. They termed the treatment "BAM" for short. BAM treatment readily turned the embryonic stem cells into functional neurons within six days. It also worked on induced pluripotent stem cells.

So then the scientists moved to their big challenge: Could they do the same with human skin cells? In experiments using skin cells from fetuses and newborns, they found that BAM treatment caused these mature skin cells to look more like neurons, but that the resulting cells were unable to generate the electrical signals that neurons use to communicate with one another.

They wondered if there was a missing ingredient. Adding a fourth transcription factor called NeuroD proved to be the tipping point: The skin cells then transformed to functional neurons in the laboratory culture dish within about four to five weeks — expressing electrical activity and even integrating into and interacting with mouse neurons grown on a laboratory dish.

Although about 20 percent of mouse skin cells can be transformed directly into neurons, only about 2 to 4 percent of human skin cells make functional neurons under the current culture conditions. And while the mouse cells accomplished their switch within just a few days, the human cells required several weeks and generated less-robust electrical signals

than naturally derived neurons.

"Clearly mice and humans are different in significant ways," said Wernig, who said that he and his colleagues are now working to optimize the technique and culture conditions to increase the efficiency and speed of the direct transformation.

The direct conversion of skin cells to neurons contrasts with similar research that first transforms skin cells to a pluripotent, or developmentally flexible, state and then coaxes them to become neurons or other specialized cells. A separate team of Stanford researchers recently used this technique to generate patient-specific neurons from a woman with Parkinson's disease. However, that process is labor-intensive and relies on cell lines that may not fully reflect the cell-to-cell diversity that occurs in a natural population. Wernig emphasized that it is important to continue to explore both research techniques.

"The iPS cell approach is doable and has been shown to work," said Wernig. "We need to keep working on both strategies. It's possible that the best approach may vary depending on the disease or the type of research being done."

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