# Major step forward in understanding cell reprogramming

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Harvard Stem Cell Institute (HSCI) and Massachusetts General Hospital (MGH) Researchers have taken a major step toward eventually being able to reprogram adult cells to an embryonic stem cell-like state without the use of viruses or cancer-causing genes.

In a paper released on-line today by the journal *Cell Stem Cell*, Konrad Hochedlinger and colleagues report that they have both discovered how long adult cells need to be exposed to reprogramming factors before they convert to an embryonic-like state, and have "defined the sequence of events that occur during reprogramming."

This work on adult mouse skin cells should help researchers narrow the field of candidate chemicals and proteins that might be used to safely turn these processes on and off. This is particularly important because at this stage in the study of these induced pluripotent (iPS) cells, researchers are using cancer-causing genes to initiate the process, and are using retroviruses, which can activate cancer genes, to insert the genes into the target cells. As long as the work involves the use of either oncogenes or retroviruses, it would not be possible to use these converted cells in patients.

Up to this point, the reprogramming process has been a virtual black box - scientists have been able to turn back the developmental clock on adult skin cells by introducing four genes into the cells, but they have not known what steps were occurring during the process.

Harvard Stem Cell Institute Co-Director Doug Melton called the work “an impressive and thoughtful study” that "marks an important first step in finding ways to create pluripotent stem cells from adult cells without the need for viruses or oncogenes.”

Hochedlinger, an Assistant Professor in Harvard’s new inter-school Department of Stem Cell and Regenerative Biology, and a leader in the study of iPS cells, is, like others converting adult cells to an embryonic-like state, using four genes to bring about the conversion.

In this new Cell Stem Cell paper, he and his colleagues at MGH’s Cancer Center and Center for Regenerative Medicine “have engineered new viral systems to introduce this into skin cells. With this new viral system we were able to control the behavior of these four genes."

When working with adult skin cells, he explains, “skin cell markers are turned off very early, in the first two or three days, and after eight or nine days,” the point at which the cells become independent of the viruses used to insert the genes now used for reprogramming, “other pluripotency genes are activated. This is the first framework for zooming in on this process, and will allow us to ask what’s happening at day five, day six, and so on.”

“The importance of this finding is that it will tell us how long we need to throw chemicals or proteins on the cells for the programming to be effective,” Hochedlinger said. “It could have been that these viruses are only necessary for two days, or three weeks,” he continued, adding that “if you know a certain chemical, or protein, becomes dangerous after 10 days, but you’ll only need to use it for eight days, you have learned something important.

“The other message,” he said, “is that we found molecular cornerstones of the reprogramming process. Using a series of surface markers we’ve

defined the sequence of events that occurs during the reprogramming. Up to this point it was unknown what the sequence of events occurring was. But using these markers, we been able to define what happens during reprogramming."

Source: Harvard University