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## Researchers tweak stem cell creation

*California team refines technique developed at UW*

BY MARK JOHNSON

Researchers from California say they have improved a groundbreaking technique that reprograms skin cells back to the embryonic state, making the procedure safer by relying less on the use of viruses and genetic modification.

The technique, first used last year by teams led by James Thomson at the University of Wisconsin-Madison and Shinya Yamanaka of Kyoto University and the Gladstone Institute of Cardiovascular Disease, turned back a cell's developmental clock by inserting four genes into the cell using a virus.

The reprogramming work by Thomson and Yamanaka was hailed in November as a major breakthrough, producing cells that mimic embryonic stem cells without the ethically controversial destruction of human embryos.

But the use of viruses and genetic modification can trigger cancer, making the procedure too risky to be used for the treatment of humans. Scientists have stressed that the creation of the new reprogrammed cells still has enormous value as a tool to test drugs and learn how diseases damage the body from within.

The latest work, published today in the journal *Cell Stem Cell*, was billed as a significant improvement by the Scripps Research Institute in La Jolla, Calif., where the work was done, but was described as more of an incremental advance by Stephen A. Duncan, director of the program in regenerative medicine at the Medical College of Wisconsin in Wauwatosa.

Duncan said the scientists at Scripps Research started by using cells that had not fully matured but were somewhere between embryonic cells and adult cells, thus making the reprogramming less challenging. If, however, researchers are able to use the same techniques to reprogram fully mature cells entirely without viruses and genetic modifications, "it would be a huge finding," Duncan said.

The insertion of genes is troubling because it can mutate genes already in the body that serve as "checkpoint regulators" to prevent cancer, Duncan said. The other risk is that this insertion process can activate genes that drive cells to make copies, causing them to proliferate out of control, he said. The end result can be cancer.

Sheng Ding, a chemist and associate professor at Scripps Research, called his team's work a highly significant proof of concept. It shows, he said, that some cells may be better than others for reprogramming, and small molecules may one day allow the transformation to take place without genetic tampering.

Ding's team, which also included scientists from the Max Planck Institute for Molecular Biomedicine in Germany, attacked the cancer risk from reprogramming on two fronts.

### **Different cell**

First, the scientists chose a different kind of cell for reprogramming: progenitor cells. These descendants of stem cells are limited in terms of the types of cells they can become and their ability to reproduce.

The researchers found that neural, or brain, progenitor cells could be reset to an embryonic state with "fewer genetic manipulations" than the skin cells reprogrammed by the Thomson and Yamanaka labs. Ding and his colleagues reprogrammed the progenitor cells using only two of the four genes Yamanaka used, omitting one that can lead to cancer.

"We're certainly not suggesting that's the best cell type to use," Ding said, explaining that the work should instead spur scientists to look for other cell types that might work better.

### **Small molecules**

The second front Ding's team investigated was the use of small molecules to replace the insertion of genes. The molecules can trigger key genes that provide the special powers of an embryonic stem cell. Embryonic stem cells are prized for their ability to become any of the more than 200 cells in the human body.

Ding's team used a synthetic molecule called BIX-01294 to replace the viral delivery of genes from outside the body and increase the efficiency of reprogramming. The molecule, identified during a screening of some 2,000 possibilities, turns on one of the body's own genes, making it unnecessary to insert a gene, Ding said.

The goal of using this technique is to one day reprogram cells using chemical cocktails instead of viruses and inserted genes.

Ding said that by combining the two methods his team investigated - the use of different cell types and different molecules - scientists may arrive more rapidly at a safe means of reprogramming cells to the embryonic state.