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## Scientists Bypass Need for Embryo to Get Stem Cells

By [GINA KOLATA](#)

Two teams of scientists reported yesterday that they had turned human skin cells into what appear to be embryonic [stem cells](#) without having to make or destroy an embryo — a feat that could quell the ethical debate troubling the field.

All they had to do, the scientists said, was add four genes. The genes reprogrammed the chromosomes of the skin cells, making the cells into blank slates that should be able to turn into any of the 220 cell types of the human body, be it heart, brain, blood or bone. Until now, the only way to get such human universal cells was to pluck them from a human embryo several days after fertilization, destroying the embryo in the process.

The need to destroy embryos has made stem cell research one of the most divisive issues in American politics, pitting President Bush against prominent Republicans like [Nancy Reagan](#), and patient advocates who hoped that stem cells could cure diseases like [Alzheimer's](#). The new studies could defuse the issue as a presidential election nears.

The reprogrammed skin cells may yet prove to have subtle differences from embryonic stem cells that come directly from human embryos, and the new method includes potentially risky steps, like introducing a [cancer](#) gene. But stem cell researchers say they are confident that it will not take long to perfect the method and that today's drawbacks will prove to be temporary.

Researchers and ethicists not involved in the findings say the work, conducted by independent teams from Japan and Wisconsin, should reshape the stem cell field. At some time in the near future, they said, today's debate over whether it is morally acceptable to create and destroy human embryos to obtain stem cells should be moot.

"Everyone was waiting for this day to come," said the Rev. Tadeusz Pacholczyk, director of education at the National Catholic Bioethics Center. "You should have a solution here that will address the moral objections that have been percolating for years," he added.

The White House said that Mr. Bush was "very pleased" about the new findings, adding that "By avoiding techniques that destroy life, while vigorously supporting alternative approaches, President Bush is encouraging scientific advancement within ethical boundaries."

The new method sidesteps other ethical quandaries, creating stem cells that genetically match the donor without having to resort to cloning or the requisite donation of women's eggs. Genetically matched cells would not be rejected by the immune system if used as replacement tissues for patients. Even more important, scientists say, is that genetically matched cells from patients would enable them to study complex diseases, like Alzheimer's, in the laboratory.

Until now, the only way most scientists thought such patient-specific stem cells could be made would be to create embryos that were clones of that person and extract their stem cells. Just last week, scientists in Oregon reported that they did this with monkeys, but the prospect of doing such experiments in humans has been ethically fraught.

But with the new method, human cloning for stem cell research, like the creation of human embryos to extract stem cells, may be unnecessary. The new cells in theory might be turned into an embryo, but not by simply implanting them in a womb.

“It really is amazing,” said Dr. Leonard Zon, director of the stem cell program at Children’s Hospital Boston at Harvard Medical School.

And, said Dr. Douglas A. Melton, co-director of the Stem Cell Institute at [Harvard University](#), it is “ethically uncomplicated.”

For all the hopes invested in it over the last decade, embryonic stem cell research has moved slowly, with no cures or major therapeutic discoveries in sight.

The new work could allow the field to vault significant problems, including the shortage of human embryonic stem cells and restrictions on federal financing for such research. Even when scientists have other sources of financing, they report that it is expensive and difficult to find women who will provide eggs for such research.

The new discovery is being published online today in *Cell*, in a paper by Shinya Yamanaka of Kyoto University and the Gladstone Institute of Cardiovascular Disease in San Francisco, and in *Science*, in a paper by James A. Thomson and his colleagues at the [University of Wisconsin](#). Dr. Thomson’s work received some federal money.

While both groups used just four genes to reprogram human skin cells, two of the genes used differed from group to group. All the genes in question, though, act in a similar way — they are master regulator genes whose role is to turn other genes on or off.

The reprogrammed cells, the scientists report, appear to behave very much like human embryonic stem cells but were called “induced pluripotent stem cells,” meaning cells that can change into many different types.

“By any means we test them they are the same as embryonic stem cells,” Dr. Thomson says.

He and Dr. Yamanaka caution, though, that they **still must confirm that the reprogrammed human skin cells really are the same as stem cells they get from embryos. And while those studies are under way, Dr. Thomson and others say, it would be premature to abandon research with stem cells taken from human embryos.**

Another caveat is that, so far, scientists use a type of virus, a retrovirus, to insert the genes into the cells’ chromosomes. Retroviruses slip genes into chromosomes at random, sometimes causing mutations that can make normal cells turn into cancers.

One gene used by the Japanese scientists actually is a cancer gene.

The cancer risk means that the resulting stem cells would not be suitable for replacement cells or tissues for patients with diseases, like [diabetes](#), in which their own cells die. But they would be ideal for the sort of studies that many researchers say are the real promise of this endeavor — studying the causes and treatments of complex diseases.

For example, researchers could make stem cells from a person with a disease like Alzheimer's and turn the stem cells into nerve cells in a petri dish. Then they might learn what goes awry in the brain and how to prevent or treat the disease.

But even the retrovirus drawback may be temporary, scientists say. Dr. Yamanaka and several other researchers are trying to get the same effect by adding chemicals or using more benign viruses to get the genes into cells. They say they are starting to see success.

"Anyone who is going to suggest that this is just a sideshow and that it won't work is wrong," Dr. Melton predicted.

The new discovery was preceded by work in mice. Last year, Dr. Yamanaka published a paper showing that he could add four genes to mouse cells and turn them into mouse embryonic stem cells.

He even completed the ultimate test to show that the resulting stem cells could become any type of mouse cell. He used them to create new mice. Twenty percent of those mice, though, developed cancer, illustrating the risk of using retroviruses and a cancer gene to make cells for replacement parts.

Scientists were electrified by the reprogramming discovery, Dr. Melton said. "Once it worked, I hit my forehead and said, 'It's so obvious,'" he said. "But it's not obvious until it's done."

The work set off an international race to repeat the work with human cells.

"Dozens, if not hundreds of labs, have been attempting to do this," said Dr. George Daley, associate director of the stem cell program at Children's Hospital.

Ever since the birth of Dolly the sheep in 1996, scientists knew that adult cells could, in theory, turn into embryonic stem cells. But they had no idea how to do it without cloning, the way Dolly was created.

With cloning, researchers put an adult cell's chromosomes into an unfertilized egg whose genetic material was removed. The egg, by some mysterious process, then does all the work. It reprograms the adult cell's chromosomes, bringing them back to the state they were in just after the egg was fertilized. A few days later, a ball of stem cells emerges in the embryo, and every cell of the embryo, including its stem cells, is an exact genetic match of the adult.

The abiding questions, though, were: How did the egg reprogram the adult cell's chromosomes? Would it be possible to reprogram an adult cell without using an egg?

About four years ago, Dr. Yamanaka and Dr. Thomson independently hit upon the same idea. They would search for genes that are being used in an embryonic stem cell that are not being used in an adult cell. Then they would see if those genes would reprogram an adult cell.

Dr. Yamanaka worked with mouse cells, and Dr. Thomson worked with human cells from foreskins.

The researchers found more than 1,000 candidate genes. So both groups took educated guesses, trying to whittle down the genes to the few dozen they thought might be the crucial ones and then asking whether any combinations of those genes could turn a skin cell into a stem cell.

“The number of factors could have been 1 or 10 or 100 or more,” Dr. Yamanaka said in a telephone interview from his laboratory in Japan.

If many genes had been required, the experiments would have failed, Dr. Thomson said, because it would have been impossible to test all the gene combinations.

As soon as Dr. Yamanaka saw that the mouse experiments succeeded, he began trying the same brute force method in human skin cells that he had ordered from a commercial laboratory. Some were face cells from a 36-year-old white woman and others were connective tissue cells from joints of a 69-year-old white man.

Dr. Yamanaka said he thought it would take a few years to find the right genes and the right conditions to make the human experiments work. Feeling the hot breath of competitors on his neck, he was in his laboratory every day for 12 to 14 hours a day, he said.

A few months later, he succeeded.

“We did work very hard,” Dr. Yamanaka said. “But we were very surprised.”

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