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Skin Cells Made To Mimic Stem Cells

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POSTED: 10:39 am EST November 20, 2007

UPDATED: 1:43 pm EST November 21, 2007

Two research groups have found different genetic recipes to give ordinary skin cells the power to turn into virtually any kind of human tissue, just as embryonic stem cells do.

If the recipes live up to their promise, they could someday end the ethical debate over embryonic stem cell research - and usher in an era when a person's own cells could be manipulated to mend a broken spinal cord, heal a damaged heart or regenerate other failing tissues.

But in their current state, the recipes are too risky for disease treatment, and even the scientists behind the latest studies cautioned that therapies are still years away. In announcing their discoveries, they emphasized that much more research still needs to be done on stem cells that have been derived from human embryos.

"It's not the time to say human embryonic stem cell research is dead," James Thomson, a biologist at the University of Wisconsin in Madison, who is behind a study appearing in the journal *Science*, told msnbc.com.

Kyoto University's Shinya Yamanaka, the principal author of a study published by the journal *Cell*, echoed that view, saying it would be "premature" to conclude that the cells created in his lab could replace embryonic stem cells.

Nevertheless, the two sets of findings quickly transformed the debate over stem cells and cloning.

Edinburgh University's Ian Wilmut - who led the research that gave rise to Dolly, the first cloned sheep, a decade ago - has been quoted as saying he's abandoning his cloning efforts to adopt the new approach. But another stem cell pioneer, Advanced Cell Technology's Robert Lanza, said he was alarmed at Wilmut's statement and worried that the new studies would drown out other stem cell research like a "tidal wave."

"This work represents a tremendous scientific milestone, the biological equivalent of the Wright brothers' first airplane," Lanza, ACT's chief scientific officer, told msnbc.com. "It's a bit like turning lead into gold. But this is not over by a long shot. It's extremely important to temper this announcement with caution."

Lanza said he would continue his work on a technique to extract stem cells from human embryos without destroying the embryo itself.

William Hurlbut, a physician and consulting professor at Stanford University Medical Center who also serves on the President's Council on Bioethics, said the research on cell reprogramming "essentially takes the stem cell issue off the political agenda."

"It's very encouraging, and it's pretty obvious we're going to find a consensus solution," Hurlbut told msnbc.com. "It's exciting, because we're not going to be fighting about this."

For years, Hurlbut has been at odds with the proponents of embryonic stem cell research because he is opposed to cloning or destroying human embryos.

No embryos required

The recipes detailed in *Cell* and *Science* don't require embryos at all - or even unfertilized human egg cells. Instead, the technique involves slipping a set of four genes into skin cells, in a specially prepared culture that coaxes the cells to behave like an embryonic stem cell.

Like embryonic stem cells, these reprogrammed cells become "pluripotent" - that is, they're capable of turning themselves into virtually any tissue type in the human body, including neurons and heart tissue. They also exhibit many of the other biochemical properties of embryonic stem cells, although they're not genetically identical to stem cells.

Yamanaka's research builds on previous work that he and his colleagues conducted with mice. They used the same four genes that made mouse cells pluripotent - Oct3/4, Sox2, c-Myc and Klf4 - but found that they had to adjust the culture to suit human cells rather than mouse cells.

Meanwhile, even before Yamanaka's group published their mouse research, the research group at Thomson's Wisconsin lab

started screening 100 genetic factors linked to embryonic development. The researchers zeroed in on four genes that produced the pluripotent cells most efficiently, said a co-author of the Science paper, Junying Yu of the Wisconsin National Primate Research Center and the Genome Center of Wisconsin.

Two of the genes turned out to be the same (Oct4 and Sox2), but two others were different (Nanog and Lin28).

"I'm very impressed that Jamie was able to identify another set of factors," Yamanaka told msnbc.com. "I really think our combination and his combination are not the only two combinations in the world. There have to be different combinations."

Thomson's research group reported that 198 stem cell-like colonies grew from 900,000 cells in one of the experiments, while Yamanaka said 50,000 cells yielded 10 colonies.

"This efficiency may sound very low, but it means that from one experiment, with a single 10-centimeter dish, you can get multiple iPS [induced pluripotent stem] cell lines," Yamanaka noted in a news release from Cell.

Perfecting the recipe

If the recipe for stem cell-like behavior can be perfected, individualized pluripotent cells could be created to reflect a particular disease condition - for example, allowing researchers to test potential treatments for Parkinson's disease on living human neurons created in a culture dish.

Eventually, your cells could be converted and grown into tissue suitable for transplantation back into your body, with no fear of immune rejection. In the process, no human embryos would be destroyed, and no human eggs would be used - easing the ethical concerns that have dogged stem cell research in the past.

But that bright future depends on a series of big ifs.

First of all, the function of the reprogrammed cells will have to be compared closely with the function of actual embryonic stem cells. "I'd be surprised if these cells do all the same tricks as stem cells derived from embryos," Lanza told msnbc.com.

Also, in both experiments, the four-gene recipe was added to the skin cells using a virus as the delivery package. "The FDA [Food and Drug Administration] would never allow us to use these virus-modified cells in patients," Lanza said.

Yu acknowledged that the viral delivery method would raise a red flag for medical treatments but said alternative gene-delivery methods may become available in the future. "A lot of groups are working on this model," she said.

Yamanaka's recipe poses an additional quandary because it includes c-Myc, a gene that has been linked to cancerous tumors. However, the newly published research hints that c-Myc may not be strictly necessary for the recipe to work. "We have been working on that very seriously," Yamanaka said. "All I can say is that we have submitted a paper regarding that aspect, and we hope that that paper will be accepted soon."

A back door to cloning?

Yamanaka also said the reprogramming technique could allow for the creation of egg cells as well as sperm cells from the same person, male or female.

"Making sperm from a male who has some kind of infertility problem, that may be very helpful," he said. "But making sperm from a female iPS cell, and eggs from a male - I think both those procedures should be banned, because the only purpose of that is to make clones."

Yamanaka said he felt a grave responsibility to make sure his technology was used properly.

"My purpose is to avoid ethical issues, but I am generating new ethical issues," he said. "So I will talk to the Japanese government to avoid the misuse of this kind of technology."

Thomson, however, said he hoped the ethical issues would give way over time to "routine science" - and eventually to routine medical treatments as well. He said that would serve as a satisfying ending to a saga that began nine years ago, when he and his colleagues at the University of Wisconsin were the first researchers to isolate human embryonic stem cells.

"You can work terribly hard in science, but sometimes a lot of dumb luck is involved," he said. "Somehow, fate has smiled on us twice."

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