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Embryonic Stem Cells—Without Embryos?

In a major breakthrough, scientists have 'reprogrammed' fully matured skin cells in mice, causing them to act exactly like embryonic stem cells.

Mary Carmichael  
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Stem-cell researchers have run into several major obstacles in the past few years, including the federal ban on funding for embryonic research and a lack of women willing to donate their eggs for possible experimentation. Four papers published on Tuesday, however, may help scientists clear both those hurdles. Teams at Harvard University, the Massachusetts Institute of Technology, The University of California-Los Angeles and Kyoto University reported in three papers that a new technique had bestowed all the powerful transformative properties of embryonic stem cells on older, more differentiated cells from adult mice. The fourth paper, meanwhile, opens up the possibility of a new and fairly large source of cells—one that won't require women to go through the painful process of egg donation purely for research. Together, the papers, published in *Nature* and *Cell Stem Cell*, move doctors much closer to the holy grail of stem-cell therapy, the regeneration of new tissue genetically identical to that of donor patients.

The first batch of papers focuses on four crucial genes in mice that control cell development by regulating the activities of other genes. By artificially activating these four genes in adult mouse skin cells, three separate teams of scientists were able to "reprogram" the cells—giving them all the flexibility of embryonic stem cells, which can develop into any of the dozens of tissue types found in the body. The new quasi-embryonic stem cells, which researchers have dubbed "induced pluripotent stem cells," are "virtually identical to a regular embryonic stem cell ... in every way we know how to test," said Marius Wernig, a postdoctoral researcher who was part of the team from MIT's Whitehead Institute. Researchers injected the cells into mouse embryos and found that they spread throughout the growing body, transforming into a wide variety of cell types, including blood cells and heart muscle. If researchers could duplicate that process with human cells, they might someday be able to grow new organs using patients' own skin cells.

The fourth paper focuses on a technique known as somatic cell nuclear transfer, or "therapeutic cloning," which replaces the DNA in an egg cell with genetic material from a patient, resulting in a new supply of stem cells with that patient's DNA profile. The technique has never been successfully used in humans. It also was previously thought to only work on unfertilized eggs, and the only source of those in humans was voluntary egg donation, a prospect so unappealing that Kevin Eggan of the Harvard Stem Cell Institute said his team had not been able to attract a single woman willing to participate. Eggan's new mouse research, however, showed that the technique could work on a fertilized egg frozen at the one-cell stage, before it had begun to divide. Getting "straight to the practical payoff," he said, the research suggests that "you might [instead] be able to use the very large number of fertilized embryos that are routinely discarded in IVF clinics at a variety of early stages" because of chromosomal abnormalities. "Those embryos can never make a child even from the moment

of conception," Eggen said. "They are waiting to be thrown away." They would vastly expand the amount of biological material doctors could work with in devising stem-cell therapies.

None of the papers focused on human cells; all the experiments were conducted in mice. Making the cross-species leap in the coming years will be challenging. The technique used to introduce the four genes into adult mouse cells—which relies on viruses to transmit the genes—may be too dangerous for human use. Two of the four genes have been implicated in cancer. Indeed, some of the mice in the new experiments developed tumors, an outcome that would clearly be unacceptable in any human therapy. Instead of inserting the four genes into human patients, researchers hope to eventually find chemicals that can boost their activity in already-existing cells.

Scientists also don't know if their technique will work in humans because the biology may simply be different than it is in mice. While allowing that he was "very optimistic that reprogramming might also work in human cells," Wernig also dryly noted that "a human is not a mouse." Scientists still know very little about human embryonic stem cells, and they certainly don't know "whether human [adult] cells are reprogrammable at all," said Konrad Hochedlinger of the Harvard Stem Cell Institute, who was involved in the research. "It's a total black box."

For that reason, the revelation of the new, induced-pluripotent cells in mice does not spell the end of embryonic stem-cell research in humans. On the contrary, said Wernig: "It is now really important to continue, if not intensify, our research on human embryonic stem cells."

Reprogramming adult cells does not require the destruction of embryos—but before they replicate the process in humans, scientists have to fully understand what it is they're trying to mimic. Eggen's research also will not mean an end to controversy. He said his research will still "be problematic for those people who feel we should not destroy these very early embryos" at the one-cell stage. Still, he added, "most scientists who do embryonic stem-cell research are not pursuing [such alternative approaches] to get around the moral complications. The reasons to pursue these approaches are scientific and logistical in nature."

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