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Groundbreaking Advance Allows for 'Reprogramming' of Adult Cells

Research Could Lead to Bevy of Cures, Sidesteps Debate Over Embryonic Stem Cells

By Rob Stein
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Scientists have transformed one type of fully developed adult cell directly into another inside a living animal, a startling advance that could lead to cures for a plethora of illnesses and sidestep the political and ethical quagmires that have plagued embryonic stem cell research.

Through a series of painstaking experiments involving mice, the Harvard biologists pinpointed three crucial molecular switches that, when flipped, completely convert a common cell in the pancreas into the more precious insulin-producing ones that diabetics need to survive.

The feat, published online today by the journal Nature, raises the tantalizing prospect that patients suffering from not only diabetes but also heart disease, strokes and many other ailments could eventually have some of their cells reprogrammed to cure their afflictions without the need for drugs, transplants or other therapies.

"It's kind of an extreme makeover of a cell," said Douglas A. Melton, co-director of the Harvard Stem Cell Institute, who led the research. "The goal is to create cells that are missing or defective in people. It's very exciting."

The findings left other researchers in a field that has become accustomed to rapid advances reaching for new superlatives to describe the potential implications.

"I'm stunned," said Robert Lanza, chief scientific officer of Advanced Cell Technology in Worcester, Mass., a developer of stem cell therapies. "It introduces a whole new paradigm for treating disease."

"I think it's hugely significant," said George Q. Daley, a stem cell researcher at Children's Hospital in Boston. "This is a very spectacular first."

Even the harshest critics of embryonic stem cell research hailed the development as a major, welcome development.

"I see no moral problem in this basic technique," said Richard Doerflinger of the U.S. Conference of Catholic Bishops, a leading opponent of embryonic stems cells because they involve destroying human embryos. "This is a 'win-win' situation for medicine and ethics."

Melton and other researchers cautioned that many years of research lay ahead to prove whether the development would translate into cures.

"It's an important proof of concept," said Lawrence Goldstein, a stem cell researcher at the University of California, San Diego. "But these things always look easier on the blackboard than when you have do them in actual patients."

Although the experiment involved mice, Melton and other researchers were optimistic the approach would work in people.

"You never know for sure -- mice aren't humans," Daley said. "But the biology of pancreative development is very closely related in mice and humans."

Melton has already started experimenting with human cells in the laboratory and hopes to start planning the first studies involving people with diabetes within a year. "I would say within five years we could be ready to start human trials," Melton said.

Other scientists have already started trying the approach on other cells, including those that could be used to treat spinal cord injuries and neurogenerative disorders such as Lou Gehrig's disease.

"The idea to be able to reprogram one adult neuron type into another for repair in the nervous system is very exciting," said Paola Arlotta, who is working in the Center for Regenerative Medicine at the Massachusetts General Hospital-Harvard Medical School, in Boston.

The research is the latest development in the explosive field of "regenerative medicine," which is trying to create replacement tissues and body parts tailored to patients. That dream appeared within reach after scientists discovered human embryonic stem cells, which can develop into any type of cell in the body. But stem cell research has been plagued by political and ethical debates because the cells can only be obtained by destroying embryos, which has been opposed by President Bush and others who believe that even the earliest stages of human life have moral standing.

Scientists last year shocked the field when they announced they had discovered how to manipulate the genes of adult cells to turn them back into the equivalent of embryonic cells -- entities dubbed "induced pluripotent stem" or "iPS" cells -- which could then be coaxed into any type of cell in the body.

The new work takes further advantage of the increasing prowess scientists have developed in harnessing the once mysterious inner workings of cells -- this time to skip the intermediary step of iPS cells and directly transform adult cells.

"This experiment proves you don't have to go all the way back to an embryonic state," Daley said. "You can use a related cell. That may be easier to do and more practical to do."

Doerflinger argued that the discovery was the latest evidence that research involving human embryos was no longer necessary.

"This adds to the large and growing list of studies helping to make embryonic stem cells irrelevant to medical progress," Doerflinger wrote in an e-mail.

But other researchers disputed that, saying it remains unclear which approach will ultimately prove most useful.

"Embryonic stem cells offer a unique window in human disease and remain a key to the long-term progress of regenerative medicine," Melton said.

For their work, Melton and his colleagues systematically studied cells from the pancreas of adult mice, slowing winnowing the list of genes necessary to make a "beta" cell that produces insulin. After narrowing the candidate genes to nine, the researchers genetically engineered viruses known as adenoviruses to ferry the genes into other pancreatic cells, known as exocrine cells, which normally secrete enzymes to help digest food. That finally enabled the researchers to identify the three crucial genes needed take control of the rest of the cell's genes to convert an exocrine cell into a beta cell.

"It was a mixture of work, luck and guessing," Melton said. "We achieved a complete transformation, or re-purposing, of cells from one type to another. We were delighted."

When the scientists tried the approach on diabetic mice, the animals became able to control their blood sugar levels.

"It didn't cure the mouse, but they were able to reduce their blood sugar levels to near normal," Melton said.

Melton and others said it remains to be seen whether it will be necessary to use genetically engineered viruses, which could face obstacles getting regulatory approval because of concerns about unforeseen risks, or whether chemicals might be found to do the same thing.

If preliminary studies in the laboratory are promising, Melton said he might first try converting liver cells to insulin-producing pancreatic cells because that would be safer than the pancreas. An alternative strategy would be to use the approach to grow beta cells in the laboratory and transplant them into patients.

Lanza said he was optimistic.

"One day, this may allow the doctor to replace the scalpel with a sort of genetic surgery," Lanza said. "If this can be perfected, it would represent one of the Holy Grails of medicine."