

Scientists Cure Mice Of Sickle Cell Using Stem Cell Technique

New Approach Is From Skin, Not Embryos

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Friday, December 7, 2007

Using a recently developed technique for turning skin cells into stem cells, scientists have cured mice of sickle cell anemia -- the first direct proof that the easily obtained cells can reverse an inherited, potentially fatal disease.

Researchers said the work, published in yesterday's online edition of the journal *Science*, points to a promising future for the novel cells. Known as iPS cells, they have been touted by [President Bush](#) and some scientists as a possible substitute for embryonic stem cells, which have been mired for years in political controversy.

But researchers also cautioned that aspects of the new approach will have to be changed before it can be tried in human patients. Most important, the technique depends on the use of gene-altered viruses that have the potential to trigger tumor growth.

"The big issue is how to replace these viruses," said Rudolf Jaenisch of the Whitehead Institute for Biomedical Research in [Cambridge, Mass.](#), who led the new work with co-worker Jacob Hanna and Tim M. Townes of the University of Alabama Schools of Medicine and Dentistry in [Birmingham](#).

"Induced pluripotent stem," or iPS, cells, are virtually identical to embryonic stem cells. They can morph into all of the more than 200 cell types in the body but are derived from skin, not from embryos. Mouse iPS cells were first derived earlier this year, and scientists reported last month to great fanfare that they had created similar cells from human skin.

The new experiment started with the removal of a few skin cells from the tail tips of mice sick with sickle cell anemia, which can cause painful circulatory problems, kidney failure and strokes.

The researchers converted those skin cells into iPS cells by infecting them with viruses engineered to change the cells' gene activity so they would resemble embryonic cells.

Using DNA splicing techniques in those cells, the researchers then snipped out the small mutated stretches of DNA that cause sickle cell disease and filled those gaps with bits of DNA bearing the proper genetic code.

Next, the researchers treated the corrected iPS cells with another kind of virus -- this time one designed to induce a genetic change that encouraged the cells to mature into bone marrow cells.

Finally, each mouse that gave up a few skin cells at the beginning of the experiment was given an infusion with the corrected marrow cells created from its own skin cells. Those cells set up permanent residence in the animals' bones and began producing blood cells -- the major function of marrow cells -- and releasing them by the millions into the circulatory system.

But now the blood cells being produced were free of the sickle cell mutation.

"All the parameters we can measure are now normal," Jaenisch said. "The mice are cured."

People with sickle cell disease can be cured with bone marrow transplants, but only about 20 percent of patients have a healthy sibling whose tissue type is a close enough match to avoid immunological complications, Townes said. Even in those cases, about 20 percent of the transplants fail, and sometimes they result in a potentially deadly reaction called graft-vs.-host disease.

Those problems do not arise with iPS cell transplants because the cells are genetically identical to the animals getting them.

"These are not just matched, they're identical," Townes said.

The mice were given low doses of radiation just before the transplants to kill some of their existing bone marrow cells and to make room for the newly injected, corrected ones. Tests indicate that about 80 percent of each animals' marrow is now made up of the new cells. And four months after treatment, no tumors have been seen.

Even a 20 percent marrow substitution can be therapeutic in people, Townes said, in part because healthy red blood cells live for about four months in the circulatory system, while their diseased counterparts last only 40 days.

"I think it is a really exciting proof-of-principle that clinical applications of iPS cells are technically feasible," said George Q. Daley, a stem cell researcher at [Children's Hospital Boston](#). "There will be lots of unanticipated setbacks before we end up in the clinic, but this work suggests that we will ultimately get there."

Jaenisch said the success with iPS cells does not mean that research on human embryonic stem cells can be dropped, as some opponents of the work have asserted.

"All the progress in this field was only possible because we had embryonic stem cells to work with first," Jaenisch said. "We need to make more ES cells and really define which are going to be the best ones for different applications."