p1106 Stranded in Spain: Government reneges on promise to hire researchers.

p1107 Fighting spirit: UN envoy Stephen Lewis speaks out against AIDS and injustice.

p1110 Criminal intent: Falsified DNA tests have led to dozens of convictions.

Scientists eye embryo-free methods to derive stem cells

On 23 August, scientists at the California-based Advanced Cell Technology (ACT) reported, to much fanfare, that they had derived human embryonic stem cells from a single cell of an embryo while leaving the embryo unharmed—which, the scientists said, could qualify the method for US federal dollars.

Fertility clinics routinely remove single cells from morulas—embryos that have eight to ten cells—to screen for genetic diseases. The ACT scientists could, in principle, have similarly removed a cell and derived embryonic stem cells from it without destroying the morula.

But to minimize the number of embryos used, they instead plucked an average of five to six cells from each of 16 morulas, generating just two stem cell colonies—and destroying the embryos in the process (*Nature* online publication).

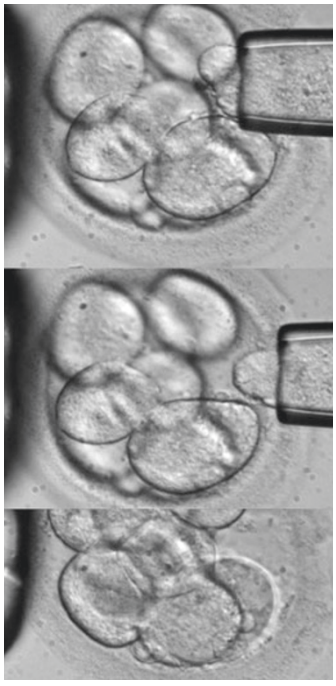
In the days that followed the announcement, experts skewered the company for its initial claim, saying it had misrepresented the finding. But the events underlined scientists' eagerness to find a way around the ethical barriers to embryonic stem cell research.

Back to the future

ACT's method relied on discarded embryos, but many researchers are engaged in finding ways to completely avoid using embryos.

The most popular approaches aim to reverse a fully differentiated mature adult cell—a hair cell, for example, or a liver cell—into an embryonic state using either existing stem cells or eggs. But it may be possible to reset the molecular switches of adult cells without using either.

"Reprogramming adult cells to the embryonic state is really possible, not science fiction," says Azim Surani, codirector of the University of Cambridge's Stem Cell Institute.



/AFP/Getty Images

Tough cell: Can stem cells be derived from an embryo without destroying it?

In the much discussed therapeutic cloning approach, researchers insert the nucleus of an adult cell into an egg from which the nucleus has been removed. This is the method that created Dolly the sheep, mice, cows and any number of other animals.

But no one has yet succeeded in doing this with human cells—as was painfully evident after South Korean Woo-Suk Hwang was shown to have fabricated his results. In most countries, therapeutic cloning is dogged by cost and safety issues related to harvesting human eggs, and by fears that the technique will be diverted to clone entire human beings.

Fusing adult cells with stem cells—which transforms the resulting hybrid to an embryonic state—has been more successful, first with mice in 2001 and then with humans last year (*Curr. Biol.* **11**, 1553–1558; 2001, *Science* **309**, 1369–1373; 2005).

One big hurdle remains, however: the fused products each have two sets of genetic material. Would expelling the embryonic genome cause the hybrid cell to revert to an adult state?

"Whether a hybrid cell's adult genome has been sufficiently reprogrammed to retain its new capabilities without the embryonic DNA is unknown," says Surani.

In any case, no one has yet convincingly shown that they can remove the embryonic genome, notes Alan Trounson, a cloning expert at Monash University in Australia. Trounson says one way might be to move the chromosomes with electromagnetic forces generated by lasers. "We've been way too conventional," he says.

Molecular switches

Rather than grapple with these uncertainties—combined with the low efficiency of fusion experiments—some scientists are trying to uncover the molecular switches that define an embryonic state.

Many researchers predicted that a huge number of factors would be needed to transform an adult cell to its embryonic origin. But in August, a Japanese team stunned the community by revealing that a set of just four proteins can confer embryonic stem cell–like qualities on adult mouse cells (*Cell* **126,** 663–676; 2006).

These 'induced pluripotent stem cells' divided unceasingly in a dish, differentiated into a large variety of tissues and, inserted in a mouse embryo before its implantation into a mouse uterus, contributed to the development of numerous organs.

The results are "shocking—a huge breakthrough," says Chad Cowan, a researcher at Massachusetts General Hospital who first demonstrated successful fusion with human cells. "If they hold up, the sky could be the limit."

None of the chimeric fetuses survived to term, and the cells showed some differences from normal embryonic stem cells, so the method needs to be refined. "I'm not saying these are *the* four factors," says lead investigator Shinya Yamanaka. "There may be better ones."

Yamanaka's team used viruses to continually churn out the four factors in the adult cells.

"It would be nice to introduce all these factors transiently and then remove them so that the cell could drive itself," says Surani.

The problem lies not with the genes, he says, but with their epigenetic status: as a cell differentiates, chemical modifications of DNA or its surrounding histone proteins lock genes into on or off positions. Reversing those epigenetic changes might be crucial in reprogramming adult cells, but scientists know little about enzymes that can do that.

Robert Blelloch at the University of California in San Francisco and his collaborators have found that mice that have lower levels of DNA methyltransferase I, a DNA-modifying enzyme, show higher rates of success with nuclear reprogramming (*Stem Cells* **24,** 2007–2013; 2006). They are also investigating the role of short RNAs that may bind to DNA and control the on-off switching.

"It's amazing what an embryo does," says Blelloch. "There's a lot more to learn."

Bruce Goldman, San Francisco