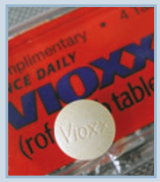
p462 Game on: Women scientists turn to sports law for equal opportunity.

p464 Seoul's star: Stem cells catapulted Woo-Suk Hwang into the spotlight.



p465 Safety first: Is the system for screening drugs broken?

Scientists seek simple remedies to cloning conundrums

In most discussions of stem cell research, staunchly conflicting sides swipe at each other over whether it is right to destroy an embryo to create stem cell lines. But at a recent scientific meeting in San Diego, scientists talked instead of alternatives that would eliminate the need for human eggs and embryos.

These researchers are trying to reverse mature cells into an embryonic state, substituting human eggs with those from animals or, perhaps the most promising for therapy, trying to create a limitless number of human eggs in the laboratory from existing embryonic stem (ES) cells.

In the conventional therapeutic cloning model, researchers take genetic material from an adult cell and fuse it with an egg that has been emptied of its nucleus. The resulting hybrid, which can be coaxed into forming an early-stage embryo, yields stem cells that can become many different tissues. The ultimate goal is that ES cells cultivated from a patient's own cells could replace his or her missing or damaged tissues such as nerve cells, heart or muscle.

The technique, also called somatic cell nuclear transfer, has thus far birthed cloned cows, pigs, goats and sheep—beginning with the departed Dolly—but only one team, led by Woo-Suk Hwang (see page 464) of South Korea, has successfully used it to derive ES cells from a human embryo (*Science* **303**, 1669–1674; 2004).

"The so-called therapeutic cloning to my mind is a non-event," says Alan Trounson, director of the Monash Institute of Reproduction and Development in Australia. As a method for developing therapies, he says, "it's just not realistic."

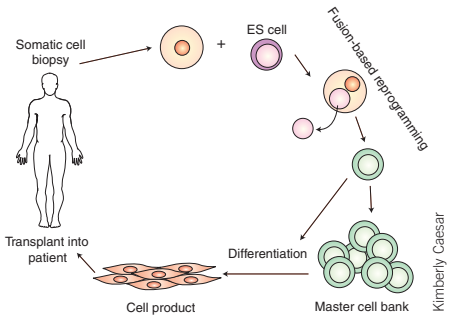
Getting human eggs for cloning experiments is expensive, technically complicated and an ethical minefield. In their experiment, the Korean team needed 242 eggs from 16 donors to create one embryo, and their work was dogged by questions about the source of the eggs. Even if all ethical considerations are met, researchers say the sheer numbers required make it an impractical approach to treat diseases.

"You can't rely on human eggs forever, there's got to be a better way," says Jose Cibelli, professor of animal biotechnology at Michigan State University. "I can predict that therapeutic cloning is going to be obsolete."

Moral trump card

People who oppose therapeutic cloning say that destroying embryos for research purposes is wrong on moral or religious grounds. Creating ES cells using this method is allowed only in a few countries, including the UK, South Korea and China; in the US, the research cannot be carried out using federal funds.

Reversing mature cells into an embryonic state trumps the moral arguments by sidestepping both eggs and embryos. German researcher Hans Schöler and his colleagues have shown that fusing adult mouse cells with mouse stem cells results in hybrids that lose their mature nature and take on the characteristics of ES cells (*Stem Cells* **22**, 941–949; 2004). Other teams are successfully replicating this with human cells, although that research has not yet been published.



Born again: Fusion with embryonic stem cells can reverse adult cells into an undifferentiated state.

But because the reprogrammed cells are created by fusing two independent cells, they continue to carry the genetic material of both. "There's still a quantum leap in this field that needs to be made: how do you get rid of the ES cell genome?" asks Kevin Eggan, junior fellow in the Harvard University Society of Fellows.

To solve this problem, some groups are testing whether the cytoplasm of ES cells might be enough to trigger the reversion of mature cells, but evidence thus far indicates that ES cell nuclear factors might be required. In any case, it might be possible to identify the specific factors required and use those to reprogram adult cells. "By looking at nuclear transfer very, very closely in animals, we can probably figure out a few key players," says Cibelli.

Peter Schultz and his colleagues at The Scripps Research Institute are screening small molecules to identify biochemical equivalents of these factors that can activate the reversion. Researchers will also need to address questions such as to what extent epigenetic information—such as methylation—is reprogrammed.

For research purposes, scientists may also fuse adult cells with empty eggs from other species such as rats, rabbits or horses. One Chinese team has derived ES cells by transferring adult cell nuclei into rabbit eggs; those cells appear similar to conventional human ES cells (*Cell Res.* **13**, 251–263; 2003).

Eggs galore

To avoid the practical hurdles surrounding egg donation, several groups are in a heated race to create eggs and sperm in the laboratory; they have already succeeded in generating eggs and sperm from mouse stem cells (*Nature* **427**, 148–154; 2004; *Science* **300**, 1251–1256; 2003).

Apart from their obvious use in treating infertility, these eggs could be used to create new embryos without requiring painful and expensive egg extraction from women. But as the method would still entail creation of embryos, it would not put the moral debates to rest. "It would lead to the creation of undeniably many more embryos," notes Eggan. "These things come from a blastocyst anyway, so the whole thing is a moral conundrum."

The ultimate goal is to use one of these methods and create stem cells to study and treat diseases. ES cells that recapitulate some genetic diseases have already been created using discarded defective embryos (*Nature* **429**, 691; 2004), but for more complex diseases, therapeutic cloning is still an option. Eggan and Harvard's Doug Melton have applied for licenses to make embryos with genetic material from patients with type 1 diabetes, Parkinson and Alzheimer diseases, and eggs donated by women.

"It's not clear who is going to step forward to be a donor where there is no compensation," says Eggan. "[But] the fact remains that the way the Koreans did it is the only way anyone has done it."

Apoorva Mandavilli, San Diego