Oz stem cell clinic turns to diseased embryos

As scientists close in on ways to create embryonic stem cell lines without destroying human embryos (see main article, right), some groups are turning to discarded embryos that carry genes for certain diseases.

Sydney IVF, an Australian *in vitro* fertilization clinic and cell line provider, screens embryos before they are implanted for more than 100 diseases caused by mutations in a single gene or by chromosomal translocations.

After a successful birth, clients can choose to allow the rejected embryos to be used for research purposes. Since it began its preimplantation genetic diagnosis program in 1997, the company has established a bank of nearly 2,000 embryos that will allow researchers to investigate single-gene diseases such as Huntington's.

The company uses a variation on the standard approach to genetic screening.

Most clinics remove one or two cells from an embryo at the eight-cell stage, which some scientists say could damage the embryo. Sydney IVF scientists instead take samples from the trophectoderm, the outer part of the embryo which will go on to form the placenta, when the embryo has grown to have more than 100 cells. "We are still the only people in the world doing this with any kind of regularity," says Robert Jansen, the company's managing director.

The researchers hope to differentiate embryonic stem cells developed in this way into particular tissues to help model single-gene diseases and screen potential therapies.

Other scientists, including Yuri Verlinsky of Chicago's Reproductive Genetics Institute, have also said they have developed stem cell lines carrying disease genes from rejected embryos (*Nature* **429**, 691; 2004).

Although the field is still in its infancy, the approach has merit, says John Rasko, head of the Gene & Stem Cell Therapy Program at The University of Sydney's Centenary Institute. "It promises the use of relevant phenotypically defined cells rather than applying normal cells or whole animal models in large-scale screening programs," Rasko says.

Sydney IVF has an AUS$2.7 million (about US$2.3 million) grant from the government to develop its approach, with the condition that its research will not involve so-called therapeutic cloning, or somatic cell nuclear transfer.

The Australian Parliament endorsed therapeutic cloning for research purposes only late last year, and state legislatures are now debating complementary laws. In early June, the government finalized guidelines for research licenses. The first of those licenses are likely to be granted before the end of the year.

Simon Grose, Canberra

Teams trail genes for human 'stemness'

The announcement in June that mature mouse cells can be reprogrammed to behave like embryonic stem cells was welcome news to US scientists hamstrung by the federal restrictions on stem cell research.

But even elsewhere in the world, researchers are scrambling to improve upon the technique, which skirts the controversial use of human eggs and embryos.

"These studies are without question among the most important advances over the past five years in the stem cell field," says the University of Southern California's Martin Pera.

George Daley, a stem cell expert at Harvard University, in an email wrote simply, "HUGE."

A Japanese team led by the Kyoto University's Shinya Yamanaka first unveiled the technique last year (*Cell* **126**, 663–676; 2006), using retroviruses to insert genes into the DNA of mouse fibroblasts. To the field's surprise—and initial skepticism—the team found that only four genes can, in combination, trigger a series of events that shunts cells back into an embryonic state, from which they are able to differentiate into any cell type in the body—an ability dubbed 'pluripotency'. Yamanaka dubbed the cells "induced pluripotent stem" (iPS) cells.

In the papers published in June (*Nature* doi:10.1038/nature05934; *Nature* **447**, 679–685; *Cell Stem Cell* 1, 55–70; 2007), three independent teams in Japan and the US used the same four factors and then selected for reprogrammed cells using the proteins Nanog and Oct4, which are characteristic of embryonic stem cells. "The [iPS] cells are as identical to embryonic stem cells as embryonic stem cells are to each other," says the University of California at Los Angeles's Kathrin Plath, who led one of the teams.

Cells are similarly reprogrammed by the unfertilized egg in so-called therapeutic cloning. So far, however, no one has succeeded in deriving stem cells from a cloned human embryo, at least in part because human eggs are complex and are all but unavailable.

Reprogramming human cells using Yamanaka's method would effectively solve the technical and ethical problems with using human eggs or embryos. The aim is to derive stem cell lines genetically matched to individuals with diseases. The cell lines would help model the diseases, test therapies for them and, ideally, produce tissues for transplant.

The ability to take a few cells from a patient's skin or a cheek swab and turn them into stem cells, says Robert Lanza, vice president of research and scientific development for California-based Advanced Cell Technology, "would be like turning lead into gold."

That's easier said than done, however.

"Mechanisms of maintenance and regulation of pluripotency are quite different between mouse and primate—monkey and human—embryonic stem cells," says Norio Nakatsuji, director of Kyoto University's Institute for Frontier Medical Sciences. "We may well need another breakthrough to obtain reprogrammed human iPS cell lines."

For example, the retroviruses used to genetically modify the mouse cells can cause cancer in humans. Rather than use these viruses to express the required proteins, synthetic molecules now being developed could move the proteins across the cell membrane, says Lanza (*Stem Cells Dev.*, in press). Another alternative would be to use small molecules to stimulate the cell's own genes that control the reprogramming process, he adds.

Another hurdle is that some of the genes, such as *Myc*, used to trigger the reprogramming process are known oncogenes. In theory, these genes should shut down naturally when the cells revert to an embryonic state. But Yamanaka found that nearly 20% of his chimeric mice had tumors that may have been caused by the *Myc* gene being turned back on.

At least in the mouse, these problems will be overcome in the next few years, says Yamanaka. But Lanza is less optimistic. "There are some very serious hurdles," Lanza says. "It could take years—if not decades—to get this work in humans in a way that could be used clinically."

The new method has led some to doubt the need to continue therapeutic cloning, especially given the need to use fresh eggs, a controversial and scarce resource. Lanza says he has only found one egg donor after several years of exhaustive search.

The new findings give reprogramming an edge, with at least a dozen groups—and probably many more—trying to derive human embryonic stem cells. According to the University of Wisconsin's James Thomson, the first scientist to isolate human embryonic stem cells, "Research in this area will now progress very rapidly given that the number of required genes appears to be small."

David Cyranoski, Tokyo