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An Offshore Haven for Human Embryonic Stem-Cell Research?

Susan Okie, M.D.

U.S. scientists studying human embryonic stem cells face unprecedented political, regulatory, and financial barriers created by the Bush administration's restrictive policies and by the ongoing national debate over the ethics of such research. The most promising method of making patient-specific and disease-specific embryonic stem-cell lines — somatic-cell nuclear transfer — is also the most ethically troubling for many people, because it requires both the creation of embryos for research purposes and the recruitment of women as egg donors. The procedure, in which the nucleus of a somatic cell is inserted into an oocyte, providing the genes for the development of an early-stage embryo, is not yet being performed in the United States.

Now, Woo Suk Hwang, the South Korean veterinarian and stem-cell biologist whose laboratory leads the world in the use of this technique, is planning to offer researchers in the United States and other countries a chance to work with such cell lines without having to make them themselves. Hwang's plan provides a possible strategy for accelerating international progress in the field and avoiding some of the legal and regulatory complications of deriving the cell lines in this country. But will U.S. scientists, ethicists, and research institutions embrace the proposal?

At the time of this writing, officials in three countries — South Korea, the United States, and the United Kingdom — were preparing to announce on October 19 the establishment of the World Stem Cell Foundation, an international consortium to be headed by Hwang and based at Seoul National University in South Korea. Under the current scheme, the consortium would operate a small satellite laboratory in the San Francisco area and another in England, and each laboratory would be associated with a nearby in vitro fertilization facility where donor oocytes would be collected. Scientists from various countries who wished to use embryonic stem cells to study a disease could apply to have cell lines created for their projects. Clinical researchers in Seoul, in England, and in San Francisco would recruit women to donate eggs and patients to donate somatic cells, after obtaining approval from the relevant oversight committees at their institutions.

Three Korean technicians trained in Hwang's laboratory

would travel regularly to the satellite stem-cell laboratories to perform all the nuclear transfer procedures. Other technicians working in the U.S. and British laboratories would grow the newly derived cell lines in culture for a few months, then ship samples to Korea, where each cell line would undergo detailed characterization and quality control. Frozen aliquots of all cell lines derived by the consortium would ultimately be stored in each of the three countries.

Reproductive and cell biologist Gerald Schatten of the University of Pittsburgh, Hwang's American collaborator and close friend, estimates that the foundation could make about 100 new disease-specific embryonic stem-cell lines per year — enough to provide 5 cell lines for each of 20 projects. Schatten, who will chair the foundation's board of trustees, emphasized that having expert Korean technicians perform the technically difficult nuclear transfers will help ensure that donated oocytes, the limiting resource for developing cell lines by this method, will be used as efficiently as possible.

"In order to move forward, we scientists need some kind of a safe haven," Schatten said. "The ethical and legal implications are important, but the most important thing for us is just to have discoveries that are independently confirmed and extended." He compared the current state of embryonic stem-cell research to the early stages in the development of organ transplantation. Once the treatment's potential became clear, he said, most religions were convinced "that it

A Tetraploid Twist on the Embryonic Stem Cell

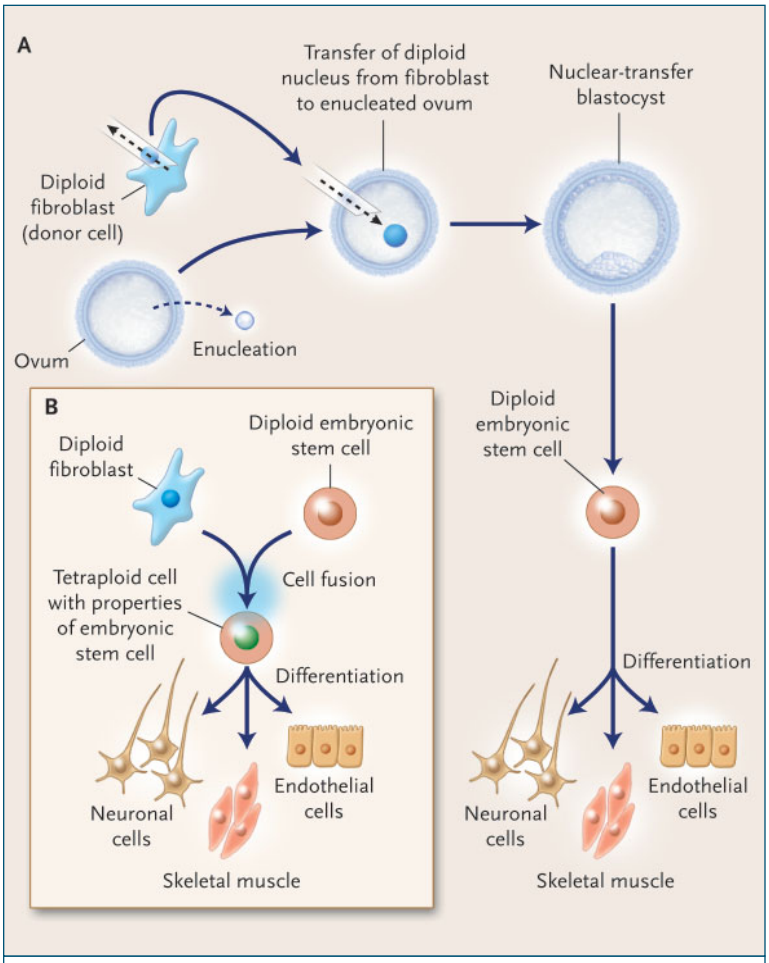
Elizabeth G. Phimister, Ph.D.

The production of human embryonic stem cells by somatic-cell nuclear transfer depends on a profound but obscure event that takes place when the nucleus of a "donor" somatic cell is injected into an enucleated ovum (see diagram). Somehow, the cytoplasm of the oocyte reprograms the chromosomes of the somatic cell's nucleus so that the newly formed cell becomes pluripotent. The cell develops into a blastocyst, from which embryonic stem cells can be derived that carry a set of chromosomes identical to that of the donor.

The "tailored" embryonic stem cells thus derived have fueled hope for new treatments for degenerative diseases such as type 1 diabetes and Parkinson's disease. They are believed to be pluripotent — that is, they can differentiate, under appropriate conditions, into cells of any type. With a nuclear complement that is identical to that found in the somatic-cell donor, they are unlikely to be rejected by that donor.

In a recent study, Cowan and colleagues[1] tested the hypothesis that, like the oocyte's cytoplasm, the human embryonic stem cell can also reprogram the chromosomes of a somatic cell. They encouraged the fusion of fibroblasts and embryonic stem cells by coculturing cells of both types in an agent that facilitates membrane fusion, and they obtained stable tetraploid hybrid cells, each of which had a single nucleus (see diagram). These cells looked and behaved like embryonic stem cells. For example, a protein characteristic of embryonic stem cells was expressed from RNA transcribed from a fibroblast chromosome; the cells seemed to be immortal (they have been passaged more than 50 times). They developed and differentiated into embryoid bodies (in vitro) and teratomas (in vivo) — each of these had tissues expressing markers characteristic of each of the three germ-cell layers (endoderm, mesoderm, and ectoderm). Thus, the hypothesis would seem to be correct: human embryonic stem cells can reprogram adult somatic-cell chromosomes after cell fusion. Additional support is provided by similar findings previously obtained with mouse cells.

There is some risk that people who are seeking to place restrictions on research into the biology of human embryonic stem cells may misinterpret these findings, arguing that the new technique represents an alternative approach to the generation of "chromosomally tailored" human embryonic stem cells that have therapeutic potential. Kevin Eggan, one of the investigators in this study, says he is "very disappointed" by this prospect and emphasizes that the



Derivation of Patient-Specific Embryonic Stem Cells by Nuclear Transfer (Panel A) and Derivation of a Tetraploid Cell with Properties of an Embryonic Stem Cell (Panel B).

Human embryonic stem cells derived by transfer of the nucleus from a somatic cell (Panel A) are considered to have therapeutic potential, in contrast with the tetraploid cells recently described by Cowan et al. (Panel B).[1] These tetraploid cells were generated by the fusion of a fibroblast and an embryonic stem cell and have the behavioral properties of an embryonic stem cell.

study "does not deliver a methodology that can replace human embryonic stem cells." Although this finding will inspire further studies to identify and determine the mechanism of action of the critical factors that reprogram chromosomes, the hybrid cells cannot generate embryonic stem cells and, because they are tetraploid, their therapeutic potential is nil.

Dr. Phimister is a deputy editor of the *Journal*.

1. Cowan CA, Atienza J, Melton DA, Eggan K. Nuclear reprogramming of somatic cells after fusion with human embryonic stem cells. Science 2005;309:1369-73.

was a blessing to donate organs. We hope that the same thing will happen here."

The legal and regulatory restrictions on embryonic stem-cell research in the United States make it appealing for U.S. scientists to participate in the Korean-led consortium, said George Q. Daley, an associate professor at Harvard Medical School and associate director of the Stem Cell Program at Children's Hospital, Boston. "Given the access that they apparently have to a very willing set of egg donors," said Daley, "they may be much more efficient at generating these cells than anybody else." Although U.S. groups, including Daley's own, are seeking approval to do somatic-cell nuclear transfer in the United States, he acknowledged that "our climate is much less supportive than theirs."

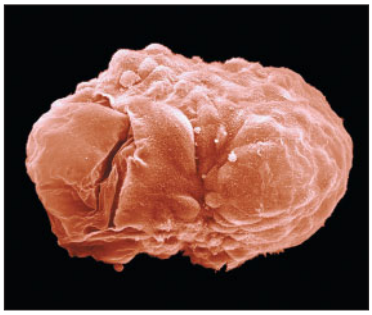
Under the administration's policy, federal funds may not be used for research on human embryonic stem cells created through somatic-cell nuclear transfer — which means that even if stem-cell researchers have grants from other sources, they may not conduct such studies using laboratory space, equipment, or supplies that were paid for by the National Institutes of Health. Five states — California, Connecticut, Massachusetts, New Jersey, and Rhode Island — have passed laws explicitly permitting scientists to make human embryonic stem-cell lines by somatic-cell nuclear transfer (sometimes called research cloning or therapeutic cloning). The governor of Illinois has legalized the procedure by executive order. In seven states — Arkansas, Indiana, Iowa, Louisi-

ana, Michigan, North Dakota, and South Dakota — research cloning is prohibited by law. Virginia may also prohibit the procedure, but the wording of its law is unclear. Only South Dakota explicitly forbids the importation of human embryonic stem cells derived elsewhere, so it appears that researchers in most states, provided that they did not use federal funds, could legally study cell lines obtained through the international consortium, according to LeRoy B. Walters of Georgetown University's Kennedy Institute of Ethics.

However, a number of prominent U.S. stem-cell researchers and scientific administrators have expressed concerns about the new international consortium as it is currently organized. Three scientists described their reservations in identical terms: "The devil is in the details."

One concern is that the policies of centralizing scientific decision making in Seoul, allowing only three technicians to perform nuclear transfer, and performing all stem-cell characterization and quality control in South Korea would greatly reduce U.S. researchers' opportunities for developing expertise in the new field. Some scientists questioned whether ethics regulations governing egg donation and embryonic stem-cell research in South Korea are sufficiently strict and said they worried that participation in the consortium would be viewed as an effort to sidestep guidelines recently issued by the National Academies, which have been widely adopted by U.S. research institutions. Some also raised questions about the cost of the cells, the funding of the enterprise, and licensing issues.

Schatten said that Korean researchers have promised not to patent new cell lines, but that the consortium does plan to charge for providing them to scientists. He said the South Korean government has promised to pay for the consortium's work in that country. However, private donations will be sought to fund its program in the United States, and perhaps also in Britain.



Blastocyst

"You learn a lot from the technology," said Michael German, a diabetes researcher at the University of California at San Francisco (UCSF), who is trying to develop insulin-producing beta cells from embryonic stem cells. "You want to get it into as many people's hands as possible. . . . The idea of a real bank of lines from different ethnic sources, different disease sources, is obviously wonderful, [but] focusing the technology in a limited number of hands is not something that we're really excited about."

International efforts are under way to standardize ethical guidelines for egg donation, embryo donation, and other research issues, and the leaders of the new consortium should be part of that process, scientific administrators said. Arnold R. Kriegstein, director of UCSF's Institute for Stem Cell Research and Tissue Biology, said that such matters would have to be worked through with the Koreans before his institute could participate in the consortium.

Researchers emphasized that Hwang has been generous about sharing his group's technical expertise and setting up collaborations with scientists in the United States and Europe. "I think the Koreans recognize that the biology itself has probably been advanced most rigorously in the States," said Evan Snyder, a pediatric neurologist who studies embryonic stem cells at the Burnham Institute in La Jolla, California. "But they see this opportunity where we've been stalled, and they have . . . made it a national priority . . . I think, now, they're incredibly sophisticated."

Snyder plans to collaborate with Hwang and Schatten, using somatic cells from patients with Lesch–Nyhan syndrome to create embryonic stem cells with the genetic mutation that causes the rare, inherited metabolic disorder. Schatten said collaborations are being planned with other scientists to make and study cell lines from patients with amyotrophic lateral sclerosis and Parkinson's disease and to try to develop lymphocytes that are genetically resistant to human immunodeficiency virus infection and could someday be used to treat people with AIDS. Many researchers believe that human embryonic stem cells may turn out to be even more valuable for studying the mechanisms of disease and for screening experi-

Yorgos Nikas/Wellcome Library.

mental drugs than for cell-based therapy, although it is their potential for providing replacements for dead or diseased cells and tissues that has captured the public imagination.

Snyder said he shares other researchers' concerns about the way the consortium is currently organized, but he predicted that it would quickly evolve to become more decentralized. "The only way the models can be made and characterized is by the community of stem-cell scholars really pulling together," Snyder said. "I would see a consortium as being a two-way street: each person brings to the table what they do best, swaps expertise and technology. Both countries start really elevating their levels of play. [When] you have success in something like this, everybody wins and everybody gets credit."

Around the nation and internationally, government policies are determining which scientists and research institutions will advance in the race to explore the potential of embryonic stem cells. According to Georgetown's Walters, 156 bills dealing with human embryonic stem-cell research and cloning have been introduced in state legislatures during 2005. States that permit research cloning are aggressively recruiting scientists who work in states that prohibit it. Among European countries, Britain, Belgium, and Sweden have the most liberal policies on stem-cell research, Walters said, whereas Italy does not permit even the freezing of extra embryos at in vitro fertilization clinics. France recently changed its regulations to allow the use of donated "leftover" embryos for research. Germany and Italy do not allow the creation of human embryonic stem cells but do permit their importation. Among Asian countries, India, China, Japan, and Singapore (as well as Korea) have liberal policies and are investing in research.

Although several major U.S. research universities are moving ahead with embryonic stem-cell research programs, Harvard's Daley said that the Bush administration policy "casts a pall over the field. . . . It makes every single negotiation for a protocol, for a human studies review, much more emotionally charged. There has never been so much sensitivity around an area of research." Researchers said the federal policy has made it difficult to get answers from Food and Drug Administration officials about what kinds of animal studies might be required to assess the safety of treatments derived from embryonic stem cells. UCSF's Kriegstein said it has also made it harder for U.S. scientists and ethicists "to have a place at the table" to discuss uniform international standards that might guide stem-cell research.

The highly politicized debate in Congress over competing stem-cell bills has also turned up the pressure on researchers to develop and test stem-cell–based therapies in human patients as soon as possible, perhaps increasing the risk that such treatments will be tested prematurely, with potentially adverse consequences. Schatten said that when he and Hwang visited Capitol Hill in September to lobby legislators about stem-cell bills that are likely to be debated in the Senate early next year, several senators and staffers told him, "Just get a medical breakthrough and you'll be home free." Stem-cell scientists said they are wary of falling into the errors made by colleagues in the field of gene therapy, who promised too much and moved too quickly into human trials.

Time will tell how the new international consortium affects this volatile mixture of science and politics. In California, where funding of the state's $3 billion stem-cell initiative is still being held up by opponents' lawsuits, the California Institute for Regenerative Medicine, the state agency that will award grants, has decided not to have a formal relationship with the consortium, according to its president, Zach Hall. UCSF, too, will probably not participate; according to Kriegstein, the university intends to raise private funds to build a new building where its scientists can create new human embryonic stem-cell lines, at least some of them by means of somatic-cell nuclear transfer. At Harvard, Daley said he and his scientific colleagues intend to collaborate with the Korean-led consortium, but they also want to become expert in making their own disease-specific cell lines using the new procedure.

"I'm going to be open to it," Daley said. "I want to be part of it. But it's not going to prevent us from trying nuclear transfer on our own as soon as the approvals go through."

Dr. Okie is a contributing editor of the *Journal*.