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Clone wars: Who'll come out ahead?

Researchers race to refine controversial technology



Jose Cibelli, holding a container of embryonic stem cells in his Michigan State University lab, has been involved with ground-breaking embryo cloning experiments.

(THE BLADE/DAVE ZAPOTOSKY)

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BOSTON — They're getting ready to clear the stragglers from the Boston World Trade Center. Even the post-meeting cocktail party is down to a scatter of empty plastic cups. But a few of the stem cell scientists linger, talking quietly.

An American scientist leans in. He has a story, a sort of scientific fright-night tale. His South Korean graduate student told it to him: In laboratories she visited in Seoul, people work day and night dissecting embryos and making stem cell lines.

"It's like assembly line stuff," said Evan Snyder, director of stem cell research at the Burnham Institute, an independent research center in La Jolla, Calif.

"We succeeded during the industrial revolution because we created the assembly line, making car after car. Now they're able to do that for science."

Shin Yong Moon, director of the Korean Stem Cell Research Center, confirms the story the next day: "They are really hard working people, working seven days a week."

If science is a contest — and it can sound like that sometimes — then South Korea won a gold medal in February when a research team there became the first to clone human embryos and derive a stem cell line from one of them.

The event focused anxieties for two dissimilar groups: American scientists who fear becoming a second-rate power in stem cell research, and those horrified by the cloning itself.

Among cloning opponents, the February announcement sent shivers of imminent danger. It marked an advance on the slippery slope to reproductive cloning — cloning to make babies. In fact, for cloning adversaries, the difference between the stem cell cloning performed in South Korea and reproductive cloning is immaterial.

"They're making a false distinction," said Wesley J. Smith, a lawyer and senior fellow at a conservative Seattle think tank. "There is only one kind of cloning." The same technique that makes an embryo for stem cells could make an embryo to create a pregnancy.

In addition, stem cell cloning requires the destruction of the embryo.

“This is pretty radical. It would create, for the first time in human history, a category of life ... that has to be destroyed,” Mr. Smith said.

The anxiety for some scientists is of a completely different nature. Most agree with University of Pennsylvania bioethicist Arthur Caplan when he says: “I think making embryos the equivalent of people from the moment of conception is scientifically false. ... A majority of embryos can’t become anything. They fail. They don’t develop in the woman’s body” and they’re incapable of complete development outside of it.

For scientists, the Korean accomplishment fed another fear — that U.S. researchers may be falling behind, hobbled by limited federal funding of embryonic stem cell work.

No federal dollars can pay for research on stem cell lines created after Aug. 9, 2001. No government research money can be used in human cloning. Yet, researchers in the United Kingdom, Singapore, China, Korea, and a half-dozen other nations enjoy government support for this work.

As long as U.S. researchers lack such backing, other countries “absolutely will beat us,” Dr. Snyder said. “They’re smart. They work hard. They do good science.”

Despite the dismay on both sides, the Korean cloning accomplishment was less a revolution than what one bioethicist called, “a subtle and sudden small shift.”

It is “only one step closer to a tantalizing goal,” Laurie Zoloth of Northwestern University said in a speech in June. “But it’s on a path in which every single tentative step matters all over the world.”

Amid the concern that a rogue fertility doctor will attempt to create pregnancies with the emerging cloning technology is a contrasting tension: Without human cloning, many believe, the promise of embryonic stem cells will not come to pass.

Life-saving potential

The eggs could not have been safer. An armed guard escorted them during the one hour drive from a Boston-area fertility clinic to the offices of Advanced Cell Technologies in Worcester, Mass., in 2001.

Michael West, chief executive officer of ACT, saw cloning as his best chance to turn stem cells into life-saving therapies.

Mr. West, a native of Niles, Mich., was among the first to recognize the commercial potential of human embryonic stem cells. When he was vice president of Geron Corp. in Menlo Park, Calif. — a company he founded — it bankrolled the breakthrough research to isolate the first human stem cells.

But even as Mr. West worked to attract investors to his California biotech, he wondered how he would put stem cells inside patients.

Surely, these cells would excite the human immune system, fostering an attack similar to what the body mounts against transplanted organs. Would stem cell therapy need the support of the immune-suppressive drugs? Such drugs make transplant patients a higher risk for infection. There had to be a better solution.

Then Dolly the sheep was cloned in 1997 and Mr. West wondered: can we use a patient’s cells to clone an embryo that would yield custom-made stem cells — cells that the immune system would ignore?

“Then we’d have a perfect match,” he said. “Then, there would be no rejection.”

Now, all he had to do is clone a human.

Biological sleight-of-hand

The human egg on the video screen glows fat and spheroid, like a rising moon.

It's a common sight in fertility labs, where the eggs are poked and prodded with tiny glass needles, and babied with baths of nutrients.

After 26 years of in vitro fertilization success, we're accustomed to the everyday magic of this globe's powers: The fusion of its nucleus with that of the sperm; the launch of new life.

But last year in a laboratory in South Korea, scientists watched as this powerful cell performed a new wonder.

First, researchers removed the DNA from this sticky egg, and replaced it with the nucleus of an adult cell.

Now, the question was, could the egg make something old new again? Would the egg work like a time machine, turning back the clock on the mature genetic program inside a grown-up nucleus?

Could it make the adult DNA behave like that of a newborn embryo?

Woo Suk Hwang was sure of it. He and his team were masters of this bit of biological sleight-of-hand. They had made clones of cows, pigs, and horses. They cloned a type of cow resistant to mad cow disease. In one animal after another, they saw the mammalian egg turn adult cells into kids again. The genes needed for adult function were turned off. The genes for embryonic development turned on.

The embryos thus formed were transplanted into surrogate mothers. A farmyard of evidence grew: Healthy cloned animals created by letting an egg reset the program of an adult cell.

But so far, no one had accomplished it in humans.

The very idea frightened people.

Embryo reprogramming

When Mr. West moved to Advanced Cell Technologies in 1999, he knew he wanted to clone. Two years of ethics review followed. ACT appointed an ethics panel that established the rules for acquiring eggs and conducting the science. None of these eggs were to be used to make a human. The extreme measure of hiring an armed guard was one defense against any of the eggs being taken and used for other purposes. Once ensconced in the ACT lab, the eggs remained behind a locked door, a video camera pointed at the entrance.

Such security measures were the easy part. The hard part was working with the difficult, fragile, human eggs.

Jose Cibelli, vice president for research at ACT in 2001, was confident cloning could work. Even before the cloning of a sheep was announced in 1997, he thought the technology had a chance.

Today, Dr. Cibelli is a professor at Michigan State University. But in 1996, he was earning his doctoral degree at the University of Massachusetts.

Then, few believed an adult cell could be reprogrammed by the embryo, which is what cloning is supposed to do.

"The dogma said [an adult] cell couldn't go back in time. I didn't buy that," he said.

To test his idea, he took one of his own cells, extracted the DNA, and put it inside a cow egg.

Although the experiment sounds odd, Dr. Cibelli was peeking into the future of cloning: "I was just trying to determine if we could go against the dogma."

He could and he did. The cow egg with his DNA divided like an embryo.

Now, in 2001, Dr. Cibelli hoped a human egg and adult cell would do the same thing — something many said was impossible.

When the well-guarded eggs arrived in the laboratory, the team had to work fast. "You have only a small window of

opportunity,” Dr. Cibelli said. You need fresh eggs.

All of the technical challenges were compounded by the fact that the team had only 17 eggs to work with. At any step along the way, they might break.

Each egg is surrounded by a cluster of cells that provide it nutrients through development. These must be cleared away.

“Right there, you can lose some eggs. You can break them,” Dr. Cibelli said.

Removing the egg DNA from an egg cell about the same width as a human hair is another difficult step. It takes a needle only one-tenth the breadth of a hair.

“You go in with a needle and pull the DNA out. That’s not difficult in species like [the cow], because the shell of that egg is hardy. The human egg, it’s very rubbery. The needle goes in, and it doesn’t really break the shell.” Once the egg is successfully punctured and its DNA captured in a needle, there’s another chance to destroy the egg. The DNA may make a big hole in the egg as it is extracted.

Finally, adult DNA is put inside the rubbery egg shell. A jolt of electricity follows. The electricity makes tiny pores in the egg membrane. As the egg repairs those holes, it pulls the new DNA inside.

“There’s not too much room for playing around with this. You can have too much electricity. You can have too little,” Dr. Cibelli said.

It was nearly 3 a.m. when the team finished its work. It would be 12 hours before they would know if they had clones.

When Dr. Cibelli finally opened the incubator, he saw the first signs of success. Many of the eggs acted as though fertilization had occurred.

On day two, when he looked again, some of the embryos were beginning to divide — a breathtaking development.

“After so much work ... it’s like what’s going on with the Red Sox right now, after losing three games in a row. ... We had so many false starts, when you get something, you’re very excited,” Dr. Cibelli said.

But on day six, the experiment was over. Two embryos had reached four cells. A third had stopped at six cells. It wasn’t enough.

The researchers needed embryos of 100 cells in order to harvest stem cells from them. Although the cloning effort failed to produce the necessary results, it was a small sign that human cloning could work.

As a public relations move, however, the experiment was a disaster. Every fear and objection to cloning, from every possible quarter, arose after publication of the experiment in the online periodical, E-BioMed Journal of Regenerative Medicine.

President Bush condemned the work: “We should not, as a society, grow life to destroy it, and that’s exactly what is taking place.”

Many in Congress voiced strong opposition. The Vatican issued “unequivocal condemnation.” The scientific and business communities were just as tough.

Thomas Okarma, chief executive officer of Geron Corp., Mr. West’s former company, was scolding in remarks to Business Week: ““The ACT paper offers a half-baked result that critics of this science can use.”

Mr. West, who rushed that Sunday morning from Meet the Press to CNN, said he knew the publicity would make enemies.

“I knew that it would hurt us, the controversy, with raising money. It did. And people I thought were our friends out there were throwing arrows at us too.

“At least we can look ourselves in the mirror and say, we did our best. We tried to do it right.”

Clearly, not everyone agreed.

South Korean advances

Even other South Korean scientists think of Woo-suk Hwang as a demon of hard work.

He takes few vacations. He works weekends.

“Actually, I want to work even Saturday, Sunday, and holiday,” he said.

He doesn’t spend much time at home. The former country boy who grew up tending cows begins his day with 4:30 a.m. yoga practice. Then he works.

While many U.S. scientists look to South Korea with some envy and, perhaps, a measure of wounded competitive pride, the fact is that country’s reputation as a powerhouse in stem cell research does not rise from generous government funding or the most liberal public policies. It is mainly the result of indefatigable researchers such as Dr. Hwang.

South Korean funding of stem cell research is a fraction of what American science receives. The Seoul government created the Stem Cell Research Center in 2002, providing it with \$7.5 million a year for the next 10 years, said Shin Yong Moon, director of the research center. U.S. funding of embryonic stem cell research totals \$24.8 million; funding for adult human stem cells tops \$190 million.

But South Korea appears to be increasing financial contribution to stem cell research, naming the field one of the country’s 10 “major growth engines.”

And Dr. Hwang is becoming something of a Korean rock star.

In August, the Korean government created a task force to financially support his work. According to the Korea Times, this followed rumors that Dr. Hwang had turned down a multi-million dollar recruitment offer from an American company.

In September, the Korean government went a step further, designating the cloning scientist an “important figure” and charging Seoul police and intelligence agencies with protecting him.

All this attention comes for an achievement that would have been illegal in the United States if a bill passed by the House of Representatives in 2001 had made it through the Senate.

Had he done the experiment in Michigan, he could have been arrested.

Bans on cloning

Michigan is one of a handful of states that outlaws human cloning, whether it’s for reproductive purposes or to create stem cells. Ohio has no law covering cloning of any type, while California bans cloning for reproduction but permits cloning to create stem cells.

If anything shows this country’s division over embryo research, it is this patchwork of legislation, where some states threaten hefty fines for cloning, a few outlaw stem cell research, and other states offer financial support to stem cell scientists.

On one hand, there is South Dakota, where embryonic stem cell research of any type is prohibited.

On the other is New Jersey, which allows cloning to make stem cells, bans reproductive cloning, and is investing \$6.5 million in the newly formed Stem Cell Institute of New Jersey.

California's stem cell efforts could trump even that. The state has a \$3 billion bond issue to fund stem cell research on the November ballot. If the initiative passes, some \$300 million per year would be available for stem cell research for the next 10 years. That would give California a stem-cell budget twice the size of the federal government's outlay for all forms of human stem-cell research.

Now, U.S. researchers are not only competing internationally, they're competing from state to state. Around the globe and the country, it is a combination of liberal legislation and financial support fueling the growth of stem cell research.

Research elsewhere

Two years ago, Lawrence Stanton, his wife, and 6-year-old son moved to the other side of the world.

He left California, where he was doing basic research in stem cell genetics for Geron Corp. Money was drying up for the kind of fundamental investigation he favored, he said. Still, he didn't expect much from Singapore.

"I came out to visit this place thinking, 'there's no chance.' I was here three days for the job interview, and before I left, I wanted this job. It's just way more progressive here. The commitment is so serious. The resources, the talent, it's really state-of-the-art science."

Singapore has what many believe is the world's most aggressive stem cell research program.

The centerpiece of Singapore's commitment is Biopolis, a \$500 million government-funded biomedical research campus that opened a year ago. The 600,000-square-foot center eventually will house some 2,000 scientists.

While Americans argue the ethics of stem cells and cloning, some Asian nations are running away with the prize, scientists say.

But this doesn't mean the United States is sure to lose leadership in this field. Nor has it yet.

"The beauty of the United States is that, although we don't have the dedicated stem cell facilities that are up and running yet, we have the biotech infrastructure that's been around since the '80s, and the brain power that goes along with it," said Ella De Trizio. Ms. De Trizio specializes in biotechnology for the international law firm Dechert LLP in Princeton, N.J.

"We've got the laboratories. We've got brilliant scientists. We have venture capitalists who understand the science. That all bodes well for the United States."

But she warns: "That doesn't necessarily mean we might not be behind the eight-ball a little bit vis-a-vis Singapore."

"The United States is still dominating this field," said James Thomson, the stem-cell pioneer at the University of Wisconsin-Madison. He notes that U.S. scientists still publish more research on stem cells than the researchers of any other country.

But the ethical and legal struggles in the United States are good news for other nations, said G. Steven Burrill, of Burrill & Company, a San Francisco biotech investment firm.

"Countries around the world, quite frankly, think the U.S. ban is an opportunity for them," he said.

Further, Congressional action has had a chilling effect on investors, he said. A bill proposed by Sen. Sam Brownback, (R., Kan.) for instance, not only would subject any scientist engaged in cloning to fines and imprisonment, but, some say, it also makes it illegal for Americans to receive treatments in other countries if the therapy arises from stem cells made from cloned embryos.

"Some of that was highly negative to the lay of the land, and people were spooked," Mr. Burrill said. "If we get laws like that and restrictions like that, there's no way anybody's ever going" to invest in this research in the United States.

Cloning and stem cell proponents say the research atmosphere here already is driving scientists to leave the country. Most mention Roger Pedersen, a stem cell researcher who left the University of California at San Francisco for a post

in Great Britain in 2001, saying U.S. restrictions were too onerous.

But it's not clear at all whether Mr. Pedersen, or Larry Stanton in Singapore, are representatives of a brain drain, or simply examples of the internationalization of science.

In fact, worries about a brain drain are hardly unique to the United States. A European Union commissioner this year said stem cell researchers from Europe were leaving for Australia, Singapore, and the United States.

A member of the team that cloned Dolly the sheep, Alan Colman, left Scotland for Singapore, saying that the United Kingdom wouldn't fund his stem cell work on diabetes the way Singapore could.

Then there's Stem Cell Sciences Holdings in Scotland. It's looking for a home in the United States, Ms. De Trizio said.

"Not surprisingly, they're looking in Massachusetts, New Jersey, and California. Those are the three friendliest states to stem cell research."

Although Massachusetts doesn't have the state efforts launched by California and New Jersey, Harvard's Stem Cell Institute hopes to raise \$100 million for research, adding to the attractiveness of a state already full of top laboratories.

Ms. De Trizio said if the United States can solve its ethical conflicts and begin investment soon, Singapore and other nations are no threat.

But she warned, "If it takes a couple more years for people to really come along, Singapore may really get ahead of us."

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When the discussion of the tiny embryo is now a matter of international consideration, the revolution in embryo science has truly come full circle in the 26 years since the arrival of the world's first test-tube baby.

The blast of publicity that accompanied the birth of Elizabeth Brown has been followed by little more than murmurs since, and the issue of embryos has been most ardently discussed by desperate patients in conference with their fertility doctors.

But now, the 400,000 human embryos on ice in the United States, with more added every day, are in everyone's focus. Suspended in liquid nitrogen, these balls of cells, a little smaller than the dot of an i, are human potential incarnate. Who can say what we may decide to do with them.
