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CLONING

South Korean Team's Remaining Human Stem Cell Claim Demolished

In an announcement that researchers worldwide both expected and feared, Woo Suk Hwang's last remaining claim to have advanced the promising field of human embryonic stem (ES) cells has been declared fraudulent. In a report released on 10 January, a committee at Seoul National University (SNU) found that Hwang and his colleagues fabricated data in their breakthrough 2004 *Science* paper reporting the first creation of a stem cell line from a cloned human blasto-

summary of the report is available on the SNU Web site at www.snu.ac.kr/engsnu.)

In the two papers published in *Science*, Hwang and his co-workers had claimed to have accomplished three firsts. The 2004 paper reported the cloning of a human blastocyst, through a process known as somatic cell nuclear transfer, and the derivation of ES cells from that cloned blastocyst; the 2005 paper reported the derivation of 11 human ES cell lines genetically matched to patients.



The verdict. Myung-Hee Chung, head of the Seoul National University panel, announces that Woo Suk Hwang's team produced no cell lines from cloned human blastocysts.

cyst. In an interim report in late December, the committee had already determined that a second paper by the team, published in 2005, was fraudulent (*Science*, 6 January, p. 22).

The final report concludes that Hwang and his colleagues did successfully clone a dog, which the scientists reported in *Nature* in August 2005. It also said that the Hwang team made some progress toward cloning early-stage human embryos. But the 2004 publication amounts to "none other than deceiving the scientific community and the public at large," the report says. (An English

ES cells, which are derived from week-old embryos, hold great medical promise because they can in theory develop into any tissue type in the body. Researchers around the world have derived dozens of cell lines from human embryos created through in vitro fertilization. But many hope that cloned embryos could produce ES cells tailor-made to match a patient's DNA. They predict that such cells could shed light on heritable diseases and offer hope for new therapies for patients suffering from maladies including spinal cord injury and diabetes.

With both papers now thoroughly discredited, "we're back to the time prior to [Hwang's 2004] publication; there is no evidence at all that we can make [stem cells] from human embryos created through nuclear transfer," says Alan Trounson, a stem cell researcher at Monash University in Clayton, Australia. Hwang's team had also claimed phenomenal advances in efficiency in its 2005 paper, reporting that it needed fewer than 20 eggs to produce each stem cell line. Work in most other mammals suggests that it usually takes 100 to 200 eggs for one stem cell line, and many researchers say the unraveling of Hwang's work resurrects the question of whether the technique will ever be efficient enough for routine clinical application.

To check the veracity of the 2004 paper, the committee collected 23 samples of the cell line supposedly described in the work, which the team called NT-1. Twenty samples came from Hwang's lab, and one each from the Korean Cell Line Bank; MizMedi Hospital in Seoul, where several collaborators worked; and the lab of Hwang's collaborator at SNU, Shin Yong Moon. The committee said it asked three independent labs to test the DNA from all 23 samples, and all three labs reported identical results.

Those results suggest that Hwang and his colleagues falsified much of the data in the paper. Hwang's team claimed that NT-1 was an exact genetic match with cells of donor A, but the committee found that the line "is quite distinct from what was reported in the *Science* article." The committee reported that 11 of Hwang's 20 samples matched the DNA of a cell line derived at MizMedi from an embryo created through in vitro fertilization. The other nine samples from Hwang's lab, as well as the three samples from outside sources, all shared a signature that could not be traced to any other known cell line.

The signature of those samples is somewhat puzzling. It is a very close match with the DNA fingerprint of a second woman who donated oocytes for the project, called donor B in the report. But the evidence suggests that it could not have come from nuclear transfer. For 40 of 48 nuclear DNA markers tested, donor B and the NT-1 samples matched. But for eight markers, donor B was heterozygous whereas the cell line was homozygous. The mitochondrial DNA of the woman is a perfect match with that of the cell line.

That suggests that the cell line might have arisen from either accidental or deliberate parthenogenetic activation, in which an

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unfertilized oocyte is triggered to divide. Several teams around the world have created ES cell lines from parthenogenetically activated oocytes from mice, and at least one team has derived a cell line from a monkey parthenote. Indeed, Hwang and his co-authors wrote in the 2004 paper that they could not rule out the possibility of a parthenogenetic cell line. (Because the team used somatic cells and oocytes from the same donor, it was difficult to tell the difference between a cloned cell line and one derived from a parthenote.)

The SNU committee confirmed that Hwang's team successfully cloned a dog to create Snuppy. The committee asked three independent test centers to compare tissue from four dogs: the egg donor, Snuppy, the adult Afghan from which somatic cells had been taken, and the surrogate mother. The labs sequenced mitochondrial DNA and checked 27 nuclear DNA markers to confirm that the adult Afghan was the source of Snuppy's nuclear DNA. Cloning a dog was considered particularly tricky because of the animal's complex reproductive cycle. "It's surprising," Trounson says. "I would have thought cloning a dog would be more difficult than a human [embryo]."

And the investigating committee found that Hwang's group did make some progress toward creating cloned embryos. The report notes that there are three main steps in producing ES cells through somatic cell nuclear transfer: nuclear transfer itself, blastocyst formation, and extraction of the cell line. The committee found that Hwang's team appears to have successfully produced cloned human blastocysts in about 10% of their cloning attempts—something that no other team had managed at the time of the first paper and which only one other team—led by Alison Murdoch in Newcastle, U.K.—has done since.

But the committee's investigation indicates that Hwang and his colleagues couldn't pull off the crucial next step. Although the report says Hwang's team claimed to see what they called cell colonies, which some on Hwang's team saw as success in establishing cell lines, "the scientific bases for claiming any success are wholly lacking." There is no evidence of extant cell lines, and "no record of further confirmatory experiments could be found," the report says.

The committee also made it clear that Hwang had lied about how his team obtained oocytes. For months, Hwang denied that any members of his team had donated eggs. After an investigative TV program reported that a



Validated. Tests confirm that Snuppy, pictured here with Hwang, is a real clone.

member of Hwang's team had told them she donated eggs, Hwang admitted that members of his team had donated but that he had only learned about it after the fact and lied to protect the women's privacy. One graduate student who voluntarily donated eggs told the committee that Hwang personally accompanied her to MizMedi Hospital for the egg-retrieval process. And 2 months later, members of the Hwang team asked female technicians working in the lab to sign a form volunteering to donate eggs.

The committee also confirmed earlier rumors that Hwang's team had used vastly more oocytes than it claimed in the two *Science* papers. The team reported using only 427 oocytes for the experiments they described in the two papers, but investigators found that the team had received 2061 human oocytes from four hospitals between November 2002 and November 2005.

The report does not clarify how many people in the lab knew about the fraud, but it does identify certain individuals who it alleges falsified data at various steps.

At SNU, the report will now be taken up by a disciplinary committee. Korean media have also reported that public prosecutors could begin an investigation as early as this weekend into Hwang's allegation that his team's stem cells were deliberately swapped with

others derived at MizMedi, allegations that members of Hwang's team were paid \$50,000 to keep quiet, and possible misuse of government subsidies. Meanwhile, an investigation at the University of Pittsburgh in Pennsylvania is expected to issue its report on the role of Gerald Schatten, a senior author on the 2005 paper, in the scandal later this month.

Science has asked MizMedi's Sung Il Roh to set up an independent investigative panel to look into MizMedi's contributions to the *Science* papers as well as papers contributed to the journal *Stem Cells*, which contained images identical to those published in the 2004 *Science* paper. Roh says he will comply.

Science, too, plans to conduct an internal investigation into its handling of both the 2004 and 2005 papers, says Editor-in-Chief Donald Kennedy, and will let readers know what it finds. The journal plans to "reconstruct the history" of each paper, examining the original submissions and changes made at every stage of review. Among other issues, *Science* will examine whether it could have "pressed" Hwang's group further for more evidence that the embryos described in the 2004 paper were cloned and not parthenogenic, says Kennedy. *Science* has also contacted members of its senior editorial board, composed of outside scientists, to seek their counsel on how the journal might modify its procedures—such as whether authors should detail their contributions—which is something else *Science* will be considering.

"It's worth finding out, 'Is there someplace I got duped?'" says Mike Rossner, managing editor of the *Journal of Cell Biology*, which has declined to publish 13 papers that passed peer review but were found to have potentially manipulated images. "I really think journal editors have to be more proactive ... rather than hiding behind the veil of review and saying, 'Our reviewers approved it, so it's OK.'"

Science's close competitor *Nature* commissioned its own analysis after questions arose about the validity of the paper it published by Hwang on the first cloned dog. In late December, *Nature* asked a scientist from the National Human Genome Research Institute in Bethesda, Maryland, to conduct independent tests to determine whether the dog, Snuppy, was a clone. Findings from those tests announced this week agree with the report from SNU that the team's report was legitimate.

—DENNIS NORMILE, GRETCHEN VOGEL, AND JENNIFER COUZIN

With reporting by Sei Chong in Seoul.