



STEM CELLS

Cloning Researcher Says Work Is Flawed but Claims Results Stand

Acknowledging that his team made “various serious errors and shortfalls,” cloning researcher Woo Suk Hwang has asked *Science* to retract his celebrated paper reporting the creation of embryonic stem (ES) cells from 11 patients suffering from diabetes, an immune system disease, and spinal cord injury. But as *Science* went to press, Hwang was insisting that, contrary to the claims of a collaborator, his team succeeded in creating these patient-specific stem cells and that they intend to replicate their results.

Pressure on Hwang and his group has been growing as scientists and the press have raised questions about the evidence presented in the paper, first published online in May this year (*Science*, 17 June, p. 1777). In another paper in 2004, Hwang and colleagues reported the first ever production of embryonic stem cells from a cloned human blastocyst. In the 2005 paper, another group led by Hwang reported that they had established 11 ES cell lines from embryos cloned from patients, a step toward someday making genetically matched replacement tissue. No lab has replicated their results.

But in early December on a Korean Web site, an anonymous writer, who claims to be a life scientist, pointed out duplications in some of the photographs of ES cells published in the 2005 paper. According to a *Science* statement, a few hours later Hwang notified *Science*'s editorial offices of what he called “an unintentional error” that led to “about 4 pictures being used redundantly.” More questions arose after critics questioned DNA traces used to demonstrate that the cell lines were a genetic match with the skin cells donated by the 11 patients to create cloned embryos (*Science*, 16 December, p. 1748). On 15 December, co-author Sung Il Roh, a fertility expert at MizMedi Hospital in

Seoul who collected oocytes from donors for Hwang's work, told Korean media that Hwang had confessed to falsifying evidence for 9 of the reported 11 cell lines.

The next day, at a packed press conference at Seoul National University (SNU), a defiant Hwang told reporters that he was “surprised and taken aback” by Roh's assertion, although he acknowledged that he had talked with Roh. Reading a prepared statement, Hwang said, “I want to make it really clear that our research team produced patient-specific (stem cells).” He acknowledged, however, that the team had problems with their cell lines. He said that last January, contamination with yeast had destroyed at least six of the lines the team had created. Based on Hwang's statement, it's not clear whether any of these original six lines were alive at the time the *Science* paper was submitted in March. The group was “lax in our



Serious errors. Cloning researcher Woo Suk Hwang has said he will withdraw a landmark paper published in *Science* earlier this year because of errors but says the conclusions are valid.

management and committed many mistakes,” said Hwang. He said they would thaw the five remaining cell lines to try to demonstrate that they match their donors, a process that Hwang said could take about 10 days.

Hwang also said that MizMedi might be responsible for mixing up cell lines from its own research with those used in the experiments that produced the *Science* paper, and he called for an investigation. Roh held an emotional press conference shortly thereafter in which he reportedly reiterated his claims and accused Hwang of lying.

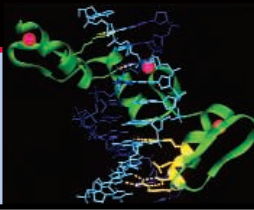
At a 16 December press briefing in Washington, D.C., *Science* Editor-in-Chief Donald Kennedy said that Hwang and Gerald Schatten of the University of Pittsburgh, who was corresponding author on the paper, had told *Science* editors in a phone call the previous day that several aspects of the data “could not be trusted” and asked that the paper be retracted, pending the agreement of the 23 other authors. Kennedy said the scope of the paper's flaws is still unclear. Kennedy added, however, that although the paper contains errors that were known at the time of submission, there is not at present evidence to conclude scientific misconduct.

When questions were first raised about duplicated images, editors at *Science* said that it appeared the duplications occurred after the paper was accepted and when new, higher-resolution images were substituted for publication. But Katrina Kelner, *Science*'s deputy editor for life sciences, says it now appears there were problems in the original submission as well. Although the four duplications that Hwang pointed out to editors were not in the original submission, she says, the original figure had at least one apparent duplication that also appeared in the final version. Figure S1 shows 68 cell photographs, which purport to show evidence of 10 of the 11 cell lines expressing up to 6 different protein markers typical of ES cells. But one image labeled as cell line number 8, expressing a marker called SSEA-4, shows the same colony of cells, though slightly shifted, as an image labeled cell line 7, marker SSEA-3. Kelner says that editors have asked the researchers to explain the images, “but we haven't gotten answers.”

It also seems that questions raised during the review process may have unwittingly helped undo the paper. In their original submission, Kelner says, the authors provided fingerprints from only some of the cell

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Repairing faulty genes



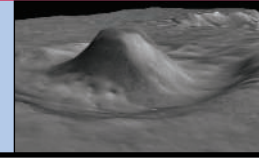
1894

The limits to tree growth



1896

News from the AGU meeting



lines. Reviewers asked for fingerprinting data from the remaining lines. It is not clear if the questionable fingerprints were in the first submission or in the additional data the reviewers requested. Editors declined to specify which lines were missing in the original submission.

The controversy has focused attention on the peer review process used by *Science* and most other scientific journals. Kelner says that even before the problems with the Hwang paper came to light, the journal had planned to institute a policy early next year to systematically examine papers for “inappropriate manipulation of images” by computer programs that leave telltale traces. But she says such techniques can only do so much. “I don’t think that would have picked up these problems. You had to be looking for duplications.”

Science editors acknowledge that the paper was reviewed and published in 2 months, about half the average time from submission to publication. But other researchers say that even with a longer review period, the peer review process is not designed to detect outright falsification. “I’m convinced by looking at the *Science* paper that it was publishable on the basis of data presented,” says Irving Weissman, a stem cell scientist at Stanford University.

Even if Hwang’s team produces convincing data that it created patient specific lines, observers have called into question other papers by Hwang and various collaborators. Postings on the same Korean Internet message board claim there is similar evidence of tampering in the supplementary data for the 2004 paper. Others are raising questions about a report in *Nature* this year describing the first cloned dog (*Science*, 5 August, p. 862). Critics say that the brief report leaves open the possibility that the two look-alike dogs resulted from embryo splitting—that they are essentially identical twins. To prove the case, the researchers should have demonstrated that the puppy and cloned adult carry different mitochondrial DNA, but the paper includes no such evidence.

Some answers may come from investigations now under way at Seoul National University and the University of Pittsburgh. The SNU committee comprises seven SNU professors, including chair Myung Hee Chung, and two scientists from other Korean institutions. In contrast to some calls from the scientific community, there are no non-Korean members. In

the initial phase of the probe, the committee intends to check lab notes, examine existing data, including micrographs of cells and DNA fingerprint traces, and interview researchers. A second phase is expected to involve testing, including new DNA fingerprinting of the five frozen cell lines Hwang claims will vindicate him. The committee may also check cell lines held at MizMedi.

The committee has clamped restrictions on the lab. Computer storage drives have been

which was set up to support stem cell research efforts when Hwang’s work came under fire, says they still have hundreds of women volunteering to donate eggs.

At least three groups have announced plans to make their own patient specific cells, a key step in validating the approach Hwang reported. Alison Murdoch and her colleagues at the University of Newcastle in the United Kingdom announced to the press in May that they had produced cloned early embryos but



Pushing forward. Hwang told a press conference that his team would produce new evidence that they had made stem cells from cloned human embryos.

seized. Researchers will not be allowed to have access to any related data and must receive prior permission for limited research, which will be under surveillance. A video camera has been set up at the culturing lab to catch any unauthorized comings and goings.

The committee got to work on 18 December, summoning 24 members of Hwang’s research team to the school for individual questioning. The committee reportedly intends to issue an interim report by 24 December.

Korean scientists are dismayed at the spectacle but split over Hwang’s culpability. “I’ve known Dr. Hwang for 10 years, and I just cannot believe [the accusations against him]; maybe I don’t want to believe them,” says an SNU colleague who did not want to be identified. A harsher view comes from a senior scientist who has no connection to Hwang or SNU: “I don’t think it makes sense that he continues his research after losing his credibility and integrity.”

Sun Min Lee, a spokesperson for the People’s Foundation for the Donation of Ova for Research and Therapeutic Purposes,

no ES cells. Ian Wilmut of the University of Edinburgh also has received government and ethical approval to begin work. A group at Harvard University is poised to start as soon as it receives ethical approval from all institutions involved.

George Daley, a member of the Harvard group, says it is too early to tell how flawed the 2005 report is. “Hwang’s group was skilled enough to be capable of doing what they claimed,” he says. “We’ll see how much of the Hwang methodology proves useful when we and others attempt to incorporate it into our own work.”

Wilmut agrees. “I very much hope that Hwang and his group can be given time to collect their thoughts,” he says. “I am sure that they did make good steps forward and derive cell lines. I hope that they can assemble their data and present it in full because it will help the rest of us to know what can be achieved.”

—DENNIS NORMILE, GRETCHEN VOGEL, AND CONSTANCE HOLDEN

With reporting by Ji-soo Kim, Mark Russell, and Yvette Wohn in Seoul.

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