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Commentary

FRAUDULENT HUMAN EMBRYONIC STEM CELL RESEARCH IN SOUTH KOREA: LESSONS LEARNED

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Now that most of the smoke has cleared from the South Korean human embryonic stem cell fraud, it is time to reflect on some lessons that one can learn from this scandal. First, a brief review of events will help to set the stage.

In June 2005, Seoul University investigator Woo Suk Hwang and 24 co-authors published what appeared to be a groundbreaking paper in *Science* in which they claimed to have established eleven embryonic stem cell lines containing nuclear DNA from somatic cells of research subjects (Hwang et al., 2005). In March 2004, Hwang's research team had published another apparently important paper in which they claimed to have established one cell line with the nuclear DNA from a research subject (Hwang et al 2004). If these two papers had been valid, they would have represented a significant step forward in human embryonic stem cell research, since they would have demonstrated the feasibility of a technique known as therapeutic

Editor's note: Although this piece is not related to the topic of this issue, we felt it was important to comment on the recent events in South Korea.

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cloning. In therapeutic cloning, researchers transfer the nucleus from a somatic cell into an enucleated oocyte to create an embryo, and stem cells are then harvested from the embryo. Therapeutic cloning holds great promise as a medical therapy, because the patient's immune system probably will not reject embryonic stem cells, since these cells are genetically compatible with the patient's own cells. Hwang's research put South Korea on the map as a biotechnology epicenter and made Hwang a national hero (Normile et al., 2006).

Trouble started brewing for Hwang's research team in November 2005, when coauthor Gerald Schatten from the University of Pittsburgh accused Hwang of misleading him about the sources of the oocytes used in the 2004 paper. In the 2004 paper, which Schatten did not coauthor, Hwang and his colleagues indicated that the oocytes had come from 16 donors. A report published in *Nature* alleged that the oocytes had come from two junior members of Hwang's laboratory (Vogel, 2005). Although not illegal, a subordinate's participation in a supervisor's research project is considered to be ethically problematic, because it can be coercive (Hawkins and Emanuel, 2005; Shamoo and Resnik, 2003). Schatten ended his collaboration with Hwang in November 2005. Hwang, who initially denied these allegations, admitted in early December 2005 that two of the donors had been junior members of his laboratory and that all of the donors had received up to $1400 in compensation for their oocytes (Holden, 2005).

As of the writing of this editorial, investigations were still underway regarding Schatten's involvement in Hwang's research, what he knew about the falsification of data and when he knew it, as well as whether he stole intellectual property from Hwang by filing a patent application on embryonic stem cell technology without listing the Korean researchers (Cryanoski and Check, 2005; Tae-gyu, 2006).

Matters became much worse for Hwang later in mid-December when *Science* received a tip from an anonymous researcher that two photos of stem cells in the 2005 paper were duplications. Soon, co-author Sung Roh told the media that Hwang had confessed to fabricating evidence for nine of the eleven cell lines. Hwang denied this charge. Schatten told *Science* that the data in the 2005 article could not be trusted, and Hwang and Schatten asked for the article to be withdrawn. A committee from Seoul

University began investigating Hwang's research. By the end of the month, the committee had determined that none of the DNA in the eleven cell lines reported in the 2005 paper matched the DNA from the somatic cell donors. The committee also determined that the data in the 2004 paper were also fabricated, and the authorship had been granted on the 2005 paper for helping to procure oocytes. However, the committee verified Hwang's claim to have created the world's first cloned dog, Snuppy, which was reported in *Nature* (Lee et al., 2005). Hwang resigned from his position at Seoul University and now faces up to ten years in prison for fraud (Normile et al., 2006).

The human embryonic stem cell research scandal is the most significant episode of fraudulent research since the Piltdown Man, because the stakes were so high. If the research had been sound, it would have been one of the most important developments in biomedicine in the twenty-first century. It would have brought money and glory to South Korea and could have earned Hwang a Nobel Prize. As it turns out, the research is one of the biggest scientific disappointments in this century, and has been a set-back the field of embryonic stem cell research (Check, 2005). Political support for this controversial research, especially support for research cloning, may subside a bit after this demoralizing incident. Perhaps some good can come from this troubling chain of events if the research community learns some lessons from it.

Lesson #1. Responsible Conduct of Research (RCR) is an international issue

Scientific research occurs across the globe and often involves collaboration among researchers in different countries. There are stem cell research centers in the U.S., the U.K., Australia, Singapore, South Korea, China, Japan, India, Israel, and Saudi Arabia (Resnik, 2004). The 2005 paper involved a collaboration among 24 South Korean researchers and one U.S. researcher (Schatten). Different countries often have different definitions of "research misconduct," "fabrication," "falsification," "plagiarism," "fraud," and other terms related to research integrity, as well as different procedures for investigating allegations of unethical or illegal research. Diversity, which benefits scientific innovation

and discovery, can undermine scientific integrity, because it leads to inconsistency and a lack of commonly accepted standards. To avoid this problem in human research, the research community has developed international guidelines for research on human subjects, such as the Helsinki Declaration (World Medical Association, 2001) and the guidelines from the Council for the International Organization of Medical Sciences (CIOMS, 2002). The stem cell research scandal demonstrates that researchers need international guidelines for RCR. The guidelines should define a set of ethical standards for the conduct (or best practices) of research, as well as procedures for interpreting and enforcing these standards. The procedures should includes rules for protecting whistleblowers, and rules for maintaining confidentiality during investigations and guaranteeing due process. It is advantageous for researchers to know the rules in advance instead of relying on ill-defined and ad-hoc standards, which can change in reaction to a given scandal. These standards could be established and promoted through the national science ministries of the cooperating states.

Lesson #2. RCR education is important

Since 1989, the U.S. Public Health Service (PHS) has required that all graduate students on PHS training grants receive RCR education. In the fall of 2000, the Office of Research Integrity (ORI) proposed that all researchers on PHS grants be required to receive education in RCR, but this proposal was suspended when a Congressional inquiry challenged the legality of the new requirements; the Bush Administration decided to not pursue them any further. Even though the ORI mandate has been dropped, many universities have gone forward with RCR educational programs for students and optional training for other researchers (Shamoo and Resnik, 2003). The National Institutes of Health (NIH) decided to follow the ORI's proposal: all researchers in the NIH's Intramural program are required take an initial, online course in research ethics as well as an annual update (Schwartz, 2004). Unfortunately, RCR education is not well-suited for online training; rather, it works best in interactive settings. Moreover, the current rate of educating researchers is so slow that it may take over fifty years to educate all of the current

researchers. Education in RCR will not prevent misconduct from occurring, but it can raise awareness about ethical issues and problems in science and how to address them. It can also promote an institutional culture of integrity and accountability (National Academy of Sciences, 2002).

Lesson #3. Peer review is no panacea, but it can be improved

The 2004 paper and the 2005 paper both went through the peer review process at *Science*. Indeed, *Science's* editors and nine outside reviewers gave a passing grade to the 2005 paper (Chong and Normile, 2006). This is not at all unusual. The peer review process almost always fails to detect research misconduct (Shamoo and Resnik, 2003). For example, in the 1980s Harvard cardiology researcher John Darsee fabricated or falsified over 17 published papers and 53 abstracts (LaFollette, 1992). In 2005, University of Vermont researcher Eric Poehlman, a well-known expert on menopause, aging, and metabolism, admitted to falsifying data in 17 peer-reviewed publications (Kinitsch, 2005). In 2002, a panel found that Jan Hendrick Schön, a Bell Laboratories physicist, fabricated or falsified data in 17 published papers. Some of the papers had been published in top journals, such as *Science, Nature*, and *Applied Physics Letters* (Service, 2002). While it is important for reviewers and editors to be vigilant and thorough in their assessment of scientific publications and to be on the alert for fabrication, falsification, or plagiarism, the peer review system was not designed to detect misconduct (Shamoo and Resnik, 2003). To detect misconduct, one usually needs access to research materials that are usually not sent to reviewers, such as laboratory notebooks, standard operating procedures, biological samples, and scientific instruments. Peer reviewers usually only examine manuscripts to determine the novelty and significance of the research, the soundness of the research methods, the consistency of the data, the validity of the analysis and interpretation of the data, and the quality of the writing.

Some of the misconduct disclosures in Hwang's research came from a careful examination of photographs submitted with the stem cell manuscripts. Identical photographs or unusually homologous elecrophoresis images derived from different sources can be an indicator of fraud. Peer reviewers, journal

editors, and their staffs should pay attention to photographs and digital images accompanying the manuscript for evidence of tampering or improbable similarities. Some journals such as the *Journal of Cell Biology* have strict guidelines about image manipulation (Rossner and Yamada, 2004).

Lesson #4. Audit data and research records

The best way to detect research misconduct is to have some quality control before a paper is submitted for publication, such as auditing data, research records, and materials (Shamoo and Annau, 1987; Shamoo, 1989; Glick and Shamoo, 1991). Auditing should occur based on suspected misconduct or other problems, and on a random basis. Therefore, auditing will not exceed 1% of all studies. Although Food and Drug Administration (FDA) regulations require pharmaceutical and biotechnology companies audit data that they plan to submit to support an application for a new drug, biologic, or medical device, to our knowledge, no academic institutions regularly audit data. There are several reasons why academic institutions do not audit data. First, they erroneously believe that auditing data requires substantial resources that most institutions would rather invest somewhere else. In reality, the cost would not exceed 1% of the study cost (Shamoo, 1989). Second, auditing data is inconvenient for researchers, most of whom would like to perform their work with as little oversight as possible. Third, many researchers believe that auditing data sends the message that they are unethical or incompetent, and they resent this insinuation. While it is easy to understand why academic institutions have resisted data auditing, their refusal to even consider this method for controlling data quality and integrity is not justified. First, academic institutions should be willing to allocate at least some resources toward data auditing. They might even be able to include auditing expenses when applying for grants or negotiating administrative costs of grants and contracts. Second, researchers should be willing to put up with some inconvenience to ensure the quality and integrity of research data. Indeed, an audit can benefit a researcher if it detects some errors or inconsistencies in his or her work. It is better to catch these problems before submitting the paper review rather than after publication. Third, researchers need to change their

attitudes toward auditing. An audit does not imply that work is fraudulent or incompetent. Indeed, auditing is an important quality control measure in many different industries, including accounting, insurance, health care, and manufacturing. The arms control principle "trust but verify" applies here. Currently, most cases of misconduct in academic science result from allegations brought by whistleblowers. Although whistleblowers perform a valuable service for the scientific community, it is time that academic researchers gave some serious consideration to data auditing. Once auditing becomes routine, it will be less intimidating. Research institutions should assure scientists that they will not be punished for honest errors or disagreements, which are not classified as misconduct.

Lesson #5. Authorship and accountability

One of the important facts uncovered by the Seoul University investigating the Hwang case was that authorship in the 2004 and 2005 papers may have been granted inappropriately. Since the 1990s, many different writers have proposed that scientific journals should adopt policies that would make authors more accountable for their work, such as requiring authors to sign a statement saying that they agree with the conclusions of the research and to provide a description of their contributions to the paper (Resnik, 1997; Rennie et al., 1997). Some journals, such as *Nature and the Journal of the American Medical Association* (*JAMA*) follow a policy adopted under the Uniform Requirements for Manuscripts Submitted to Biomedical Journals issued by International Committee of Medical Journal Editors (ICJME) that promotes a high degree of accountability among authors. *Science* editor Donald Kennedy (2006) announced that *Science* was also considering changing its authorship policies. According to the ICMJE policy:

> Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. One or more authors should take responsibility for the integrity of the work as a whole, from inception to published article. Authorship credit should be based only on (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; and (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Conditions 1, 2, and 3 must all

> be met.1-2. All authors (i.e., the corresponding author and each coauthor) must complete and submit an authorship form with signed statements on (1) authorship responsibility, criteria, and contributions, (2) financial disclosure, and (3) either copyright transfer or federal employment . . . In addition, authors are required to identify their contributions to the work described in the manuscript. (JAMA, 2006)

Although holding authors accountable for their contributions to scientific papers will not prevent misconduct, it promotes integrity, accountability, and responsibility in research. Policies like JAMA's send a clear message that researchers should adhere to the highest standards of ethics in research and that authorship should be earned, not granted as a gift or a favor.

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References

Check, E. (2005). Where now for stem-cell cloners? *Nature*, 438: 1058–59.

Chong, S., and Normile, D. (2006). And how the problems eluded peer reviewers and editors, *Science*, 311: 23–24.

CIOMS. (2002). International Ethical Guidelines for Biomedical Research Involving Human Subjects. Available at http://www.cioms.ch/frame_guidelines_nov_2002.htm. Accessed: January 19, 2006.

Cyranoski, D., and Check, E. (2005). Stem-cell brothers divide, *Nature*, 438: 262–3.

Glick, J. L., and Shamoo, A. E. (1991). Auditing Biochemical Research Data: A Case Study, *Accountability in Research*, 1: 223–43.

Hawkins, J., and Emanuel, E. (2005). Clarifying confusions about coercion, *Hastings Cent Rep*, 35(5): 16–19.

Holden, C. (2005). Korean cloner admits lying about oocyte donations, *Science*, 310: 1402–1403.

Hwang, W., Roh, S., Lee, B., Kang, S., Kwon, D., Kim, S., Kim, S., Park, S., Kwon, H., Lee, C., Lee, J., Kim, J., Ahn, C., Paek, S., Chang, S., Koo, J., Yoon, H., Hwang, J., Hwang, Y., Park, Y., Oh, S., Kim, H., Park, J., Moon, S., and Schatten, G. (2005). Patient-specific embryonic stem cells derived from human SCNT blastocysts, *Science*, 308: 1777–83 (RETRACTED).

Hwang, W., Ryu, Y., Park, J., Park, E., Lee, E., Koo, J., Jeon, H., Lee, B., Kang, S., Kim, S., Ahn, C., Hwang, J., Park, K., Cibelli, J., and Moon, S. (2004). Evidence of a pluripotent human embryonic stem cell Line derived from a cloned blastocyst, *Science*, 303: 1669–1674 (RETRACTED).

JAMA. (2006). Instructions for authors. Available at http://jama.ama-assn.org/ifora_current.dtl. Accessed: January 21, 2006.

Kennedy, D. (2006). News Release, January 10, 2006. Available at http://www.aaas.org/news/releases/2006/0110stemstatement. shtml. Accessed: January 21, 2006.

Kinitisch, E. (2005). Researcher faces prison for fraud in NIH grant applications and papers, *Science*, 307: 1851.

LaFollette, M. (1992). *Stealing into Print*. Berkeley, CA: University of California Press.

Lee, B., Kim, M., Jang, G., Oh, H., Yuda, F., Kim, H., Shamim, M., Kim, J., Kang, S., Schatten, G., and Hwang, W. (2005). Dogs cloned from adult somatic cell, *Nature*, 436: 641.

National Academy of Sciences. (2002). *Integrity in Research*. Washington, DC: National Academy Press.

Normile, D., Vogel, G., and Couzin, J. (2006). South Korean team's remaining human stem cell claim demolished, *Science*, 311: 156–57.

Rennie, D., Yank, V., and Emanuel, L. (1997). When Authorship Fails: A Proposal to Make Contributors Accountable, *JAMA*, 278: 579–85.

Resnik, D. (1997). A Proposal for a New System of Credit Allocation in Science, *Science and Engineering Ethics*, 3: 237–43.

Resnik, D. (2004). The need for international stem cell agreements, *Nat. Biotechnol.*, 22: 1207.

Rossner, M., and Yamada, K. (2004). What's in a picture? The temptation of image manipulation, *J. Cell Biology*, 166(1): 11–15.

Schwartz, J. (2004). The Responsible Conduct of Research: a New Online Course. The NIH Catalyst (July-August, 2004). Available at http://www.nih.gov/catalyst/2004/04.07.01/page4.html. Accessed: January 20, 2006.

Service, R. (2002). Bell labs star physicist found guilty of forging data, *Science*, 298: 30–31.

Shamoo, A. E. (1989). *Principles of Research Data Audit*. New York: Gordon and Breach.

Shamoo, A. E., and Annau, Z. (1989). Ensuring Scientific Integrity [correspondence], *Nature*, 327: 550.

Shamoo, A. E., and Resnik, D. (2003). *Responsible Conduct of Research*. New York: Oxford University Press.

Tae-gyu, K. (2006). Schatten Stole Hwang Patent. *The Korea Times*, (Jan. 8) at Al.

Vogel, G. (2005). Collaborators split over ethics allegations, *Science*, 310: 1100.

World Medical Association. (2001). Ethical Principles for Medical Research Involving Human Subjects. Available at http://www.wma.net/e/policy/b3.htm. Accessed: January 19, 2006.