COMMENTS

The cloning controversy

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Abstract

Stem cell research has captured the imagination of many, including the scientific and medical community. But the medical community received a rude wake-up call early this year when a well-known researcher publicly confessed to deception. While the core question relates to honesty and integrity, it is equally necessary to examine the system that made such deception possible.

Background

The embryonic stem cell is the most pluripotent of all stem cells. It has the ability to differentiate itself into other cell types such as nerve, bone and muscle. In contrast, the highly differentiated organ-specific stem cell is unipotent. Embryonic stem cells are usually culled from embryos left over from in-vitro fertilisation (IVF) treatment, which have been stored in clinics beyond a stipulated period. These embryos are therefore sought after, but many ethical controversies surround how they may be used, especially for cloning.

Reproductive cloning has been used for many years to clone animals. The most publicised example – though not the first one – was Dolly the sheep, who was born in 1996. A number of animals have been cloned since then. But many people are apprehensive about cloning. Much of the opposition to embryonic stem cell research comes from the fear that human beings could be cloned. However, cloning can also be used for therapeutic purposes. Therapeutic cloning uses the same procedure of somatic cell nuclear transfer (SCNT) that is used in reproductive cloning, with a modification in the last steps, to create stem cell lines.

In reproductive cloning, cells from the blastocyst stage of the embryo are re-implanted into the womb of the surrogate mother and the pregnancy progresses to grow into the corresponding animal. Therapeutic cloning depends on stem cell lines produced from cells from the blastocyst stage and cultured in the laboratory. Scientists believe that it will eventually be possible to use SCNT to grow custom-made cell lines suited to a specific individual's needs. Custom-made cell lines might provide treatment for individuals who have developed a fatal illness and do not have a sibling who can be a potential donor.

SCNT for stem cell therapy

A healthy, unfertilised ovum is identified and the nucleus is removed. The individual requiring treatment is identified. Somatic cells (from a non-reproductive organ) are collected from the individual. Nuclear material is transferred from the somatic cell into the "empty" ovum. The cell is provided with the necessary growth conditions. The egg cell re-programmes the DNA contained within the nucleus of the donated somatic cell. After a while these cells from the individual requiring therapy start multiplying inside the ovum with a genetic make-up identical to that of the donor. In the blastocyst stage, the inner cell mass is removed and grown on culture plates in the laboratory. When these cells reach sufficient quantities, they can be differentiated into different cell types and used for treatment for the donor's illness.

SCNT is expensive. It is individualised and a large number of ova is required if cell lines suitable for a number of people and illnesses are to be made available. Some issues central to embryonic stem cell research have not been comprehensively addressed. Scientists and researches are concerned that young women, not completely informed of the risks involved, might volunteer to be ovum donors in return for monetary compensation.

The Hwang controversy

The Korean public heard of Hwang Woo-Suk in 1999 when he first cloned a dairy cow. By early 2004, he claimed to have produced the first human embryonic stem cell line using the SCNT process. While other researchers had used frozen embryos, Dr Hwang used fresh non-frozen unfertilised ova and reported a better success rate. His work was published in the March 12, 2004 issue of the journal *Science*. Dr Hwang said he had used 242 ova donated by a single woman; he had also used somatic cell nuclear material from the same person.

In June 2005, Dr Hwang and his team reported even greater success when they announced the production of 11 different, non-identical human embryonic stem cell lines using just 185 ova. This meant a more than 10-fold increase in their success rate. The donors of the somatic cell nuclear material, as reported by the team, were eight males and three females, ranging in age from 2 to 56 years. These donors suffered from congenital hypogammaglobulinemia, spinal cord injury, and juvenile diabetes – conditions that could be treated with stem cells. Therapeutic cloning was successful in nine out of 11 patients with cells containing nuclei from nine donors developing to the blastocyst stage. One or two embryonic stem cell lines were obtained from each of these blastocysts. This improvement was attributed in part to the use of oocytes from younger donors (1).

More dramatically, the donor of the ova and the source of somatic cell nuclear material were different people and in some

situations were also of a different sex. The implications were enormous. It meant that just about anyone requiring stem cell therapy could have a line created specifically to suit their needs, without having to worry about the existing embryonic stem cell lines. This is what scientists all over the world were hoping to achieve. The work was published in the June 17, 2005 issue of *Science*. This was soon followed by one more success, this time in the form of the cloned Afghan hound SNUPPY, an acronym for Seoul National University Puppy.

By now Dr Hwang had become a national hero. The media covered his work. He repeatedly stated that the work was free from bias and the donors of the ova were not in any other way involved with the study.

Established ethical guidelines

The Declaration of Helsinki (2), a policy statement of the World Medical Association, elucidates the ethical principles for medical research involving human subjects. According to this document, the design and performance of each experimental procedure involving human volunteers should be clearly outlined and submitted to a specially appointed ethics review committee.

The Guidelines for Human Embryonic Stem Cell Research published by the National Academic Press (3) go a step further and recommend that women who undergo hormonal therapy for oocyte donation should only be reimbursed for direct expenses as determined by the Institutional Review Board (IRB) of the organisation conducting the study. The guidelines also clearly state that no payments either in cash or kind need to be made for donating oocytes. Dr Hwang's study breached several of these guidelines.

The aftermath of the controversy

In November 2005, Gerald Schatten, a professor at the University of Pittsburgh and a collaborator, disassociated himself from the study, expressing concerns about the acquisition of the ova for the earlier study in 2004. Soon after, another close collaborator, Roh Sung-il, head of the Miz-Medi women's hospital, in Seoul, disclosed that the women who had contributed their ova for the study had been given monetary compensation, but that Dr Hwang had been unaware of these transactions. The ministry of health in South Korea assured everyone that no laws or ethical guidelines had been breached because there were no commercial interests in the research. Dr Hwang resigned from his post soon after. The university conducted a detailed probe and by December 2005 it announced that Dr Hwang's claim of creating 11 cell lines was a fabrication. In January 2006, after further verification, the university insisted that both his papers (of 2004 and 2005) should be retracted.

Questions raised by the controversy

How was Dr Hwang able to get IRB approval for the study without disclosing the fact that the women who were donating the ova were involved in the study and had been financially remunerated? Dr Hwang's statement that he was unaware of the Declaration of Helsinki is hard to believe considering that he has been a researcher for several years. While some of Dr Hwang's work is invaluable, his deception has unfortunately brought all his work under a cloud.

It is also noteworthy that one of his close collaborators clearly distanced himself from the study, while another disclosed controversial details. These two collaborators have got off lightly when compared to Dr Hwang. Could it have been possible for Dr Hwang to conduct a study of such import, single-handedly, without taking other key players into confidence? What prompted these collaborators to come out into the open?

Conclusion

Scientific journals must establish more stringent criteria for checking the veracity of any scientific publication. While it may not be possible to reproduce every detail of a study, those aspects of work that can be independently replicated and all verifiable documentation must be checked before any article is published. The media play a vital role in dissemination and must be more responsible when reporting information about science or medicine.

In India, the Indian Council of Medical Research (ICMR) has drawn up guidelines on biomedical research ethics, which make it mandatory for practitioners to seek approval for such research. (4) However several doctors and premier institutions have attempted stem cell therapy on patients with various illnesses without this approval. They claim there has been no violation of medical ethics as the legislation based on these guidelines is still awaiting cabinet approval. The ICMR and the department of biotechnology are working to tighten stem cell research rules, but progress has been slow.

Guidelines for stem cell research and therapy must be carefully instituted, implemented and followed at all times. The credentials of researchers and therapists must be examined, protocols must be adhered to and extreme caution should be exercised before making reports of research available to others. Otherwise, we can soon expect another controversy in another laboratory in some other part of the world.

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