Issues in Oocyte Donation for Stem Cell Research

David Magnus and Mildred K. Cho*

As described by Hwang et al. in Science (1), somatic cell nuclear transfer (SCNT) to create human embryonic stem cell (hESC) lines represents a step toward realizing the promise of stem cell research. They have shown the generalizability and efficiency of the approach in creating 11 cell lines from the nuclei of skin cells of individuals with serious diseases or disabilities and the oocytes of donors. This work raises ethical and policy questions. As hESC research proceeds internationally, these issues must be adequately addressed for public confidence to be maintained. We discuss three areas that particularly deserve attention: (i) ethical oversight of collaborations between scientists working in countries with different standards, (ii) protection of oocyte donors, and (iii) avoidance of unrealistic expectations.

International Oversight

The research described in Hwang et al. took place in South Korea. It was conducted with oversight and approval from Korean institutions required by South Korean law. However, one of the researchers is a U.S. scientist. No U.S. Federal funding was used, and the creation of human embryonic stem cells for research under these conditions is not prohibited in either country (2, 3). This scientist obtained Institutional Review Board (IRB) review from his university, in which the IRB determined that the research did not involve human subjects on the basis of the Federal definition of human subjects research. These regulations exempt research from full IRB review if samples cannot be traced back to their donors (4). If this had been a clinical trial, his institution in the United States would have been mandated also to provide full IRB oversight for the research. Full IRB review might have been warranted in this case, because at least one of the researchers must be able to ascertain the identity of the donor from the clinician’s encoded information if family members were to receive priority for future hESC transplants, in compliance with the Korean Network for Organ Sharing Regulation Code 18-1 [see SOM for (1)]. However, until recently, specific guidance to IRBs for review of procurement of oocytes for stem cell research has been minimal.

IRBs now can look to the new U.S. National Research Council—Institute of Medicine (NRC-IOM) report on stem cell research recommending that all such research have IRB approval and additional oversight by a special hESC research ethics oversight committee (5). If such oversight is not required by law, but is routine within the United States, should we expect that U.S. researchers working in other countries will voluntarily comply with these requirements? Or should they follow the laws and regulations of the country where the research is taking place unless mandated by U.S. law to do otherwise? This research was conducted before the NRC-IOM recommendations and at this point, it is not clear what the involvement of the U.S. IRB should have been.

Differing ethical standards in international collaborative research are not new, and solutions for reconciling differences have been proposed (6, 7). Therefore, the evolving oversight of hESC research will require that, as new mechanisms are put in place [such as for research funded by the passage of the state’s Proposition 71 (8) in 2004], U.S. researchers would be wise to seek approval from all relevant bodies and to ensure compatibility with the highest standards. This can help researchers obtain approval of the FDA or other similar bodies of clinical application of their research.

Nonmedical Oocyte Donation

A major challenge facing hESC research will be procurement of oocytes from “nonmedical” donors, meaning those who are donating oocytes neither for reproductive, nor medical purposes. The use of excess embryos and oocytes from in vitro fertilization procedures for research has a clear precedent. It uses a clinical informed consent process for women who are considering using assisted reproductive technology that includes discussion of the risks and benefits with the patient. In addition, there is a research informed consent process, as the patient (now a subject) agrees to allow her gametes to be used for research purposes (9, 10). Agreement will be required on the confidentiality and the use of the material. In other words, for these patients, there is a two-part process—a clinical consent that covers the (not insignificant) risks and benefits of the procedure used to procure the oocytes for reproductive purposes (drugs for hyperstimulation, removal of the follicles, etc.) and then a research consent that focuses on the subject as a tissue donor. If cell lines derived from this material are eventually used in clinical trials, then the consent process for a new clinical trial comes into play.

The clinical consent model does not seem to fit women who agree to donate oocytes entirely for research purposes. These women are not pursuing the procedure for any reproductive or medical benefit to themselves; rather, they are exposing themselves to risk entirely for the benefit of others. If we were to think of them as simply clinical patients, their physician’s fiduciary obligations would seem to require counsel against undergoing such a procedure for no benefit (11). Between 0.3 and 5% (12) or up to 10% (13) of women who undergo ovarian stimulation to procure oocytes experience severe ovarian hyperstimulation syndrome, which can cause pain, and occasionally leads to hospitalization, renal failure, potential future infertility, and even death.

Alternatively, these individuals can be viewed purely as research subjects. After all, research often requires individuals to expose themselves to risk for the benefit of others (albeit often with the possibility of direct benefit to themselves). This model may also be inadequate for addressing the status of these women, because the consent process is likely to focus on the post-procurement research risks and benefits. Thus, the risks of the actual procurement process may not be adequately highlighted. There is nothing experimental being tested on these women. The only research aspect of their experience is use of their tissues.

Finally, once current technical limits are overcome, cell lines derived from this research may actually be used in therapy. There may be very little difference for the oocyte donors between donating their...
gametes for research or for clinical purposes—yet the consent processes would seem to require different approaches. All of these factors doubtless contribute to the fact that Hwang and colleagues’ discussion of the consent process and their consent forms (1) reveal little attention to the risks of the procedure and focus on the research aspects of their contribution.

We may need a new category to deal with this unusual class of participants who expose themselves to substantial risk only for the benefit of others, where the risk is incurred not in the actual research but in the procurement of materials for the research. When the oocytes that are donated are anonymized, current U.S. regulations no longer recognize these donors as research subjects. However, the donors are also not patients. We recommend use of the term “research donors” as distinct from “research subjects” to signify their dissimilar roles. This new category does not apply to donors of sperm used to create hESCs, because they are not exposed to similar risks. It also does not apply to donors of tissue for genetic research projects such as the HapMap (14), even though direct benefits do not accrue to those donors, because of the low physical risks involved.

When someone volunteers to donate an organ (such as a kidney or a liver lobe), there is a similar conceptual difficulty (15–17). These procedures are not now considered research, but it is difficult to see the donors truly as patients in the way that recipients are seen (18). Simply taking the best interests of the donor into account, it is hard to justify organ donation.

In dealing with the problem of benefit, the transplant community has moved fairly cautiously, and a great deal of conceptual and procedural work has gone into protecting the individuals who are making a sacrifice for others (15–19). In general, scrutiny of the motives for undergoing such donation is far greater than would normally be required for an elective procedure, and whole classes of potential live donors are ruled out on principle. For example, altruistic directed donation by live donors (i.e., to strangers) has generally been regarded as problematic, both ethically and practically (16, 20). In general, it has been found that it is much easier to justify donation to close family members and friends.

However, it seems that clinicians and stem cell researchers envision this type of altruistic donation as the primary vehicle for generating hESC lines for research and eventual clinical application. Applying this model to the procurement of oocytes would mean that researchers would have to exercise a great deal of caution and to be rigorous in their assessment of whether someone is an appropriate donor as well as being clear about all of the risks.

Recruiting oocyte donors from families of afflicted patients would follow the pattern of justification typically cited in living organ donation. However, it does raise the question of whether oocyte donors feel coerced by their family situations into donating. Furthermore, there is one significant difference that leads to a final problem—organ donation has fairly clearly established benefits to the recipient; hESC research based on SCNT does not.

**Misconception of Therapeutic Use**

As the NRC-IMOM report highlights, it is necessary that prospective donors recognize the large gap between research and therapy. This is particularly important in frontier areas of research where therapeutic impact in humans is unknown. Because it is likely that oocyte donors will be recruited from individuals with diseases and disabilities or their close family members, researchers must make every effort to communicate to these volunteers that it is extremely unlikely that their contributions will directly benefit themselves or their loved ones. Also, it is nearly certain that the clinical benefits of the research are years or maybe decades away. This is a message that desperate families and patients will not want to hear. Their vulnerability and the risks of oocyte donation make it imperative that prospective donors are adequately counseled and that risks are weighed carefully against a realistic assessment of benefits before allowing research to proceed. Donors who are family members or friends of patients hoping to benefit from downstream stem cell research are more vulnerable than the so-called altruistic donors who are strangers.

The language used to describe the research can reinforce the therapeutic misconception (27), misleading donors and subjects into believing that research is therapy. This was recognized as a serious problem in so-called “gene therapy” research (20, 22, 23) and has led to recommendations that this research should more accurately be described as “gene transfer research.” Similarly, it is important not to use the term “therapy” when what is meant is “research” and not to refer to hESC research as “therapeutic cloning.” There is currently no such thing as “therapeutic cloning” and this is not “therapeutic cloning research,” nor can we say with any certainty that “cell therapy” is in the near future. Similarly, referring to research subjects as “patients” contributes to confusion (2). Introducing such terminology increases the likelihood that individuals have been or will be misled into exposing themselves to risk. It is permissible and perhaps even laudatory for women to contribute voluntarily to moving the field forward. But it would be a mistake to allow our language and the enthusiasm of researchers to allow that research to take place through exploitation of vulnerable patients and their friends and family members.

**Responsibilities of Journals**

Journals have an ethical obligation to publish research such as Hwang et al.’s if it is scientifically sound. However, journals must also be satisfied that the research was conducted ethically and must call attention to ethical issues raised by the work that they publish. Research that crosses the boundary into the illegal or clearly ethically unacceptable (e.g., if this research had been conducted without consent) should not be published. Although Hwang et al. did not cross those boundaries, their work is in such a novel and controversial area that it is unsurprising that it raises new ethical challenges, and is beset by some ambiguities. Journals are obligated to publish such research and to encourage ethical reflection on how future research should be conducted.

**References and Notes**


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