Advisory Committee to the Director (ACD)
Working Group (WG) for Human Embryonic Stem Cell Eligibility Review

Findings and Summary Regarding
Guangzhou Medical College Submission 2010-ACD-002

December 3, 2010

Finding regarding all lines in Guangzhou Medical College Submission 2010-ACD-002

The ACD should consider recommending that the NIH Director approve the lines in this submission (FY-hES-1, 3, 5, 7, 8, and FY-3PN) for use in NIH-funded research.

First Discussion

This new submission requests approval of six cell lines for use in NIH funded research. Although the request is generally well documented, it appears that the translation of key documents from the original Chinese has resulted in several ambiguities. In addition, the Working Group felt that their review of the submission would benefit from the advice of a person familiar with accepted practices in Chinese IVF clinics.

Both the consent form and the "Flow Chart of Establishment of Human Embryonic Stem Cell Lines" (each translated from the original Chinese version) raised questions of when the consent was obtained to donate embryos for research. The Working Group needed more information regarding the timing of the consent process: time from creation of embryo to donation of embryo. The flow chart indicates that embryos may be moved to research on day 3 post-fertilization. However, it appears that other embryos may be donated for research after cryopreservation. The embryo donation consent forms do not clarify this. In addition, although the publication included with the submission indicates that these are poor quality embryos, this is not clear in the actual consent forms.

The consent form to donate embryos to research (as translated by the NIH Clinical Center Library) states that "specimens" cannot be provided to individuals or research institution without the consent of the Third Affiliated Hospital of Guangzhou Medical University. It is unclear if this applies to cell lines or just to embryos. The Working Group requested clarification of this provision.

Finally, there are questions about the donors' decision making within the context of the Chinese culture. For example, the clinical treatment consent states that pregnancy reduction is necessary if more than two fetuses are conceived. Also, in the consent for embryo freezing and thawing, it is stated that the first paid storage period is one year after freezing of the embryo, renewable each year. However, the donors' ownership rights are relinquished if the renewal fee is not paid. Upon nonpayment, the embryos will be discarded or used for research, and it is unclear if patients make that choice. The Working Group suggested that NIH staff consult with an expert regarding

the acceptability of these practices within Chinese culture. Also, it would be helpful to know the percentage of IVF couples in China that do not consent to donate remaining embryos for research.

The Working Group agreed to table this request pending receipt of clarification of the timing of consent to donate discarded embryos. This is particularly important in the case of fresh embryos. In addition, the Working Group suggested that NIH staff consult with an expert in Chinese culture to consider more closely the patients' rights and the overall acceptability of the practices described in the request.

Second Discussion

Since the last Working Group meeting, the submitter confirmed that all six lines were derived from 3-day old embryos that were graded as poor quality and would have been discarded otherwise. The submitter also confirmed that consents for clinical treatment and donation of embryos for research were obtained at the same time.

Several concerns remain from the previous discussion. First, consent for embryo donation was obtained in advance of IVF treatment, and in addition, it was not clear whether donors had opportunities to withdraw their consent for embryo donation. Second, the translated consent form provided by the submitter states that the "discarded embryos" may not be provided to any individual or research institution without the donor couples' consent. However, the U.S. translator contracted by the NIH said that the correct translation was not "discarded embryo" but rather was "specimen," raising questions about what the donors understood. Finally, the consent for IVF treatment includes a statement about "necessary" pregnancy reduction if a woman is carrying more than twins. It also appeared that IVF treatments occurred at the same hospital where the stem cell derivation occurred, which the Working Group asked NIH staff to confirm, and also to ask whether the hESC researchers were involved in the clinical treatment of patients.

Several group members expressed concern about approving lines generated within a system where the state has so much control over couples' reproductive decisions. Two key issues of concern related to China's one-child policy were noted: 1) how a multiple pregnancy resulting from IVF treatment is managed; and 2) the restriction of options for excess embryos, as compared to the U.S. In addition to the one-child policy, Chinese assisted reproductive technology guidelines appear to prohibit transfer of embryos to another couple for reproductive purposes. The lack of certain options for use of cryopreserved clinical-grade embryos could be considered a general issue in evaluating submissions from China, although in this specific case the lines were derived from poor-quality embryos, so certain options would not be directly relevant.

The working group discussed whether embryo donation consents in this situation could be considered truly voluntary. Members noted that research on prisoners in the U.S. is limited, given concerns that voluntary consent in such a situation may not be achievable, and that the voluntariness of consent for clinical research in resource-poor countries with very limited health care has long been debated. Another member noted that the Working Group had previously

considered whether patients in a private IVF clinic that also conducts hESC research had full autonomy in deciding whether to donate their embryos to that clinic for research purposes.

The Working Group also noted differences between China and the United States in how embryos were viewed. However, other group members cautioned against imposing one set of cultural standards on another culture. The group members further noted that other countries place limits: for example, in the United States, embryos cannot be created solely for research or by cloning with NIH funds. In addition, the Working Group noted that many nations conducting research, including China, emphasize the key principles of voluntary informed consent. The workgroup discussed considering whether the consent forms in this particular application meet standards within China.

Lastly, the primary reviewer raised a question about whether the IRB provided continuing review beyond the initial approval included in the submission.

Due to the complexity of the issues, the Working Group agreed to seek additional information from the submitter and continue consideration of this submission. NIH agreed to request a call with a recommended bioethicist in China to learn more about China's IVF practices and cultural norms. NIH also agreed to provide information about past NIH decisions from submissions reviewed administratively regarding the timing for donation of poor quality embryos.

Third Discussion

The Working Group continued its consideration of this request.

In addition, information on Chinese culture as it relates to human embryonic stem cell research was obtained by the Working Group through consultation with outside experts. The latter information was sought in an effort to ensure that the Working Group's recommendations would be as informed as possible and considered in the proper context. One member of the Working Group consulted with several prominent bioethicists in China, who noted that most patients undergoing IVF treatment in China have probably used their entire savings to pay for IVF treatment, so they are not likely to have funds remaining for paying cryopreservation fees for remaining embryos. In addition, China is making a strong effort to support human embryonic stem cell research.

The Working Group's previous questions to the submitter were answered satisfactorily. All six lines were derived from 3-day old fresh embryos that were graded as poor quality and would have been discarded otherwise. This group does over 1,000 IVF cycles per year and the embryo donation rate is 7-8%. These numbers are reassuring, as they indicate that the embryo donation consent process appears voluntary. The submitter stated that the couples signed the donation consent at the same time as the IVF treatment consent, which the Working Group agreed was acceptable for the donation of poor quality embryos. Altogether, the Working Group felt that the embryo donor consent form was thorough, although some question remained about the intent of the language of "specimens" in the embryo donation consent form.

The Working Group discussed concerns raised by the IVF treatment consent form. The most troubling aspect of the IVF treatment consent form is the stated mandatory multifetal pregnancy reduction in the case of pregnancy with more than two fetuses. The Working Group discussed this point at length, and agreed that it would not be an acceptable provision in the United States. Also, in signing the form, the couple agreed to the following statement: "We are certain that the sperms and eggs to be used in the process of this IVF-ET treatment were all obtained from us, and that the children born are completely our own, both genetically and legally." The Working Group noted that clinics do make mistakes (although rarely) during identification of specimens in the IVF process. This language could be viewed as exculpatory in that scenario. It also may be a reflection on the predominant desire for taking home a male child. Also, there are several factual inaccuracies in the consent forms. For example, the intracytoplasmic sperm injection consent states: "There is no significant difference in the fetal malformation occurrence rate between the cases where this technology is used and in the cases of natural pregnancy, and that therefore there is no guarantee that each "test tube baby" will be born healthy." This is not consistent with current knowledge about children born using this technology.

Finally, the Working Group continued its discussion of the limited options available to patients in Chinese IVF clinics for use of embryos remaining after fertility treatment under the one-child policy. Most members agreed that the issue does not impact upon this specific situation: the hESC lines are derived from poor-quality embryos that would have been discarded and not transferred to the uterus. Thus, use of those embryos for reproductive purposes was not an option. Therefore, the majority of the members agreed that the Working Group's concerns about the one child policy and limited options for use of embryos remaining after IVF treatment could be separated from the Working Group's consideration of these particular lines, since they are from poor-quality embryos.

The Working Group voted to recommend approval of these cell lines for use in NIH-funded research by a vote of 7 to 2. Members voting the minority felt that the restrictions on choice in the clinical consent process were potentially coercive and therefore sufficiently concerning that the application did not merit a positive finding. Members voting in the majority also expressed concern about the clinical consent restrictions, but felt that the consent process for research in the context of non-clinical grade embryos was sufficiently strong to merit a positive finding.

Fourth Discussion

At the prior meeting, the Working Group voted to suggest that the ACD recommended approval of this request for six hESC lines to be used in NIH-funded research. Following that meeting, NIH requested that the Working Group look again at two sentences in the consent from Guangzhou (translated to English from Chinese by the submitter):

- "The discarded embryos can not be available to any individual or research units without our consent" and
- "The discarded embryos can not be used to other experiment without our consent."

Specifically, the Working Group was asked to revisit this consent form to consider whether those signing the consent would distinguish between "embryos" and the stem cells derived from the embryos.

The Working Group agreed that both sentences should be read to apply to embryos, since it is the embryos and not the stems cells that are being discarded, and earlier in the consent the establishment of a human embryonic stem cell bank is described.

The wording of the first point is somewhat unclear and that the phrase “any *other* individual or institution” would have been preferable. The second sentence was interpreted by the Working Group as merely documenting that the embryos cannot be used for any purpose other than the establishment of a hESC bank for the purposes of scientific research. With this interpretation of the two sentences, the Working Group had no concerns and their previous vote still stands.

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