November 28, 2011

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

Findings and Minutes of Discussions Regarding
Guangzhou Medical College Submission 2010-ACD-002

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

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

Executive Summary

This submission is for six cell lines derived from non-clinical grade embryos (not usable for fertility treatment) donated in 2007 by patients at the Third Hospital Affiliated to Guangzhou Medical University to researchers at the same institution. The embryo donation consent was signed at the same time as the consent for IVF treatment. The hospital institutional review board provided approval of the research and did ongoing monitoring of the project.

The initial Working Group discussions focused on several issues:

- The Working Group noted that couples may have limited options with respect to clinical grade embryos in China due to the one-child reproduction policy. However, since these lines were derived from embryos that were not going to be used for reproductive purposes, the Working Group agreed that any issues related to the one-child policy were not relevant for the purposes of considering these particular lines.
- The Working Group agreed that is reasonable to donate nonclinical grade embryos in advance of reproductive treatment.
- The Working Group noted that the rate of embryo donation to research, 7-8%, was supporting evidence that the embryo donations were voluntary.
- The Working Group identified several problematic statements in the IVF treatment consent form, in particular that multifetal pregnancy reduction was necessary in the case of a pregnancy with more than two fetuses. The Working Group believes that such a provision would be unacceptable in the U.S.
- The Working Group considered the embryo donation consent to be adequate, although they noted that there were different translations of key terms in the section titled *The Subject's Acknowledgement*: "embryo" in the translation by Guangzhou, and "specimen" in the NIH translation.

The Working Group subsequently 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. 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.

At the December 9, 2010, meeting of the Advisory Committee to the Director, NIH, Dr. Botkin presented the Working Group's analysis of this submission and mentioned the difference in the two translations regarding the use of "embryo" or "specimen" near the end of the consent form. The ACD raised concerns about what donors understood about the use of the embryos. The ACD voted to table the submission and send it back to the Working Group for further consideration.

In response, the Working Group decided to focus on the question of whether couples reading the donation consent form would understand the actual meaning of the consent and the potential fate of the embryo. The Working Group developed a list of questions to send to four external reviewers, who are fluent in Chinese, knowledgeable in IVF practices, and with an intimate knowledge of Chinese culture to provide his/her sense of the adequacy of the consent form and provide advice on the specific language that the Working Group has identified for clarification.

All four outside reviewers stated that the highlighted text within the consent form was more accurately translated as "specimen" (NIH translation) as opposed to "embryo" (submitter's translation). This is a serious concern, given the donors' critical need to understand that the part of the consent refers to the distribution of embryos. Two reviewers stated that the language regarding the sharing of the stem cell lines with investigators at outside institutions was ambiguous. Two of the four reviewers judged the overall consent form to be ambiguous and inadequate to enable couples to make an informed choice about the use of their embryos for stem cell research.

Based on this input, the Working Group agreed that the consent was ambiguous about what would be the product of the research and what could be distributed outside Guangzhou. With this concern, in addition to the original concern about potential coercion in the clinical consent process, the Working Group reconsidered their earlier recommendation and voted unanimously to present a negative finding to the ACD.

Summaries of Discussions

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 are 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

Since the previous meeting, 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

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.

ACD Meeting

At the December 9, 2010, meeting of the Advisory Committee to the Director, NIH, Dr. Botkin presented the Working Group’s analysis of this submission and mentioned the difference in the two translations regarding the use of “embryo” or “specimen” near the end of the consent form. The ACD raised concerns about what donors understood about the use of the embryos. The ACD voted to table the submission and send it back to the Working Group for further consideration. The motion made it clear that it was up to the Working Group to determine what to do next and convince the ACD of its findings.

Fifth Discussion

At the next Working Group meeting, the Working Group resumed the discussion of this submission and decided to focus on the question of whether couples reading the donation consent form would understand the actual meaning of the consent and the potential fate of the embryo. That is, would a reasonable person understand the practical meaning of the consent? Did the signer of the consent form understand that material genetically similar to the donor would be propagated and potentially shared around the world? The Working Group agreed that simply obtaining additional translations would miss the point, which is to consider whether the consent language was understandable by the actual patients. Based on this point, the Working Group agreed that it will be important to have someone close to the Chinese culture and knowledgeable

in IVF practices read, translate, and interpret the consent form with regard to how the people there are reading this. In other words, a better assessment is needed of the donors' likely interpretation of the overall consent. How is someone in that culture reading this, and how does the consent language come across? How does the consent form compare with others of similar nature within the same time period and context?

The point was raised that people with the financial resources and geographical mobility to go through IVF are not the average Chinese couple; they probably are urban, relatively wealthy, and educated. Therefore the term "average" is not the most accurate term to use in this case. The Working Group did agree that it is reassuring that only about 8 percent of the IVF patients signed the consent. This relatively small number indicates that perhaps they read the consent form in a critical, informed manner and that they did understand the potential consequences of signing.

The Working Group remained generally positive about the overall submission, which they tabled pending further consultation. Several members of the Working Group agreed to consult with NIH staff to identify one or more individuals fluent in the Chinese language, knowledgeable in IVF practices, and with an intimate knowledge of Chinese culture to provide his/her sense of the adequacy of the consent form and to provide advice on the specific language that the Working Group has identified for clarification. The subgroup would also discuss further the questions that will be asked of the consulted individual(s).

Finally, the Working Group briefly restated their position that if it is concluded that a donor would not have understood that the stem cell lines would be shared beyond Guangzhou (without further consent), that would be a restriction on use of the cell lines. Considering restrictions are beyond the Working Group's charge and not relevant to determining whether a submission met the NIH Guidelines.

Sixth Discussion

NIH staff reported that three individuals have been identified as potential reviewers by Working Group members and two of these have been contacted by Working Group members, at least indirectly. All three are native Chinese speakers; two are physician/fertility specialists, and the third person is an educated consumer. The Working Group agreed that additional discussion was required regarding the optimum number of reviewers to be recruited for this activity and the ideal balance of expertise and experience.

The Working Group then discussed the broader issue of possible approaches for obtaining the best information from the reviewers. It was agreed that the documentation of the overall process and the instructions to the reviewers need to be as explicit and standardized as possible; the Working Groups needs to be able to defend the process, if challenged. NIH staff replied that they already have begun to draft standardized questions to be addressed by translators. The draft set of questions will be reviewed by the Chair before distributing it to the overall Working Group. It was pointed out that the questions as well as the responses will be part of the official record. Therefore, the clarity of the questions posed to the reviewers and the lack of bias will be critical. For example, the reviewer may be asked his/her opinion of what a potential donor's understanding of a given document would be without identifying the specific item of

controversy. Through this approach, the reviewer would raise any issues/concerns independently, free of leading questions. The Working Group agreed that this generic approach may not be feasible in all cases and that further discussion on this point is needed.

In terms of strategies for approaching a potential translator, one Working Group member suggested that the Chair make the initial contact by telephone in collaboration with NIH staff. Through this initial contact the individual's willingness to participate would be determined and the task would be described to him/her at the outset.

It was suggested that individuals who agree to participate as reviewers would then be sent selected text (e.g., the consent form for the Guangzhou submission), along with a series of questions for him/her to address. The reviewer would be contacted by phone again once he/she has had a chance to review the materials. Through this second call the Chair, along with other members of the Working Group (as needed), would clarify any issues to facilitate the reviewer's completion of the task. It was suggested that NIH provide a person who would take notes on the discussion highlights to document the exchange of information during the teleconference. An alternate approach would be to omit this second teleconference and simply rely on the written feedback of the reviewers; ask them to review the written materials and answer the questions without a verbal interview. This approach may be more defensible in terms of standardization across individual cases because the teleconference could veer from the script and introduce extraneous factors. The Working Group agreed that there are pros and cons to both approaches and that further discussion is needed before setting either one into practice. The final discussion item centered on the issue of the confidentiality of the reviewer's identities.

After considering all of these issues the Working Group Chair agreed to work with NIH staff to draft the questions to reviewers and the overall protocol for obtaining the feedback. The draft questions and protocol will be circulated to the entire Working Group for their comments, and the issue will be discussed again at the next conference call. Ideally, this will allow the questions and protocol to be piloted on the Guangzhou submission in April/May in preparation for a presentation at the June 2011 ACD meeting.

Seventh Discussion

Before beginning today's discussion, NIH staff requested that the Working Group not identify the external reviewers in today's discussions and the meeting summary. With this in mind, the Chair reported that he had received feedback from one external reviewer who was raised in China and is fluent in Mandarin. Although he/she is not a clinician, he/she has knowledge of and experience with IVF services. The Working Group decided it will be better to have at least two, and preferably three, external reviews in hand before considering any responses to the questions. Therefore, the Working Group agreed not to engage in a detailed discussion of the single external review at this point. The Chair will attempt to obtain additional external feedback over the next few days; he has several leads, including recommendations from the Working Group members. The plan is to bring the external reviews to the Working Group via a brief phone conference or email discussion, followed by a vote.

The Working Group understands that the process described above may not be able to be carried out in time to bring the find to the June 9-10th ACD meeting since the materials for that meeting are sent to the ACD members about one week before the meeting. It was agreed that the process will not be rushed at the expense of the integrity of the findings, and that the external reviews can be brought to the next meeting of the Working Group, if necessary.

The Working Group members were reminded that the last vote on this submission - 7 positive and 2 negative - reflected lack of clarity in the translation of "specimen" versus "discarded embryo" in the consent form, and the broader question as to whether the overall consent form would be understandable to the average donor couple. If the language is ambiguous, that would affect the quality of the consent form, which is a key element in the review of submissions. However, the Working Group members understand that they need to be cautious with the use of the external responses. It is important to remember that the consent forms included with other submissions have not been held to evaluation by external individuals. This is particularly important to note if the external reviewers deem the consent form to be not understandable to the average donor couple.

Another question posed to the external reviewers pertains to potential restrictions on approved lines. Although restrictions on the lines are important to note on the Registry, this element is outside of the Section IIB review criteria and should not enter into the Working Group's findings. That is, the Working Group should continue to make an effort to note potential restriction on lines, although this element is not to be considered in their findings.

Eighth Discussion

After the previous meeting, specific questions for external reviewers were finalized. The items ranged from specific to broad, and included the following:

- The reviewer's background and familiarity with Mandarin and his/her understanding of the approach in China to reproductive services;
- The identification of any unclear words or phrases in the consent form;
- The comparative accuracy of the two differing translations;
- The understandability of the consent form by most couples who receive assisted reproductive services in China;
- Whether couples signing this form would understand that stem cells would be shared with investigators beyond the institution where consent was obtained.

Separate responses from four outside reviewers were presented to the Working Group. All four outside reviewers stated that the highlighted text within the consent form was more accurately translated as "specimen" (NIH translation) as opposed to "embryo" (submitter's translation). Therefore, the NIH translator and the outside reviewers all disagreed with the submitter's translation. This is a serious concern, given the donors' critical need to understand that the consent refers to the distribution of embryos.

In response to another question, two reviewers stated that the language regarding the sharing of the lines with investigators at outside institutions was ambiguous. (The two other reviewers

didn't directly address this question.) Given this ambiguity, it is possible that couples could donate out of loyalty to Guangzhou Medical College and be unaware that the lines could be distributed elsewhere. NIH staff reminded the Working Group that NIH has agreed to honor restrictions written in the consent forms (e.g., a restriction to diabetes research only). That is, although restrictions on the lines are important to note on the Registry, this element is outside of the Section IIB review criteria and should not enter into the Working Group's findings. However, the Working Group made the point that in this case the issue cannot be resolved by simply placing a "Provider Restriction" in the Registry; the ambiguity of the consent form's distribution language directly erodes the integrity of the overall submission. Although restrictions are in principle separate from the issue of eligibility, restrictions stated in an ambiguous manner within the consent form have a direct effect on the overall eligibility of the cell lines.

Most importantly, two of the four reviewers judged the overall consent form to be ambiguous and inadequate to enable couples to make an informed choice about the use of their embryos for stem cell research.

Based on this input, the Working Group agreed that the consent was ambiguous about what would be the product of the research and what could be distributed outside Guangzhou. With this concern, in addition to the original concern about potential coercion in the clinical consent process, the Working Group reconsidered their earlier recommendation and voted unanimously to present a negative finding to the ACD.

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