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

Findings and Summary Regarding
Children's Memorial Hospital Submission 2009-ACD-009

December 3, 2010

Finding regarding the lines CM2, CM6, and CM7 in Children's Memorial Hospital (CMH) Submission 2009-ACD-009

The ACD should consider recommending that the NIH Director NOT approve the lines CM2, CM6, and CM7 for use in NIH-funded research because of problems in the informed consent process.

Note: the Working Group has not yet finished its review of the lines from embryos donated by patients at one the two IVF clinics pertinent to this submission (lines CM1, 5, 8, 11, 12, 13, 14, and 16). Those lines will not be discussed at the December 9, 2010 ACD meeting, and discussion about issues specific to those lines are not included below in this report.

First Discussion

This a request for approval of 11 human embryonic stem cell lines for use in NIH-funded research from Children's Memorial Hospital (CMH) in Chicago. Between 1998 and 2009, almost 300 embryos were shipped to Children's Memorial Research Center (CMRC) from off-campus IVF centers, without identifiers, to be placed in an embryonic stem cell line bank. The major donor sites were from clinic #1 *(name redacted as clinic association is not public)* and Midwest Fertility Center, Illinois.

The WG expressed concerns about the lack of documentation in key areas, primarily the omission of an actual protocol under which lines were derived and the dates of derivation. Furthermore, the documentation does not provide sufficient information on the consent forms that were actually used. Based on a preliminary review by the primary reviewer and the chair, the WG requested additional information:

- Clarification of the date each hESC line was derived and the source of embryos for each line.

- The protocol(s) as approved by the Children's Memorial Research Center IRB and/or the Northwestern University Committee on Human Stem Cell Research.

- Documentation of the IRB approval for the years when each line was derived, whether there were any lapses in renewal, or changes in the protocol or its exempt status.

- A more detailed explanation about the arrangements between Children's Memorial Research Center and the IVF clinics, particularly regarding when informed consent took place and what options were presented to patients at each clinic regarding embryos remaining after reproductive treatment.

- Clarification of whether any lines were derived from discarded PGD embryos rather than from frozen embryos that were not implanted.

- For each of the hESC lines, documentation of informed consent for embryo donation.

- Clarification of whether the sample consent forms provided were those used when the embryos used to derive the hESC lines were donated.

After reviewing this additional information, the WG had several concerns in these areas:

First, the sample consent forms that were provided to the WG include very general wording. For example, there is a box for "research," without mentioning stem cell research in particular. Therefore, it is not clear that the donors were adequately informed about what would happen to the embryos. (Some people may be willing to donate the embryos for genetic research or infertility research, but not for stem cell research.)

The sample consent forms that were provided do not cover all the time periods when each clinic was sending embryos to CMRC, and there is not enough documentation to assure the WG that no inducement was provided or that people were aware that there would be no benefit to them. Of additional concern is the investigator's statement that the IVF centers were encouraged to transfer donated embryos for research to CMRC instead of discarding them. The WG needs more evidence to provide assurance that the centers did not provide undue inducement for patients to donate embryos.

The WB would like to see evidence that the embryo donor for each hESC line gave informed consent for hESC research. In the additional material submitted before the WG meeting, the investigator stated that they may not be able to provide copies of informed consent for a particular embryo because de-identification and confidentiality agreements preclude the investigators from linking each hESC line to specific protocols and consent forms. Despite this hurdle, the WG still believes that it is important to see documentation that the embryo donor of each specific line gave written informed consent. It would be helpful to have more information on the attempts that the investigators made to get a consent form linked to the embryo donor for each hESC line (a redacted form or a clinic doctor's statement that s/he saw it). It still is unclear why the investigators cannot provide specific documentation of consent and what efforts they have made to do so. Several approaches might be taken. First, the investigators could ask the IVF clinics to attempt to track back to the embryo donor for each hESC line in order to provide redacted consent forms. Second, if de-identification precludes the submission of an actual, redacted consent form linked to the donor of each hESC line, then the investigators could attempt to track back to the time window around the embryo donation and verify that all IVF patients who donated embryos to gave consent for hESC research, using a form that has been provided to the WG. If line x came from clinic y, the IVF clinic director at clinic y could review files of all

embryo donors to CMRC at that time should be reviewed. The IVF clinic director should attest that he or she reviewed all files and verified that consent for hESC research was given.

It appears that some of the embryos donated were fresh post-PGD, but it is not clear. If fresh embryos were donated, it will be important to know if the timeframe allowed families to make decisions about consent and donation.

The WG agreed to defer a finding on this request, pending receipt of additional information. The WG will request additional information on the points described above. Specifically:

- Specific dates of embryo donation and hESC derivation for each hESC line.
- A copy of the research protocols, redacted if necessary, with information on whether fresh embryos were used, whether the embryos were poor quality, leftover from PGD, and/or clinical grade embryos, and what procedures were used for identifying those embryos and shipping them to CMRC.
- Documentation that for each hESC line the embryo donor gave written informed consent (rather than just the sample consents already provided). This could be accomplished in any of the ways described above.
- Documentation of whether donors were given more specific information (including in oral form) about the nature of the hESC research. This could be documented in attestations from IVF clinic medical directors.
- Further information on whether clinics encouraged patients to donate embryos.
- Whether any financial arrangements existed between the IVF clinics and CMRC.

Second Discussion

The Working Group reviewed additional information submitted by the applicant, which resolved some issues and raised new ones.

<u>Midwest Fertility Center (MFC) lines</u>

The forms from the MFC lack specificity regarding the intended research use of the embryos. The three MFC lines (CM2, 6, and 7) were derived from embryos donated in 2006 and 2007. The Working Group found the failure of the MFC to provide consent forms with specific language pertaining to hESC research particularly troubling, given that these embryos were donated after the publication of the 2005 National Academy of Sciences Guidelines which set a standard in the U.S. for specificity in embryo donation consents. The Working Group also noted that Section IIA of the NIH Guidelines requires: "During the consent process, the donor(s) were informed of the following: that the embryos would be used to derive hESCs for research." It is plausible that some individuals who would consent to donate for general embryo research purposes would not agree to donate for hESC research.

Additional issues were noted pertaining to each cell line:

- For CM2, there was no "donate for research" option on the printed informed consent form: rather, someone hand-wrote "Donate to Northwestern for research."

- For CM6, the submitter points to clinical notes in which it is hand written that the donors of the embryo from which the CM6 line was derived gave oral consent for embryo donation for "research." Section IIB of the NIH Guidelines requires written consent. There are also conflicting statements within the submission about the date of embryo donation.

- For CM7, multiple signed donation forms were submitted, since it is not known which donated embryo was the source of the line. One donation form stated that "Your account will be sent to a collection agency in the amount of $3,000.00 unless payment or this notice is returned with the order for discard or research." That form also had a handwritten note, presumably from the donor, stating that "in the past several times (6) I have received letters and stated if we did not respond they would be discarded. I am not sure why this did not take place!"

Apparent lack of rigor in documentation and the embryo donation process brings the adequacy of communication and consent into question.

Based on the concerns expressed above, the Working Group voted unanimously to suggest that the ACD not recommend approval of these cell lines for use in NIH-funded research.

Third Discussion

At the prior meeting, the Working Group arrived at a negative finding for this request from Children's Memorial Hospital in Chicago regarding the 3 cell lines from embryos shipped from Midwest Fertility Center (MFC), Illinois to Children's Memorial Research Center (CMRC). Following the prior discussion, NIH staff asked the Working Group for a more specific explanation of how they found the consent for line CM2 (from MFC) lacking.

The Working Group determined that the consent process for embryos donated for the MFC lines did not meet the standards set in the 2005 National Academy of Sciences (NAS) report, which recommended that the consent process for blastocyst donors should state "that the blastocysts or gametes will be used to derive hESC cells for research." Furthermore, the NAS report states "Written informed consent must be obtained from all those who elect to donate blastocysts or gametes." The Working Group regards this NAS report, which made consensus recommendations from an interdisciplinary panel and was peer reviewed, as setting national standards of practice for embryonic stem cell research and in particular for donation of materials used to derive hESC lines. The MFC consent process for donation of embryos (all donated after the NAS report) fails to meet these standards, as discussed below.

Line CM7 was derived from embryos frozen between 1996 and 2005. The printed consent forms from the donors list the following options: donate for research purposes, discard, and continue to freeze. The forms do not specifically mention hESC derivation or research. Moreover, on one consent form for donation signed 1/24/2007 there is a handwritten notation: *"in the past several times (6) I have received letters and stated if we did not respond they would be discarded. I am not sure why this did not take place!"* This notation suggests that embryos were not discarded

after the IVF patient failed to respond, raising further questions about the consent process. This consent also included a statement that "Your account will be sent to a collection agency in the amount of $3,000.00 unless payment or this notice is returned with the order for discard or research."

MFC lines CM2 and CM6 were derived from fresh embryos after PGD screening, with line CM6 donated from embryos donated in 2008 or 2007 (NIH received conflicting paperwork). There is a handwritten note on the embryology lab sheet "Donated for research. Parents consented verbally."

Line CM2 was derived from embryos donated for research in 2007. The signed CM2 consent form lists the following options:

- We do not have any embryos remaining for freezing
- We want all of the remaining embryos discarded
- We want those suitable for cryopreservation frozen and others discarded
- "Donate to Northwestern for research" *(hand-written additional option)*

NIH staff asked the Working Group if the 2007 CM2 consent form described above answered their concerns about this line; the Working Group members stated that it did not. For all three MFC lines, the consent process fails to meet the 2005 NAS standards of written consent for hESC derivation. For example, people struggling with fertility problems may think they are donating for fertility-related research, whereas stem cell research may be of concern to them.

Although the requester stated that the IVF Director explained to the donors orally that the embryos would be directed for stem cell research, the Working Group saw this attestation of oral declaration as insufficient, given the irregularities throughout the request. It might be more assuring if a written script had been followed in every case. An additional concern regarding line CM2 is that the item specifying donation to Northwestern might preclude use at other sites.

The Working Group agreed unanimously to support their previous recommendation of a negative finding for the lines derived from embryos at MFC.

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