6 June 2012

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

Findings and Minutes of Discussions Regarding
California Stem Cell, Inc. Submission 2012-ACD-001

Finding regarding line in California Stem Cell, Inc. Submission 2012-ACD-001

The ACD should consider recommending that the NIH Director disapprove the use of this cell line in NIH-funded research under the Section IIB criteria of the NIH Guidelines for Human Stem Cell Research.

Summary of Discussions

First Discussion

This new submission from California Stem Cell, Inc. (CSCI) requests approval of one cell line for use in NIH-funded research. The embryo was donated for research in 2006 by a couple who no longer wished to keep the embryo in a cryopreserved state.

The submission, which was initially submitted for administrative review, was moved to Working Group review when it was determined that it did not meet all criteria within Section IIA of the Guidelines. It was unclear whether the donors had been informed of their ability to withdraw the donation of the embryos until the embryos were actually used to derive embryonic stem cells or until information that could link the identity of the donor(s) with the embryos was no longer retained, if applicable.

The question of the opportunity for withdrawal of consent was discussed at length by the Working Group. Of major concern was the lack of a statement within the actual informed consent document that consent could be withdrawn after it had been provided. In addition, the consent form does not provide a name or contact information for individuals who decide to withdraw consent. The study protocol does state that if the couple decides to withdraw from the study within the 30-day waiting period, the frozen material will be returned to the couple's possession and will not be transported to CSCI. However, it is not clear how or whether that information was communicated to the donors, since it is not covered within the consent materials. Therefore, it was doubtful to the Working Group that the ability to withdraw consent was communicated to the donors. The Working Group also requests clarification of the one-page document entitled "Procedure for Presenting Informed Consent to Study Members." It is unclear whether this undated document, which actually provides all of the needed information, was provided to the donor couple.

A second major concern expressed by the Working Group related to the gap between the dates of embryo donation and IRB approval of the protocol. According to the documents available to the Working Group, the actual protocol was approved by the IRB retrospectively in 2009, 3 years

after the donation date. It is not clear whether the protocol was even in place when the individuals gave consent for their embryos to be used. It was noted that the Working Group has never rendered a positive finding for a submission documenting a lapse in IRB approval or a gap between consent and IRB approval. NIH had already asked CSCI to explain when the protocol was developed and whether it was in effect at the time of the embryo donation. In addition, the Working Group asked that NIH inquire whether IRB approval for this protocol was sought at the time that the embryo was donated, and if it was not, why not.

Concerns also were raised about the consent form's lack of alternatives to research donation. There is some indication in the consent form that embryos would be stored or otherwise handled according to terms/conditions of the program participation agreement. Alternatives are described in the protocol, which states that the donors had the additional options of donation of the embryo(s) to other couples for IVF treatment, donation of the embryo(s) for other research, or disposal. Also, a cryopreservation bill to the donors with the subject "Disposition of Frozen Embryos/Oocytes" provided some information on possible alternatives, along with a request for $500; if money was not remitted or a choice was not made, then the embryos would be considered abandoned and theoretically destroyed. The Working Group was concerned that the 30-day period could be too brief for a couple to provide the money or to make a final decision about disposition. NIH has requested a copy of the actual cryopreservation program participation agreement, which may provide more information than the "bill" about the options that were made available to the couple.

The Working Group acknowledged that the consent process is sometimes presented to donors in two stages: Couples will sign a consent to have the embryos donated to research and then receive information about different options. After signing that initial consent, they are provided with a separate consent explaining what will happen to the embryos. In the two-stage model, there is a sequence of choices, with information about the different options at each stage. With these factors in mind, the Working Group agreed to ask for additional information from CSCI on its consent process.

The Working Group members also expressed concern about possible exculpatory language within the "Commercial Developments" section of the consent form. The language is actually contradictory because it appears to deny rights that were never the donors' to begin with. That is, the form states that, by signing this agreement, the donors give up the right under Federal law to control the use of stem cell lines derived from the embryos. While the language itself is exculpatory, there is no Federal law governing the right to control the use of stem cell lines derived from the donor's embryos. Therefore, taking that right away is a strange claim to make. The Working Group's primary concern with this matter is that the cited language could add to the donors' confusion about their ability to withdraw the donation.

Finally, minor concerns were expressed about hedging language in the consent form, stating that Dr. Keirstead "may" have an ownership interest in CSCI. Although this statement by itself is not of major concern, it appears to reflect the less than optimal transparency present in the areas of more major concern mentioned above. In a way, the statement appears to put the onus on the couple if they are interested in pursuing that issue.

Based on the several unclear aspects of the submission, the Working Group agreed to table the review of this submission pending NIH's receipt of information on the points described above. NIH staff will draft the questions for review by the Working Group Chair and primary reviewer before sending the questions to CSCI.

Second Discussion

At the April 2012 meeting, the Working Group tabled the review of this submission based on several unclear issues, which are outlined in the meeting summary. Shortly after that meeting, the NIH staff sent questions to California Stem Cell, Inc. (CSCI) in an attempt to clarify the specific points raised by the Working Group. At the May meeting, the Working Group reviewed the responses from the applicant.

A concern expressed at the April 2012 meeting related to insufficient documentation in the initial submission that the donors had been informed of their ability to withdraw consent up to the time that the embryos were used to derive stem cells. Postmeeting communications from CSCI provided no additional evidence that such language was in effect and had been distributed to the donors. Although the study protocol provides some information on this topic, there is no documentation that it was in place at the time of embryo derivation. Nor was there any evidence that the document entitled "Process for Presenting Informed Consent to Study Subjects," which unlike the informed consent document includes information about who to contact if withdrawal of consent is desired, was in effect at the time of consent. An additional documentation issue is the relatively minor but continuing concern that the "Commercial Developments" section of the consent form contains contradictory language that could have added to the donors' confusion about their ability to withdraw the donation.

A separate document, the cryopreservation bill, includes brief language on other options for use of the embryos, including a statement that, if a fee were not paid within 30 days, the embryos would be destroyed. In response to a request for more information, CSCI provided the Working Group with the Cryopreservation Program Participation Agreement (referenced in the bill). This document states that if the agreement is terminated, the donors will receive a notice 90 days before the embryos are destroyed. The Cryopreservation Program Participation Agreement form also asks the couple to indicate their choice for the dispensation of the embryos if either or both donors die.

The Working Group discussed at length the issues of withdrawal of consent by donors and information to donors on other options. Working Group members acknowledged that, although the processes and documentation used by CSCI appear to be far from ideal, the Working Group's reviews of other submissions under Section IIB criteria have revealed that applicants used a range of processes and documents before the 2009 Guidelines were in effect. In cases where key points had been omitted from the actual consent form, but were provided to the donors through other materials, the Working Group has considered the entire package of documents in arriving at its findings.

A second concern expressed at the April 2012 meeting related to the 3-year gap between the date of embryo donation and IRB approval of the protocol. It is understood that CSCI is not officially

required to have IRB approval because it does not receive HHS funds. Although no regulations were violated, the absence of IRB approval prior to the donation of sensitive materials presents more than just a regulation issue; the lack of an impartial review of the protocol presents an ethical problem. Although the Working Group has arrived at positive findings for lines from foreign entities that followed their own country's policies regarding IRB approval, the Working Group has never rendered a positive finding for a U.S. submission that documented a lapse in IRB approval or a gap between consent and IRB approval. On a related point, it was agreed that in cases where an exempt designation is claimed, that designation should be determined by the IRB, as an independent body, based on the study protocol. The fact that CSCI did not obtain IRB approval of the protocol in advance is of significant concern. There is no such thing as retroactive IRB approval.

Based on the multiple concerns expressed above, the Working Group voted unanimously to present a negative finding to the NIH Advisory Committee to the Director (ACD) for the use of this cell line in NIH-funded research.

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