3 December 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-004

Finding regarding line in California Stem Cell, Inc. Submission 2012-ACD-004

The NIH Advisory Committee to the Director (ACD) should consider recommending, to the NIH Director, that the initial decision to disapprove line CSC14 from California Stem Cell Inc. (CSCI) for use in NIH-funded research under the Section IIB criteria of the NIH Guidelines for Human Stem Cell Research remain unchanged as the new information submitted does not adequately address the deficiencies in the consent process previously identified.

Discussion Summary

At its May 2012 meeting, the Working Group for Human Embryonic Stem Cell Eligibility Review voted unanimously to present a negative finding to the ACD for the use of this cell line in NIH-funded research. The negative finding was based on multiple concerns expressed in discussions at two meetings of the Working Group. The ACD accepted the Working Group's finding at its June 2012 meeting. (See Attachment A: Findings and Minutes of Discussions Regarding California Stem Cell, Inc. Submission 2012-ACD-001.) The present submission from CSCI represents the first resubmission received by NIH for a disapproved line.

The negative finding from the May 2012 Working Group meeting was primarily based on concerns regarding the donors' understanding of their ability to withdraw consent up to the time that the embryos were used to derive stem cells. The existence of contradictory and possibly exculpatory language in the consent form was considered by the Working Group to possibly further confuse the donors with regard to their ability to withdraw the embryo donation. In addition, there was a 3-year gap between the date of the embryo donation and IRB approval of the protocol which was deemed by the Working Group to reflect negatively on ethical standards of the investigators, even though CSCI was not required by the U.S. Department of Health and Human Services (DHHS) to have IRB approval since no DHHS funds were used and CSCI was not covered by a federal-wide assurance. Although no regulations were violated in not undergoing IRB review, the absence of an impartial review prior to obtaining donor consent and of ongoing impartial oversight during the consent process underlines the confusing nature of the consent documents and weakened the confidence of the Working Group in the rigor with which CSCI protected the rights of donors.

In the resubmission materials, the point-by-point responses by CSCI to the concerns raised by the Working Group refer to a new document: a signed declaration by Antoine La, the embryologist at the IVF clinic that provided reproductive treatment to the embryo donors. In this document Mr. La attests that he and the persons working in the Embryology Laboratory were

trained on the undated procedural documents for presenting informed consent and procurement of embryos. (CSCI had previously indicated that they were unable to verify that those documents were in use at the time of embryo donation.) Mr. La also states that the procedural documents were in place and implemented prior to embryo donation, that the right to withdraw consent was conveyed orally to the donors, and that the donors were told who to contact if withdrawal of consent was desired.

The Working Group considered the declaration and additional information in detail, but determined that concerns with the consent process remained. While the Working Group respects the declaration of Mr. La, the other available information cannot be used to substantiate the information in the declaration. The fact remains that the procedural documents are undated and the Working Group previously received information that the applicant could not determine whether these documents were in use at the time that consent was obtained for this line. Further, the declaration and procedural documents do not identify who, at the IVF clinic, actually conducted consent sessions and provided the oral information regarding withdrawal, and whether that person(s) had relevant training in informed consent principles. In addition, there is no information on the content of the orally-conveyed consent information, so it is not possible to determine whether the information conveyed orally was consistent with the written materials. Also, although it is stated that the donors were provided (orally) with the name of a person to contact for withdrawal of consent, neither the name or contact information were written in the consent document, which is the only document mentioned in the protocol that the donors were to be given. Providing detailed contact information exclusively in oral form is not satisfactory.

CSCI responded to the Working Group's concern about potentially exculpatory/contradictory language within the "Commercial Developments" section of the informed consent form (see language below in italics) by stating that this was remedied by the information that was conveyed orally.

> *"Under federal law, if you do not sign this agreement, you would have the right to control the use of the stem cell lines derived from your embryo(s). However, by signing this agreement, you are giving up that right and authorizing the use of your embryo(s) for the research described in the PURPOSES/PROCEDURES section of this agreement."*

However, as stated above, the declaration provided by Mr. La offers no information on the specific language of the withdrawal information provided to the donors. Therefore, the exculpatory/contradictory language remains troubling because it could have confounded the donors' understanding of their ability to withdraw consent. The paucity of information in the Declaration does not support the CSCI's position that the information conveyed orally to the donors would eliminate confusion from the contradictory information in the written materials.

The IRB matter cited by the Working Group in previous reviews of this submission is of ethical concern only in the context of several other issues raised by this application. Although IRB review was not strictly required for CSCI studies at the time as explained earlier, the central question is whether CSCI followed the ethical standards in 45 CFR 46. The lack of prospective IRB review and explanation by CSCI of the purpose of retrospective IRB review does suggest a failure to recognize the utility of the IRB review process to provide impartial oversight, and

thereby to help ensure that the design of an informed consent process is robust before donors give consent.

Finally, the resubmission states that the "flexible standard" regarding withdrawal, that the Working Group applied to the GENEA submissions (2012-ACD-002, -003), should be applied to the CSCI resubmission. However, the overall GENEA submissions were well conceived and tightly constructed, other than a minor inconsistency in the withdrawal language. In contrast, the omissions and flaws in the CSCI resubmission represent several significant concerns.

The potential for confusion regarding the donor's right to withdraw, resulting from possibly exculpatory language in the consent, and the absence of written information on who to contact (and how) regarding withdrawal, remain significant weaknesses in the consent process. With all of these factors considered, the Working Group voted unanimously to present a negative finding to the ACD for the single line included in this submission.

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Attachment A

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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