

26 August 2014

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

**Findings and Summaries of Discussions Regarding  
California Stem Cell, Inc. Submission 2012-ACD-004**

**Executive Summary**

The Advisory Committee to the Director, NIH (ACD) is asked to reconsider its recommendation regarding a submission from California Stem Cell, Inc. (CSCI), now NeoStem, for human embryonic stem cell line CSC14, based on new data. The cell line is currently on the list of [Cell Lines Not Approved for NIH Funding Eligibility](#). After reviewing two additional consents signed by the embryo donors, the majority of the members of the Working Group for Human Embryonic Stem Cell Eligibility Review (4 of 7) now suggest that the ACD recommend approval of the cell line CSC14 for use in NIH-funded research under the Section IIB criteria of the NIH Guidelines for Human Stem Cell Research.

Cell line CSC14 was derived from an embryo donated in 2006 by a couple who had received reproductive treatment at an IVF clinic separate from CSCI. The embryo donation consent form did not describe an option for the donor couple to withdraw their embryo donation. The form did include arguably exculpatory language: “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...” An undated protocol included details on how donors could withdraw consent, but at the time of the first ACD review, in June 2012, CSCI was unable to present any evidence that the protocol was in effect at the time of embryo donation. CSCI had obtained an Institutional Review Board (IRB) review of the protocol in 2009, three years after the embryo donation. CSCI was not a recipient of Department of Health and Human Services (HHS) funds at the time of embryo donation and did not have a federal assurance with the HHS Office for Human Research Protections.

In the first report to the ACD, at the June 15, 2012, meeting, the Working Group presented a negative finding based primarily on concerns regarding whether the donors were provided clear and adequate information regarding 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 regards to their ability to withdraw the embryo donation. In addition, the absence of impartial, independent review, prior to obtaining donor consent and during the consent process weakened the confidence of the Working Group in the rigor with which CSCI protected

the rights of donors. The ACD accepted the Working Group's finding and recommended disapproval of the cell line. Dr. Collins disapproved the cell line on June 20, 2012.

In November of 2012, CSCI submitted an attestation from the embryologist at the IVF clinic stating that the protocol was in effect at the time of embryo donation, that staff were trained using the protocol, and that the donors were informed of their right to withdraw consent up until the time derivation occurred and who to contact in order to withdraw consent. A letter from CSCI specifically stated that the donors were informed verbally. The Working Group remained concerned that there was potential for confusion about the donor's right to withdraw, resulting from the possibly exculpatory language in the consent form and the absence of written information on whom to contact and how regarding withdrawal. Therefore, the Working Group remained uncertain that the rights of donors were protected adequately. So the Working Group voted unanimously to present a second negative finding to the ACD. On December 7, 2012, the ACD recommended continued disapproval of line CSC14.

CSCI subsequently requested a meeting with NIH; a teleconference occurred in February 2013, at which CSCI indicated that there were other records that might be relevant to NIH's decision. In July 2013, CSCI submitted a new consent form signed by the embryo donors to NIH, along with a number of documents, most of which pertained to review and approval, by animal care and stem cell research oversight committees at the University of California, Irvine, of preclinical research in animal models using the already-derived stem cell line or derivatives. Thus the University of California, Irvine reviews did not pertain to the embryo donation process or concerns raised by the Working Group.

The Working Group considered the second consent, signed by the embryo donors in July of 2013. The stated purpose of the second consent was to affirm the donors' willingness to allow the use of the cell line in NIH-funded research and allow the listing of CSC14 on the NIH Stem Cell Registry. The consent described CSCI's plans to use the cell line to proceed with their therapeutic programs in Spinal Muscular Atrophy and Amyotrophic Lateral Sclerosis. The consent stated that "Programs have been developed over the past six years at a cost of millions of dollars and show huge promise for addressing the unmet medical needs of tens of thousands of Americans. Continued development of these programs could result in regulatory approval to begin treating patients in clinical trials as early as late 2013. International clinical development activities in these indications also require approval of CSC14 on the NIH Registry." The consent also stated that "The only risk is the loss of confidentiality" and "You may decide not to participate or you may leave the study at any time."

The Working Group viewed the second consent as fundamentally different from other consents that have been previously reviewed, since the cell line was already derived and donors were being asked to allow use of the line in NIH-funded research. The Working Group noted that in

past discussions re-consent was viewed as a way not to address past actions but to obtain consent for future actions and an “opportunity to firm up ethical foundations” of a researcher’s work. With this in mind, the Working Group was concerned that it was not known how the donors interpreted the open-ended withdrawal language in the second consent, and discussed what it would mean if the couple did withdraw their consent, e.g., would the line be removed from the NIH Registry? The Working Group also discussed whether it would be feasible to remove a cell line from NIH-funded laboratories, as well as any derivatives and data.

Many members of the Working Group thought that the claims of scientific progress and impact could make it hard for the embryo donors to decline to sign the consent form. However, members also felt it would be unfortunate to deny embryo donors the choice to contribute to scientific research due to the inadequacies in the consent form. Minor concerns were also raised about the perceived sparse language in the consent regarding the risk of loss of confidentiality.

At that point, the unanimous view of the Working Group was that the cell line should remain disapproved, due to the possible pressure placed on donors from the exaggerated claims of scientific progress and impact, and confusing language related to the donors’ ability to withdraw consent. Members also remained concerned that consent obtained *after* stem cell derivation could not redress concerns about the adequacy of information provided to individuals deciding about frozen embryo disposition, *before* stem cell derivation, since at the time of the second consent options other than stem cell derivation (reproductive donation, disposal, other research) were no longer available to them.

NIH staff also had questions about what could be done if consent was withdrawn for a cell line listed on the NIH Registry. Therefore when contacted by CSCI regarding the adequacy of this second consent, NIH communicated the concern that the current consent implied that the donors could withdraw their lines from the NIH Registry at any time and it might be better if the embryo donors confirmed their willingness to have the cell line used in research, knowing that they cannot withdraw the line once it is distributed.

The embryo donors signed a third consent document in June 2014, in which they agreed to allow the use of CSC14 by NIH-funded researchers, and were informed that the cell line could not be withdrawn from research once it is distributed to NIH-funded laboratories. This third consent did not include the claims of scientific importance that were in the second consent.

The ACD Working Group met by teleconference in June 2014 to consider this third consent and had a split vote (3-3) on a motion to suggest that the ACD recommend continued disapproval of the line. Members in support of approval of the line were willing to accept the third consent, together with earlier consents and materials, as adequate evidence of an informed decision by the couple to have the cell line used in NIH-funded research. Those members felt that while the

consent process was flawed in several respects, they did not want to undermine the donor couples' desire to contribute to stem cell science, which they had made clear through their willingness to sign three consents.

Those in favor of continued disapproval were concerned that the second and third consents could not remedy the original shortcomings of the first consent, and they could not have confidence that the donors had an accurate understanding of their choice at the time of embryo destruction. They were also concerned that approval of the cell line now would suggest that other flawed consents could be remedied by re-contacting donors and obtaining revised consent.

One Working Group member who could not participate in the teleconference reviewed the material and the meeting minutes, and voted to support approval of the line, commenting that the third consent was satisfactory and that it would be a disservice to the couple not to follow through at this point. In total, 4 out of the 7 voting members suggest that the ACD recommend approval of the cell line CSC14 for use in NIH-funded research under the Section IIB criteria of the NIH Guidelines for Human Stem Cell Research.

#### *Attachments*

*A: Report to be Presented to ACD on September 5, 2014*

*B: Report Presented to ACD on December 7, 2012*

*C: Report Presented to ACD on June 15, 2012*

## **Attachment A**

### **Report to ACD for September 5, 2014**

#### 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 line CSC14 from California Stem Cell Inc. (CSCI), now NeoStem, be approved for use in NIH-funded research under the Section IIB criteria of the NIH Guidelines for Human Stem Cell Research.

#### Summaries of Discussions (August, October, and November 2013; June 2014)

##### *August 2013 Discussion*

The Working Group continued its discussion of the submission from California Stem Cell, Inc. (CSCI), requesting approval of one cell line to be listed on the NIH Registry. The embryo was donated for research in 2006 by a couple who no longer wished to keep the embryo in a cryopreserved state.

The discussion opened with a brief summary of the issues that led to the Working Group's negative finding at the November 2012 meeting, discussed in the "Report to the ACD Presented December 7, 2012."

In December 2012, the ACD accepted the Working Group's findings and recommended that submission 2012-ACD-004 remain disapproved. Following the December 2012 ACD meeting, CSCI wrote to the NIH Director, disputing the recommendation. A teleconference with NIH and CSCI staff in February 2013 led to CSCI's July 9, 2013 submission of additional materials, including a new consent by the original donors to have the cell line listed on the NIH Registry. A number of additional materials were submitted, but those were not from the time of embryo donation and not relevant to the original concerns. On August 13, 2013, NIH staff sent questions to CSCI in an attempt to clarify outstanding questions: the roles of the investigators at the University of California, Irvine; whether there was institutional review by the University of California, Irvine of the protocol; and whether the protocol that was submitted is definitely the protocol that was in place in 2006, when the embryo was donated.

At the time of this meeting, Working Group meeting, NIH was still waiting for answers to the August 13 questions. It was decided to proceed with the meeting, to briefly review the history of this submission, discuss the new consent document, and identify any additional questions. A more formal review and vote is planned for the next Working Group meeting.

The discussion centered on the re-consent document submitted to NIH on July 9, 2013. The main discussion points included the impact of the re-consent and whether it addresses the concerns expressed by the Working Group in the previous reviews. NIH staff reminded the Working Group of its past discussion of the potential value of re-consent in the context of the disapproved submissions from the Reproductive Genetics Institute in Chicago. In that case, the Working Group agreed that the purpose of the re-consent would not be to address past actions, but to explain the current status of the research and obtain consent for use in NIH-funded research.

In the current case, concerns remain about whether the embryo donors were given all the information needed to make a well-informed decision about embryo donation in 2006. However, the Working Group noted that now that the stem cell line exists and there is potential for therapeutic use, the donors have indicated that they are willing to have the cell line listed on the NIH Registry. The question posed in the second consent--to agree with the use of an existing cell line in NIH-funded research or not—is quite different from the first consent. Working Group members noted that the very fact that the cell line has been successfully derived and is in use could have affected the donors' re-consent. One Working Group member suggested that perhaps the re-consent should be weighted differently, since the donors no longer have the full range of options.

Several Working Group members pointed out that the re-consent makes it clear that the donors want research with this cell line to go forward. However, the members have concerns about approving a less than rigorous consent process. Working Group members agreed that a better resolution would be if the donors could affirm that in 2006 they knew that they could withdraw their consent, and at no time wished to withdraw their embryo from the research.

The Working Group members agreed that their deliberations will have implications in terms of precedent. NIH staff reminded the attendees that this submission, as with all submissions referred to the Working Group so far, is to be reviewed under the IIB criteria of the NIH Guidelines for Human Stem Cell Research (Guidelines), which are more general than the IIA criteria. The submissions referred to the Working Group for review under Section IIB of the Guidelines focus on the generation of human embryonic stem cells before the Guidelines were issued in 2009. Previous to the effective date, consents varied in their content, and by present standards, some may appear to be somewhat ambiguous. However, even considering the time frame, the Working Group believes that this was not a well-designed consent process. Approval of this submission could invite entities with less than rigorous original consent processes to re-contact the donors once the lines have been derived and show promise, and ask the donors for their consent to have the lines placed on the NIH Registry. Such action could downgrade the importance of the initial consent process. In concluding the discussion on this point, the

Working Group members stated the importance of maintaining high standards, so approved submissions are above reproach.

Several additional points were raised about the re-consent. First, the wording of the document is not entirely objective, citing the “huge promise” of the research plan if the couple allows the stem cells to continue to be available for use. Second, the document does not describe clearly what it means to have the cell line listed on the NIH Registry in terms of practical or ethical concerns the donor couple might have. Third, the re-consent form states that CSCI will use the cells to study Spinal Muscular Atrophy and Amyotrophic Lateral Sclerosis; this may have suggested to the donors that the cells can be used only for those areas of research. However, several places in the consent document state more broadly that the cells will be used for NIH-funded research. NIH staff reminded the Working Group that while they may point out possibly restrictive language, NIH makes the determination as to whether a restriction in use should be applied to NIH-funded research.

In summary, the Working Group members agreed that while this re-consent could not address the deficiencies of the original consent process, it can inform us of the donors’ mindset about the present choice at hand: the donors have given their permission for the cell line to be placed on the NIH Registry. NIH staff will inform the Working Group members when additional information from CSCI is received. At that point a follow-on discussion will be scheduled to revisit the members’ positions on the issues and determine whether there is sufficient information to arrive at a formal vote on this submission.

#### *October 2013 Discussion*

The discussion opened with a reminder by NIH staff that the Working Group is not required to reach consensus on any submission. Rather, the goal is to review submissions according to the Section IIB criteria of the NIH Guidelines for Human Stem Cell Research (Guidelines) and to convey all major discussion points to the ACD; the findings should reflect the thoughts of all members. The specific goal of the meeting was to develop findings about the current submission from California Stem Cell, Inc. (CSCI).

The members briefly summarized the history of the CSCI submission, which requests the approval of one cell line to be listed on the NIH Registry. The embryo was donated for research in 2006 by a couple who no longer wished to keep the embryo in a cryopreserved state. The “Report to the ACD Presented December 7, 2012” provided a detailed background of the history of this submission, including the Working Group’s reasons for arriving at a negative finding for the original submission. At the August 2013 meeting, the Working Group focused on a second consent (“re-consent”) document submitted by CSCI in July 2013. An accompanying letter from CSCI explained that the purpose of this new consent was not to address past issues, but to affirm

the donors' willingness to have the cell line used in NIH funded research. Although the August 2013 discussion provided an opportunity for the Working Group members to share and clarify their views on the re-consent process, they did not attempt at that time to finalize their findings. This discussion centered on CSCI's approach to obtaining consent after the derivation of the stem cells. Concerns expressed by the Working Group members included: a) potentially exaggerated claims of scientific progress and impact in the "Purpose" section of the consent form; b) perceived confusing language in the "Voluntary" section of the form; and, c) perceived sparse language about potential re-identification in the "Risks" section of that document.

The Working Group debated the utility and validity of the re-consent obtained after the embryo had been destroyed, stem cell lines had been derived, and research efforts were underway. The Working Group concluded that this context differed significantly from the context of the original consent, which was obtained before destruction of the embryo, and that this might unduly influence the donor to agree to future research use of the stem cell lines.

On one side, although the Working Group found that the second consent form was not ideal and includes overstatements in terms of scientific promise (see quotes below), it was IRB-approved. One member expressed the view that because the donors are now aware that a stem cell line has been successfully derived, they have made an informed decision to allow the stem cell line to be listed on the NIH Registry. The Working Group assumed that the donor couple had the opportunity to read and consider the second consent form in private. Several members added that it is important to consider the wishes of the donors, although the process must still meet the Section IIB criteria.

Based on the points mentioned above, several members of the Working Group presented their initial position that the weight of the evidence suggests that the donors are supportive of the stem cell derivation and that the donors wish to have the opportunity to contribute to scientific research. Thus, they felt that it would be unfortunate to deny the donors this opportunity if they genuinely want to contribute to scientific research.

On the other side, some members of the Working Group felt that the wording of the second consent form could have placed undue pressure on the donors. Specifically, the "Purpose" section of the form states that the research programs "...have been developed over the past six years at a cost of millions of dollars and show huge promise for addressing the unmet medical needs of hundreds of thousands of Americans." Several members thought this was overstated and would make it hard to decline to sign the consent.

A second major concern of the Working Group focused on the "Voluntary" section of the consent document, which includes the following statement: "You may decide not to participate or you may leave the study at any time." A primary reason for the Working Group's arrival at a

negative finding in consideration of the original consent to donate the embryo was the uncertainty of the donors' understanding of their ability to withdraw their consent for the donation of the embryo for stem cell research. Now that the embryo has been destroyed and stem cells have been derived, it is not clear how the donors could "leave the study at any time." This section of the consent form could have been standard or boilerplate consent language that was not carefully considered by the submitter. Still, if the donors were to learn of a CSCI cell line study which they oppose, the Working Group speculated, they might think they have the right to have the cells withdrawn from that work, or even the NIH Registry. The Working Group further wondered if, after a cell line has been listed on the Registry and cells have been distributed to various labs, whether it would be possible to comply with donors' wishes for a line to be withdrawn and ongoing research with cell lines or derivatives suspended. It was noted that CSCI does have at least one Material Transfer Agreement (MTA) with the University of California, Irvine for transfer of CSCI derived cell lines, and MTAs are a standard business practice, so that it may be feasible for CSCI to identify labs to which it sends cell lines or derivatives.

Ultimately, the Working Group members agreed that what really matters is what the donor couple understood by the withdrawal statement, and the Working Group did not feel confident that it could draw conclusions about the donor's understanding from the information provided. The Working Group members agreed, however, that to suggest that CSCI contact the donors to clarify their understanding could border on badgering the donors.

A third, and relatively minor concern of the Working Group, related to the "Risks" section of the consent form, which includes only a single statement: "The only risk is the loss of confidentiality." This sparse text does not actually explain the effects of the possible loss of confidentiality and probability of identification of the donors through current technology. NIH staff informed the members that more sophisticated discussions regarding potential identifiability of cell lines have mostly been seen in recently written consent documents, and was not required in consents that were previously accepted as meeting the requirements of the Guidelines. Considering this, the Working Group agreed that this issue by itself is not a major shortcoming of the submission.

After considering all of the concerns mentioned above, the Working Group voted unanimously to present a negative finding to the ACD for this cell line. This recommendation is based primarily on perceived consent form deficiencies, including exaggerated claims of scientific progress and impact and confusing language related to the donors' ability to withdraw consent.

#### *November 2013 Discussion*

NIH staff opened the session by stating that the purpose of the meeting was not to revisit the findings from the prior Working Group's meeting for the California Stem Cell, Inc. (CSCI)

submission. Rather, the members were asked at this meeting to consider their findings on the CSCI submission in the context of how the withdrawal provisions in previously reviewed submissions have been analyzed. To facilitate the discussion, a document prepared by NIH staff, entitled “Prior Decisions regarding Withdrawal of Consent” was sent to the Working Group in advance of the meeting. The document summarized withdrawal language in previously approved and disapproved submissions. Within that document, NIH staff had organized previously reviewed submissions into six categories, ranging from: a) consents with language sufficiently clear and complete to meet Section IIA requirements; to b) submissions with complete absence of language regarding withdrawal of consent. Between these two extremes, submissions reviewed under the Section IIB criteria have contained a variety of types of withdrawal of consent language, including inaccurate, inconsistent, or boilerplate “you may withdraw at any time” wording, sometimes with accompanying assurances or other documentation regarding information about withdrawal that was conveyed to embryo donors in the consent process.

The discussion began with a reminder that the negative finding for the CSCI submission was based in part on perceived deficiencies in both consent forms regarding withdrawal language, namely: 1) the question of whether donors understood that they had a window during which they could withdraw their original consent for donation of the embryo, and 2) how to consider the open-ended withdrawal language in the second consent. After Working Group reviewed the “Prior Decisions regarding Withdrawal of Consent” document, they agreed that the CSCI issues are unique. The second CSCI consent is the first time that the Working Group has seen a submitter go back to the embryo donors and specifically ask for their consent to allow a cell line to be listed on the NIH Registry. No other submission is directly analogous.<sup>1</sup>

The Working Group reiterated its concerns with the open-ended withdrawal language in the second consent. The Working Group noted that the second CSCI consent cannot provide the couple with the opportunity to withdrawal consent to donate embryos, because the embryo has already been destroyed in the derivation of the stem cells. Therefore, the withdrawal language in the second consent could only apply to the stem cells derived from the embryo. However, the second consent does not discuss what would happen if the donor withdraws that consent. For example, the consent form does not discuss whether donors could have the line deleted from the NIH Human Embryonic Stem Cell Registry, or the cell line retrieved from laboratories. While

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<sup>1</sup> One somewhat similar case was a submission from Cellartis, in which the embryo donors signed a series of four consents over several years, allowing for continued research using the lines. Cellartis had stated that donors obtained information that they had an opportunity to withdraw consent until donor identities were delinked. (It was not clear whether Cellartis was referring to withdrawal of cell lines or embryos, although there was a documented process of delinking donor identifiers and cell lines years after derivation.)

NIH could remove the listing of a cell line from the NIH Registry website, withdrawing the cell line (and possibly derivative products or data) after distribution to various labs was not considered feasible. These complexities raise the question of whether the couple truly understood the nuances of the options offered through the second consent process. Further, it appears that the couple was offered an option to withdraw in the second consent that is not possible to honor.

As the discussion drew to a close, all members agreed that the CSCI findings did not conflict with any past findings. The members also agreed that their discussion of their findings on the CSCI submission relative to other submissions was worthwhile.

### *June 2014 Discussion*

The company has now obtained the donors' signatures on a third consent document, which attempts to address the language in the second consent regarding withdrawal and the extraordinary research promise. Some Working Group members expressed concern regarding the precedents that might be set if deficiencies in an initial consent could be addressed with multiple re-consents, allowing applicants to re-consent donors if and when their original consenting practices were flawed. Allowing re-consents could lead to pressuring the donors or introducing distress in a situation the donors thought was behind them. Another concern involved the implication (despite a consistent message from the Working Group), that NIH would reconsider its decision about the line if the submitter provided documentation of an improved process.

Regarding the issue of precedence, NIH staff noted a scenario they had encountered during administrative review, in which the donor signed a second consent several years after making the initial donation (both consents were provided to NIH at the same time). In this case, both documents were fairly consistent, but the second consent provided additional information, e.g., more was known about the therapeutic potential and commercial aspects of the line. NIH approved that cell line. NIH staff also reminded the Working Group about the Cellartis submission reviewed by the Working Group, where the donors were consented four times. However, in this case, Swedish law required regular re-consent of donors.

Working Group members noted that the latest consent document adequately addresses the questions about the current right to withdraw consent for use of the cell line and omitted language about the promise of the research that could be conducted with the cell line. However, the members noted that the repeated re-consents do not address the concerns about the initial consenting process. One member questioned the point at which re-consenting the donors could be considered harassment. The emotional context in which the donors were asked to sign the consents is not known, and unlike the Cellartis case, these donors would not expect to be contacted regularly for re-consent. The company has developed a consent document that addresses the misleading language from the second consent, but in the time it took to do so, it

might have repeatedly contacted a couple who wanted to place this part of their lives behind them. NIH staff noted that another view could be that the donors were willing to sign the two later consents because of their desire to donate their embryos, but the donors' intent has been undermined by poorly written consents.

Working Group members were sensitive to the competing goals of setting a high ethical standard for approved stem cell lines on the one hand, and not undermining the donors' perhaps heart-felt desire to contribute to stem cell research on the other. Some members were willing to accept the third consent, along with the other two consent documents and assurances, as adequate evidence of an informed decision by the couple to have the cell line derived from their embryo used in NIH-funded research. Some Working Group members felt that while the consent process was flawed in several respects, the couple's informed approval of the listing should be honored. Other Working Group members remained concerned that because the original consent was inadequate, and they cannot have confidence that the donors had an accurate understanding of their choices at the time of embryo destruction, the re-consent process does not remedy the original shortcomings of this application.

The Working Group also considered the implications of continued disapproval of the cell line. NIH staff reminded the Working Group that disapproved lines and their derivatives are not available to investigators to use in NIH-funded research, although the lines and derivatives would remain useful for non-NIH funded research.

A motion to continue suggesting that the ACD recommend that the line remain disapproved was made. Three of the Working Group members voted for the motion, while the other three voted against it. An additional Working Group member who was unable to attend the meeting voted against the motion.<sup>2</sup> This discussion and vote will be presented to the ACD at a future ACD meeting.

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<sup>2</sup> This member noted that the couple has consistently agreed to have the line listed on the NIH Registry. The member believes that the couple's approval through three consent processes should be honored and that it would be a disservice to the couple not to follow through at this point.

## **Attachment B**

### **Report to the ACD Presented December 7, 2012**

#### 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 GENE A submissions (2012-ACD-002, -003), should be applied to the CSCI resubmission. However, the overall GENE A 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 C**

### **Report to the ACD Presented June 15, 2012**

#### 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 form 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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