Report from ACD Working Group for Human Embryonic Stem Cell (hESC) Eligibility Review

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Advisory Committee to the Director
September 5, 2014

Overview

- Review of NIH Guidelines for Human Stem Cell Research criteria
- Summary of previous discussions and recommendations regarding cell line CSC14 from NeoStem, New York (formerly California Stem Cell Inc. (CSCI))
  - CSC14 is currently disapproved for use in NIH-funded research
- Working Group analysis and finding for use of CSC14 cell line in NIH-funded research based on two additional consent documents
- ACD consideration of Working Group finding regarding CSC14

Advisory Committee to the Director, NIH, Working Group for hESC Eligibility Review

- Jeffrey Botkin, M.D., M.P.H., University of Utah School of Medicine
- Dena Davis, J.D., Ph.D., Lehigh University
- David Grainger, M.D., M.P.H., University of Kansas School of Medicine-Wichita and Center for Reproductive Medicine, Wichita
- Cato Laurencin, M.D., Ph.D., The University of Connecticut
- Bernard Lo, M.D., The Greenwall Foundation and University of California, San Francisco
- Anne Drapkin Lyerly, M.D., MA., University of North Carolina Chapel Hill
- Terry Magnuson, Ph.D., University of North Carolina Chapel Hill
- John O'Shea, M.D., National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH

NIH Guidelines for Human Stem Cell Research

- Effective July 7, 2009

- All hESCs must be:
  - Derived from embryos created by IVF for reproductive purposes and no longer needed for that purpose
  - Donated by individual(s) who sought reproductive treatment and who gave voluntary written consent for human embryos to be used for research purposes

- ACD Working Group review for lines derived before 7/7/09: "Section IIB" criteria (flexible)

- NIH Director makes final decisions

Section IIB of NIH Guidelines for Human Stem Cell Research

- ACD Working Group will take into account:
  - Principles in Section IIA
  - 45 CFR 46 Subpart A (Common Rule)
  - Points to Consider: During informed consent process, whether donor(s) were:
    - Informed of other available options pertaining to use of embryos
    - Offered any inducements for the donation
    - Informed about what would happen to the embryos

The submission presented today is being reviewed under IIB

Resubmission for ACD Consideration

- Resubmission # 2012-ACD-004 from NeoStem, New York
  - formerly California Stem Cell Inc. (CSCI)
- Single hESC line CSC14, derived from frozen embryo donated in 2006 at separate California IVF clinic
- This is the third ACD discussion of this line under Section IIB

Prior ACD Discussions

June 2012	Working Group (WG) concerned about - lack of withdrawal language in consent - possibly exculpatory language - retrospective IRB review - CSCI could not verify that undated procedural document (with withdrawal information) was in effect at time of donation.	- ACD accepted WG findings; recommended disapproval - NIH disapproved cell line
Dec 2012	- CSCI submitted attestation from embryologist that procedural document was effect at time of donation and donors were informed of their right to withdraw and who to contact. - WG remained uncertain that rights of donors were protected adequately.	- ACD accepted WG findings and recommended that line remain disapproved.

Today: Discuss Two Consents Signed by Embryo Donors

- Second consent, signed by embryo donors, submitted to NIH in July 2013

- Heading: “Consent to Affirm Your Willingness to Allow the Use of CSC14, an Embryonic Stem Cell Line Derived from one of Your Embryos, in NIH Funded Research, and to Affirm Your Willingness to Allow the listing of CSC14 on the NIH Registry”

- CSCI stated in letter to NIH that purpose was not intended to address past issues or “fix” the old consent, but to inform donors about the current state of research with the cell line and affirm the donors’ willingness to allow use of the line in NIH-funded research.

Key Statements in Second Consent

- Describes CSCI plan to use the cell line to proceed with Spinal Muscular Atrophy and Amyotrophic Lateral Sclerosis programs.
  - "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 only risk is the loss of confidentiality."

- "Your participation in allowing the CSC14 to be included on the NIH registry is voluntary. You may decide not to participate or you may leave the study at any time."

Working Group Analysis of Second Consent

- This consent is fundamentally different from most others reviewed since cell line has been derived and donors are being asked to allow use of line in NIH-funded research.

- Working Group concerned that it is not known how donors interpreted the open-ended withdrawal language.
  - What would it mean if couple said they withdrew this consent?
    - Remove line from NIH Registry?
    - Remove the line from NIH-funded laboratories? Also remove any derivatives and data? Is this feasible?

- Working Group considered its views regarding withdrawal information in the two consents compared to past assessments, and concluded that this submission raised unique issues.

Working Group Analysis of 2nd Consent (cont.)

- Many Working Group members felt that claims of scientific progress and impact could make it hard for the embryo donors to decline to sign the consent form.
- However, the Working Group was also concerned about denying embryo donors the choice to contribute to scientific research due to inadequacies in the consent form.
- The Working Group voted unanimously to present a negative finding to the ACD on cell line CSC14.
- NIH was contacted by CSCI on status of review; NIH communicated concern about implication that donors could withdraw line from NIH-funded research and laboratories.

Third Consent

- Third consent, signed by embryo donors, submitted to NIH in June 2014

- Heading: “Consent to Affirm Your Willingness to Allow the Use of CSC14, an Embryonic Stem Cell Line Derived from one of Your Embryos, in NIH Funded Research, with the Understanding that the Cell Line Cannot be Withdrawn Once it is Distributed to NIH-funded Laboratories, and to Affirm Your Willingness to Allow the listing of CSC14 on the NIH Registry”

- Does not include claims of scientific importance

- “Your participation in allowing the CSC14 to be included on the NIH registry is voluntary. If you decide to so do, your consent will make the stem cells derived from your previously donated embryo available to researchers outside of California Stem Cell, Inc., meaning that they will be widely distributed and used in various projects for many years. Additionally, your consent will mean that it will no longer be possible to withdraw consent for the use of these cells for research or for the treatment of others.”

Working Group Analysis of Third Consent

- Some members willing to accept third consent, together with prior materials, as evidence of an informed decision by the couple.
  - Those members felt that consent process was flawed in several respects, although they did not want to undermine the donor couple's desire to contribute to stem cell science, which had now been reaffirmed through the signing of multiple consents.

- Some members were concerned that 2nd and 3rd consents could not remedy shortcomings of 1st consent.
  - Those members were concerned that approval of cell line would suggest that other flawed consents could be remedied by reconsenting.

- Final tally: 4-3 in favor of suggesting that ACD recommend approval of cell line CSC14 for use in NIH-funded research.

NIH Human Embryonic Stem Cell Registry
as of August 28, 2014

- Approved: 283 lines
  - 57 lines approved after ACD review (Section IIB)
  - 226 lines approved after NIH administrative review (Section IIA)

- Disapproved: 66 lines
  - All lines disapproved after ACD review (Section IIB)
  - Includes lines referred to ACD after NIH staff determined did not meet administrative review criteria (Section IIA)

Prior WG Discussion on Re-consent

- Re-consent was discussed at the June 2010 ACD meeting regarding the submissions from Reproductive Genetics Institute, which were disapproved due in part to exculpatory language.

- Working Group thought purpose of re-consent was not to address past actions, but obtain consent for future actions. Re-consent could inform donors of current status of the research and request consent to make cells widely available for federally funded research.

Slides on Prior ACD Discussions on CSC14 (June and December 2012)

ACD Discussion June 2012

- No information in the original consent form regarding withdrawal; company stated that there was no evidence that donors were informed.
- Undated protocol and process documents discuss withdrawal procedures, but company presented no evidence that either document was in effect at the time of embryo donation.

ACD Discussion June 2012

- Consent contained apparent 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 and authorizing the use of your embryo(s) for the research described in the PURPOSE/PROCEDURES section of this agreement."

- While no such law exists, such language seen by ACD as having the potential to cause confusion about the ability to withdraw consent for donation.

ACD Discussion June 2012

- IRB approval of protocol occurred three years after embryo donation
  - Company reported that it was not required to obtain IRB review since no HHS funds or federal assurance with the HHS Office for Human Research Protections.
  - However, ACD concluded that the lack of impartial, independent review, given additional concerns, presented an ethical concern, since that is an important safeguard for protecting the rights of donors.
- Based on these multiple concerns, ACD recommended disapproval. The NIH Director disapproved the line for listing on the NIH Registry.

ACD Discussion December 2012

- Considered declaration from IVF clinic embryologist
  - States that staff were trained using the protocol and consent procedure documents, both of which contain information on the right to withdraw, as well as contact information.
  - States that those procedures were followed for the donation of the embryo from which CSC14 was derived.
  - States that information was provided to the embryo donors regarding:
    - their right to withdraw consent up until the time derivation occurred
    - who to contact in order to withdraw consent.

ACD Discussion December 2012

- Company addressed apparent exculpatory language
  - Suggested any potentially adverse effect of the language was remedied by withdrawal information conveyed verbally to embryo donors.

- Company explained why it obtained retrospective IRB review
  - CSCI noted that IRB review was not required for embryo donation process by NIH Guidelines.
  - CSCI stated that retrospective IRB review was an appropriate retrospective evaluation, similar to the ACD Working Group review.

ACD Discussion December 2012

- ACD continued to find significant weaknesses in consent process:
  - The ACD felt that information conveyed orally was not sufficient to eliminate possible confusion about the donor's right to withdraw the embryo donation, based on:
    - The absence of written information for donors on who to contact regarding withdrawal and how to contact them.
    - The oral information provided (per the declaration) was inconsistent with the written consent provided to donors.
    - Apparent exculpatory language in the consent form.
    - The undated protocol did not indicate exactly what information regarding withdrawal would be provided to the donors.

ACD Discussion December 2012

- The ACD recognized that IRB review was not strictly required, but opined that the relevant question is whether ethical principles of 45 CFR 46 were followed.

- CSCI argued that approach used in considering GENEA withdrawal information (inconsistency between information in consent form and actual policy, conveyed orally) should be applied. However, ACD, in GENEA, considered the discrepancy between the written consent and what was told to embryo donors regarding withdrawal to be minor.

ACD Discussion December 2012

- Given the problems with the consent process, the ACD was not certain that the rights of donors were protected adequately.

- ACD recommended that the Director not change the decision to disapprove this line for listing on the NIH Registry.