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

Jeffrey C. Murray, M.D.
Member, ACD Working Group for hESC Eligibility Review and ACD

Advisory Committee to the Director
December 7, 2012

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
- Pamela Davis, M.D., Ph.D., Case Western Reserve University
- David Grainger, M.D., M.P.H., University of Kansas School of Medicine-Wichita and Center for Reproductive Medicine, Wichita
- 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
- Jeffrey Murray, M.D., University of Iowa Children's Hospital
- 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

Types of Review

- NIH administrative review under "Section IIA": specific requirements for donation process
  - required for current/future US donations
  - optional review path for older lines or foreign lines
- ACD Working Group review for older lines under "Section IIB": more flexible
- ACD Working Group review for current/future lines from outside of U.S. under "Section IIC": equivalency
- NIH Director makes final decisions on eligibility of all hESC lines for use by NIH-funded researchers

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 was reviewed under IIB

NIH Human Embryonic Stem Cell Registry

- Approved: 186 lines
  - 57 lines approved after ACD review (Section IIB)
  - 129 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)

Resubmission for ACD Consideration

- Resubmission # 2012-ACD-004 from California Stem Cell Inc., Irvine, CA
- Single hESC line CSC14, derived from frozen embryo donated in 2006 at separate California IVF clinic
- At the June 2012 meeting, the ACD accepted the negative finding of the Working Group and recommended that the line not be accepted for the NIH registry due to failure to meet the criteria under IIB
- Dr. Collins disapproved line per ACD recommendation

Concerns from First Review

- No information in the consent 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.

- Consent contained exculpatory language: donors give up rights under Federal law to control use of cell lines.
  - While no such law exists, such language had the potential to cause confusion about the ability to withdraw consent for donation.

Concerns from First Review

- IRB approval occurred 3 years after embryo donation
  - Company not required to obtain IRB review since no HHS funds or federal assurance with the HHS Office for Human Research Protections.
  - However, lack of impartial review presents an ethical concern, since that is an important safeguard for protecting the rights of donors.

- Based on these multiple concerns, Working Group voted unanimously to present a negative finding to ACD. The ACD accepted the finding and recommended disapproval. The NIH Director disapproved the line for listing on the registry.

California Stem Cell Inc. Resubmission Contents

- Information provided previously:
  - Embryo donation consent
  - Cryopreservation agreement
  - Embryo disposition form
  - Protocol and consent procedures documents (undated)
  - IRB approval (3 years after embryo donation)

- New:
  - Letter from company about ACD review
  - Declaration from IVF clinic embryologist
    - Information about withdrawal provided orally
    - Attested that the undated protocol and consent procedures documents were used at time of embryo donation

Resubmission/Response from California Stem Cell

- Declaration from Mr. La, IVF clinic embryologist
  - States that staff were trained using the protocol and consent procedures documents.
  - States that those procedures were followed for the donation of the embryo from which CSC14 was derived.
  - States that information was provided orally to the embryo donors regarding:
    - their right to withdraw consent up until the time derivation occurred
    - who to contact in order to withdraw consent.

Resubmission/Response from California Stem Cell

- Company explained prospective IRB review
  - IRB review was not required for embryo donation process by NIH Guidelines.
  - Retrospective IRB review was an appropriate retrospective evaluation, similar to the ACD Working Group review.
- Company addressed exculpatory language
  - Any potentially adverse effect of the language was remedied by withdrawal information conveyed verbally to embryo donors.

Second Consideration by Working Group

- Working Group considered the embryologist declaration and letter from company, but concerns remain about consent process:
  - Withdrawal information was only provided orally
    - Contact information to enable donors to notify California Stem Cell about withdrawal was only provided orally.
    - The oral information provided (per the declaration) was inconsistent with the written consent provided to donors.
  - Undated protocol and process documents do not indicate exactly what information would be provided to donors regarding withdrawal or who would provide this information.

Second Consideration by Working Group

- Working Group is not convinced that information conveyed orally remedied contradictory written information. Consent has no information on withdrawal, and exculpatory language could further confuse donors regarding right to withdraw.

- As noted before, IRB review was not strictly required, but relevant question is whether ethical standards of 45 CFR 46 were followed.

- California Stem Cell argues that same approach used in considering GENEA withdrawal information should be applied here. However, GENEA's submission was generally well conceived and constructed, and the discrepancy between the written consent and what was told to embryo donors regarding withdrawal was minor.

Working Group Finding

- Significant weaknesses in consent process:
  - The potential for confusion about the donor's right to withdraw, resulting from:
    - Exculpatory language in the consent
    - Absence of written information on who to contact (and how) regarding withdrawal
  - Working Group uncertain whether rights of donors were protected adequately.

- The Working Group voted unanimously to present a negative finding to the ACD.

Proposed Actions for ACD

- Recommend to NIH Director that the initial decision to disapprove line CSC14 from California Stem Cell Inc. (new submission 2012-ACD-004) for use in NIH-supported research remain unchanged, as the new information submitted does not adequately address the deficiencies in the consent process previously identified.