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

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

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- Dena Davis, J.D., Ph.D., Cleveland-Marshall College of Law
- Pamela Davis, M.D., Ph.D., Case Western Reserve University
- David Grainger, M.D., M.P.H., University of Kansas School of Medicine-Wichita; Center for Reproductive Medicine
- Bernard Lo, M.D., 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

Findings For ACD Consideration

Working Group findings on 12 lines from 3 institutions:

- Hadassah Hebrew University Medical Center, Jerusalem, Israel 3 lines
- Reprogenetics, Livingston, NJ, 4 separate submissions with 6 lines total
- VistaGen Therapeutics, South San Francisco, CA, 3 lines

Section IIB of NIH Guidelines for Human Stem Cell Research

For embryos donated before July 7, 2009 (if Section IIA is not met):

- Embryos were created for reproductive purposes by IVF and no longer need for that purpose
- Donated by donors who gave voluntary written consent for the embryos to be used for research purposes

ACD Working Group also 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

All submissions presented today reviewed under IIB

Hadassah Hebrew University Medical Center Submission

- 3 lines from embryos donated in 2006-2008 after minimum of 5 years cryopreservation

- Other options were to keep embryos frozen for up to 10 years or destroy (donation to another couple is not an option in Israel)

WG Discussion of Hadassah Hebrew University Submission

- Working Group found donor consent form to be generally clear and complete.
- Working Group's questions to submitter about confidentiality provisions for donor's health information were answered satisfactorily.
- The Working Group voted unanimously to suggest that the ACD recommend approval of these lines for use in NIH-funded research.

Reprogenetics Submission #1

- 3 lines, RNJ18-20, donated in 2009 from couple at private IVF clinic under consent to donate clinically unusable embryos.
- Embryos tested positive by preimplantation genetic testing for a mutation causing congenital nephrotic syndrome.
- Embryo donation consent in effect for one year after signature; embryos donated over two IVF cycles. For second cycle, oral confirmation of continued consent to donate embryos obtained.

WG Discussion
Reprogenetics Submission #1

- Consent form is clear overall; benefits section adequate although not particularly well-stated

- The Working Group discussed whether use of single consent form for both treatment cycles was adequate. Working Group concluded this is not a major issue since the embryos were not clinically usable.

- The Working Group voted unanimously to suggest that the ACD recommend approval of RNJ18-20 for use in NIH-funded research.

Reprogenetics Submission #2

- 1 line, RNJ7, from nonviable embryo donated in 2008 by IVF patients at hospital at which researchers previously worked and had continued affiliations.

- A reconsent document intended to address potential financial interests of researchers and remove limitations on research use was sent to embryo donors; donors did not return the form.

- Working Group initially voted 4-4 to present a negative finding to the ACD; those voting for a negative finding believed the lack of reconsent called into question whether original consent remained valid.

Reprogenetics Submission #2

- Discussion reopened when it became apparent that submitter had provided an incorrect version of the first embryo donation consent.
  - The actual version used was from 2002, so the IRB approval of consent form would have been expired when used in 2008.
  - Also, a different modified consent form approved by the IRB in 2004 was not put into use, apparently due to an oversight by the IVF clinic.
  - Thus, the embryo donation consent form used did not have current IRB approval.

WG Discussion
Reprogenetics Submission #2

- The Working Group recalled a previous ACD recommendation to disapprove a line derived from an embryo donated during a lapse in IRB approval.

- The Working Group voted unanimously to suggest that the ACD not recommend approval of RNJ7, due to the use of an expired consent form and concerns over the failure of the donors to respond to reconsent efforts.

Reprogenetics Submissions #3 and 4

- 2 lines (RNJ11, 12) from nonviable embryos donated in 2008 by IVF patients at hospital at which researchers previously worked and had continued affiliations.

- Reconsent documents signed in 2009 by embryo donors; intended to address potential financial interests of researchers and remove limitations on research use.

WG Discussion
Reprogenetics Submissions #3 and 4

- Working Group voted in the majority (6-3) to suggest that the ACD not recommend approval of RNJ11 and12, due to concerns that:
  1) reconsent form did not adequately disclose the financial interests of the researchers
  2) there was an inaccurate description regarding donor withdrawal of consent*
  3) it was not stated whether information that could identify the donors would be available to researchers*

* Relates to Section IIA criteria

VistaGen Therapeutics Submission

- 3 lines from cryopreserved embryos donated in 1999
- Consent is a three-sentence "Agreement for Disposal of Embryos (allowing research on embryos prior to disposal)"
- Consent does not specify stem cell research
- Researcher who conducted initial stages of derivation was a cofounder of the IVF clinic and an advisor to VistaGen. Derivation began at his university laboratory before shipment of cultures to VistaGen.

VistaGen Therapeutics Submission

- Consent does not mention potential commercial interests of deriving researcher or VistaGen
- VistaGen states that donors were informed orally that options for embryos no longer needed for treatment were 1) destruction, 2) donation to research, or 3) anonymous donation to another couple

WG Discussion of VistaGen Submission

- Working Group has serious concerns about the brevity and lack of clarity in the consent form. The consent form is extremely general and fails to state that embryos may be used for stem cell research. The form also does not mention potential commercial interests, despite the nature of VistaGen's research.

- The Working Group voted unanimously to suggest that the ACD not recommend approval of the lines in this submission due to the lack of sufficient evidence that donors were making an informed choice about use of the embryos for stem cell research.

Update on Guangzhou Submission

- On December 9, 2010, the ACD tabled consideration of submission from Guangzhou Medical College pending further consideration by Working Group.

- Issue: two translations of embryo donation consent used different words ("embryos" and "specimens") regarding additional donor consent for distribution to other institutions.

- Working Group is consulting with several native Chinese-speaking individuals, one of whom was an IVF patient.
  - Not all responses have been received and considered by Working Group, so presentation will occur at future ACD meeting.

Summary Working Group Findings

ACD should consider recommending to NIH Director that these lines be approved for use in NIH-supported research:

- Hadassah Hebrew University Medical Center, Jerusalem, Israel, 3 lines
- Reprogenetics #1, Livingston, NJ, 3 lines (RNJ18, 19, 20)

Summary Working Group Findings

ACD should consider recommending to NIH Director that these lines be disapproved for use in NIH-supported research:

- Reprogenetics #2: Livingston, NJ, 1 line (RNJ7)
- Reprogenetics #3, 4: Livingston, NJ, 2 lines (RNJ11, 12)
- VistaGen Therapeutics, South San Francisco, CA, 3 lines