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

- Jeffrey Botkin, M.D., M.P.H., University of Utah School of Medicine
- 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
- 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., Scientific Director, NIAMS
- Carlos Pavão, M.P.A., Education Development Center Inc, Atlanta

Findings For ACD Consideration

Working Group findings on 16 lines from 5 institutions:

- Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, India, 2 lines
- Cellartis, Sweden, 3 lines (including a subclone)
- Guangzhou Medical College, Guangdong, China, 6 lines
- Children's Memorial Hospital, Chicago, IL, 3 lines
- University of Texas Health Science Center at Houston, Houston, TX, 2 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

Jawaharlal Nehru Centre for Advanced Scientific Research Submission

- Two lines from embryos donated in 2007
- Poor quality embryos not usable for fertility treatment
- Submitter states complies with 2007 guidelines from the Indian Council of Medical Research
- Initially submitted for administrative review; NIH considered and moved to ACD

WG Discussion of Jawaharlal Submission

- Straightforward embryo donation consent;

  states that embryos will be used for research and stem cells are mentioned, but direct connection not made

- Embryo donation form is template; submitter provided assurance that signed consents were reviewed by IVF clinic officials

- Working Group voted unanimously to put forward a positive finding to the ACD.

Cellartis Submission

- Two lines (and one subclone) from embryos donated initially in 2000
- Lines were on NIH Registry under prior federal policy
- Embryos were near 5-year limit for cryopreservation per Swedish law; patients may request extension from national board
- Embryo quality unclear
- Donors consented 4 times over 4 years for use of cells for specific periods of time. Last consent had no end date and allowed for sharing lines beyond Sweden.
- Initially submitted for administrative review; NIH considered and moved to ACD

Discussion of Cellartis Submission

- WG discussed whether statutory limit on cryopreservation affected voluntariness of consent to donate embryos for research.
  - A variety of factors beyond reproductive planning may be relevant to cryopreservation time including cost to couples

- WG noted that many other countries and regions have laws either limiting or prohibiting cryopreservation of embryos, including Australia.

- Endeavour-2 line currently on NIH Registry was from embryo donated in New South Wales, which was subject to 10 year cryopreservation limit as stated in the IVF consent document.

Discussion of Cellartis Submission

- WG voted unanimously to present a positive finding to the ACD, but noted that the specifics of embryo storage limits and other factors that could influence people to choose a donation to research should continue to be considered.

Guangzhou Medical College Submission

- Six lines from embryos donated in 2007
  - non-clinical grade embryos not usable for fertility treatment
- Embryo donation consent signed at the same time as IVF consent
- Approval and ongoing monitoring by hospital IRB
- Working Group noted that couples may have limited options with respect to clinical grade embryos in China due to the one child policy
  - Not a relevant issue for these lines derived from non-clinical grade embryos

WG Discussion of Guangzhou Submission

- Reasonable to agree to donate nonclinical grade embryos in advance of treatment
- Embryo donation consent adequate
- Donation rate is 7-8% for research
  - Supports voluntariness of decisions
- Problematic statements in IVF treatment consents:
  - Multifetal pregnancy reduction necessary in case of pregnancy with more than two fetuses *(WG believes such a provision would be unacceptable in the U.S.)*
  - Patient agrees that 'children born are completely our own" *(WG notes clinics make mistakes, although rarely)*
  - No significant difference in fetal malformation rate using intracytoplasmic sperm injection compared to natural pregnancies *(WG notes not consistent with current knowledge)*

WG Discussion of Guangzhou Submission

- Most WG members agreed concerns about limits on options for use of remaining embryos not relevant in this specific case since embryos were not clinical grade.

- Working Group voted 7-2 to put forward a positive finding to the ACD.

- Members voting in the minority felt that restrictions on choice in the clinical IVF clinical consent process were potentially coercive. Members voting in majority also expressed concern, but felt consent process for embryo donation in the context of non-clinical grade embryos was sufficiently strong to merit a positive finding.

Children's Memorial Hospital, Chicago Submission

- Lines from embryos donated by patients at 2 different IVF clinics
  - Only lines from embryos donated by Midwest Fertility Center (MFC) patients to be discussed today: CM2, CM6, CM7
- No financial arrangements between IVF clinic and research institution
- All embryos were donated after the release of the 2005 NAS Guidelines

Children's Memorial Hospital Submission

- Midwest Fertility Center, Illinois: have actual consents for embryos donated to create CM2 and CM7

- CM2 from nonfrozen embryo donated after PGD screening in 2007 by handwritten note “donate to Northwestern for research” in embryo disposition form; no other details documented regarding research. Other options listed for embryos are freeze or discard.

- CM6 from nonfrozen embryo donated after PGD screening in 2007 or 2008 (conflicting dates in submission); consent information was given verbally and patients consented verbally.

Children's Memorial Hospital Submission

- CM7 from embryos frozen between 1996-2005, donated between 2006-2007. Several Embryo Storage Notice forms presented.
  - Checkbox “Use … for Research Purposes” on some
  - Options on one form are “Continue to store...”, “Discard…,” or “Other” in which “Please donate for research” was handwritten.

Children's Memorial Hospital Submission

- CM 7: One consent states that account will be sent to collection agency for $3,000 unless payment made or notice returned with order for discard or research. Handwritten note (presumably by donor) that past six letters stated if no response, embryos would be discarded, and the writer is not sure why this did not take place.

Discussion of Children's Memorial Hospital Submission

- WG noted donation forms signed by MFC patients lack the specificity expected at the time regarding stem cell research.
- Apparent lack of rigor in documentation and the embryo donation process brings the adequacy of communication and consent into question.

Discussion of Children's Memorial Hospital Submission

- The WG voted unanimously to suggest that the ACD not recommend approval of the CM2, CM6, and CM7 lines due to the lack of sufficient evidence that donors were making an informed choice about the use of the embryos for stem cell research.

University of Texas Health Science Center at Houston Submission

- 2 lines from embryos donated in 2004
- Embryos initially to be sent to USCF; investigator at USCF left, so embryos were sent to U-TX
- Clinic used “consent to release embryos” forms rather than typical “consent to donate embryos for research” form
- No printed documentation on consent forms that donations were for research purposes
  - references to research were handwritten

Discussion of University of Texas Health Science Center at Houston Submission

- Embryo #1260/line CR1:
  - 'consent to discard embryo' form has handwritten note "Please donate for stem cell research at USCF" without date or initials; UCSF was then crossed out, "Rel to Univ of Texas stem cell" handwritten (dated and initialed apparently by clinic)
  - "consent to release embryo" form has "UCSF/UTX" handwritten as recipient (without initials or date)
  - No description of stem cell research

Discussion of University of Texas Health Science Center at Houston Submission

- Embryo #1260/line CR1 (cont.):
  - Form states other options for use of embryo were considered and are unacceptable (including research, which submitter clarified as referring to in-house fertility research)
- Embryo #548/line CR2:
  - "Consent to release embryo" form appears to have "USCF" handwritten in the space for recipient name and then crossed out with "UTX esc program/Eva Zsigmond" added, without dates or initials
  - No description of stem cell research

Discussion of University of Texas Health Science Center at Houston Submission

- Embryo #548/line CR2 (cont.):
  - no other options for use of embryos written on form; submitter states that clinic director says donors were presented with all options available

- For both lines: it is unclear exactly what was written on the forms at the time that the donors signed them.
- It is unclear who made the alterations on the forms, and who saw those changes.
- Documented information provided to the donors is neither clear nor complete.

Discussion of University of Texas Health Science Center at Houston Submission

- The WG voted unanimously to suggest that the ACD not recommend approval of the CR1 and CR2 lines due to the lack of sufficient evidence that donors were making an informed choice about use of the embryos for stem cell research.

Summary Working Group Findings

- ACD should consider recommending to NIH Director that these lines be approved for use in NIH-supported research:
  - Jawaharlal Nehru Centre for Advanced Scientific Research: BJNhem19, 20
  - Guangzhou Medical College: FY-hES1, 3, 5, 7, 8, FY-3PN
  - Cellartis: SA001, SA002/SAOO2.5*

(*SA002.5 is subclone—subclones are not specifically listed on Registry as all subclones of Registry lines are eligible for use)

Summary Working Group Findings

- ACD should consider recommending to NIH Director that these lines be disapproved for use in NIH-supported research:
  - Children's Memorial Hospital, Chicago, IL: CM2, CM6, CM7
  - University of Texas Health Science Center at Houston: CR1, CR2