November 24, 2009

Working Group for Human Embryonic Stem Cell Eligibility Review
Report to the Advisory Committee to the Director

Findings and Summary
Harvard University Submission 2009-ACD-003

Findings

1) The ACD should consider recommending that the NIH Director make the Harvard embryonic stem cell lines available for use with NIH funds, with the exception of Line 25.

2) The ACD should note that:
    a. the consent form says the cells will be used for endoderm development, with a focus on pancreatic formation, and diabetes research
    b. the Harvard IRB determined it was acceptable to use the cells more broadly on the basis of Common Rule usage of anonymized tissue, and
    c. that the broadening of consents due to unexpected advances in medical science is under active discussion at other federal agencies at present.

Summary of First Discussion

The Working Group (WG) reviewed all documents submitted in support of this request for 28 human embryonic stem cell lines to be approved for use in NIH funded research. HUES (Human Embryonic Stem Cells) 1-28 are Harvard's oldest lines and, as described in the submitted documents, were all derived under a single IRB-approved protocol and informed consent form. After consideration of all submitted documents, the WG agreed to table the submission pending request for and receipt of additional information.

Foremost, it was determined that before the WG could arrive at a finding as to whether the cell lines were responsibly derived, a clarification of the consenting process was needed. The WG requested receipt of representative clinical treatment consents from the Boston-area Collaborating IVF Clinic and other IVF clinics. In addition, the WG requested a breakdown of which cell lines came from the Collaborating IVF Clinic and which came from other IVF clinics, if this information was available. Because they felt that the timing of events between clinical services and consenting for embryo donation for research was unclear, they also requested a description of the process for obtaining consent for embryo donation for research by the Collaborating IVF Clinic and the other clinics.

The ACD WG also requested documentation of the research role of the Collaborating IVF Clinic Scientific Director. Specifically, the WG requested clarification of the role of the Scientific Director and staff in the research process and their roles in the consenting of patients. Information on the financial relationship between IVF clinics and research,

and policies for intellectual property rights and co-authorship (academic relationship) was also requested. The WG felt that these documents would assist WG in their consideration of the separation between the clinical and research roles.

It was noted that HUES #25 was obtained during a lapse in IRB approval of the protocol. Finally, the WG noted that the consent form states that the purpose of the study is pancreatic formation and its exocrine function. The WG discussed whether NIH should note this if the HUES lines are listed on the NIH Registry.

The WG voted unanimously to table this submission.

Summary of Second Discussion

After the first meeting, the WG had requested more information on the consenting process, including representative clinical treatment consents and clarification of the timing of events between clinical services and consenting for embryo donation, and clarification of the role of the Scientific Director and staff in the research process and their roles in consenting patients.

Harvard's response letter noted that Harvard had been concerned with protecting donors and had used a higher than usual level of donor anonymity. As a result there are no links that would allow them to identify from which specific clinic the embryos that had resulted in a specific cell line had been obtained or to obtain those specific clinical consents. However, the letter noted that the consent standards of the time had been carefully followed (the 2000 *NIH Guidelines for Research Using Human Pluripotent Stem Cells*), that all embryos had been frozen, that with only one exception research consents had been done by the Coordinating Clinic, that the role of the Scientific Director had been limited to the thawing and culturing of the embryos, that the Clinic had been reimbursed for reasonable costs only, that there were no patenting plans, and that the cells would be placed in the public domain.

The WG discussed the timing of the period during which donors could choose to withdraw from the study. For example, they noted that it would be possible for a donor to withdraw from the study during the period of time between the transfer of the embryos from the first to the second clinic. This time period was after the embryos had been donated for research but before they had been actually transferred to the laboratory. Once transferred to the laboratory after de-identification, it would be possible that the embryos would remain frozen for a period of time before actually being used. During this time, however, it would not be possible to withdraw. To this point, the consent form does not address this period between de-identification and derivation. However, the form does make clear that there would be some point at which withdrawal would no longer be possible. The WG arrived at a finding that although the fine details were not included, the intent is clear and, therefore, the consent is acceptable in this respect.

Non-monetary incentives such as authorship of papers were examined. It was noted that although the role of the Scientific Director had been limited to the thawing and culturing

of the embryos, this did require some expertise and co-authorship would be appropriate at some level.

The issue of the adequate disclosure of available options to donors was discussed. The protocol was written in such a way that people were not approached for donation of embryos to research until their fertility treatment was complete and a decision had been made to destroy the embryos. The earlier decision point – when the donors had been asked whether to continue storage of the embryos or to consider donating to another couple, if that option was available, – had occurred prior to the research consenting process and was therefore not documented other than by the protocol and the assurance from Harvard. It can be inferred that if a couple's embryos were frozen, the couple understood that the embryos could still be used and the options of donating to another person or using the embryos themselves must have been clear.

The WG concluded that although the clinical consent forms were not available for specific lines, they thought the Harvard lines should be considered by the ACD for recommending approval by the NIH Director, contingent upon receiving an assurance from the Director of the Collaborating IVF Clinic that describes what options were presented to patients at that clinic regarding embryos created using IVF for reproductive purposes and no longer needed for that purpose. In addition, the WG wanted to know if the Director of the Collaborating Clinic believes that those options were likely to have been consistent with the options presented to patients at the other IVF clinics. They agreed that if the documentation was consistent with the stated protocol, they would not need to reconvene to consider this documentation but would defer to the Chair and the primary reviewer. If there is a privacy concern, Harvard could examine the documents, redact them, and attest to their source.

The WG then discussed Line 25. This cell line was derived from an embryo that had been donated during a period of time in which the IRB approval had lapsed. Because the renewed IRB protocol was identical to the previous protocol, the Harvard IRB had approved the continued use of the cell line. However, although there was no regulatory violation, the WG excluded Line 25 from their contingent approval finding of the other lines.

Finally the WG addressed the issue of whether, if these cell lines are approved for NIH funding, a restriction on their use for certain forms of research will be necessary. The consent form states that the derived cells will be used "to study the embryonic development of endoderm with a focus on pancreatic formation. The long-term goal is to create human pancreatic islets that contain β cells, the cells that produce insulin, for transplantation into diabetes." The Harvard IRB later determined that it was acceptable to use the cells more broadly and they are now used for all kinds of diseases and tissues. In the WG discussion, there was a range of opinion. It was noted that the consent was not explicit in excluding other types of research, that embryonic stem cells divide indefinitely so that the use of cells in other areas of research does not limit their use in diabetes research, and that broader use of the cells would be consistent with the Common Rule. This is an area of active discussion in other federal agencies at present. However, it is

possible that donors were influenced because family members had diabetes, but might not have been willing to donate for other diseases. They agreed, however, that this was not a matter directly related to whether the lines should be eligible for funding, rather something for NIH to consider regarding how the lines are used.

Harvard University subsequently submitted an attestation from the Medical Director of Harvard's Collaborating IVF Clinic. The WG chair and the primary reviewer agreed that the attestation satisfied the questions raised by the Working Group.

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