June 3, 2011

Advisory Committee to the Director (ACD)
Working Group for Human Embryonic Stem Cell Eligibility Review

Reports to the ACD for June 9, 2011 Meeting

Working Group Findings and Summary Regarding Hadassah Hebrew University Medical Center Submission 2011-ACD-004

June 2, 2011

Finding Regarding All Lines in Hadassah Hebrew University Medical Center Submission (2011-ACD-004)

The ACD should consider recommending that the NIH Director approve all lines in this submission (HAD-C 100, 102, and 106) for use in NIH-funded research.

First Discussion

This new submission from the Hadassah Hebrew University Medical Center requests approval of three cell lines for use in NIH-funded research. The submission was initially received for Section II (A) administrative review, but was moved to review under Section II (B) as the submission did not meet one of the administrative review requirements but was eligible for review under Section II (B) of the Guidelines. On this point, NIH staff reminded the Working Group that while the submission did not fully meet the specific Section IIA requirements, the Working Group needs to review it anew under Section IIB requirements. When writing the Guidelines, NIH anticipated that many lines derived before the July 7, 2009 publication date of the NIH Guidelines on Human Embryonic Stem Cell Research would not meet the Section II (A) criteria, but could have been ethically derived. Therefore, NIH staff have advised potential submitters who were not sure of the appropriate review mode to send the documents in for administrative review, and if needed, the submission would be referred for Section II (B) review.

The three lines from Hadassah Hebrew University were derived from human embryos donated in 2006, 2007 and 2008 as part of protocol that envisioned creating lines suitable for transplant in patients. The documents state that all embryos had been frozen for at least 5 years and were donated by married couples. In fact, Israeli policy states that viable embryos can be donated only if they have been frozen for at least 5 years. The donors were approached by individuals who were not part of the IVF treatment group to ensure a clear separation between the IVF team and the team developing stem cells. The couples were informed that the options, other than donation for research, were to keep the embryos frozen for up to a total of 10 years or to have the embryos destroyed. In Israel, donation of remaining embryos to another couple for reproductive purposes is not an option.

Although the donor consent form is generally clear and complete, it is embedded within in a broader protocol which requests health information about the couples beyond the requirements for embryo donor consent. In anticipation of potential future therapeutic applications of the hESC lines, the broader protocol includes interviewing the donors to clarify personal and familial medical history; sending the donors the results of blood tests for infectious diseases; and retaining the frozen blood samples in case future testing of the donors is needed. Although none of these items in itself is troubling, the Working Group wants clarification on the process

followed regarding security and confidentiality of the collected information. Specifically, the Working Group felt that there may be possible risks for emotional distress and privacy infringement, particularly since some of the health information includes STDs. For example, the protocol does not specify how the collected information would be kept private from the donor's spouse. Through its review of the materials the Working Group was able to identify some language within the consent form related to confidentiality and coding ("Methods" section, numbers 11 and 12), but the wording is different from that usually seen in the U.S. It is possible that the security and confidentiality issues are covered under the "law of genetic information" and the "laws and procedures of confidentiality" that are cited in the consent form, but this needs to be clarified.

A second area of the broader consent form that needs clarification relates to the donors' ability to withdraw from the clinical portion of the study and/or to participate in other studies. The form states that "… we do not participate, at the time of signing of this document, in any other clinical study, and that we are committed to not participate in any other clinical trial during the whole period of this study." It is not clear that this is enforceable, and it appears to be restrictive. Additionally, in another section of the form it is stated that donors might be approached in the future to obtain more medical information to further ascertain the suitability of the stem cells. It is not clear when the study would actually conclude if the researchers could contact the donors at any point in the future. It is possible that the restrictive text is standard language for Israeli research consents, but this needs to be clarified.

The Working Group expressed relatively minor concerns about the wording of the donor consent form. First, it was not obvious to the Working Group that the right to discontinue donation of the embryo was clearly stated and understandable to the donors. Section II (A) of the NIH Guidelines requires that "Donor(s) should have been informed that they retained the right to withdraw consent for the donation of the embryo until the embryos were actually used to derive embryonic stem cells or until information which could link the identity of the donor(s) with the embryo was no longer retained, if applicable." As part of the previous administrative review under Section II (A), NIH staff contacted the submitter in advance of the Working Group meeting, requesting that they address how this element was met. The submitter replied by citing two separate statements within the consent form: a) a general statement that "… we are free to discontinue at any time our participation in the study"; and, b) "The embryos will not continue to exist after the production of the stem cells." Based on these two statements the submitter stated that they believed that it was clear to the donors that they could withdraw their consent to donate the embryo up to the point of the production of stem cells. The Working Group interpreted the first of the two sentences as standard language for clinical studies and not directly applicable to embryo donation. The Working Group agreed that the second cited sentence does apply to embryo donation, but felt that the phrase "not continue to exist" was not well chosen. Although the phrase is technically correct, it would have been preferable to directly state that the donors would not be able to withdraw participation from research once the embryos had been destroyed and the stem cells had been created and disseminated.

As a final issue, the Working Group noted that it would be helpful to receive assurance that that the donors received the information in their native/preferred language or in a language in which

they were sufficiently fluent. The Common Rule speaks to the need to provide information in language with which participants are fluent or familiar.

In summary, the Working Group is generally comfortable that the consent form is thorough, and that reasonable people would understand the point about withdrawing participation. However, the Working Group agreed to defer a formal vote, pending receipt of information on several relatively minor points: assurance/clarification regarding the process for handling sensitive health information; assurance that donors were given consent materials in language in which they were comfortable; clarification on how Hadassah ascertains the donors' possible participation in other clinical studies; and lastly, it is not clear in this case when the study would officially conclude since the donors can be contacted at any point in the future for further testing.

Second Discussion

Hadassah's responses to the questions above were discussed. Overall, the questions were addressed to the Working Group's satisfaction. Specifically, the language of the consent form was identified as Hebrew, and it was stated that all donors were comfortable with this language. The study period was defined as "…the time from signing the informed consent, until the donors complete the process of undergoing physical examination, blood/swab sampling, and are interviewed by the staff." Hadassah estimated this to be only 1 to 2 hours in duration. Therefore, the consent form language regarding the donors' possible participation in other clinical studies probably does not apply here.

The bulk of the Working Group's discussion centered on the question "Are blood test results communicated privately with one spouse and not available to the other?" The question was initially included based on the Working Group's concerns related to potentially sensitive information, for example results of STD screening. The response from Hadassah focused on privacy between the couple and outside entities, and not on privacy between the two spouses. The question may have been ambiguous in this regard. By the end of the discussion, the Working Group agreed that it may be a moot point since in the U.S., the couple is typically treated as a unit. In other words, information is communicated to both individuals. Although, this issue is no longer of concern to the Working Group with regard to the Hadassah submission, the discussion may be valuable to the consideration of similar situations that may arise in the review of future submissions.

As a side note related to the general issue of embryo donor screening, NIH staff mentioned that FDA requirements apply to screening of couples who are donating embryos for research where stem cells might be derived and used later as a therapeutic product.

The Working Group voted unanimously to present a positive finding to the ACD for the three lines included in this submission.

Working Group Findings and Summary Regarding Reprogenetics LLC Submission #1, 2011-ACD-005

Finding Regarding Lines RNJ18-20 in Reprogenetics LLC Submission 2011-ACD-005

The ACD should consider recommending that the NIH Director approve all lines in this submission (RNJ18-20) for use in NIH-funded research.

Discussion

This new submission from Reprogenetics requests approval of three cell lines for use in NIH-funded research. This request was initially submitted for review under Section IIA of the Guidelines but did not meet all of the IIA criteria, so was referred to the Working Group for review under Section IIB. As a point of information, the IVF clinic was a different facility than the clinic in the other submissions from Reprogenetics.

The three cell lines, RNJ 18, RNJ19, and RNJ20, were derived from the same patient during two treatment cycles; line RNJ18 was derived from an embryo received on 2/24/2009 and lines RNJ19 and RNJ20 were derived from embryos received on 6/12/2009. Because the two cycles took place within one year, Reprogenetics considered the research consent form to be valid for both cycles. In addition, the submitter states that the donors orally confirmed their consent for embryo donation during the second cycle. The IRB approval is dated 6/13/2008, so the consent form was technically valid for both cycles.

The embryos were determined to be not clinical grade, based on PGD testing for congenital nephrotic syndrome. The consent form is clear overall, with well-phrased statements regarding voluntary participation/withdrawal and disclosure of the researchers' potential financial interests. Although the "benefits" section is not particularly well-stated, it is adequate.

The only concern with this submission is the use of a single consent form for both treatment cycles. However, this is not seen as a major issue since the embryos were not viable. Moreover, since the Working Group believes this is the first time that this issue has surfaced, they did not want to hold this application to a different standard.

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

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Working Group Findings and Summary Regarding Reprogenetics LLC Submission 2010-ACD-006

Finding Regarding line RNJ7 in Reprogenetics LLC Submission 2010-ACD-006

The ACD should consider recommending that the NIH Director not approve RNJ7 for use in NIH-funded research, due to the use of an expired consent form and concerns over the failure of the donors to respond to reconsent efforts.

First Discussion

The Working Group reviewed all documents in support of this request for a single cell line, RNJ7, to be approved for use in NIH funded research. The single line was derived from an IVF patient in a donation made in 2008 in which the embryo was determined to be nonviable.

After considering all submitted documents, the Working Group expressed concerns in several areas. There appears to be the potential for bias in determining whether embryos were not suitable for reproductive use. Did any of the embryology staff who made decisions as to which embryos were suitable for reproductive purposes have any financial interest in Reprogenetics or have they been co-authors on any abstracts or publications resulting from this hESC research? Also, when they determined whether specific embryos were suitable for reproductive purposes, were they blinded as to whether the IVF patient had agreed to donate unsuitable embryos for research?

The sponsor has clarified that the scientists at Reprogenetics had no role in the consenting process. However, the Working Group needs verification that Dr. Garrisi and the treating physician for the IVF patient who donated the embryo for RNJ7 have no financial interest in Reprogenetics. Also, verification is needed that the Saint Barnabas Medical Center and the IVF practice have no financial interest in Reprogenetics.

The second general area of concern relates to the revised informed consent form. Reprogenetics received permission from the IRB in 2009 to re-consent. However, the revised form simply deleted the statement that lines would not be used for production of commercial cell lines; the revised version has no affirming statement that this might be a possible use. The Working Group is troubled by the failure to be more transparent. In other words, language was merely eliminated instead of taking the opportunity to clarify what will actually happen. When the donor signed the re-consent the company had already been founded and the doctors had already left their primary affiliation. Therefore, it is unclear why the possibility of commercialization was not mentioned in the re-consent form. It is considered acceptable by IRBs to allow investigators to say they might benefit financially when there is already a clear interest. The Working Group felt this should be stated as a fact; the investigator has financial interest in the outcome. Profits and gains are uncertain but the interest should be made clear.

It also is unclear why the 2009 re-consent form did not contain specific language stating that the cell line might be used for allogeneic transplantation.

The Working Group requests a redacted copy of the revised consent form with the signature of the patient whose embryo was used to create line RNJ7. Alternatively, the sponsor can send a letter attesting that the signee has personally seen the signature of the donor on the revised consent form.

On the issue of no payment for donated embryos, the investigators point to language that there is no direct benefit to be expected from participation in research. However, in that context, direct benefit generally refers to clinical benefit. The Working Group requests from Reprogenetics an explicit statement that in this IVF practice no financial payment were made.

Given the remaining questions about this submission, the Working Group voted unanimously to table the request instead of presenting a positive finding contingent on submission of additional information. The failure of Reprogenetics to be more transparent in the revised consent form is of concern.

Second Discussion

Additional materials submitted from Reprogenetics addressed nearly all of the questions from the first discussion. The institutional separation and potential conflicts of interest across the clinical and research entities were clarified to the Working Group's satisfaction. However, the Working Group had remaining concerns about the possibility of potential bias in the selection of embryos for transfer, if the embryologist is not blinded to the decision of the IVF patient. Although the highest quality embryos certainly would be reserved for IVF and the lowest quality clearly would be deemed not suitable for use for reproductive purposes, the fate of the embryos in the second tier might entail a more subjective judgment call. This is particularly important in the case of fresh embryos, and it is a timing issue; at the moment of determination, did the embryologist know what the fate of the embryo would be if it were deemed unsuitable for reproductive purposes? Given this hypothetical set of issues, it might be preferable, or even exemplary, to have the embryologist blinded in grading the embryos when research is offered as an option for "lower grade" embryos. However, to the knowledge of the Working Group, there is no accepted, standard practice in the field. Therefore, the Working Group agreed that blinding of the embryologist making the determination should not be required in the case of Reprogenetics, because it would hold them to a standard different from that of the field in general.

The remainder of the discussion centered on Reprogenetics' consent process. They have asked the donors to reconsent with a newer version of the form which deletes the statement that lines would not be used for production of commercial cell lines. It also removes the statement that cell lines will not be donated to other individuals, centers, or corporations. However, the donors have not yet signed the form to reconsent. Therefore, Reprogenetics has asked NIH to disregard the reconsent and instead review the request on the basis of the original consent form, which continues to impose the original limitations of no therapeutic use and no commercial use on this particular cell line. This raises the question of the availability of the cell lines, since reverting to the previous version of the consent form retains the exclusivity statement that would make the cells available only within the St. Barnabas-Reprogenetics complex.

A broader concern is that at the time of the first Working Group discussion, the couple for reasons unknown had not signed the new consent although they had had approximately one month to make a decision about the consent with the language removed; it is unclear how this should be interpreted. Should it be assumed that the original consent they signed is the active one and ignore that they haven't signed the new one? Or might the donor couple have a problem with some aspect of stem cell research or the idea of commercialization? In summary, the fact they have not responded to reconsent calls into question whether the initial consent should no longer be considered valid.

To resolve the questions centered on the reconsent, the Working Group requests a copy of the letter that was sent to the couple as part of the reconsent process. The Working Group believes that the information to the donor couple should clarify if this is an actual reconsent or an extension of the previous consent. Also, it should reveal specifically what the donors were told, and what they were asked to do.

Based solely on the reconsent issue, the submission remains tabled, pending receipt and review of the letter/instructions to the donors that accompanied the reconsent materials.

Third Discussion

In response to the Working Group's questions, Reprogenetics stated that they were not involved in the conversations between the physicians and their patients, so they do not have direct knowledge of the content of those discussions. Instead, Reprogenetics provided NIH with the following written description of the consent form changes, which was sent to the one of the physicians for transmittal to her patients: "The new consents remove three restrictions from the original consent and allow the following:

- Therapeutic use of the cell lines (but at this time therapeutic use is not intended):
- Commercial use of the cell lines; and,
- Donation/transfer of the cell lines to other entities."

In addition, a statement has been added declaring potential financial interest of the researchers in the cell lines. This new information did not help the Working Group to interpret the donors' lack of response to Reprogenetics' request for reconsent.

The Working Group also discussed the relative significance of disclosure of potential financial interest and the evolution of conflict of interest policies in recent years. For example, the 2005 stem cell guidelines from the National Academies did not mention financial conflict of interest.

The Working Group voted 4 to 4 on a motion that the ACD recommend disapproval of the line because the lack of reconsent calls into question whether the original consent remained valid. Those members voting against the motion shared all of the stated concerns with the other members, but they were not willing to conclude that the couple's failure to reconsent necessarily invalidated their original consent. The Working Group members all agreed to reconsider their findings if further information is provided regarding the reconsent process prior to the next ACD meeting.

On a separate matter, the Working Group noted the extreme restrictions placed by Reprogenetics on access to the cell lines. This issue is referred to NIH staff because it is outside of the Working Group's overall charge, which is to evaluate the ethical derivation of the cell lines. This consideration did not impact the Working Group's findings.

Fourth Discussion

In communications between NIH and Reprogenetics regarding other submissions, it came to light that Reprogenetics had previously provided the NIH with the incorrect consent form. Specifically, the embryo donation consent version dated 5/12/2006, which was previously believed to be the correct version, was not used for the donation of this embryo. The actual embryo donation consent used was the version dated 8/23/2002. The 8/23/2002 version has the following differences from the 5/12/2006 version:

- The 8/23/2002 version has the title "discarded non-viable embryos" instead of "discarded and abnormal embryos."
- The 8/23/2002 version has a paragraph in Section B regarding non-viable embryo selection criteria
- The 8/23/2002 version has a sentence: "Thawed stem-cells would be tested for viability and characteristics as well as their ability to transform into other cell types."
- The 8/23/2002 version Section B includes a sentence at end of the fifth paragraph: "Frozen-thawed stem-cells and embryos will be subjected to the same research protocols as described above."

Of concern to the Working Group is the fact that the IVF clinic inadvertently continued to use the 2002 consent form, although its IRB approval would have been expired in 2008. In addition, Reprogenetics noted that a new consent was approved by the IRB in 2004 and was not put into use by the clinic. Meanwhile, this leaves the Working Group with even greater concern than in the previous reviews. That is, in addition to the previous concern about the donors' failure to re-consent, the Working Group now understands that the 2002 consent form was not IRB-approved at the time that it was signed by the donors in 2008. The Working Group recalled the ACD recommendation against approving a line from Harvard University derived from an embryo donated during a short lapse in IRB approval of the protocol; Dr. Collins accepted the ACD's recommendation and disapproved that line.

The revised protocol approved in 2004 led to the derivation of RNJ7 (as well cell lines RNJ11 and RNJ12 in submissions 2011-ACD-002 and 2011-ACD-003). The revisions to the protocol expanded the study to include abnormal embryos as determined by pre-implantation genetic diagnosis (PGD) analysis. However, the submitter has confirmed that the embryo used to derive RNJ7 was not derived from an embryo that underwent PGD analysis.

A remaining concern is the absence of a clear statement within the consent form of Reprogenetics' interests in commercialization within this area.

The Working Group voted unanimously to present a negative finding to the ACD due to the use of an expired consent form and concerns over the failure of the donors to respond to reconsent efforts.

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Working Group Findings and Summary Regarding Reprogenetics LLC Submissions 2011-ACD-002 and 2011-ACD-003

Finding Regarding lines RNJ11 and RNJ12 in Reprogenetics LLC Submissions 2011-ACD-002 and -003

The ACD should consider recommending that the NIH Director not approve RNJ11 and 12 for use in NIH-funded research, 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

Discussion Submission 2011-ACD-002

This new submission from Reprogenetics requests approval of one cell line, RNJ11, for use in NIH-funded research. This request was initially submitted for review under Section IIA of the Guidelines but did not meet all of the IIA criteria, so was referred to the Working Group for review under Section IIB.

The donor patients were initially consented on 10/16/2008 and were then re-consented on 12/20/2009. The embryos were determined to be not clinical grade.

The Working Group expressed several concerns about the re-consent form. First and foremost, "Disclosure of researchers' potential financial interests" (Section E) is not straightforward or transparent. Although the financial interests are described as potential or hypothetical, these interests were real at the time of the consent; the researchers had a relationship with a for-profit entity. Therefore, the researchers were less than candid on this point. Several members of the Working Group saw this as a relatively minor oversight and they wondered how many of the previous submitters who used the qualifiers "may" or "might" were held to the same standard in the review of this element. As a practical issue, the question was raised whether data are available on the willingness of patients to donate to a for-profit entity versus to a university or other nonprofit organization. One member stated that participation in clinical trials appears to be unaffected by these factors, but the Working Group was not aware of data on the effect of these factors relative to the willingness to donate embryos.

Additional concerns related to the re-consent form pertain to: a) the timing of the right to withdraw; and, b) whether information that could identify the donor(s) would be available to the researchers. Although these two items are technically part of the Section IIA administrative review criteria, the basic principles should be considered under Section IIB review. The re-consent form does not address either of these points, and the Working Group made note of it in their overall review of the submission.

A motion to present a positive finding to the ACD, received a vote of six against and three for the motion. Based on this, the Working Group will present a negative finding to the ACD for this submission.

Discussion Submission 2011-ACD-003

This new submission from Reprogenetics is identical to Submission 2011-ACD-002 with two exceptions: the consent form and the cell line. Other than the letterhead, the content of the consent form is identical to that of the other submission. However, since the donors are different, the redaction also differs.

The submitter requests approval of one cell line, RNJ12, for use in NIH-funded research. Like submission 2011-ACD-002, this request was initially submitted for review under Section IIA of the Guidelines but did not meet all of the IIA criteria, so was referred to the Working Group for review under Section IIB.

All of the comments within the review of submission 2011-ACD-002 also apply to this submission. A motion to present a negative finding to the ACD, received a vote of six for and three against the motion. Based on this, the Working Group will present a negative finding to the ACD for this submission.

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June 3, 2011

Working Group Findings and Summary Regarding VistaGen Submission 2011-ACD-001

Finding Regarding All Lines in VistaGen Therapeutics, Inc. Submission 2011-ACD-001

The ACD should consider recommending that the NIH Director not approve the lines in this submission (K117, J618, and J713) for use in NIH-funded research.

Discussion

This new submission from VistaGen Therapeutics, Inc. requests approval of three cell lines for use in NIH-funded research. The embryos were donated for research in 1999 by patients who no longer wished to keep the embryos in a cryopreserved state. The patients were orally informed that they had the additional options of having their excess embryos destroyed or donated to other couples.

Dr. Jonathan Van Blerkom was responsible for the laboratory phase of *in vitro* fertilization, including fertilization, embryo culture, transfer, and cryopreservation. Dr. Van Blerkom is a co-founder of the IVF clinic where the embryo donors were treated. He also is on the faculty of the University of Colorado, Boulder, and advisor to VistaGen. As stated in the submission materials, the IVF clinic was a private infertility practice not affiliated with the University of Colorado. Cultures of the cell colonies with the appearance of embryonic stem cells were shipped to VistaGen.

The Working Group expressed serious concerns about the brevity and lack of clarity of the consent form. With only three sentences of text, the consent form is extremely general; in particular, it fails to state that the embryos may be used for stem cell research. Considering that the form was used in 1999, it is puzzling that stem cell research was not mentioned. In addition, the form does not mention potential commercial interests, despite the nature of VistaGen's work. Although the overall submission meets most of the IIB criteria, the consent form is unacceptable.

The Working Group arrived at a negative finding by unanimous vote due to the lack of sufficient evidence that the donors were making an informed choice about use of the embryos for stem cell research.

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