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

Findings and Summary Regarding
Reproductive Genetics Institute
Submissions 2009-ACD-006, 2009-ACD-007
June 2, 2010

Finding regarding all hESC lines in Submissions 2009-ACD-006 and 2009-ACD-007

The ACD should consider recommending that the NIH Director does not approve these hESC lines for use in NIH funded research.[1]

First Discussion

Reproductive Genetics Institute (RGI) requested the inclusion of 47 human embryonic stem cell (hESC) lines in the new NIH Registry. These lines were derived from embryos obtained by *in vitro* fertilization (IVF) using gametes from couples at risk for conceiving children with genetic diseases such as cystic fibrosis, Huntington's disease, and hemoglobinopathies. Embryos from which the cell lines were derived included embryos predicted by pre-implantation genetic diagnosis (PGD) to carry the disease, as well some heterozygotes and normal embryos.

The Working Group (WG) discussed several issues during its first review of the RGI documents. RGI provided a blank research consent which was not on letterhead and did not have an IRB stamp and date. A clinical consent was not submitted and as such the WG could not see what the patients were told about risks associated with clinical procedures. It was also not clear whether the donors' agreement to donate the embryos for research occurred simultaneously with their giving consent for the clinical procedures.

A letter from RGI's Institutional Review Board (IRB) stated that the IRB approved the research protocol on June 28, 2002, and was re-approved on March 24, 2004. The WG wanted assurance that IRB approval had not lapsed during the time in which embryos were donated.

The consent form stated that embryos would be used only by RGI and not distributed, sold, or made available to outside entities. Although the WG interpreted the statement to mean that embryos would remain at RGI while derived stem cell lines would not, it was not clear whether donors assumed that stem cell lines derived from these embryos would also be restricted to exclusive use by RGI. The WG determined that this discrepancy would not affect its determination regarding whether the stem cell lines were derived responsibly, but that restrictions regarding sharing the embryos outside of RGI might have to be noted in the NIH Registry. RGI noted some restrictions in its Registry submission: "cell line limited for research

[1] Note Addendum on page 6 regarding re-consenting.

purposes by Material Transfer Agreement and cannot be used for experiment nuclear transfer and chimera production".

Because these embryos were derived from donors at risk of conceiving children with genetic diseases, it may be difficult to de-identify their donations and ensure confidentiality within RGI. However, the WG agreed that the concerns about confidentiality outside of RGI were adequately addressed.

Under "Discoveries and Patents," the consent stated, "We further agree that we, our heirs, successors, relatives, representatives, and/or agents will not bring any action in law or in equity, or in any administrative setting, related to our participation in this study." WG members expressed concern that this language might be interpreted broadly to be exculpatory, meaning that donors were asked to relinquish their rights to sue for negligence or harm. However, they also speculated that this statement related to donors' understanding that they would not gain financially from research using the donated embryos.

The WG agreed to defer further evaluation of this submission pending receipt of:

- Signed and dated research and clinical consent forms (with patient names redacted) for two specific cell lines. These lines were selected at random by the WG to represent the consent forms for this submission.

- Clarification about dates of IRB approval.

- Assurance from RGI that donation to other couples was not an option readily available at the time consent was given.

Second Discussion

The WG reviewed the additional materials submitted by RGI, which raised several concerns. A central concern was derived from the fact that RGI, as a private company, is not required to adhere to provisions in 45 CFR part 46, Subpart A. RGI articulated this point specifically with regard to the fact that the IRB did not hold annual meetings to review ongoing research projects.

That notwithstanding, during the discussion by the WG, it was noted that even if RGI is not required to comply with 45 CFR part 46, Subpart A, they should present evidence that they are responsive to the guiding principles of 45 CFR part 46, subpart A or a similar document (e.g., the Belmont report). This was not done in the materials provided.

During the review of materials the following additional specific concerns were raised and discussed by the WG:

- It is unclear whether the RGI IRB is sufficiently independent of the RGI organization. As such the rigor and format of their review was discussed. Not enough information was provided to the WG or was available on the RGI web site for the WG to make a determination about the appropriateness of their membership, policies, and procedures.

- The WG discussed the fact that the consent form raised serious concerns. First, the exculpatory language made it appear that the purpose of the document was to protect the practice more than patient. Second, language in the clinical consent form, "continued participation is at the discretion of the ART Team," could be perceived by the patient as encouraging the donation of embryos for research. It was noted by the WG that both of these points appear to challenge a key principle of informed consent to protect the interests of the donors.

- The WG noted that it was not clear from materials provided whether the clinicians were also involved in the research on the donated embryos. If so, the WG pointed out that this could represent a conflict of interest and that there was nothing mentioned how such a conflict was addressed and monitored by the IRB.

- Concern was expressed about the timing of the clinical and research consents, an issue of particular importance in the use of fresh embryos. The WG discussion made it clear that re-consenting patients who have already donated embryos would not resolve the issue, since the embryos have already been used for research purposes. A table with the dates of clinical and research consents for each of the cell lines would be very helpful in understanding the timing of the two types of consents.

- The WG noted that there didn't appear to be an informed consent form specifically for PGD and it was not clear how those embryos got biopsied and ultimately donated for research.

- The new information on the IRB procedures indicated that annual review of the protocols was not required and that lines were derived under a protocol that had not been reviewed by the IRB for two to three years. This omission abrogated the opportunity for the IRB to review concerns and complaints that may have arisen after consent was obtained. Although bodily harm to the signatories is unlikely from the donation of embryos, it might be that psychosocial harms could have occurred, such as breaches of confidentiality or regret over the decision to donate embryos.

Based on these concerns, the WG agreed that in light of the concerns about the IRB process, more information was needed about the policies and procedures assuring independence of IRB review from RGI investigators and how RGI assured that their IRB review process was consistent with the principles enunciated in 45 CFR part 46, even if not all of the elements of the Common Rule are followed. A request for additional information was sent to RGI soliciting additional information in the following areas:

- Composition and policies and procedures of the IRB, including information or documentation addressing the independence of the IRB and separation of the IRB's reviews from the scientific investigators at RGI.

- Assurance that RGI followed all relevant local, state, and federal law, as appropriate.

- A table showing, for each of the hESC lines in the RGI submissions, the date of consent for clinical treatment and the date of the consent to donate remaining embryos for research.

- A description of the general process for obtaining consent for donations of embryos remaining after PGD, including when embryos were biopsied for PGD and when the patient provided consent to donate embryos for research.

Third Discussion

The requested materials were received and reviewed. With regard to the IRB, it was still not clear that this group was sufficiently independent of RGI since four members are employees of RGI.

The WG remained concerned about the lack of an annual review. The documents showed that there was an interval of at least 2 years between reviews, and that reviews took place only if there was a change in the protocol. Given the importance and novelty of the research at the time, the WG thought it was surprising that the IRB did not meet at least annually. Most IRBs look at standard issues each year and more frequently as needed for serious adverse events (SAEs), complaints about recruitment and consent process and the overall level of satisfaction of the participants with their engagement in the process. Since it was clear that the IRB was not conducting an annual review, the WG questioned whether there was a process in place to monitor for SAEs, including those which might be psychosocial in nature or be threats to the dignity of the human subjects.

In response to the WG's request, RGI provided for each of the stem cell lines the date of consent for clinical treatment and the date of donation of remaining embryos for research. Of the 47 lines, one showed the date of oocyte retrieval and the date of research consent as the same day; the clinical chart could not be retrieved. In an additional four cases the date of consent for clinical treatment and date of consent to donate for research were the same day. For the remaining stem cell lines, the interval was usually five days or more. Therefore, even if consents done on the same day were disallowed, a significant number of cell lines still could qualify.

Several concerns remained about the consent form, which included what appeared to be exculpatory language which is not allowed under the Common Rule. However, the WG understands that RGI was not bound by the Common Rule. There were different opinions within the WG on the relative seriousness of this language. There was also a statement in one of the clinical consent forms that continued treatment was at the discretion of the ART team; this could be seen as unduly influential and potentially affect the donor's decision to donate embryos. In both of these cases the important question is whether RGI's policies and practices were in agreement with the principles embodied within the Common Rule. This also applied to the RGI IRB.

Regarding the WG's request for a description of the general process for obtaining consent for donations of embryos remaining after PGD, the investigator stated that the patients admitted for fertility treatments or PGD make decisions at different times. Some patients initially come for

IVF only, and then decide to do aneuploidy PGD. Other patients come for molecular PGD and then make the decision to donate the affected embryos during the cycle. Yet other individuals donate frozen embryos after a successful pregnancy. Based on the additional information, the WG had no major concerns about this item.

Based primarily on the concerns about exculpatory language in the consent form and the failure to review the research protocol on an annual basis, the WG voted 4 to 1 against putting forward a positive finding to the ACD to recommend approval of these cell lines for use in NIH-funded research.

In the opinion of the member with the dissenting vote, the language in the RGI informed consent documents was not exculpatory and was not ethically problematic. That member's position is that language at issue comes quite clearly under the subheading of "Discoveries and Patents" and therefore puts subjects on notice that neither they nor their heirs will have any property rights in any discoveries or patents stemming from the research use of their embryos. The member believes that this was quite appropriate so that subjects understand what they are (potentially) relinquishing in the way of property rights.

In the member's view, this language was not problematic because:

- there is no agreed-upon legal or moral right to the financial rewards stemming from donation of human tissue, therefore subjects are not being asked to relinquish any right;
- the language's placement under the subheading makes it clear that it relates to property interests, not to the right to sue for negligence or harm;
- the word "exculpatory" means to "excuse from guilt," or "hold harmless," but there is no guilt or harm involved here, as there would be if the language related to the researchers' possible negligence or potential harm to subjects.

As noted, other WG members were of the opinion that the language was exculpatory in that it appears to address legal actions for negligence or harm despite its location on the document under "Discoveries and Property Rights." Further, the other language in this section would appear to be sufficient to address the question of property rights in this context, suggesting that the last sentence was intended to address the broader issue of liability for negligence or harm.

General Discussion

The WG's discussion of requests from entities not bound by the Common Rule raised the broader issue of the Common Rule's principles versus its specific language as they apply to the charge to the WG. For example, some agreed that the WG could recommend approval of a request, if it upholds the principles embodied in the Common Rule, even if the request does not meet the specific language of Common Rule. However, some members of the WG stated the need to exercise caution and not undermine the premise that the specific stipulations in the Common Rule are based on ethics. The WG agreed that not being bound by the Common Rule does not mean that the principles of the Common Rule do not need to be met.

Most importantly, the WG agreed that it needs to be transparent on these issues in fairness to all requestors, to guide the WG in future meetings, and to ensure that the NIH makes the best decisions on the cell lines. The WG members agreed that their charge is to look at the overarching principles of ethical research.

Addendum

In response to a question from NIH, the Working Group had an additional discussion on whether re-consenting the donors would alter the Working Group's findings on these submissions. NIH staff had asked RGI whether re-contacting the embryo donors was feasible. RGI replied that they could try to recontact donors if they could get the treating physicians to release contact information from the patient's clinical charts, which the physicians may not be willing to do. The Working Group noted that RGI had obtained the clinical consent forms from several patients in response to an earlier request from the Working Group, which suggests they are able to match clinical consents with particular lines (at least in certain cases).

Assuming that it is feasible for the clinicians to identify the donors, the remaining questions are: is re-consenting appropriate and will it resolve the issue?

The purpose of the re-consent would not be to address past actions (i.e. creation of lines) but to obtain consent for future actions. For example, the re-consent could state that the work has been successful, but it now is clear that the expanse of research done with these lines could be broad. In this way, the donors could be informed that as the research is progressing to a new stage, RGI is now asking for their consent. The Working Group members agreed that re-consenting could have the positive effect of bringing the individuals up to date on the status of the lines and the consideration of making them widely available for federally funded research. The donors may not have been aware of these issues at the time of original consent, and it could be explained to the donors that one purpose of the re-consent is to make sure that this is what these individuals wanted. RGI should look at the re-consent as an opportunity to firm up ethical foundations of their work.

The Working Group agreed that re-consenting with appropriate materials will resolve the concerns regarding exculpatory language. It is assumed that the consent would have to go back through RGI's IRB for an amended protocol along with the new consent.

The Working Group voted unanimously that a re-consent process, of feasible, would sufficiently address the Working Group's concerns such that the Working Group could come to a positive finding. (While the Working Group also had concerns about RGI's IRB process, including that the IRB had not conducted annual review of research protocols, those concerns alone would not result in a negative finding.) If the ACD recommends re-consenting and if this is approved by the NIH Director, the Working Group recommends that NIH staff follow up with RGI to ensure that the re-consent materials meet the NIH's standards.

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