

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

**Findings and Summary Regarding  
Cellartis AB Submission 2010-ACD-010**

**November 26, 2010**

Finding regarding all hESC lines in Cellartis AB Submission 2010-ACD-010

The ACD should consider recommending that the NIH Director approve the lines in this submission (SA001 and SA002, which would also allow use of subclone SA002.5) for use in NIH-funded research.

*First Discussion*

This new submission requests approval of two lines, SA001 and SA002, and a subclone of SA002, SA002.5. SA002 was derived from an embryo that had been frozen for 5 years. Because Swedish law states that embryos can be stored only for 5 years, this embryo was no longer eligible for uterine transfer and would have been discarded if it had not been donated. Details about SA001, which was cryopreserved, were less clear. The Working Group asked NIH to confirm the details about the embryos which were used to produce both lines.

Written consent was obtained from both donating couples. The submitter provided copies of IRB approvals and the consents to donate embryos for research purposes. Couples were asked for and gave their consent at four time points. The principal investigator for the research project had no contact with the couples, and the attending physician at the time of the donations was not involved with the research. The submission mentioned a letter provided to patients with cryopreserved embryos approaching the 5-year point; NIH requested a copy of that letter.

The primary reviewer noted that one of the lines, sub-clone SA002.5 was created from the parent line, SA002, which contained a trisomy. The sub-clone SA002.5 has a normal genotype. The Working Group then asked about NIH policy regarding approval of sub-clones for use in NIH-funded research. NIH stated that once parent line approval is obtained, then all sub-clones and modifications of the parent line are considered approved.

The Working Group noted that although the donating couple gave consent at several time points, what they were told as the embryo reached the 5-year limit was not known. It was also not clear whether the embryos donated for the lines were clinically viable. In an earlier communication with NIH, the submitter said that embryos stored in liquid nitrogen for the maximum time (5 years) were excluded for uterine transfer. The group also discussed whether the 5-year limit on cryopreservation affected the voluntariness of the decision to donate embryos for research. Other members noted that the limit may be set out of concern that the embryos would be damaged by the 5-year freezing point and could be considered a good medical practice decision. Others added that it may also serve as a mechanism to manage the bulk of embryos stored for an indeterminate

amount of time as long-term storage of embryos can be a complicated issue. In addition, although the 5-year limit is a national law in Sweden, the reasons for this limit are not clear. The Working Group requested follow-up with the submitters to understand the basis of the 5-year limit law in Sweden, as well as clarify the original clinical viability of the donated embryos used to derive these lines.

The Working Group agreed to table recommendations for this submission pending receipt of the following information or clarifications:

- The grade of the embryos used to derive SA001 and SA002.
- A copy of the letter sent to patients with frozen embryos nearing the 5-year legal limit.
- The justification for the Swedish national 5-year limit for cryopreserved embryo storage.

### *Second Discussion*

The Working Group continued discussion of this request based on additional information provided.

The response from Cellartis regarding the grade of the embryo from which SA001 was derived was not completely clear, although a protocol dated later indicated that they freeze only clinical grade embryos. Cellartis provided a copy of the letter sent to patients with embryos approaching the 5-year storage limit. Cellartis also stated they believe IVF treatment consents are not necessary in Sweden.

According to an email from Cellartis, their IVF clinic representatives indicated that it was their belief that the 5-year limit was established primarily to avoid large gaps between the ages of siblings, and also to minimize storage space and handling requirements. Research done by NIH staff suggested that patients are able to apply for an extension to the 5-year limit, under exceptional grounds, for consideration by Sweden's National Board of Health and Welfare. (NIH staff were unable to identify Swedish legislative history or other documents explaining the justification for the 5 year limit.) It is not known whether a cryopreservation fee is paid by patients with frozen embryos in Sweden.

NIH staff also provided the Working Group with an extensive 2010 survey report from the International Federation of Fertility Societies listing current cryopreservation policies in many countries and a draft paper written by NIH staff which summarized various embryo storage limits across a number of countries. Both of these documents showed existing limits for the storage of cryopreserved embryos vary, from no embryo freezing allowed to up to 10 years.

The Working Group recalled that it had already reviewed and provided a positive finding for a submission from the New South Wales, Australia (submission 2010-ACD-008 concerning hESC line Endeavor-2) with a 10-year limit on the storage of cryopreserved embryos. The ACD reviewed and recommended approval of this line, which was subsequently approved and listed on the NIH Registry in June 2010.

The Working Group discussed whether the Swedish embryo storage limit may have influenced patients in their decisions to donate embryos to research, and decided that in this case they were

comfortable with the limit. The Working Group had no other concerns about the consent process for this submission.

The Working Group agreed that while there is likely no specific time limit which would trigger a concern, the storage limit issue is part of a broader question: does a required decision at some time - due either to a time limit or possibly the imposition of a storage fee - tend to influence people to donate their embryos to research if they are not otherwise predisposed to it? The Working Group also recalled that the Guangzhou Medical College in China has a policy that the donors' ownership rights are relinquished if the renewal fee is not paid.

In closing, the Working Group agreed that as they go forward they need to work particularly closely with NIH on the issue of other nations' policies on embryo storage time limits to ensure that the reviews are informed, fair, and transparent.

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

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