Regarding item # 11: Consideration of adoption of interim regulation regarding covered stem cell lines.

On Wednesday July 24, 2013, the CIRM Scientific and Medical Accountability Standards Working Group will convene to consider an interim regulation regarding covered stem cell lines. Background materials for this meeting are attached. We will report the SWG's recommendation regarding the interim regulation for the Board's consideration at its meeting on July 25th.

CALIFORNIA'S STEM CELL AGENCY

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

July 1, 2013

To: CIRM Medical and Ethical Standards Working Group
From: CIRM
Re: Consideration of Exception for Covered Stem Cell Lines

Introduction:

In May 2013, Shoukhrat Mitalipov's Oregon Health & Science University (OHSU) research group reported the derivation of human embryonic stem cells by somatic cell nuclear transfer (SCNT). This report has generated scientific interest among CIRM grantees and the desire to utilize derived SCNT lines. CIRM's current policy prohibits the use of the OHSU SCNT lines because oocyte donors were financially compensated. CIRM requests the Medical and Ethical Standards Working Group (SWG) revaluate this prohibition with regard to CIRM grantees ability to utilize the resulting lines in light of recent scientific and policy developments.

CIRM Policy History:

Proposition 71's "prohibition on compensation" compels the ICOC to adopt standards "prohibiting compensation to research donors." This requirement has been consistently interpreted to prohibit the use of CIRM funds to financially compensate oocyte (or other cell or tissue) donors. In 2006, this interpretation was extended to exclude from use, in CIRM-funded research, any stem cell line where research donors were financially compensated, even if the derivation was done without the use of CIRM funds. Proposition 71, however, does not compel the ICOC to prohibit the use of stem cell lines where financial compensation is provided to the oocyte donors, provided that CIRM funds are not used to compensate the donors or derive the lines.

The policy to extend the prohibition to all stem cell lines was proposed by CIRM president Dr. Zach Hall in January 2006. At the time that Dr. Hall recommended this policy, there was scientific uncertainty concerning the feasibility and value of SCNT experiments and limited experience with oocyte donation programs for research. This uncertainty contributed to the prevailing view that CIRM should have a "uniform" (SWG 1/30/06, pp. 143-146) compensation standard.

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Scientific and Policy Developments

There have been scientific and policy developments since 2006 that address some of the prior uncertainties, including:

- The development of CIRM oocyte donation guidelines for human stem cell research
- The successful derivation of induced pluripotent stem cells (IPSCs) utilizing genetic reprogramming methods
- The successful derivation of stem cell lines in New York and Oregon utilizing SCNT methodologies.
- The development of a paid oocyte donation program in New York incorporating recommendations for voluntary informed consent and policies to avoid undue inducement.
- The initiation of CIRM disease team awards involving iPSC- and hESC-derived cell therapies

Policy Proposal

CIRM requests the Medical and Ethical Standards Working Group (SWG) consider a regulatory amendment to allow an exception for covered stem cell lines not considered "acceptably derived" under Title 17, California Code of Regulations, section 100080. Section 100080 pertains to stem cell lines use by CIRM-funded researchers (e.g. lines derived without CIRM funding). A report regarding CIRM's review of the OHSU lines is attached as Appendix 1 to provide an example of type of review and analysis CIRM would conduct under the proposed interim regulation.

The proposed *Exception for Covered Stem Cell Lines* would take the form of a procedural requirement where the CIRM President would present the results of a scientific and ethical evaluation to the ICOC. Based on this evaluation, the ICOC would determine whether the covered stem cell lines will advance CIRM's mission and would have the discretion to approve their use by CIRM-funded researchers.

CIRM Staff Recommendation:

Recommend Board approval of an *Exception for Covered Stem Cell Lines* (regulatory amendment section 100082) as an interim regulation.

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Appendix 1:
Consideration of Scientific, Ethical and Policy Consideration for Exception for Covered Stem Cell Lines

CIRM performed an evaluation of the OHSU SCNT derivation protocol. This evaluation was consistent with CIRM's MES Compliance Plan Policy and included a site visit to OHSU. The site visit included:

- A review of ESCRO membership and expertise
- Consideration of the scientific rational for the need to use human oocytes
- A description of the study protocol with regard to donor recruitment
- A review of the informed consent documents
- Interview of IRB, ESCRO and Research Integrity Officers
- Discussion of specific steps taken to support participant safety and autonomy consistent with CIRM regulatory requirements for oocyte donation
- Evaluation of scientific interest in the derived SCNT-derived stem cell lines

The OHSU ESCRO is consistent with the CIRM regulations and includes members with expertise in assisted reproduction. Prior to approving this protocol, Dr. Mitalipov was approved to conduct research on failed-to-fertilize and/or immature oocytes emanating from infertility treatment. After unsuccessful attempts to derive SCNT cell lines under this protocol, the ESCRO approved the use of oocytes from research donors. The study protocol was subsequently reviewed and approved by the OHSU IRB.

The research donor recruitment protocol involved multiple steps including but not limited to (1) telephone screening of interested participants responding to notices about the study, (2) required attendance in an informational seminar where the study and the protocol were described, (3) a period of time to deliberate between the informational seminar and consent process, and (4) donor informed consent consistent with CIRM and National Academy of Sciences (NAS) requirements. Once informed consent was obtained, the protocol did not deviate from the standard of care for all oocyte donors and included a psychological assessment.

CIRM reviewed the informed consent process and document utilized for oocyte and somatic cell donation and found them to be consistent with CIRM and NAS requirements. Interviews with the recruitment team revealed that

when presented with an option for research use, some research participants expressed a preference for donation for research over reproductive use.

The IRB and clinical staff confirmed the protocol was consistent with the CIRM oocyte donation guidelines for human stem cell research. The protocol is also reported in the group's publication in Cell. Consistent with CIRM donor protection policy, an insurance policy was purchased by the researchers to cover any adverse events that may occur as a result of participation in the study. No adverse events were reported.

Since the reported derivation, CIRM grantees have expressed interest in utilizing the SCNT lines. These cell lines are one of only three types of pluripotent stem cell lines, and one of only two types of pluripotent lines that can be used for autologous cell transplants. Since so little is known about how any of these cell types will perform for applications such as cell transplantation and disease modeling, it would be scientifically advantageous to consider the following:

- Differentiation potential: SCNT-derived cell lines differ from other pluripotent cell lines, which raises a question about whether they are capable of forming cell types with more mature characteristics than those derived from other pluripotent cell lines?
- Genetic/genomic stability in culture: IPSCs have been reported to be unstable in culture and subject to chromosomal aberrations like copy number variation. How does the genomic stability of SCNT-derived cell lines compare?
- X chromosome inactivation: ESCs and iPSCs differ in their X chromosome inactivation state. Would understanding X chromosome behavior in SCNT-derived cell lines further expand knowledge useful to move forward with all three cell types?
- Mitochondrial disease: Using SCNT, it is possible to generate cell lines in which the mitochondria and nuclear genomes come from different individuals. This could provide a useful tool for understanding the genetic contribution of each in a variety of diseases where mitochondrial defects are implicated.
- Efficiency and yield: Comparing different lines over a long culture period could identify factors that might improve efficiency and yield of direct reprogramming.
- Engraftment: SCNT-derived cell lines could differ from ESCs or IPCs in their detection by immune surveillance, which could impact the engraftment efficiency and durability of their cellular derivatives.

§ 100082. Exception for Covered Stem Cell Lines

(a) A covered stem cell line that is not considered "acceptably derived" under Title 17, California Code of Regulations, section 100080, may be used in CIRM-funded research if the ICOC determines in a public meeting that use of the covered stem cell line in CIRM-funded research will advance CIRM's mission. Factors to be considered by the ICOC in determining whether use of the covered stem cell line in CIRM-funded research will advance CIRM's mission include, but are not limited to, the following:

(1) the strength of the scientific or clinical rationale for use of the covered stem cell line, and how use of the covered stem cell line will advance CIRM's mission;

(2) the nature and adequacy of the consents given by the donors of human gametes, embryos, somatic cells or tissue used to create the covered stem cell line;

(3) the nature of the valuable consideration provided to the donors of human gametes, embryos, somatic cells or tissue used to create the covered stem cell line in exchange for their donation, including reimbursement for the cost of storage prior to donation;

(4) whether the donation of human gametes, embryos, somatic cells or tissue used to create the covered stem cell line was overseen by an IRB or equivalent; and

(5) whether the donation of human gametes, embryos, somatic cells or tissue used to create the covered stem cell line was consistent with "best practices" at the time of donation.

(b) The President of CIRM may request an exception by presenting a proposal to the ICOC in public session describing how use of the covered stem cell line will advance CIRM's mission based on the factors identified in subdivision (a).

(c) A CIRM grantee or potential grantee may request an exception by submitting a petition that includes the information specified in section 100081(a)(1)-(8) and that describes how use of the covered stem cell line will advance CIRM's mission based on the factors identified in subdivision (a)

(d) The ICOC must consider the merits of a request from the President or a petitioner in open session, and must vote to grant or deny the request or petition in open session. Members of the ICOC may consider confidential and proprietary information relating to the request or petition in closed session before taking action on the request or petition.