CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Scientific and Medical Accountability Standards
Draft Working Group Briefing Paper:
Use of Cell Lines Derived Prior to Effective-Date of CIRM MES Regulations

Background Acceptably Derived Cell Lines

The CIRM MES regulations contain provisions governing the derivation and use of hESC lines. Section 100080 established performance criteria for "acceptably derived" cell lines. Section 100080(a)(2)(A) specifies that gamete donors must provide informed consent for cell lines utilized in CIRM-funded research.

> § 100080 Acceptable Research Materials
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> All covered stem cell lines used in CIRM-funded research must be "acceptably derived."
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> (a) To be "acceptably derived," the stem cell line must meet one of the following criteria:
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> (2) The stem cell line is derived from human gametes, embryos, somatic cells, or tissue under the following conditions:
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> (A) Donors of human gametes, embryos, somatic cells or tissue gave voluntary and informed consent; and
> (B) Donors of human gametes, embryos, somatic cells or tissue did not receive valuable consideration. This provision does not prohibit reimbursement for permissible expenses as defined in California Code of Regulations, title 17, section 100020, subdivision (h), as determined by an IRB; and
> (C) Donation of human gametes, embryos, somatic cells or tissue was overseen by an IRB (or, in the case of foreign sources, an IRB-equivalent); and
> (D) Individuals who consented to donate stored human gametes, embryos, somatic cells or tissue were not reimbursed for the cost of storage prior to donation.

The provisions serve a major policy recommendation of the Standards Working Group – it requires comprehensive consent for materials utilized to derive cell lines.

One impact of this requirement is that cells or cell lines derived before the effective date of the regulations (November 2006) may not conform to the consent standard. The typical example involves cells or cell lines for which donor sources been made anonymous; consequently the ability to re-contact the donor(s) does not exist. This situation arose in the context of (1) the NIH hESC lines and (2) archived somatic cell lines that where deemed desirable for iPS experiments. In both cases materials could not be "re-consented" in accordance with detailed CIRM requirements because there are no identifiers associated with the cells. In these examples, the SWG recommended that the particular NIH hESC lines and somatic cell lines conforming to federal standards be available to researchers.

CIRM has identified an additional hESC line derived prior to November 2006 that does not conform to Section 100080(a)(2)(A).

Scientific Considerations

The line in question is a clinical grade hESC cell line. The line was derived under clinical manufacturing (cGMP) conditions with the intent of utilizing the line in Phase I clinical trials.

The cell line was derived from an embryo originally created for reproductive use in 2000 from an oocyte donated by a third-party. There was no payment to the original oocyte donor. In March 2005, (prior to the NAS Guidelines being issued) consent for stem cell line derivation was obtained from the couple with custody of the embryo. Obtaining consent from the original oocyte donor is not feasible now due to patient confidentiality.

The line's producer worked to ensure the line was suitable for use in clinical trials. They had informal discussions with the FDA, and the FDA indicated that extant consents are appropriate and sufficient for the use of the line in clinical applications.

Policy Context

The NAS guidelines require consent of all gamete donors for new stem cell line derivations, consistent with the CIRM regulations. The NAS guidelines include an "acceptably derived" standard.

> "Acceptably derived" means that the cell lines were derived from gamete or embryos for which
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> (1) The donation protocol was reviewed and approved by an IRB or, in the case of donations taking place outside the United States, a substantially equivalent oversight body;
> (2) Consent to donate was voluntary and informed;
> (3) Donation was made with reimbursement policies consistent with these Guidelines; and
> (4) Donation and derivation complied with the extant legal requirements of the relevant jurisdiction.

The NAS guidelines would deem lines derived before the standards took effect as "acceptably derived" if the consent process was consistent with the extant consent process.

Policy Considerations

CIRM has encountered situations where cells and hESC lines obtained prior to the effective date of the CIRM regulations have scientific utility but do not conform to the precise standards recommended by the SWG. In certain cases, the SWG has

recommended a direct regulatory remedy to enable use of materials for research. For example, hESC lines approved for use by the NIH were deemed "acceptably derived." In July 2007, the SWG recommended a policy that deems "covered stem cell lines" derived from somatic cells that conform to federal guidelines as "acceptably derived."

In the case of hESC lines derived before the effective date of the regulations, there may be an ongoing need to evaluate materials for use in CIRM-funded research. This evaluation might include "grandfathering" lines deemed appropriate or "disqualifying" lines deemed inappropriate. It is anticipated that the universe of lines subject to evaluation would be limited to a small number of lines with scientific significance or unique ethical concerns.

Considerations relating to the decision to approve or disqualify a particular hESC line would likely be unique to the specific line. Under these conditions a regulatory remedy may not be practical. Rather, an administrative evaluation procedure that enables consideration of the unique considerations relating to a specific line is advisable. Administrative remedies could include a process where lines were evaluated against scientific and ethical considerations in a consistent and transparent manner.