CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

7/17/2006

To: Scientific and Medical Accountability Standards Working Group (SWG)

From: CIRM

Re: Briefing Materials for July 27 SWG Meeting

Background:

On 11/22/06 the CIRM Medical and Ethical Standard (MES) regulations recommended by the Standards Working Group (SWG) became state law. On 2/16/07, the ICOC approved 72 grants totaling approximately $45 million over two years, to researchers at 20 academic and non-profit research centers.

These recently approved grants have served as the impetus for stem cell research oversight (SCRO) committees to begin to apply the MES regulations to specific research applications approved for funding. Over the course of SCRO committee reviews CIRM received a number of inquiries regarding specific regulatory requirements. These inquiries identified issues related to the regulations that warrant consideration by the SWG.

On 5/10/07 the SWG discussed additional regulatory consideration identified through CIRM's Evaluation Initiative. During these deliberations the SWG directed CIRM staff to evaluate the *Japanese Guidelines for Derivation and Utilization of Human Embryonic Stem Cells* for consistency with the MES regulations.

This briefing memo summarizes the regulatory considerations identified through SCRO committee review and summarizes the Japanese guidelines for consistency with the CIRM MES regulations.

Regulatory Considerations (ordered by section):

For the purpose of the 7/27/07 SWG meeting, three specific items have been identified for consideration in the agenda.

1. **Use of cell lines derived under *Japanese Guidelines for Derivation and Utilization of Human Embryonic Stem Cells***
2. **Limitations on payment for cells**
3. **Requirements for use of somatic cells and human tissue**

Each issue is summarized below. In addition, model language is suggested for addressing items 1 and 2. Item 3 involves criteria for the use of somatic cells and human tissue in CIRM-funded research with no language suggested.

1. Use of Cell Lines Derived Under *Japanese Guidelines for Derivation and Utilization of Human Embryonic Stem Cells*

Section: 100080 Acceptable Research Materials

Summary: At the5/9/07 SWG meeting, CIRM staff were requested to review the *Japanese Guidelines for Derivation and Utilization of Human Embryonic Stem Cells* for consistency with the MES regulations (see Attachment 1).

Issue: Consider whether to recommend to the ICOC that the MES regulations include stem cell lines derived under the *Japanese Guidelines* as acceptable "research materials."

Researchers have expressed interest in identifying additional cell lines that can be utilized in CIRM funded research without additional reviews. A delegation of Japanese scientists expressed the desire to include these cell lines as acceptable research materials.

Comment: Adding lines derived under the *Japanese Guidelines* would extend existing policy to additional research materials. Identifying such materials in the regulations facilitates research by reducing the need for SCRO committee review of cell lines.

Model Language:

Acceptable Research Materials

All covered stem cell lines used in CIRM-funded research must be "acceptably derived." To be "acceptably derived," the stem cell line must:

(f) Been derived in accordance with the Japanese Guidelines for Derivation and Utilization of Human Embryonic Stem Cells

2. Limitations on Payment for Cells (excluding "covered stem cell lines")

Section: 100080, subd. (e)(3) Acceptable Research Materials

Summary: Questions have arisen regarding the ability to purchase commercially available biological products for CIRM-funded research, particularly somatic cells and tissue that do not constitute "covered stem cell lines." Researchers have found confusing different sections of the California Health and Safety Code. Section 100080, subdivision (e)(3) states:

A person may not knowingly, for valuable consideration, purchase or sell gametes, embryos, somatic cells, or human tissue for research purposes pursuant to this chapter. This provision does not prohibit reimbursement for permissible expenditures as approved by a SCRO committee or IRB, or permissible expenses as determined by an IRB. "Permissible expenditures" means necessary and reasonable costs directly incurred as a result of persons, not including human subjects or donors, providing gametes, embryos, somatic cells, or human tissue for research purposes. Permissible expenditures may include but are not limited to costs associated with processing, quality control, storage, or transportation of materials.

100080(e)(3) is intended to place limitations on payments for cells. However, this section is redundant because the California Stem Cell Research and Cures Act (Proposition 71) defined permissible expenditures. The language contained in the act has been incorporated into CA H&S Code section 125290.35(b)(5) and reads:

Standards limiting payments for the purchase of stem cells or stem cell lines to reasonable payment for the removal, processing, disposal, preservation, quality control, storage, transplantation, or implantation or legal transaction or other administrative costs associated with these medical procedures and specifically including any required payments for medical or scientific technologies, products, or processes for royalties, patent, or licensing fees or other costs for intellectual property.

Issue:

It may be redundant and ambiguous to have two separate standards governing the use of materials. A single standard based on the explicit language in California Stem Cell Research and Cures Act (Proposition 71) is desirable.

Comment: The recommendation is intended to achieve exclusivity in the regulations and to enhance clarity this recommendation does not constitute a policy change. This proposed language has no impact on the existing prohibiting valuable consideration to donors of gametes, embryos, somatic cells or human tissue.

Model Language:

Limitations on Payments for Cells

Payments for the purchase of covered stem cell lines, gametes, embryos, somatic cells, or human tissue to persons other than the original donors of gametes, embryos, somatic cells or human tissue shall be limited to those cost identified in CA H&S code 125290.35.

3. Requirements for Use of Somatic Cells and Human Tissue

Section: 100090 Additional Requirements for CIRM-Funded Derivation

Summary: Section 100090 requires that CIRM-funded research that is designed to derive human stem cell lines comply with sections 100080 (acceptable research materials) and 100100 (informed consent requirements):

Where CIRM funds are to be used to derive new human stem cell lines, in addition to the requirements of Code of California Regulations, title 17, section 100080, subdivision (e), the SCRO committee must confirm that donors of gametes, embryos, somatic cells or human tissue have given voluntary and informed consent in accordance with Code of California Regulations, title 17, section 100100.

Section 100090 has the effect of applying retroactively the exact consent requirements of section 100100 to any research intended to derive a new covered stem cell line. As a consequence, existing somatic cell lines obtained with informed consent may not be available for reprogramming experiments unless consent was obtained in accordance with the exact requirements of section 100100.

The reprogramming of somatic cells to an ES-like state represents a promising approach to stem cell research. The recent publications by Maherali et al., (Cell Stem Cell 1, July 2007) and Wernig et al., (Nature, June, 2007) highlight the potential for reprogramming to give rise to cells with induced pluripotent potential.

At least one CIRM funded institution has a number of investigators who have been studying epigenetic control of gene expression for many years and their work often utilizes commercially available human somatic cell lines. This same institution has proposed reprogramming experments that have been approved for funding by the ICOC. Under the current requirements of section 100090, continuation of this work with the intent to derive ES-line cell is not feasible. Based on a review of the record, it is not clear that the SWG intended to apply CIRM-specific consent requirements retroactively to commercial cell lines that are not embryonic stem cell.

Issue:

The SWG might consider a more flexible standard for use of somatic cells. Interviews with leading researchers suggest the inability to utilize commonly available commercial somatic cells (non-covered stem cell lines) lines would limit CIRM-funded researchers from attempting to replicate studies.

Policy options:

To be discussed.

Attachment 1

May 16, 2007

To: Scientific & Medical Accountability Standards Working Group (SWG)
Fr: CIRM
Re: Consistency of Japanese Guidelines for Derivation and Utilization of Human Embryonic Stem Cells CIRM MES Regulations Title 17 California Code of Regulations Section 100010-100110

Currently the Japanese Regulatory Body (a ministry) imposes a series of procedures for the derivation and use of human embryonic stem cells. These procedures are detailed in the Japanese Guidelines for Derivation and Utilization of Human Embryonic Stem Cells (hESC) (attachment 1). On May 10, 2007 it was the sense of the CIRM Scientific and Medical Accountability Standards Working Group that CIRM should evaluate the compatibly of the Japanese Guidelines for Derivation and Utilization of hESC with the CIRM MES regulations Title 17 California Code of Regulations Section 100010-100110.

It was previously determined that the UK Human Fertilisation and Embryology Authority (HFEA) Code of Practice and Canadian Institutes of Health Research (CIHR) Guidelines for Human Pluripotent Stem Cell Research are consistent with the informed consent and oversight provisions section 100080, subdivisions (e)(1 and 4), in the CIRM MES regulations. Based on this determination, covered stem cell lines created under the HFEA and CIHR authority are deemed to be "acceptably derived" for use in CIRM-funded research. The purpose of this evaluation is to consider whether hESC lines derived under the Japanese guidelines conform to the informed consent and oversight provisions section 100080, subdivisions (e)(1 and 4), in the CIRM MES regulations.

- Informed Consent

The Japanese regulations limit source material for hESC derivation to embryos created for reproductive purposes. Paragraph II articles 22-23 contain extensive consent provisions applicable to all gamete donors. In addition, consent may be withdrawn prior to hESC derivation and there are requirements for protecting personal information.

- Payments and Expenses for Donors

Article 4 stipulates that embryos shall be donated "gratuitously" for derivation of human ES cells. There is a provision allowing for necessary expenses. This provision is consistent with the definition of "permissible expenses" in the CIRM regulations. It is typically used to provide for transportation expenses for a donor who is asked to come to a hospital or the other facility to consent for donation.

- Oversight

Article 13 details the review and oversight obligations of the deriving institute. These obligations combine the SCRO and IRB responsibilities and requirements of the CIRM regulations.

- Other Issues

Article 6(4) requires embryos to be used within 14 days of fertilization. The 14 day requirement is consistent with the NAS guidelines. Proposition 71 sets an upper limit of 12 days after cell division begins.