Proposed Procedure for Developing CIRM's Response to the National Institutes of Health Guidelines for Human Stem Cell Research

Introduction

On April 17, 2009, the National Institutes of Health released draft guidelines to implement President Obama's Executive Order relating to stem cell research (see Attachment A). The guidelines, once adopted, will govern the conduct of NIH-funded research involving human stem cells. NIH has requested public comment on the proposed guidelines within 30 days of publication in the Federal Register, or by May 24, 2009. (The draft guidelines are included as Attachment A.)

As the largest funder of human embryonic stem cell research in the world, CIRM has an interest in ensuring that the NIH rules are consistent with CIRM's medical and ethical standards, which were modeled upon guidelines adopted by the National Academies of Science, and with the best interests of science and patients.

CIRM staff has evaluated the draft NIH guidelines, compared them to CIRM's medical and ethical standards and those of other stem cell research funders, and explored the potential effect of the guidelines on CIRM-funded researchers. In attachment B, we identify those provisions in the draft guidelines that are either inconsistent with CIRM's medical and ethical standards or that may pose barriers to CIRM-funded researchers. We also discuss CIRM's proposed response to the guidelines.

In light of the short time frame within which CIRM must respond and the complexity of the issues to be addressed, we propose that the Board designate a taskforce to work with CIRM staff to craft CIRM's response to the proposed guidelines on behalf of the Board. As a delegated committee of the Board, the taskforce would be subject to Bagley-Keene and would conduct its meetings in public and invite public comment.

PROPOSAL: Appoint a task force to work with CIRM staff to develop CIRM's response to the proposed NIH guidelines and authorize the task force to approve the comments submitted by CIRM. The task force will conduct its meetings in public and invite public comment.

Policy Evaluation Process

On the request of the CIRM Executive Committee, staff initiated a policy evaluation process. This process included the following steps:

- Policy Review: The Draft National Institutes of Health Guidelines for Human Stem Cell Research were evaluated against the CIRM Medical and Ethical Standards Regulations.
- Key Informant Interviews: CIRM interviewed leading researchers at California-based institutions. These interviews were intended to identify policy considerations among current and potential CIRM grantees and better enable prioritization of comments.
- Impact Analysis: CIRM contacted a number of stem cell research oversight committees in California to consider how the draft guidelines might impact the availably of materials used in NIH-funded grants.

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- Communications with National Partners: CIRM assisted in a survey of the membership of the Interstate Alliance on Stem Cell Research to consider whether the policy would impact collaboration and exchange. CIRM participated in a member meeting of the Committee for the Advancement of Medical Research in which members of the NIH policy team took questions from the membership.
- Identification of Opportunities to Support Collaboration and Exchange: CIRM in conjunction with its national partners identified policy options for constructively addressing considerations identified through this evaluation.

The result of the policy evaluation process is summarized in the following sections. This evaluation is ongoing and subject to revisions as additional information becomes available.

Policy Review:

Attachment B *Comparison between NIH Draft Guidelines and CIRM MES Regulations* compares each policy on a point-by-point basis. The focus is on areas of policy deviation indentified at this time. This comparison serves to identify specific topics worthy of comment or clarification in future correspondence with NIH. The remainder of this section focuses on broader consideration relating to the CIRM/NIH policy frameworks.

Federal Restrictions on hESC Derivation

It is important to note Executive Order 13505 stated:

> *Sec. 2. Research. The Secretary of Health and Human Services (Secretary), through the Director of NIH, may support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell research, to the extent permitted by law.*

Under current law, NIH is constrained by the Dickey-Wicker amendment which states the following:

> *SEC. 509. (a) None of the funds made available in this Act may be used for--*
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> *(1) the creation of a human embryo or embryos for research purposes; or*
> *(2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and Section 498(b) of the Public Health Service Act [1](42 U.S.C. 289g(b)) (Title 42, Section 289g(b), United States Code).*
>
> *(b) For purposes of this section, the term "human embryo or embryos" includes any organism, not protected as a human subject under 45 CFR 46 (the Human Subject Protection regulations) . . . that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes (sperm or egg) or human diploid cells (cells that have two sets of chromosomes, such as somatic cells).*

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The draft NIH policy is consistent with federal law in so far as it only authorized the utilization of hESC lines but not their actual derivation at the blastocyst stage. NIH funds may not be used for derivation because such work results in the destruction of a human blastocyst.

NIH Discretionary Policy

NIH appears to have exercised some discretion in the draft policy by prohibiting the use of existing cell lines derived via parthenogenesis or IVF if derived specifically for research and potential future lines derived through somatic cell nuclear transfer. NIH has indicated that this limitation is consistent with past legislation enacted by congress.

"Acceptably Derived" Standard a Core Difference Between Draft NIH Policy and CIRM Regulations

The following sections identifies key informants concerns and provide an impact analysis suggesting that the draft policy may disqualify some established hESC lines. It is helpful to understand how the CIRM regulations (and the NAS guidelines) balanced the desire to allow the utilization of hESC lines derived prior the establishment of regulations or utilization of lines from outside jurisdictions governed by different guidelines or laws.

CIRM (and the NAS) adopt a two-part framework for determining whether a hESC line may be utilized for research.

CIRM/NAS have established an "acceptably derived" standard for lines derived prior to the effective date of the regulations or lines derived outside CIRM jurisdiction. The "acceptably derived" standard stipulates hESC lines must meet 3 criteria:

1. Donors provided informed consent (without specifying specific consent criteria)
2. Donors were not paid to provide balstocysts for research use
3. There was oversight by an IRB or equivalent

For derivations funded by CIRM, more detailed consent and oversight requirements, largely consistent with the draft NIH guidelines apply. This specific and limited context is the basis for stating: "the conditions required by the NIH are largely consistent with requirements CIRM has developed for derivation performed by our grantees."

Key Informant Interviews:

CIRM conducted interviews with stem cell program directors (3), research administrators / SCRO committees (5), research advocacy organizations (1) and other state-based research programs (1). A number of themes consistently emerged from these interviews:

- The draft policy appears to be generally consistent with existing CIRM/CDPH practice for the derivation of new hESC lines from surplus IVF embryos. There were some concerns over how NIH will interpret some of the exact standards, but moving forward, prospectively, it appears current practice under the CIRM/CDPH/NAS regulatory framework can be adapted to satisfy the draft NIH policy. For areas of uncertainty (see policy comparison table), it will be helpful to obtain clarification and guidance from NIH.

Understanding acceptable practice for specific criterion will be important for the research community.

- The draft policy sets "a high bar" for consent and disclosure. There are concerns that established cell lines may not meet the proposed standard. Substantial foundational research has been performed utilizing established lines. NIH should consider a "grandfathering" clause or other mechanism that enables continued use of established lines. NIH should give consideration to whether a particular line was derived in accordance with consensus guidelines or the legal requirements at the time of consent or derivation.

- The draft policy places the burden of proof on institutions and researchers. A number of concerns arise from requiring individual institutions to perform independent evaluations. First, each evaluation is resource intensive resulting in inefficiency. It would be more efficient to develop a centralized evaluation mechanism designed to identify compliant lines – establish an official registry. Further, experience suggests there may be uncertainty to whether specific cell lines conform to every requirement of the draft guidelines. This uncertainty may result in qualifying lines not being utilized. There was broad consensus that a registry of compliant lines would be the most efficient method for identifying lines and ensuring promising research materials are not unnecessarily disqualified.

- For grantee institutions the promulgation of NIH guidelines raises question related to the implementation of grants where a mix of funding is involved. For example, one institution identified the case where research involves a comparative analysis of multiple hESC lines. It is conceivable that such a study could involve lines not recognized or approved by every funding source. Harmonization of rules, to the extent allowed by law, would be desirable from this grantees perspective.

- For state programs that have adopted the NAS Guidelines or institutions adopting them voluntarily, the draft policy appears to be generally consistent with existing practice for the derivation of new hESC lines from surplus IVF embryos. NAS staff has prepared a separate draft policy review comparing their guidelines to the draft NIH guidelines.

Impact Analysis:

CIRM staff sampled hESC utilization by grantees in the New Faculty I and New Cell Lines research programs (thus they conform to the NAS guidelines and the CIRM regulations). Based on this sample, we indentified providers of interest[1]. For a sample of these suppliers, we were able to obtain correspondence describing the consent and derivation procedures for hESC derivation. Our conclusion from this preliminary analysis is that the consent protocol for some lines does not include all items identified by NIH in its eligibility criteria, suggesting some scientifically significant lines may not qualify. All lines evaluated were derived from balstocysts created for reproductive purposes but no longer required for family planning.

Communications with National Partners:

[1] We have refrained from identifying specific suppliers to avoid any premature determination of compliance with a draft guideline. Further, the evaluation involved correspondence from suppliers. A more complete evaluation is necessary for any formal determination.

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CIRM is continuing to correspond with our national and international partners through the Interstate Alliance on Stem Cell Research (IASCR). At this time, our partners in other states supporting stem cell research have arrived at conclusions, regarding policy and impact analysis, substantially similar to those articulated in this document. The IASCR will be meeting on May 5 with NIH to review the draft policy. The IASCR may provide additional comments to NIH pending further deliberations and analysis.

Identification of Opportunities to Support Collaboration and Exchange:

CIRM has developed a proposed mechanism for state programs through stem cell research oversight committees to certify hESC lines have been derived in accordance with the CIRM regulations. A complementary mechanism is being considered by the Interstate Alliance on Stem Cell Research. (see Attachment C: Certification Form for Human Pluripotent Stem Cell Line Derivation). This certification process was developed in recognition of the need to identify to lines that meets CIRM/NAS standards. Certified lines would be "research ready" eliminating the need for multiple reviews by institutions. This approach may be an approach NIH could consider to support the registration of compliant lines.

Options & Possible Next Steps:

- Based on the *Comparison between NIH Draft Guidelines and CIRM MES Regulations* and additional data that become available, develop specific comments or points of clarification related to the draft guidelines.

- Consider whether the Standards Working Group should make suggestions for revisions to the MES regulations to support the regulatory consistency.

- Work with state and national partners to coordinate the development of proposals that serve to address barriers or sources of inefficiency.