CALIFORNIA'S STEM CELL AGENCY

SCIENTIFIC AND MEDICAL ACCOUNTABILITY STANDARDS WORKING GROUP
BACKGROUND: REVIEW AND OVERSIGHT OF ANIMAL STUDIES

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Background

In 2006, CIRM enacted the first comprehensive regulatory requirements for the review and oversight of human stem cell research.[1] CIRM's policies are based on the National Academies' (NAS) Guidelines for Human Embryonic Stem Cell Research.[2] In certain instances, CIRM policies are more prescriptive than the NAS recommendations due, in part, to California state requirements for regulatory clarity.[3] Whereas guidelines tend to suggest issues for consideration, regulations must establish clear performance goals.

One example where CIRM's regulations are more prescriptive and expansive in scope than the NAS Guidelines are studies where human stem cells are transplanted into animals. CIRM requires a stem cell research oversight committee (SCRO) to review and approve certain animal studies. In contrast, the NAS Guidelines state that the same studies do not *require extensive ESCRO (SCRO) committee review.*

In response to a CIRM survey, seven SCRO committees reported reviewing 77 protocols involving transplantation of human stem cells to animals. SCROs ask for clarifying information (such as length or study, number of animals or whether experiments would be repeated) as a condition of approval, but none of the respondents reported requiring changes to the scientific protocol based on SCRO review. The same survey and additional interviews with SCRO committees outside California did not identify overt behavioral or physical changes in animals as a result of the transplantation of human stem cells.

The SCRO committee review requirement has created a barrier for some organizations seeking to initiate FDA-mandated pre-clinical animal studies. These organizations are commercial or non-profit entities. CIRM 2.0 is designed to attract national and international applicants from jurisdictions where SCRO committees are not part of the system for research review and oversight. Thus, CIRM is concerned that the absence of a SCRO committee may delay the initiation of awards.

CIRM is recommending that the SWG consider amending this policy to allow greater flexibility for the review and oversight of animal studies. Additional policy

[1] http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0040114
[2] http://www.nap.edu/openbook.php?record_id=11278
[3] Regulations must be clear so the persons directly affected by them will easily understand their meaning.

recommendations for aligning the CIRM regulations with the NAS recommendations are provided. Policy options are described below.

NAS Guidelines and CIRM Regulations

With regard to the review and oversight of studies where human stem cells are transplanted to animals, the CIRM regulatory requirements state:

> *Research introducing covered stem cell lines into non-human animals or introducing neural-progenitor cells into the brain of non-human animals … may not commence without SCRO committee review and approval.*[4]

Whereas the 2010 Amendments to the NAS Guidelines state:

> *Transplantation of differentiated derivatives of hES cells or even hES cells themselves into adult animals will not require extensive ESCRO committee review. If there is a possibility that the human cells could contribute in a major organized way to the brain of the recipient animal, however, the scientific justification for the experiment must be strong, and proof of principle using nonhuman cells, is desirable.*[5]

However, the 2010 Amendments to the NAS Guidelines also state:

> *Experiments in which hES cells, their derivatives, or other pluripotent cells are introduced into nonhuman fetuses and allowed to develop into adult chimeras need more careful consideration because the extent of human contribution to the resulting animal may be higher. Consideration of any major functional contribution to the brain should be a main focus of review.*[6]

Policy Considerations and Options

1. CIRM recommends the SWG recommend policy changes designed to provide flexibility in the review and oversight of studies involving the transplantation of human stem cells into **adult** animals. Options include the following:

    a) No Additional Review: Consider removing the requirement for review of animal transplantation studies involving (1) covered stem cell lines and/or (2) cells derived from covered stem cell lines. Animal research will still be subject to IACUC review and oversight.

[4] California Code of Regulations Section 100700 (e).

[5] 2010 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research section 6.5 *Research Use of hES Cell Lines*

[6] 2010 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research section 6.7 *Research Use of hES Cell Lines*

b) Exempt Certain Studies: Consider exempting rodent studies from SCRO review and/or studies mandated pursuant to a regulatory requirement (e.g. FDA-mandated pre-clinical studies). Rodent studies will still be subject to IACUC review and oversight.

c) Specify Studies of Interest: Consider identifying types of studies where additional review and oversight is warranted. For examples, studies designed to transplant or engraft human organs or features.

d) Flexible Additional Review: Consider maintaining the current review requirement and give awardees the option of having their IACUC perform the review of animal protocols as specified in the CIRM regulations.

2. CIRM recommends the SWG continue to recommend SCRO review and oversight of chimeric studies involving the transplantation of human stem cells into animal blastocysts or fetuses pursuant to the NAS recommendations. Such studies may not fall under the jurisdiction of an IACUC if vertebrate animals are not involved.