CIRM Standards Working Group Summary and Guidance for Oversight of Human Stem Cell-Based Embryo Models

On February 9, 2024, the California Institute for Regenerative Medicine convened the Scientific and Medical Accountability Standards Working Group. The record for this meeting may be found here. The working group charge was to:

- Consider the use of human pluripotent stem cell (hPSC)-based embryo model systems in research.
- Review CIRM's standards involving the oversight of research protocols in light of advances in hPSC-based embryo models.
- Consider whether further guidance is warranted.

Participants included members of the Standards Working Group, CIRM leadership, and representatives from grantee organizations responsible for the review and oversight of CIRM-funded research (institutional officials).

Background On Stem Cell-Based Embryo Models:

Advances in stem cell science have resulted in the development of "integrated embryo models", i.e. models that include both embryonic and supporting extraembryonic tissues, for the study of human development and disease etiology. These models are organized three-dimensional structures derived from human pluripotent stem cells that mimic developmental processes that occur in early human embryos.[1] During the 2/9/24 meeting a definition was presented:

> **Stem cell-based embryo models:** *In vitro 3D cultures of pluripotent stem cells +/- other cell lines that reproducibly and robustly generate organized structures that model specific stages or structures of the in-vivo embryo.*

"Different stem cell-based embryo models, obtained with different methods, …exhibit different levels of completeness when compared to embryos".[2] However, at this time, even the most advanced mouse embryo models fail to form viable offspring and therefore, stem cell-based embryo models are currently not considered equivalent to embryos[2]. While the potential to produce offspring cannot be tested in human for ethical reasons, it is possible, and probably likely, that some non-human embryo models will be shown to have that capacity in the future. At that time, and considering additional factors, such as the high degree of resemblance of the human embryo model to the human embryo at the morphological, cellular and molecular levels, human stem cell-based embryo models may be considered equivalent to human embryos for oversight purposes.[3]

[1] https://www.isscr.org/isscr-news/isscr-statement-on-new-research-with-embryo-models
[2] https://www.nature.com/articles/s41556-023-01289-4
[3] https://www.cell.com/cell/fulltext/S0092-8674(23)00807-3

Regulatory Policy Context:

Because human pluripotent stem cells serve as the building blocks for these models, CIRM-funded stem cell-based embryo model protocols are governed by our Medical and Ethical Standards Regulations which require scientific and ethical oversight by Stem Cell Research Oversight (SCRO) committees. This regulatory framework was described at the 2/9/24 meeting.

CIRM's regulations require different levels of oversight depending on the nature and purpose of the experiment. They either require (1) written notification of the SCRO committee (hereafter 'SCRO notification') or they require (2) heightened oversight by convening of the SCRO committee for annual review and approval (hereafter 'annual SCRO review and approval'). For instance, protocols involving the in vitro use of pluripotent stem cells require SCRO notification, while protocols involving the use of human embryos require heightened oversight including annual SCRO review and approval, consistent with established research guidelines.[4] Institutional officials informed the working group that research protocols where SCRO notification is required undergo an administrative review by the SCRO committee administrator(s).

SCRO committees have requested clarification of how protocols involving human stem cell-based embryo models should be overseen in the context of CIRM's regulations. These models currently fall in the category of in vitro research involving pluripotent stem cells requiring SCRO notification. However, the recent development of integrated embryo models has resulted in constructs with advanced developmental potential relative to previous models.[3] Therefore, the International Society for Stem Cell Research and scholars have suggested a deliberative oversight framework, consistent with annual SCRO review and approval, for protocols involving integrated embryo models.[5,6] This framework includes the recommendation that there be a compelling scientific justification for the use of integrated embryo models that cannot be otherwise addressed by alternative approaches. Consistent with this recommendation, CIRM's existing Medical and Ethical Standards include a requirement that the SCRO committee be provided an "acceptable scientific rationale" as part of the annual SCRO review and approval of research protocols.[7]

[4] https://www.nationalacademies.org/our-work/guidelines-for-human-embryonic-stem-cell-research
[5] https://www.isscr.org/guidelines/blog-post-title-one-ed2td-6fcdk
[6] https://www.nature.com/articles/d41586-023-03062-x
[7] Note institutional officials indicated that the scientific rationale is considered in both administrative and full review of protocols.

CIRM SWG Guidance:

Given the recent and fast-changing nature of human stem cell-based embryo model research, CIRM recommends that the following guidance be applied to protocols involving **not only integrated but also other "complex" human stem cell-derived embryo models that mimic peri- and post-implantation stages of development.** CIRM recommends that:

(1) protocols involving such models be subject to annual SCRO review and approval, and
(2) the reason for the use of the integrated or otherwise complex model shall be included in the scientific rationale.
(3) the experimental stopping point should be defined ahead of time and not be open-ended.

As part of its review, the SCRO committee should consider the complexity of the model and whether the proposed experimental stopping point is appropriate for the scientific question under study.

Consistent with existing CIRM regulations and international guidelines, transplantation of a human stem cell-based embryo model into a uterus is not eligible for CIRM funding. To the extent a CIRM awardee is licensing or otherwise providing a CIRM-funded Stem Cell-Based Embryo Models to a third party we recommend including adherence to this guidance as part of the transfer agreement.

Implementation Considerations:

To facilitate implementation of this guidance, CIRM will administer a voluntary subscription listserv for SCRO committees. Meeting participants indicated that listservs have historically provided a venue for sharing operational experience implementing stem cell guidelines and regulations. There was consensus that a revitalized listserv would help to support consistent application of a CIRM guidance.

As experience is gained with stem cell-based embryo models, this guidance should be reevaluated. For example, it may be appropriate for certain protocols to undergo administrative review by the SCRO committee (as opposed to annual SCRO review and approval) in the future. Conversely, if research reaches the point of demonstrating that certain embryo models are equivalent to the embryo, as described above under 'Background On Stem Cell-Based Embryo Models', applicable human stem cell-based embryo models will have to be overseen as embryo research.