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Draft Recommendations for the CIRM Scientific and Medical Accountability Standards Working Group (SWG) Workshop on Human Gene Editing

On February 4, 2016 the CIRM Scientific and Medical Accountability Standards Working Group (SWG) Workshop of Human Gene Editing was conducted:

<https://www.cirm.ca.gov/agendas/01122016/standards-working-group-meeting>. At the workshop, a list of policy issues and questions emerged. The CIRM Team was tasked with working with the co-chairs to draft a written response to these issue and questions. This document represents the draft response.

The Draft Recommendations are being circulated to the SWG membership for comment. The Draft Recommendations may be modified based on SWG comments. A majority of the Draft Recommendations may be addressed without further action by the SWG or the ICOC. Certain recommendations, notably number 6.1, would require the development of new policies and further action by the SWG and CIRM's Board. Based on SWG member comments, the CIRM Team will work the SWG co-chairs to draft Final Recommendations to be submitted to the CIRM Board.

1. **Consent for Embryo Donation (New Collection)**: Is embryo donor consent adequate and effective?

The CIRM regulations do not explicitly require that human embryo donors be informed that donated embryos may be genetically modified. The current language states that "derived cells or cell products may be used in research involving genetic manipulation."

Recommendation 1.1: CIRM can immediately develop a guidance document highlighting the fact that the existing language does not explicitly address the genetic manipulation of human embryos. This guidance document should suggest that researchers prospectively obtain permission for gene editing, to allow widest scientific uses for donated embryos. Embryo donor programs could develop informed consent protocols that include model language addressing the editing of human embryos. Such language should ensure donor consent specifically addresses the ranges of research uses eligible for CIRM funding.

2. **Risk to Germline from Somatic Cell Editing**: Are there off-target effects from somatic cell genome editing that impact the germline?

Working Group members expressed concerns over potential off-target impacts where the patient germ line is affected by somatic cell gene editing. Dr. David Baltimore suggested the potential for off-target impacts should be investigated. During the workshop a report was provided on the National Academy of Sciences and National Academy of Medicine consensus study on the scientific, medical, and ethical

considerations of human gene editing – including germline editing. Off-target impacts are within the scope of this study.

Recommendation 2.1: The concerns raised at the Workshop have been forwarded to the National Academy of Sciences and National Academy of Medicine committee. The CIRM Team should continue to track this study and report any new information regarding off-target effects to the SWG. In addition, if researchers submit protocols with the explicit aim of studying the potential for off-target modifications to germ line (e.g., isolating primordial germ cells and maturing them in vitro), this should be described explicitly in consent process.

3. **Oversight and Donor Protection:** Is gamete and embryo genome editing research subject to effective oversight?

CIRM regulations require review and oversight of embryo research and specify requirements for informed consent. Review and oversight is performed by stem cell research oversight (SCRO) committees. In addition, the CIRM grant review process includes a comprehensive evaluation of the scientific merit of a proposed project.

Recommendation 3.1: Continue review and oversight by SCRO committees, and provide additional guidance as necessary (e.g., Recommendation 1).

4. **Prohibition on Implantation:** Should CIRM reconsider the regulatory prohibition on implantation of a “genetically modified” embryo to the uterus?

CIRM’s regulations prohibit funding of research / clinical interventions where a genetically modified embryo is implanted into a uterus for reproductive purposes. During the workshop, it was reported that the International Summit on Human Gene Editing Organizing Committee reported: “It would be irresponsible to proceed with any clinical use of germ line editing unless and until (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application.”

During the workshop, it was suggested that CIRM adopt the Summit standard. However, others advocated for the existing CIRM standard which prohibits nuclear genome editing for reproductive purposes. Further, a standard based on “broad societal consensus” may be considered ambiguous and not appropriate as a regulatory standard. Workshop participants also noted that the FDA may be prohibited from considering clinical trials for germ line/embryo genome editing. Finally, the SWG and the ICOC maintain the ability to reconsider CIRM regulatory requirements.

Recommendation 4.1: No change to the existing regulatory prohibition.

5. Modification of mDNA: Is mDNA modification within the scope of the CIRM prohibition described in 4?

During the workshop, the substantial differences between mDNA and nuclear DNA was discussed. In addition, the ISSCR Guidelines distinguish between mDNA and nuclear DNA with the aim of supporting clinical research to address mitochondrial disease while imposing a moratorium on clinical use of nuclear DNA editing. During the development of the CIRM prohibition there was not reference to mDNA; the discussion was limited to nuclear DNA.

Policy Determination 5.1: The CIRM prohibition does not apply to mDNA. Any CIRM-funded research involving modification of mDNA in a clinical context must comply with applicable state and federal laws and regulations.

6. Assurances Against Ineligible Activities: Can CIRM provide assurance that grantees will not utilize inventions for prohibited activities in the future?

The CIRM team was asked to consider whether CIRM could provide assurance against ineligible activities. One option is to develop a policy that would prohibit and penalize a grantee for utilizing CIRM-funded inventions for prohibited activities in the future. For example, a grantee could be funded to develop a clinical protocol with the aim of performing mitochondrial repair utilizing genome editing, but under this new language, the grantee would be prohibited from performing nuclear genome editing for reproductive purposes and be penalized for violating the prohibition (e.g., return of CIRM award/ineligible for future CIRM funding).

Recommendation 6.1: Develop a policy proposal to receive feedback and comment from interested parties.

7. Patient & Public Engagement: What are the views of patients and the public regarding embryo genome editing?

The National Academy of Sciences and National Academy of Medicine consensus study on the scientific, medical, and ethical considerations of human gene editing includes mechanism for including the public and assessing views on genome editing.

There may be specific patient populations that should be engaged to ascertain their views on gamete and embryo genome editing research. For example, patients effected by mitochondrial disease may perceive genome editing research to be of direct benefit to them.

Recommendation 7.1: With regard to the views of the general public, continue to track the National Academy of Sciences and National Academy of Medicine consensus study.