

Subject: [EXT] Comments for the January 29 ICOC meeting on CIRM Preferences

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From: Okada, Hideho

To: Lana Morales

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Dear Ms. Morales-

Could you please forward my email letter below to the ICOC Board Meeting on January 29th? – Thank you so much in advance.

Hideho Okada

Dear Chair, members of the Board, and members of the ICOC Science Subcommittee,
My name is Hideho Okada. I am a Professor of Neurosurgery at UCSF and a physician–scientist working in the field of malignant glioma immunotherapy. I am deeply grateful for CIRM’s longstanding support of our shared mission to develop transformative therapies for patients with devastating diseases. I have been fortunate to receive support through the DISC2, TRAN1, and CLIN2 mechanisms.

In our current CLIN2-funded phase I study (CLIN2-15562), we are evaluating autologous T cells engineered with lentiviral EGFRvIII-primed synNotch–CAR circuit (E-SYNC) in patients with glioblastoma. Although this study began less than two years ago, we are already observing an excellent safety profile and encouraging early signals of efficacy, with two participants achieving progression-free survival beyond 18 and 15 months, an uncommon outcome in this patient population. Building on these results, we are developing a second-generation approach using a brain-specific antigen (BCAN-primed synNotch–CAR; B-SYNC) to broaden applicability and enhance efficacy.

Against this backdrop, I would like to respectfully share concerns regarding the current CIRM Preferences implemented with approval from the ICOC on September 26, 2024, for administrative triaging of proposal applications, specifically the simultaneous prioritization of pluripotent stem cells (PSC), in vivo gene therapy, and non-viral nucleic acid delivery within the PDEV and CLIN2 programs.

From the perspective of early-phase cancer immunotherapy trials, the primary objective must remain the clear demonstration of safety and biological efficacy. For all good reasons, clinical trial design needs to be incremental: introducing one novel component at a time while relying on established platforms for other elements allows investigators, regulators, and patients to understand what drives success or failure. In our current CLIN2 study, for example, the novelty lies in the E-SYNC circuit, while autologous T cells and ex vivo lentiviral gene transfer provide a well-characterized and clinically validated backbone.

I fully agree with CIRM that PSC-based therapies, in vivo gene delivery, and non-viral systems represent important future directions for the field. However, these technologies are not yet sufficiently mature for

broad deployment in early-phase clinical trials, particularly for complex engineered cell therapies with large genetic payloads. Non-viral platforms, for instance, currently face practical limitations for delivering large circuits such as E-SYNC or B-SYNC at a clinical scale. While we are actively developing non-viral versions of these approaches, they are not yet ready for patient-facing studies.

For these reasons, I believe that prioritizing these emerging technologies first within DISC-type preclinical mechanisms, and then transitioning them stepwise into PDEV and CLIN programs as the field matures, would better align with the realities of cancer immunotherapy development. Abruptly introducing multiple unestablished technologies at the clinical trial stage risks being disruptive rather than constructive, potentially slowing progress toward meaningful patient impact.

I offer these comments in the spirit of partnership and shared commitment to CIRM's mission. I hope this perspective will be helpful as CIRM continues to refine its programs to best support the development of safe, effective therapies for patients with urgent unmet needs.

Thank you very much for your time and consideration.

Sincerely,

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