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September 21, 2025

To: California Institute of Regenerative Medicine (CIRM) governing board, and members of the Independent Citizens Oversight Committee (ICOC)

We appreciate the opportunity to communicate concerns regarding our proposal (DISC0-17579) titled "Gene-edited CD19 CAR-T cells with superior proliferation, persistence and serial-killing activity."

The proposal, originally submitted in the fall of 2023, received an outstanding review and score of 83 – just two points shy of the funding threshold. While we understand that CIRM-provided review comments are not exhaustive, our best interpretation of the review content was that there were three primary criticisms of our 2023 submission:

1. **The GWG raised concerns about the X-linked nature of our gene of interest**
2. **Some reviewers found that our application was lacking in attention to details about safety**
3. **Concerns about our proposal related to diversity, equity and inclusion (DEI) were raised**

We thoroughly revised the proposal to address the reviewers' criticisms (please see attached response statement redacted for proprietary reasons). This included a significant effort to generate additional preliminary data. The work was carried out using private funds, as we believed that given our proximity to the funding threshold, the further investment in time and resources would result in a proposal that CIRM deemed worthy of supporting.

To our shock and dismay, the revised proposal did not produce a fundable score and was in fact graded lower than the previous submission (80 versus the previous 83).

There are **several concerning aspects** of the present review that we ask the board members to consider:

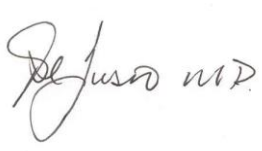
1. **The reviewers did not acknowledge the prior review, criticisms or our response**
   The guidelines on the CIRM website state that at least one reviewer from the previous submission will review resubmitted proposals. Specifically: "The proposal template includes a section for addressing prior reviewer critiques in overview. CIRM staff seek to have at least one prior reviewer critique a revised, resubmitted application. The GWG will have access to this Review Summary." **We are not convinced this occurred.**

2. **At least one of the provided negative review comments was completely inaccurate and implies that a reviewer(s) either a) did not thoroughly review the proposal or b) did not have a good understanding of the proposed studies**
   Specifically, the comment stated that "The proposal includes in vivo data demonstrating that monogenic mutations in this gene result in a lymphoproliferative disease and an immunodeficiency syndrome." The data presented did *not* demonstrate a lymphoproliferative disease nor immune deficiency. In fact, neither of these conditions were assessed. We primarily demonstrated enhanced proliferation and cytotoxicity after tumor rechallenge. Obviously, factually incorrect responses such as the comment above, are critically damaging to all applicants' expectation of achieving a fair review of their work.

3. **Yet another negative review comment is factually incorrect, with multiple excerpts from the written proposal directly refuting the statement. Again, how can any applicant accept that reviews are fair or accurate when <u>demonstrably false criticisms</u> are presented?**
   The false statement here, which is particularly damaging because it purports to speak to an overall deficit of our proposal is: "A weakness of the plan is that efforts to evaluate toxicity (CRS, ICANS, GvHD transformation, etc.) are not included."
   Again, this is inaccurate and suggests that the reviewer(s) did not thoroughly read the proposal before passing judgment. As mentioned above, we can cite multiple excerpts *from the proposal itself* to refute the contention that 'efforts to evaluate toxicity are not included.' Among several examples:
   a. From page 14 of the proposal: "…and f) ascertain potential graft vs. host effects to establish safety"
   b. From the top of page 15 of the proposal is an **entire paragraph** discussing special attention to xenogeneic vs true GVHD in mice, and the expertise of a collaborator in discerning this
   c. From page 15: "Sacrificed cohorts will allow early evaluation of CAR-T engraftment, distribution **and toxicity (H&E staining)**" [Emphasis added in this response]
   d. **The entirety of Milestone 2 is dedicated to evaluating sources of potential toxicity**. While the milestone 2 experiments are in vitro, we strongly contend that they are clearly part of a comprehensive effort to ascertain the safety of our modified CAR-Ts.

We are sure that the CIRM committee members are fully aware that an enormous amount of time, effort and resources go into these proposals, just as we understand that there is never a guarantee of funding. However, consistent and equitable assessments of revised, and indeed, any, proposals is a reasonable expectation of all applicants. In this case, the prior criticisms seemed to be completely ignored, and new criticisms, **many of which are factually and demonstrably incorrect,** were produced. At the very least, we believe we have provided evidence supporting that our revised submission should be reconsidered for its merits. On a broader scale, we contend that we have highlighted deficiencies in the review process that could affect all applicants. We urge fairness, consistency and accuracy in all CIRM review processes, and believe that in our case, there are clear issues that negatively impacted our opportunity to receive DISC0 funding. We respectfully ask the board members to correct the lapses we have cited in the review of our proposal.

Sincerely,



Joseph M. Tuscano
Director of Bone Marrow and Stem Cell Transplantation
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Resubmission Statement (up to [redacted] page; excess pages will be discarded)

Are you resubmitting a substantially similar proposal that addresses Grants Working Group (GWG) reviewer comments on a previous CIRM application?

☒ Yes. ☐ No, this is a new application.

We wish to thank the GWG for the carefully considered review of our previous DISC0 application. We were grateful for the highly favorable score of 83 that left us **just 2 points shy** of the funding cutoff. We appreciated reviewers' praise such as '*The logic is very convincing. The preliminary data suggest the target as relevant and support the aims*,' and '*Could provide an interesting new approach to substantially modulate CAR-Ts and prevent exhaustion*.' The GWG critiques focused on three concerns, and we have addressed those in the revised proposal, as outlined below.

1. The GWG raised concerns about the X-linked nature of our gene of interest [redacted]

The reviewers raise valid concerns regarding the ability to target [redacted] given its position on the X chromosome. We have now included preliminary data demonstrating that our genetic modification is highly efficacious in CAR-Ts derived from **both male and female donors**. **Figure 2** in the resubmission establishes that we can efficiently [redacted] in male and female donors, and we have observed similar outcomes for other female donors (not shown due to space). We also show in **Figures 5 and 6** and **Table 1** that [redacted] disruption in a female donor leads to the same *functional* improvements as seen in edited male-donor CAR-Ts. Our revised proposal includes donor sex as a variable.

2. Some reviewers found that our application was lacking in attention to details about safety

Our updated proposal includes multiple assays that specifically focus on the safety of our modified CAR-T product. Additionally, we have updated the design of our CAR-T construct to include a 'safety switch' which allows for the rapid ablation of cells using the well-defined Rapamycin-based system. Milestone 2 is now completely dedicated to CAR-T safety, with additional safety experiments added in Milestone 3.

3. Concerns about our proposal related to population impact were raised

We verified with our donor blood vendor, Vitalant, that we can request blood provided by donors of specific sex and ethnicity. We will obtain blood samples from a donor pool that matches the ethnic diversity of California's population.

We also want to rationalize some additional improvements, made in response to exciting preliminary data obtained during the 18 months following our initial submission. Specifically, we have observed that under the pressure of *in vivo* tumor rechallenge, there is genetic selection of a highly desirable CAR-T phenotype. This prompted us to modify Milestone 1. Instead of testing only two [redacted] mutated CAR-T variants *in vitro*, we now propose **comprehensive *in vivo/in vitro* screens** that will select superior CAR-Ts from a library of CRISPR-generated variants, while continuing forward with the original promising clone as a fallback. This is an innovative approach that allows the development of CAR-T therapies at the apex of efficacy and safety. We have also omitted and redistributed studies from original Milestones 2 and 3. We removed Milestone 2 because our hypothesis has evolved to focus on CAR-T genotype as a driving force behind the expansion of beneficial T-cell memory subtypes. Also, the prior Milestone 3 goal, testing [redacted] CAR-Ts against clinically relevant B-cell cancer lines with varied surface receptors, is still achieved here, with all originally proposed target lines being used across the three current Milestones. Our preliminary findings and research plan are summarized in **Figure 10** in the proposal.

In summary, we believe this more focused research plan will generate clearly defined deliverables, each moving our CAR-Ts toward satisfying the requirements of a release candidate for an IND application.