

MEMORANDUM

TO: Members of the Application Review Subcommittee (ARS) and Independent Citizens' Oversight Committee (ICOC), California Institute for Regenerative Medicine (CIRM)

FROM: Mehrdad Abedi, MD, Principal Investigator, University of California, Davis

DATE: September 12, 2026

SUBJECT: Programmatic Appeal and Response to GWG Review for CLIN2-20389: *Phase I Clinical Trial of a Trispecific CAR T-Cell Therapy for Multi-Antigen Targeting in CNS and B-Cell Lymphomas*

Dear Members of the ARS and ICOC,

We sincerely thank the Grants Working Group (GWG) for their rigorous and constructive review of our CLIN2 application. We submit this letter to respectfully request that the ARS exercise its programmatic authority to fund this project, considering that its score fell below the funding score by only 1 point and its importance to the CCCE sites with which we are affiliated. Our request pivots around two important considerations:

- 1- The perceived operational risks have been proactively mitigated through our FDA-cleared IND and our extensive experience with point-of-care manufacturing both with Miltenyi Inc. and Caring Cross; and
- 2- More importantly, our proposal is specifically designed to align with CIRM's Strategic Allocation Framework (SAF), specifically the mandate to expand equitable patient access through the Community Care Centers of Excellence (CCCE) network.

In other words, this project is critically needed for our CIRM-funded collaboration with both Loma Linda and Fresno CCCEs to manufacture and administer gene-modified cell therapy products in a sophisticated community hospital.

We are highly encouraged that the panel recognized the unique and transformative potential of our trispecific CAR architecture, the critical unmet medical need, and the value of our projected \$70,000 Cost of Goods Sold (COGS) in comparison with the current almost half-million-dollar commercial products.

Our application received a median score of 84, placing it just one point below the funding threshold of 85. A detailed analysis of the GWG report indicates that this score was primarily driven by perceived operational risks regarding our decentralized clinical execution and Chemistry, Manufacturing, and Controls (CMC) comparability that we believe are easily addressable:

Response to the main reviewers' concerns:

1. CCCE Operational Readiness and Patient Access

GWG Critique: "The biggest weakness in my view is considering the clinical/commercial execution. How will non-specialty centers have the resources they need to prepare for appropriate care? ... A reasonably significant outreach effort is likely required."

Response: We appreciate GWG's vigilance regarding lack of appropriate resources at decentralized sites. We wish to assure the Board that our partner sites (e.g., in Fresno and Loma Linda) are not standard, under-resourced community hospitals; Both programs have an already established cell therapy program that is in the process of significant expansion thanks to both hospitals' dedication and their newly awarded CIRM-funded Community Care Centers of Excellence (CCCEs). The CCCE grants are specifically awarded to address the reviewers' concerns, i.e., to provide the resources necessary for this exact line of work. UC Davis partners with both centers to establish their GMP and clinical trial programs. Without this grant, we currently have no candidate to manufacture any GMP product, which could jeopardize meeting milestones for both grants on time.

Beyond their CIRM-funded infrastructure, these centers have been rigorously vetted for clinical readiness, and they both administer commercial CAR T cell products. Loma Linda already has a FACT-accredited BMT and cellular therapy program, and Fresno is in the middle of its FACT evaluation and approval. They have established SOPs for administering and managing toxicities for several cell therapy products and have the requisite 24/7 ICU capabilities, neurology consult service, etc., to support these patients.

Most importantly, this proposal, in conjunction with already funded CCCE grants, will synergistically address the local manufacturing and administration of cellular and gene therapy products in those local communities. CCCE grants for both Fresno and Loma Linda were funded to develop the infrastructure needed to manufacture and administer the major community hubs, not only for access but also to be able to manufacture and infuse the products within days of cell collection, which has huge clinical and perhaps life-saving advantages such as avoiding unnecessary and harmful bridging chemotherapy and decreasing tumor burden at the time of cell infusion. The CIRM grants will address the infrastructure but do not fund projects, and without a project, CCCE progress will stall. Our proposal is specifically designed around local cell manufacturing and provides an appropriate candidate to test this concept in the community. We do agree that this is a bold concept, but we genuinely believe that, if our proposal is funded, we will have all the components needed to get this project to the finish line.

Furthermore, to address the GWG's note on outreach, these CCCEs both have a huge catchment area with patients who prefer to stay and be treated locally. They are already deploying CIRM-funded bilingual patient navigators and leveraging established community oncology referral networks to ensure robust, equitable enrollment. By funding this trial, CIRM will operationalize the CCCE network in the Central Valley, delivering a highly potent, affordable CAR-T therapy to underserved rural populations and fulfilling CIRM's mandate for equitable statewide access. In addition, we recently partnered with a rural healthcare system in Chico, CA, which recently received a fundable score on our joint CIRM CCCE grant application.

2. Clarification of CMC Complexity and Comparability

GWG Critique: "CMC plan allows for up to 4 drug product configurations (8- or 12-day culture/fresh or frozen), describes NIH as a parallel manufacturing site... Considerations for demonstrating comparability to support pooling of all the clinical data are not well defined."

Response: We acknowledge the GWG's valid regulatory concern regarding Phase 1 CMC variability, and we apologize for the lack of clarification in the proposal. For patients treated at UC

Davis, Fresno, and Loma Linda, we have proposed not 4 but just a single product configuration: i.e., fresh infusion of CAR T cells after an 8-day manufacturing process. However, based on our experience with a different homegrown CAR T cell manufacturing product, in about 10% of cases, additional days of culturing are needed to meet release criteria for a specified cell number. As a contingency plan, cells can be expanded and harvested at 12 days if needed. Similarly, in exceptional situations, if patients are not ready to receive the cells, cells will be frozen and infused later, once the patient's condition allows infusion. We are planning to take advantage of these exceptional situations and analyze differences between early and late, and fresh versus frozen, cell infusions only if enough cases are available for analysis.

To ensure that safety and efficacy signals are not confounded, the trial is statistically designed and sufficiently sized to evaluate the safety and feasibility of the UC Davis 8-day fresh cohort independently of the NIH cohort. The 12-day culture and cryopreservation options are strictly pre-specified contingencies designed to maximize patients' chance of receiving the product. We assure the Board that a formal comparability protocol is already established within our FDA-cleared IND to address the parallel NIH manufacturing site. These variables are tightly controlled, and our FDA clearance reflects the agency's agreement with this comparability and pooling strategy.

3. Clinical Trial Design and Statistical Power

GWG Critique: *"What's the power analysis to justify an additional 10 patients per cohort after identifying an MTD? Why not just run a Simon two-stage design to initiate Phase II efficacy with an expansion cohort?"*

Response: The 10-patient expansion cohort utilizes a standard, FDA-precedented sample size for confirming safety and establishing the Recommended Phase 2 Dose (RP2D) in early-phase CAR-T trials. To avoid introducing regulatory delays via a major post-clearance protocol amendment to the FDA, we will maintain the currently cleared 3+3 and 10-patient expansion design for Phase 1. However, we fully agree with the GWG's astute recommendation regarding the Simon Two-Stage design; we will formally incorporate this rigorous, efficacy-driven statistical framework into our pivotal Phase 2 protocol following our End-of-Phase 1 FDA meeting.

Regarding indication heterogeneity, the trispecific nature of TriCAR19.20.22 is mechanistically designed to be indication-agnostic across B-cell malignancies. The expansion cohorts are designed to enroll a more homogeneous patient population. We plan several interim analyses; in collaboration with the FDA, DSMC, and our consulting committee, we will decide whether the cohort patient populations need to be adjusted.

4. Scientific Rationale: Trispecific vs. Bispecific Superiority

GWG Critique: *"The idea that trispecific CARs are superior for overcoming heterogeneity has not been proven in vivo in comparison to bispecific CARs. At some point one would theorize that more CAR targets would begin to elicit a plateauing effect..."*

Response: We acknowledge the GWG's point that *in vivo* murine models have inherent limitations for conducting head-to-head comparisons of multi-antigen escape dynamics. However, our *in vitro* CRISPR knockout data (Proposal Figure 7) provide definitive mechanistic proof of concept: when tumor cells successfully lose both CD19 and CD20, the independent CD22 CAR

arm maintains complete cytotoxic clearance. This functional redundancy is designed to create an evolutionary bottleneck that mathematically eliminates antigen escape, rather than risking a plateauing effect. Clinically, we routinely encounter cases where a single antigen escape occurs when other antigens are missing. This proposed Phase 1 trial is the necessary and definitive *in vivo* human evaluation required to validate this hypothesis. Critically, the ultimate goal of this therapeutic candidate is not only to treat antigen escape cases but to bring it to earlier treatment stages when any antigen escape can be prevented.

5. Commercialization Timelines and Urgency

GWG Critique: "... The commercialization timeline (BLA submission by Year 7) is long relative to typical for-profit development plans."

Response: We share CIRM's urgency to accelerate treatments to patients. The 7-year BLA timeline presented in the proposal is a highly conservative, worst-case projection. In fact, CRING Cross has already outlined a much-expedited timeline for BLA, enabling higher-phase trials in preliminary discussions with the FDA. Our clinical strategy is built for speed: we plan to utilize preliminary Phase 1 data to apply for Regenerative Medicine Advanced Therapy (RMAT) designation as early as Year 2, which is explicitly designed to compress this timeline and accelerate pivotal development. While our partnership with Caring Cross uses a non-profit model to ensure a sustainable \$70,000 COGS, this does not mean a slower development pace.

Conclusion

CLIN2-20389 represents a rare convergence of advanced cellular immunology, rigorous FDA-cleared regulatory planning, and a highly disruptive, equitable commercialization model. We respectfully request that the ARS consider the critical and immediate clinical impact and the profound programmatic value this trial brings to the CIRM CCCE network that is essential for the success of their grants and ultimately help the patients of California.

Sincerely,

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