CLINICAL

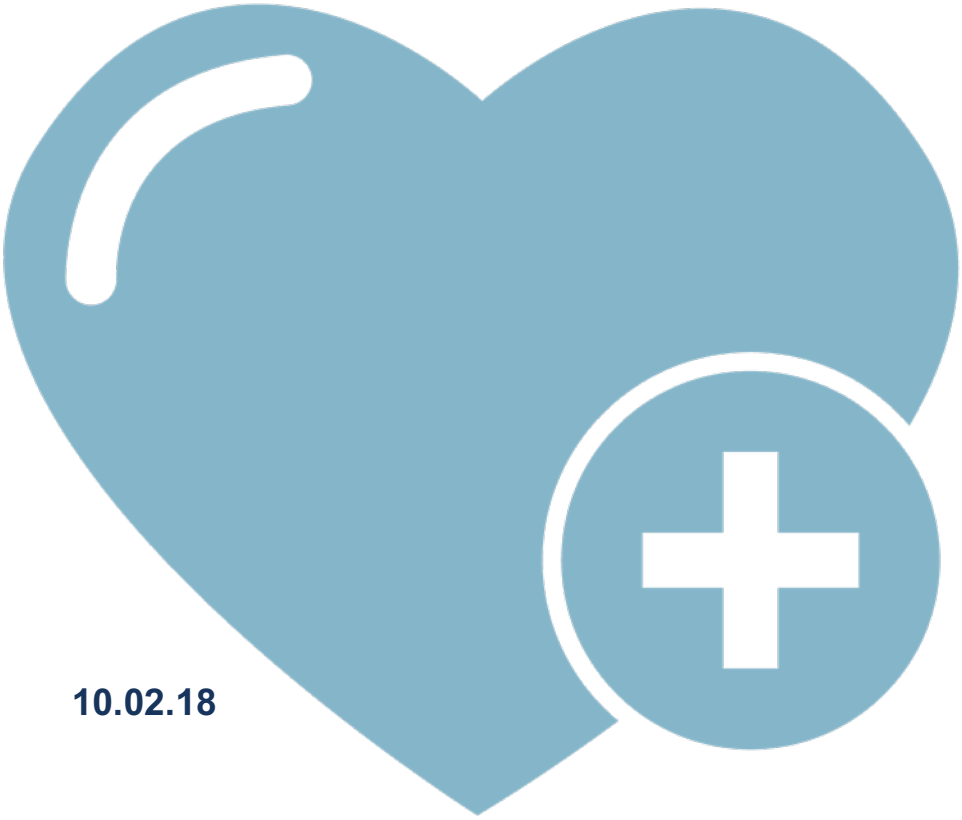
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

CMV-specific T cells expressing anti-HIV CAR and CMV vaccine boost as immunotherapy for HIV/AIDS

Application Number: CLIN1-11223	Review Date: 27 September 2018

Late Stage Preclinical Project Proposal (CLIN1)



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CMV-specific T cells expressing anti-HIV CAR and CMV vaccine boost as immunotherapy for HIV/AIDS

APPLICATION NUMBER: CLIN1-11223

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PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate or Device

Cytomegalovirus (CMV)-reactive T cells that express chimeric antibody receptors (CARs) to recognize and kill HIV-infected cells

Indication

HIV/AIDS

Therapeutic Mechanism

Antiretroviral drug therapy (ART) suppresses HIV to undetectable levels but does not eradicate the cellular reservoirs of the virus. We will engineer HIV-specific CAR T cells that will kill reactivated HIV-infected cells after ART withdrawal. These cells are also engineered to proliferate in response to a cytomegalovirus (CMV) . We will use a CMV vaccine to maintain these CAR T cells when HIV viremia is low, i.e., before ART withdrawal or when the HIV reactivation is controlled.

Unmet Medical Need

There is no cure for HIV and only half of the HIV patients adhere to ART in North America. Every year, ~16,000 HIV individuals die in the U.S. Our long-term goal is to develop a highly effective immunotherapy which significantly improves outcomes for HIV individuals and eliminate the need for ART.

Project Objective

IND filing and initiation of Phase 1 trial sites

Major Proposed Activities

Optimize the clinical-manufacturing of the therapeutic product

Complete the characterization of the efficacy and safety profiles of the therapeutic product

Submit the regulatory documentation to initiate the clinical trial

Funds Requested

$3,812,797 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 12 GWG members

Votes for Score 2 = 0 GWG members

Votes for Score 3 = 0 GWG members

- A score of “1” means that the application has exceptional merit and warrants funding;
- A score of “2” means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement;
- A score of “3” means that the application is sufficiently flawed that it does not warrant funding, and the same project should not be resubmitted for review for at least six months after the date of the GWG’s recommendation.

Review Overview

Reviewers agreed that while HIV is currently controlled by antiretroviral therapy (ART), the lack of a cure and the drawbacks of daily ART administration represent a significant unmet medical need for HIV patients. Overall, reviewers were very enthusiastic of this novel, albeit high risk, bispecific CAR-T cell therapy approach to curing or effectively controlling HIV infection. Reviewers thought that the rationale for using cytomegalovirus (CMV) specific T-cells and engineering them to target HIV-infected cells was based on sound scientific rationale and was supported by the preliminary data.

Reviewers agreed that the proposed project is appropriately designed to address FDA feedback and achieve IND submission within 18 months. They noted minor concerns including regulatory risk of the experimental CMV vaccine necessary for the treatment approach and the feasibility of manufacturing scale-up. They also provided several recommendations for improving the clinical study design. Noting high enthusiasm for the project and minor, addressable concerns, reviewers unanimously recommended the application for funding.

Review Summary

Does the project hold the necessary significance and potential for impact?

YES	**12**	**NO**	**0**

a) Consider whether the proposed treatment fulfills an unmet medical need.

- There is currently no cure for HIV. While antiretroviral therapy (ART) successfully controls HIV infection, it is associated with morbidities including bone/renal toxicity, dyslipidemia, insulin resistance, cancer, cardiovascular disease and shortened life expectancy.
- The eradication of HIV infection or its control without requiring daily administration of ART ("functional cure") are important unmet medical needs addressed by the proposed treatment.

b) Consider whether the approach is likely to provide an improvement over the standard of care for the intended patient population.

- The proposed CAR-T cell therapy approach, if successful, could eliminate the need for daily ART administration and could substantially improve patient outcome and quality of life.

c) Consider whether the proposed treatment offers a sufficient value proposition such that the value created by it supports its adoption by patients and/or health care providers.

- If shown to be effective at achieving eradication or functional cure of HIV while having minimal toxicity risk, the proposed single infusion CAR-T therapy would present much greater value to patients and health care providers than ART.
- The proposed CAR-T cell therapy could be very attractive if this single delivery therapy can control the HIV virus and prevent re-infection with minimal toxicity in hard to treat patients.
- Based on ART cost calculations provided by the applicants, HIV CAR-T therapy could provide cost savings to the health care system. Even though the cost of CAR-T manufacturing is higher, the cost of the therapy per year could be significantly lower due to the single infusion mode of treatment.

c) If a Phase 3 Trial is proposed is the therapy for a pediatric or rare indication or, if not, is the project unlikely to receive funding from other sources?

- N/A

Is the rationale sound?

YES	12	NO	0

a) Consider whether the proposed project is based on a sound scientific and/or clinical rationale, and whether the project plan is supported by the body of available data.

- The proposed therapeutic approach is highly novel and based on sound scientific rationale. The applicants have provided a substantial body of preliminary data to support their rationale.
- The project's reliance on an investigational CMV vaccine, for which there is limited clinical data to date and eventual FDA approval is uncertain, is a weakness of the overall approach.
- Some reviewers noted that minimal data was provided on stem cell memory and central memory T cell populations in the CAR-T cell product.

b) Consider whether the data supports the continued development of the treatment at this stage.

- The preliminary data supports continued development of this treatment.
- While the project is scientifically compelling, it is highly risky and the likelihood of eventual success may be low. However, given the potential for substantial improvement over the standard of care, it is worth pursuing.

Is the project well planned and designed?

YES	12	NO	0

a) Consider whether the project is appropriately planned and designed to meet the objective of the program announcement and to achieve meaningful outcomes to support further development of the therapeutic candidate.

- The project is appropriately planned and designed to complete pre-clinical development of the CAR-T cell therapy and enable filing of the IND for clinical study.
- The project plan has appropriately considered and incorporated FDA feedback from the pre-IND meeting.
- Reviewers noted that the proposed studies will provide additional proof-of-concept and preclinical efficacy data in animal models to support continued development of the CAR-T cell therapy.
- Based on limited manufacturing data from HIV patient samples, it was unclear to reviewers whether patient-to-patient variability will impact the CD4/CD8 composition of the CAR-T cell product.

b) Consider whether the proposed experiments are essential and whether they create value that advances CIRM's mission.

- The approach of using the CMV vaccine to expand CMV specific T-cells may eliminate the current use of preconditioning chemotherapy that is widely adopted for T cell therapies. If this is successful, it could broaden the application of T cell therapy beyond HIV and cancer to other

infectious diseases.

- Reviewers noted that, per new proposed FDA rules, NIH Recombinant DNA Advisory Committee (RAC) oversight is no longer applicable and can be removed from the project activities.

c) Consider whether the project timeline is appropriate to complete the essential work and whether it demonstrates an urgency that is commensurate with CIRM's mission.

- The project timeline is appropriate to achieve IND submission within 18 month of project start.

Is the project feasible?

YES	12	NO	0

a) Consider whether the intended objectives are likely to be achieved within the proposed timeline.

- The preclinical IND-enabling studies are likely to be achieved in the proposed timeline.
- Reviewers noted that process optimization activities for large-scale GMP manufacturing could be a significant source of delay for the project.

b) Consider whether the proposed team is appropriately qualified and staffed and whether the team has access to all the necessary resources to conduct the proposed activities.

- The proposed team is highly experienced and qualified to conduct the activities proposed in the project.

c) Consider whether the team has a viable contingency plan to manage risks and delays.

- The team identified appropriate risks and proposed viable contingency plans to manage these risks. However, the contingency plan did not assess the impact of potential delays on the project timeline.

CIRM Recommendation to Application Review Subcommittee

The CIRM recommendation to the Application Review Subcommittee is considered after the GWG review and did not affect the GWG outcome or summary. This section will be posted publicly.

RECOMMENDATION: Fund (CIRM concurs with the GWG recommendation).