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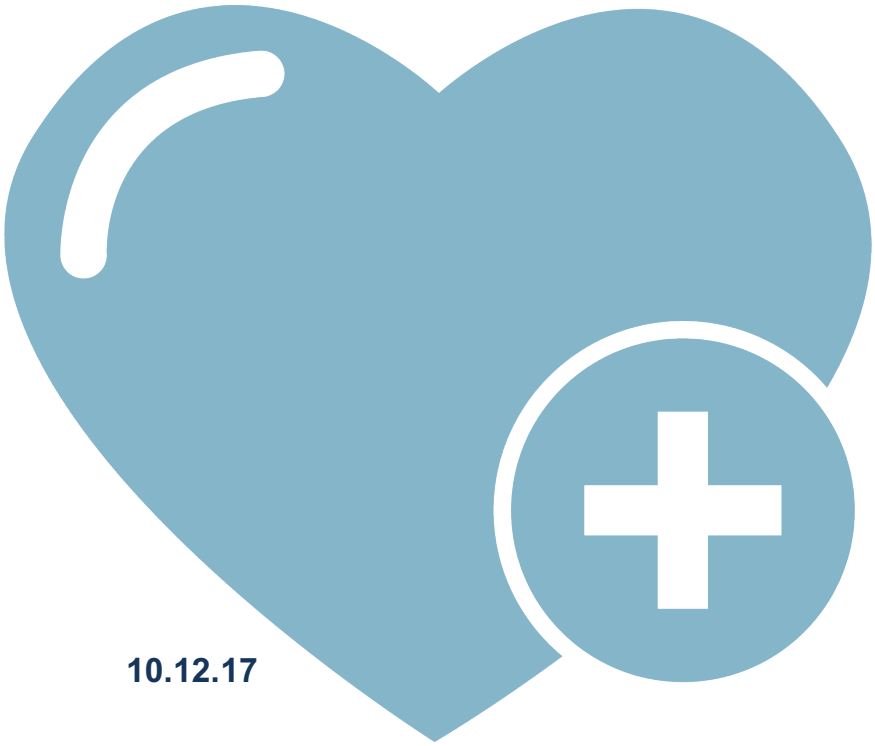
# Grants Working Group Public Review Summary

## Antiviral Cellular Therapy for Enhancing T-cell Reconstitution Before or After Hematopoietic Stem Cell Transplantation (ACES)

| Application Number: CLIN2-10392 (Revised Application) | Review Date: 26 September 2017 |
|---|---|

Clinical Trial Stage Project Proposal (CLIN2)



**10.12.17**

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# Antiviral Cellular Therapy for Enhancing T-cell Reconstitution Before or After Hematopoietic Stem Cell Transplantation (ACES)

**APPLICATION NUMBER: CLIN2-10392 (Revised application)**

**REVIEW DATE: 26 September 2017**

**PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects**

## Therapeutic Candidate or Device

Partially HLA-matched virus-specific T-cell therapy targeting cytomegalovirus, Epstein-Barr virus, and adenovirus.

## Indication

This study will treat persistent viral infections with CMV, EBV, and/or adenovirus in patients with immunodeficiency.

## Therapeutic Mechanism

The goal of this study is to use banked virus-specific T-cell therapy in A) patients who have persistent viral infections after bone marrow or cord blood transplant, and B) patients with primary immunodeficiency conditions who have persistent viral infections and have not undergone transplantation.

## Unmet Medical Need

Viruses account for up to 40% of deaths in patients with immunodeficiency, and antiviral medications are limited by toxicities and resistance. Restoration of T-cell immunity by adoptive immunotherapy could provide lasting control of targeted viral infections.

## Project Objective

Phase 1/2 trial completed

## Major Proposed Activities

To determine the feasibility and safety of administering partially HLA-matched T-cells to treat persistent viral infections.

To determine the antiviral efficacy of partially HLA-matched T-cells in immunodeficient patients with CMV, EBV, and/or adenoviral infection.

To determine the effects of partially HLA-matched VST infusion on overall survival at 6 months and 12 months following infusion.

## Funds Requested

$4,825,587 ($0 Co-funding)

## Recommendation

Score: 1

Votes for Score 1 = 9 GWG members

Votes for Score 2 = 1 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.

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## Review Overview

This is a revised application that previously received a score of "2". Persistent viral infections are a significant unmet medical need in a small subset of immunodeficient patients who are resistant to antiviral medications. The proposed multicenter clinical study builds on positive results with adoptive virus-specific T cell therapy from single site studies in this patient population.

In the initial review of the application, reviewers were concerned that the trial design was too ambitious and lacked clear inclusion criteria with respect to antiviral medication use in the study population.

The applicant responded with specific criteria for defining failure of antiviral therapy in the study population and requirements for concomitant usage of antiviral medications during the course of the study. Reviewers thought that the study design modifications were appropriate and recommended the application for funding.

## Review Summary

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

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

- Antiviral medication resistance in immunodeficient patients with persistent viral infections is an unmet medical need.

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

- If the T cells are effective in eliminating viral disease in the small subset of patients who are resistant to standard of care antiviral medications, this would represent an improvement.

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

- The proposed treatment, if successful, would demonstrate the value of treating immunocompromised patients from a central bank of virus-specific T cells.

**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?**

**a) Consider whether the proposed project is based on a sound scientific**

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**and/or clinical rationale, and whether the project plan is supported by the body of available data.**

- There is very good scientific rationale and clinical experience from several groups demonstrating the feasibility and clinical activity of this approach.
- In the initial review of the application, reviewers noted that the predictive algorithms for HLA restriction were not well defined. The applicant provided additional details of the HLA restriction mapping and cell selection methodology. Reviewers noted that clinical matching of banked cells to patients would still be reliant on the experience and expertise of the clinical investigators.
- In the initial review of the application, reviewers expressed concern whether the small stem cell memory (Tscm) fraction of the T-cell product contributed to its functionality. Reviewers were satisfied with the applicant's response, which noted that the Tscm fraction is expected to be proliferative and persistent *in vivo* and that correlative studies will be performed to measure Tscm function.

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

- The clinical data gathered to date supports this multicenter study of centrally banked virus-specific T cells.

**Is the project well planned and designed?**

**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.**

- In the initial review of the application, reviewers were concerned that the target patient population and allowance for concomitant use of antiviral drugs were not well-defined. Reviewers were satisfied with the study design modifications made by the applicant including specific criteria for antiviral therapy failure and better-defined criteria for concomitant use of antiviral medication.
- In the initial review of the application, reviewers were concerned that the project was too ambitious by targeting three viral infections. The applicant modified the study design to enroll a higher proportion of CMV and adenovirus patients. Reviewers found the response adequate, noting that the endpoints and anti-viral therapy regimens are similar in CMV and adenovirus patients.
- Reviewers expressed a minor concern that the post-thaw characterization of the product will not assess T cell functionality.

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

- The proposed experiments will demonstrate the value of a central virus-specific

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T cell bank for treating medication-resistant viral infections in immunodeficient patients.

**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.

**Is the project feasible?**

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

- The intended objectives are likely to be achieved within the proposed timeline.

**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 team is highly qualified to conduct the clinical study.

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

- The contingency plan is acceptable.

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## 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).