CLINICAL

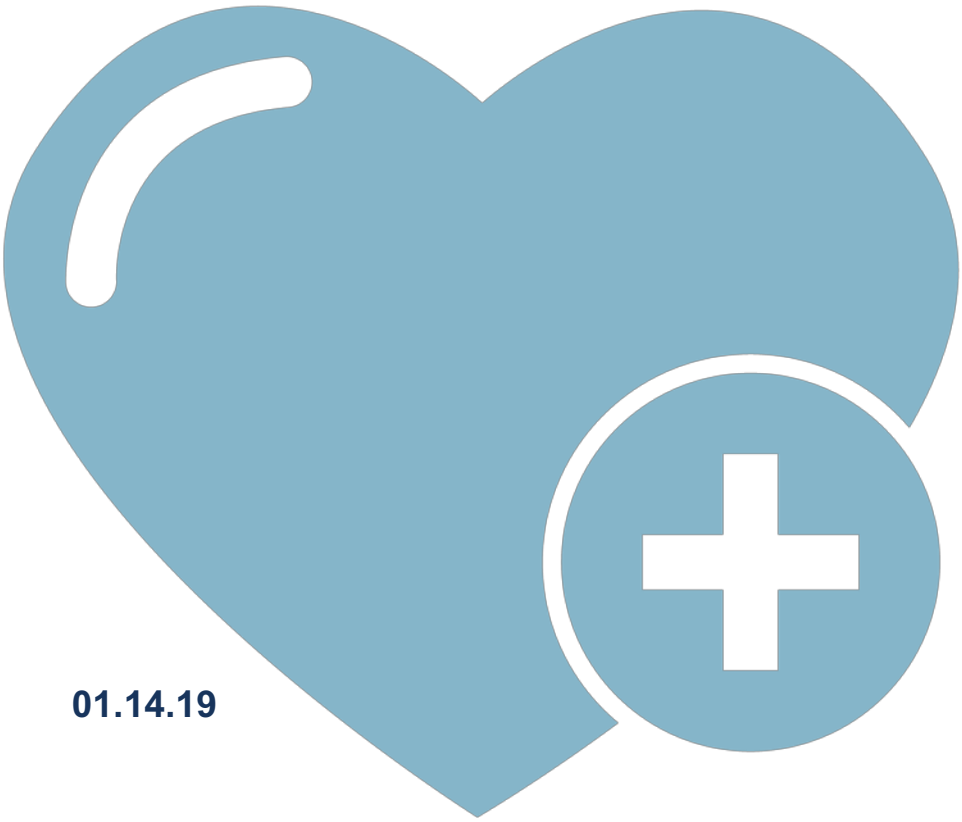
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

Induction of Tolerance by Combinatorial Therapy w/ Donor Stem Cells and Expanded Recipient Treg cells in HLA-mismatched Kidney Transplant Recipients

Application Number: CLIN2-11400 (Revised Application)	Review Date: 20 December 2018

Clinical Trial Stage Project Proposal (CLIN2)



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Induction of Tolerance by Combinatorial Therapy w/ Donor Stem Cells and Expanded Recipient Treg cells in HLA-mismatched Kidney Transplant Recipients

APPLICATION NUMBER: CLIN2-11400 (Revised application)

REVIEW DATE: 20 December 2018

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Combined hematopoietic stem cell graft and recipient T regulatory cells

Indication

Kidney disease requiring kidney transplantation

Therapeutic Mechanism

The study will determine whether patients treated with TLI and rATG, and given a haploidentical living donor hematopoietic progenitor cell transplant (HSCT) , along with in vitro expanded recipient Treg cells (what we term as combinatorial therapeutic cell therapy) can achieve sustained donor mixed chimerism and be withdrawn from immunosuppressive drugs while maintaining normal renal function after renal transplantation.

Unmet Medical Need

The goal is “one kidney for life” off drugs with safety for all patients. The overall health status of patients off immunosuppresive (IS) drugs will improve due to reduction in side effects associated with IS drugs, and due to reduced graft loss afforded by tolerance induction that will prevent chronic rejection.

Project Objective

Phase 1 trial completed

Major Proposed Activities

Assessment and adjustment of the Treg dose required to sustain chimerism in the recipients without causing adverse reactions such as GVHD

Assessing the impact of immunosuppressive drug dose reductions toward withdrawal without graft rejection or adversely affecting kidney function

Assess kidney duration post-transplant compared to patients undergoing standare of care kidney transplants without cell therapy to induce immune tolerance

Funds Requested

$11,969,435 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 14 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

This is a revised application that previously received a score of “2”. Reviewers agreed that reducing the risk of immune rejection and the reliance on chronic immunosuppression are critical unmet medical needs for kidney transplant recipients. The proposed treatment attempts to improve the success rate of the experimental approach of inducing mixed chimerism in transplant recipients, which combines donor-derived CD34+ cell infusion with the kidney transplant, by also co-infusing expanded recipient T regulatory (Treg) cells.

In the initial review of the application, reviewers expressed concerns regarding Treg cell manufacturing and transport, inconsistent descriptions of endpoints in the application and coordination between the two trial sites. In addition, some reviewers thought that the preclinical data was not convincing. The applicant’s detailed responses in the revised submission sufficiently addressed the reviewers’ concerns. Reviewers unanimously recommended the application for funding.

Review Summary

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

YES	**14**	**NO**	**0**

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

- Kidney transplantation remains the best treatment option for patients with renal failure. However, transplant rejection and the requirement for prolonged immunosuppression are significant clinical concerns.
- There is currently no treatment available that induces tolerance in non-HLA identical donor/recipient combinations. This project addresses the need for long-term immunosuppressive-free renal transplantation from living haploidentical donors.

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

- The current standard of care requires long-term immunosuppression, which poses significant risks for the patient. The proposed approach has the potential to greatly improve standard of care by inducing long-term transplant tolerance without the need for immunosuppression.

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 successful, the proposed treatment would be compelling to patients and health care providers by improving kidney transplant tolerance rates and by reducing or eliminating chronic immunosuppression regimens and its associated risks.
- The proposed treatment could also provide compelling value for organ transplantation in general.

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	14	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.

- Reviewers agreed that the scientific rationale for combining donor kidney transplant with hematopoietic progenitor cell transplant to induce mixed chimerism and tolerance was sound and supported by preclinical and clinical data. Reviewers also agreed that, based on the outcomes to date in the ongoing CIRM-supported clinical study, there is good rationale for adding expanded recipient Tregs in order to improve success of achieving mixed chimerism.
- In the initial review of the application, viewers disagreed on whether there was sufficient preclinical data to support addition of ex vivo expanded recipient Tregs to enhance mixed chimerism.
    - Reviewers thought that the applicant's response detailing clinical experience as well as published preclinical studies, while not fully convincing, was sufficient to warrant clinical study of the approach.

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

- Reviewers agreed that the clinical data to date supports continued clinical development of the proposed treatment.

Is the project well planned and designed?

YES	14	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.

- In the initial review of the application, reviewers raised the following concerns with the clinical trial design: discrepancies in success criteria, alternative approaches if mixed chimerism is not achieved in initial cohort, rationale for donor CD3 T cell dose, and potential impact of the conditioning regimen on infused Tregs.
    - Reviewers thought that the applicant's response, which corrected success criteria discrepancies, detailed alternative strategies for achieving mixed chimerism and provided additional information regarding dosing and conditioning sufficiently addressed their concerns.
- In the initial review of the application, reviewers were unclear whether cryopreservation and transport of cells between the two proposed clinical sites would impact viability and activity of the product.
    - Reviewers thought that the applicant's response, which clarified the manufacturing and transport processes, sufficiently addressed reviewer concerns.
- It was unclear to some reviewers why the clinical protocol indicated a much larger number of subjects in both the control and treatment arms compared to the clinical study described in the application proposal.

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

- In the initial review of the application, reviewers questioned the relevance and necessity of the correlative studies.
    - Reviewers thought that the revised submission was more effective in describing the correlative studies and providing stronger rationale for their inclusion in the project.

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.

- In the initial review of the application reviewers were concerned that the projected enrollment rate was slower than would be expected for the two proposed clinical sites.
    - The revised application provided sufficient additional justification and explanation for the projected enrollment rate at both clinical sites.

Is the project feasible?

YES	**14**	**NO**	**0**

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

- The proposed phase 1 clinical trial activities are likely to be achieved in 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 experienced and very well qualified to conduct the clinical study. Both proposed clinical sites have the appropriate resources to perform the trial activities.
- In the initial review of the application, reviewers had advised the applicant to ensure that a comprehensive communication plan is in place between the two clinical sites.
    - Reviewers were satisfied with the applicant's description of the communication plan in the revised submission.

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

- In the initial review of the application, reviewers had advised that the applicant develop a contingency plan to address delays in manufacturing or processing one of the cell products.
    - Reviewers were satisfied with the contingency plan proposed by the applicant in the revised submission.

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).