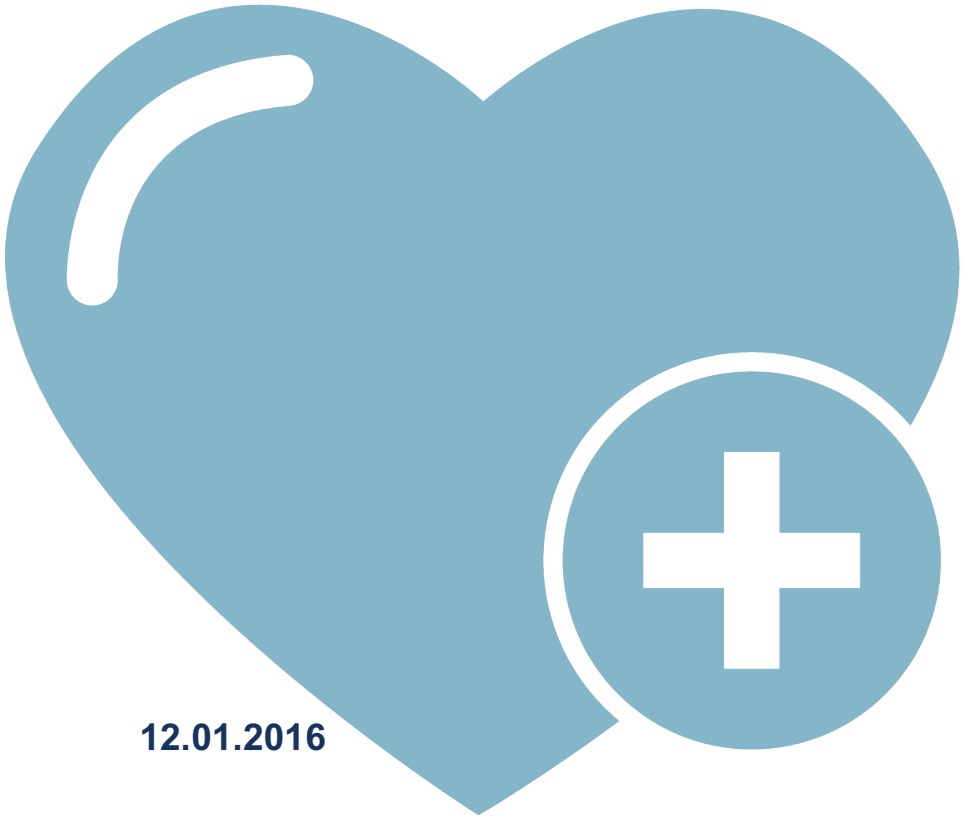
CLINICAL

Grants Working Group Public Review Summary

Induction of Tolerance to Combined Kidney and Hematopoietic Progenitor Cell Transplants from HLA Haplotype Matched Living Donors

Application Number: CLIN2-09439	Review Date: November 29, 2016

Clinical Trial Stage Project Proposal (CLIN2)



12.01.2016

CLINICAL

Induction of Tolerance to Combined Kidney and Hematopoietic Progenitor Cell Transplants from HLA Haplotype Matched Living Donors

APPLICATION NUMBER: CLIN2-09439

REVIEW DATE: November 29, 2016

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate

Blood stem cells and T cells from organ transplant donors

Indication

Kidney transplant

Therapeutic Mechanism

Injection of the donor blood stem cells and T cells into recipients will prevent recipient immune cells from rejecting the donor kidney transplant enabling withdrawal of immunosuppressant drugs from kidney transplant recipients

Unmet Medical Need

The proposed treatment eliminates the life-long need of immunosuppressive drugs to prevent kidney transplant rejection. Immunosuppressive drugs increase the risks of cancer, infection, and heart disease.

Project Objective

Complete the Phase 1 clinical trial

Major Proposed Activities

Manufacture optimum donor cell product for injection into kidney transplant recipients

Assess the clinical safety of the donor cell injection

Assess the ability to withdraw immunosuppressive drugs

Funds Requested

$ 6,653,266 ($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.

CIRM 2.0

CALIFORNIA’S STEM CELL AGENCY

Public Review Summary

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

Review Overview

Reviewers were highly enthusiastic regarding this potentially transformative approach to inducing tolerance in kidney transplant recipients. The treatment would provide a substantial value proposition to patients and health care providers if successfully developed. Reviewers thought the investigator to be outstanding, the project highly feasible, and the plan appropriate to move this product toward clinical use. Reviewers unanimously recommended this project for funding.

Review Summary

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

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

- Complications from renal transplant such as graft rejection are significant, and the proposed treatment holds the potential to fulfill this unmet medical need.
- Renal transplant recipients take life-long immunosuppressant drugs that have deleterious side effects. A treatment approach allowing reduction or withdrawal of these drugs, such as the one proposed, would fulfill 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.

- This treatment, if successful in inducing life-long tolerance in HLA mismatched renal transplant recipients, would offer improvements to quality of life and patient outcomes over the current standard of care for this patient population.
- This treatment approach holds the potential to transform the standard of care in renal transplant and, possibly, organ transplant generally.

c) Consider whether the proposed therapeutic offers a sufficient, impactful, and practical value proposition for patients and/or health care providers.

- There is a significant healthcare burden, morbidity, and mortality that could be reduced if this treatment induces life-long tolerance and enables withdrawal of immunosuppressant drugs. This provides a sufficient, impactful, and practical value proposition to both renal transplant recipients and healthcare providers.
- Partnerships are in place to move forward commercially should the proposed clinical trial yield positive outcomes.

Is the rationale sound?

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

- There is a large, compelling body of data in various preclinical and clinical settings underpinning the scientific rationale and supporting the proposed project.
- Data describing likely mechanisms of tolerance induction using this treatment approach is presented in the application, though there is still much to learn through the proposed project.
- Previous clinical experience demonstrates that in fully HLA matched renal transplant recipients, long-term tolerance induction and withdrawal of immunosuppressant agents is possible using this treatment. This has been difficult to replicate in partially HLA matched renal transplant recipients, but the provided data supports the proposed approach to achieving long-term

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

tolerance in this patient population.

- Previous clinical data from patients who have already been followed for relatively long periods of time provides confidence that this approach holds the potential to provide long-term benefits to patients.

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

- The data strongly supports continued development of the proposed treatment.

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 achieve meaningful outcomes to support further development of the therapeutic candidate.

- Proof of principle for this approach has been demonstrated in HLA matched patients, and the patient population that is under investigation in the proposed study is the next logical step. The proposed clinical plan to induce tolerance in these patients is appropriate and well thought out.
- There is risk that the dose of T cells in the product required to induce tolerance will also induce graft versus host disease (GVHD), an unacceptable complication in this patient population. However, the proposed project plan considers this risk and utilizes a safe and logical approach to determining if an efficacious and safe dose can be identified.

b) Consider whether this is a well-constructed, quality program.

- This is an extremely well-constructed and high quality program.

c) Consider whether the project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission.

- The project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission. In fact, the purpose of this funding request is to significantly accelerate an ongoing clinical trial.

Is the project feasible?

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

- It is likely that intended objectives will be achieved within proposed timelines.
- The project plan is feasible and likely to be executed as described.

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 principal investigator is an established leader in the field who is experienced in this type of clinical trial and has contributed significantly to understanding long-term tolerance in renal transplant patients.
- The team is outstanding and has access to all necessary resources.

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

- Risks are presented and discussed adequately, and there is a viable contingency plan in place.

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

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).