CLINICAL

# Grants Working Group Public Review Summary

Treatment of sickle cell disease by induction of mixed chimerism and immune tolerance using CD4+ T-depleted haploidentical blood stem cell transplant

| Application Number: CLIN2-10847 | Review Date: 25 January 2018 |
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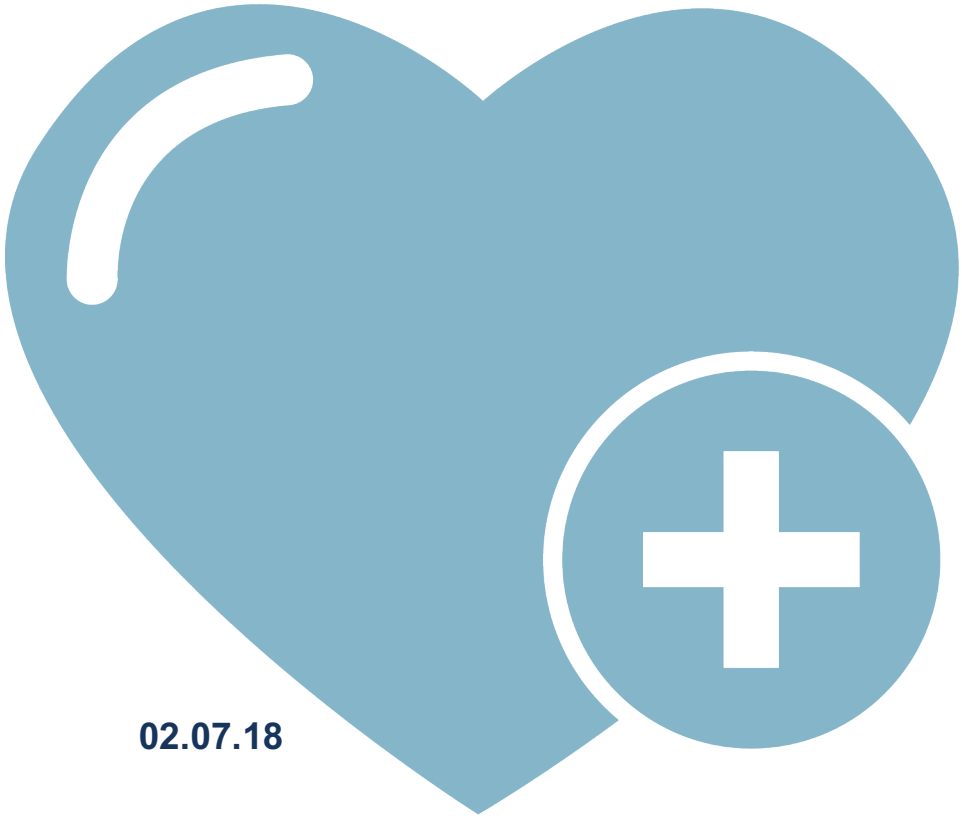
Clinical Trial Stage Project Proposal (CLIN2)



02.07.18

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# Treatment of sickle cell disease by induction of mixed chimerism and immune tolerance using CD4+ T-depleted haploidentical blood stem cell transplant

**APPLICATION NUMBER: CLIN2-10847**

**REVIEW DATE: 25 January 2018**

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

## Therapeutic Candidate or Device

Haploidentical (half-match) T cell depleted blood stem cell transplant with a low-toxic conditioning regimen

## Indication

Adult patients with severe sickle cell disease who are excluded from the potentially curative current standard stem cell transplant.

## Therapeutic Mechanism

The proposed therapy is intended to achieve mixed chimerism and immune tolerance. Mixed chimerism is when a combination of donor and host blood cells co-exist in the transplanted host. The right mix of donor to host blood cells can reverse sickle cell disease. Immune tolerance will prevent rejection of the donor blood stem cell graft and allow patients to be free of sickle cell disease for a long time.

## Unmet Medical Need

This proposal will allow more people with severe sickle cell disease to have a potentially curative stem cell transplant. Our method will allow patients to receive less-toxic conditioning drugs before the transplant, and to get stem cells from half-match donors.

## Project Objective

Complete the Phase 1 clinical trial

## Major Proposed Activities

Manufacture a half-match T-cell-depleted blood stem cell donor product

Conduct a clinical trial with severe sickle cell disease patients

Assess safety and ability to induce mixed chimerism

## Funds Requested

$5,742,180 ($435,834 Co-funding)

## Recommendation

Score: 1

Votes for Score 1 = 7 GWG members

Votes for Score 2 = 5 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

Patients with sickle cell disease (SCD) can potentially be cured with allogeneic hematopoietic stem cell transplantation (HSCT). However, the treatment is associated with high mortality and morbidity and subsets of patients, particularly adults, are not eligible. Reviewers thought that the proposed product has the potential to address this important unmet medical need. Reviewers generally agreed that the preclinical studies adequately demonstrated proof of concept to advance to human testing. However, they noted that additional data in large animal models would have provided stronger support for the rationale. The phase 1 trial design was found to be reasonable but reviewers disagreed whether the small sample size would inform on the safety and feasibility of the approach.

There was also disagreement between reviewers on whether the proposed product advances CIRM's mission. Some reviewers noted that the HSC product lacks novelty and doesn't represent an advancement in stem cell therapy. Others noted that the overall treatment approach for this indication is novel and would expand SCD patient access to curative HSC therapy. The majority of reviewers thought that the project merited support and recommended it 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.**

- Severe SCD is a major unmet medical need. Current treatment options do not adequately control or cure the disease for a substantial subset of SCD patients.
- Curative HSCT is largely limited to pediatric patients and has significant treatment related mortality and morbidity. The proposed treatment fulfills this unmet medical need by potentially enabling safer haploidentical HSCT in SCD patients.

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

- If successful, the proposed approach is likely to provide improvement over the current standard of care in SCD patients, particularly the subset of patients who are not well-served by the currently available therapies.

**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 be a one-time curative treatment and would expand the donor pool for the target patient population to haploidentical HSCT. Thus, the proposed approach has the potential to reduce overall cost of care and increase access to curative treatment in the target patient population.
- The conditioning regimen and withdrawal of immunosuppression will need to be uniquely managed for each patient, which could add to the cost of care.



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

- Reviewers noted that while the mouse models used in the preclinical studies weren't entirely representative of the human SCD setting, the results demonstrated adequate proof of concept for the proposed combined cell therapy and conditioning regimen approach.
- The rationale for mixed chimerism and immune tolerance induction is generally supported by clinical studies in other transplant settings but those studies aren't necessarily predictive of the success of the proposed approach.
- Reviewers thought that additional preclinical studies in large animal models would have provided further support for the proposed approach.

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

- The preclinical data gathered to date and the clinical experience in SCD and other transplant settings support continued development of the 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 to achieve meaningful outcomes to support further development of the therapeutic candidate.**

- The phase 1 trial design is reasonable and appropriately conservative to assess safety of the proposed treatment.
- Some reviewers questioned whether the small sample size in the phase 1 study would adequately inform on safety and go/no go criteria.
- The clinical protocol does not provide guidance on management of immunosuppression beyond the 2-year follow up period.
- Given uncertainty about the durability of mixed chimerism and immune tolerance, reviewers thought that longer term follow up could be beneficial.
- It was uncertain what effect cryopreservation of the product would have on cell viability and functionality.
- Some reviewers were unclear on how anti-donor antibody reactivity in SCD patients will impact donor selection.
- Reviewers were not convinced that the conditioning regimen posed no risk of infertility. The applications should consider supporting sperm banking for enrolled patients.

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

- Reviewers disagreed on whether the project creates value that advances CIRM's mission. Some reviewers questioned whether the proposed product supports advancement of transformative stem cell therapies. Others noted that the combined cell therapy and conditioning regimen represents a novel curative approach that will expand SCD patient access to stem cell therapy.

**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 and demonstrates adequate urgency.

**Is the project feasible?**

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

- The project is feasible.

**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 excellent and has extensive experience in stem cell transplants and SCD treatment.

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

- The team has a viable contingency plan to manage risks.

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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).