CLINICAL

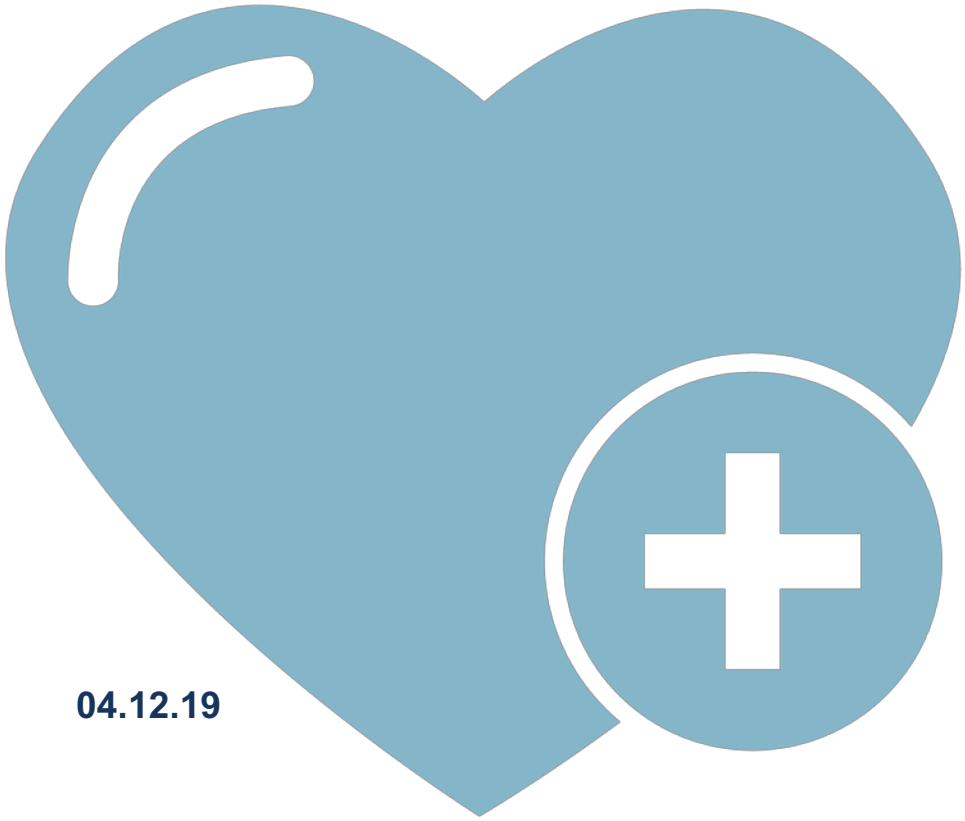
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

Curing Sickle Cell Disease with CRISPR-Cas9 Genome Editing

Application Number: CLIN1-11497	Review Date: 04 April 2019

Late Stage Preclinical Project Proposal (CLIN1)



04.12.19

Curing Sickle Cell Disease with CRISPR-Cas9 Genome Editing

APPLICATION NUMBER: CLIN1-11497

REVIEW DATE: 04 April 2019

PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate or Device

Blood stem cells collected from individuals with sickle cell disease will have the sickle gene corrected and then given back to the same individual.

Indication

Sickle cell disease is a hereditary blood disorder associated with pain and other serious medical complications including a shortened life-span.

Therapeutic Mechanism

It is possible to cure sickle cell disease by a bone marrow transplantation. Unfortunately, most patients do not have a donor for this treatment. In addition, a bone marrow transplant is a risky treatment. Our new treatment first collects a sickle cell person's own blood stem cells and uses a new technology called CRISPR to correct the sickle gene in the blood stem cells. These are returned to the same person after first destroying the sickle-producing blood cells. It might stop the disease.

Unmet Medical Need

Currently, there are only two approved treatments for sickle cell disease, which are drugs that help treat symptoms but do not cure the disorder. There is an unmet need to approve new treatments that eliminate the cause of the disorder that arises in the blood cells, with potential of cure.

Project Objective

Obtain an IND for an early phase clinical trial

Major Proposed Activities

Find all the sites in human DNA where the CRISPR changes the code and confirm these changes are not dangerous or cause cancer

Find all the types of the hemoglobin protein that might be made after the CRISPR fixes the sickle gene and confirm the hemoglobin in red cells is safe

Make enough of the gene-corrected blood stem cells to treat 3 patients and show these are safe in mice and have a good shelf-life after freezing

Funds Requested

$4,490,777 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 14 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.

Review Overview

The review panel was very enthusiastic about the proposed sickle cell disease project. The potential for a curative treatment for a disease that currently has poor treatment options provides a high value proposition. The strong preliminary data and rigorous preclinical plan to an IND led to overall support for the proposed project. Reviewers noted several concerns with the preliminary clinical trial design that they hope the applicant can address quickly given the tight timeline of the project but were not critical to have addressed for the proposed preclinical stage activities and GWG recommended the application for funding.

Review Summary

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

YES	15	NO	0

Reviewers considered the following:

a) Whether the proposed treatment fulfills an unmet medical need.

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

c) 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.

d) 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?

Summary of Reviewers' Comments:

- Sickle cell disease (SCD) is an inherited condition with limited curative options. Although hematopoietic stem cell transplantation is curative, many patients do not have suitable donors. Gene therapies may provide a curative option for a broad base of this patient population.
- The costs of treating SCD over a lifetime are much higher than the cost of a single curative therapy.
- The proposed gene editing approach, which aims to correct the sickle mutation, is competing with lentiviral gene therapy strategies or genome editing approaches that aim to re-activate fetal globin expression. However, there are some unique aspects to the proposed approach that warrant further study.

2. Is the rationale sound?

YES	15	NO	0

Reviewers considered the following:

a) 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.

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

Summary of Reviewers' Comments:

- The preclinical data for genome editing as well as the initial clinical development data strongly support the proposed project.
    - Proof of concept data show gene correction, engraftment, and persistence of modified cells.
    - Product characterization and the approach to establishing safety prior to clinical study appears robust.
    - A downside of the proposed gene editing approach is the relatively low number of corrected alleles (20-30%) versus disrupted alleles (50-60%) that may create a beta-thalassemia phenotype. This concern should be addressed prior to IND filing.
- Gene editing of autologous cells to correct the sickle cell mutation would be more specific and less expensive than other forms of gene therapy. Using the patient's own cells avoids the task of finding an HLA-matched donor.

3. Is the project well planned and designed?

YES	14	NO	1

Reviewers considered the following:

a) 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.

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

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

Summary of Reviewers' Comments:

- Overall the project is well-planned and designed. The proposed studies are essential and closely incorporate FDA feedback. The toxicity study in particular is rigorously designed, though the timeline may be delayed if it is not successful. The timeline and risk mitigation for the proposed studies are appropriate.
- Reviewers recognized and accepted that the clinical protocol was a work in progress. They noted several areas of concerns and provided recommendations to improve the trial design.
    - Although this is a first-in-human (FIH) study, the primary objective of the clinical trial is event-free survival (EFS) which appears to be an efficacy endpoint rather than the assessment of safety and tolerability as FDA would expect in a phase 1. The safety and

tolerability endpoints are described as secondary endpoints. Reviewers recommended that the secondary safety endpoints be incorporated into the primary objective of evaluating safety and tolerability. EFS could be separate primary endpoint or the first secondary endpoint.

- As this is a small open-label study in 8 subjects, it may be helpful for data interpretation to enroll a concurrent natural history matched control group that receives standard-of-care, this would particularly aid the assessment of event-free survival.
- A strategy is needed for patients who may have poor mobilization with the proposed Plerixafor, which is not very effective and is generally an adjunct to G-CSF for mobilization.
- The preservation and monitoring of reproduction and fertility of patients will need to be incorporated into the protocol.

4. Is the project feasible?

YES	15	NO	0

Reviewers considered the following:

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

b) 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.

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

Summary of Reviewers' Comments:

- The timeline will be tight but sufficiently aggressive.
- The team is well qualified to perform the studies and has excellent resources and facilities.
- Major risks are outlined and mitigation strategies are discussed.

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).