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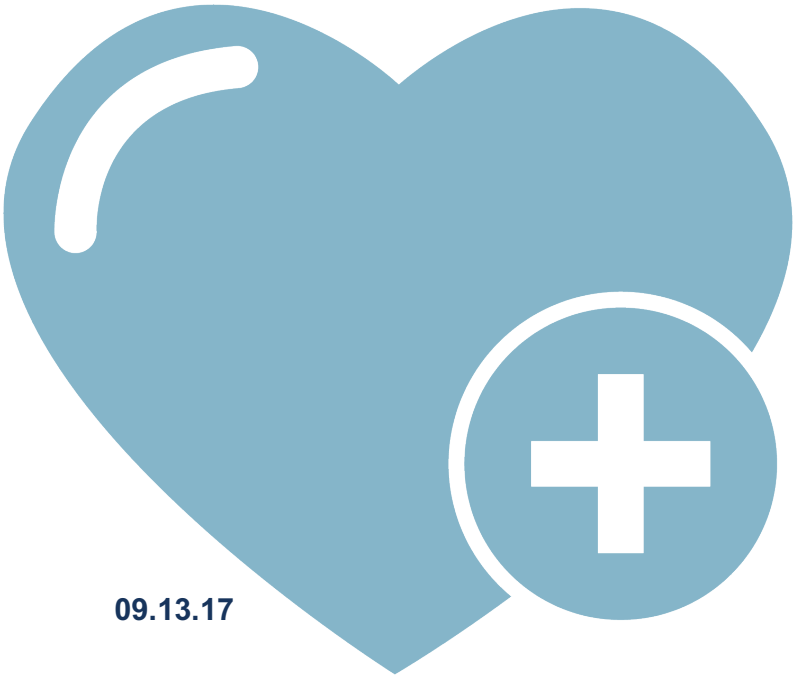
# Grants Working Group Public Review Summary

## Genome Editing of Autologous Hematopoietic Stem Cells to Treat Sickle Cell Disease

| Application Number: CLIN1-10084 (Revised Application) | Review Date: 29 August 2017 |
|---|---|

Late Stage Preclinical Project Proposal (CLIN1)



**09.13.17**

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# Genome Editing of Autologous Hematopoietic Stem Cells to Treat Sickle Cell Disease

**APPLICATION NUMBER: CLIN1-10084 (Revised application)**

**REVIEW DATE: 29 August 2017**

**PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects**

## Therapeutic Candidate or Device

Autologous blood stem cells edited to correct the sickle cell disease mutation to be given back to the patient as an autologous stem cell transplant

## Indication

Severe sickle cell disease

## Therapeutic Mechanism

The mechanism of the proposed therapy for sickle cell disease is that the genetically engineered autologous HSCs (pathologic S allele corrected) will replace the endogenous HSCs using an autologous hematopoietic stem cell transplantation (HSCT). We will use ablative chemotherapy to eliminate the endogenous HSCs and create space for the genetically corrected HSCs. The genetically corrected HSCs will then produce red blood cells with Hgb A and should not sickle and cause disease.

## Unmet Medical Need

Sickle cell disease patients have an average lifespan in the mid-40s with a life with frequent painful crisis. The only curative therapy is allogeneic HSCT but it has significant side effects and is only available to a small number of patients. Thus, there remains an unmet medical need.

## Project Objective

Filing of IND application with the FDA

## Major Proposed Activities

Generate viral vector (AAV) that will be utilized by the blood stem cell to change the sickle cell disease mutation to a non-disease causing base

Establish the reproducibility of the stem cell manufacturing process by repeating the clinical scale manufacturing process three times

File an Investigator New Drug (IND) application with the FDA to get approval to start a phase I/II clinical trial

## Funds Requested

$5,194,431 ($0 Co-funding)

## Recommendation

Score: 1

Votes for Score 1 = 13 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". Reviewers expressed enthusiasm about the potential of this novel autologous gene correction approach for curing patients with sickle cell disease. In the initial review of the application, reviewers were concerned about potential misalignment with the FDA on modifications to a preclinical study protocol as well as feasibility of the novel vector manufacturing method. Both of these concerns represented substantial risks to achieving IND filing within 18 months of project start. The applicant was responsive to the reviewers' concerns by providing additional information on the preclinical study modification, manufacturing method details, and a manufacturing backup plan. Reviewers thought that the revised submission addressed their concerns 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.**

- The proposed gene-corrected autologous hematopoietic stem cell (HSC) treatment would be curative for patients with sickle cell disease (SCD).

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

- SCD patients without a suitable matched donor for allogeneic HSC transplantation have increased mortality. If the proposed therapy is successful, it would address lack of donor availability and improve patient outcomes.

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

- If successful, this gene-corrected autologous transplant would offer an impactful and practical benefit for patients and healthcare providers.
- This curative treatment would reduce the high costs associated with chronic care and management of SCD patients.

**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.**

- The proposed project is based on sound scientific rationale. The *in vitro* and preclinical data gathered by the team demonstrate the highest level of gene correction in SCD HSC obtained to date.

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- Reviewers questioned whether a high level of gene correction could be achieved in long-term repopulating HSC.
- Some reviewers expressed concern that there wasn't strong clinical rationale for mobilizing HSC in SCD patients, which would be necessary step for harvesting and gene-correcting the patient's cells.

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

- The *in vitro* and preclinical data gathered to date strongly support continued development of the candidate.

**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.**

- The proposed project is appropriately designed to enable clinical testing and validation of a novel gene correction method.
- The proposed preclinical testing program represents an appropriate path to IND and appears to be reasonably consistent with detailed feedback provided by the FDA at the pre-IND meeting.
- In the initial review of the application, reviewers were concerned that the applicant was still awaiting feedback from the FDA on a study design modification. The applicant included the complete correspondence to the FDA in the revised submission. Reviewers were satisfied with the applicant's rationale and justification for the study modification.
- In the initial review of the application, reviewers expressed concern about the robustness of the proposed assay for detecting off-target gene edits. The applicant adequately addressed this concern in the revised submission by increasing the sensitivity of the assay.

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

- This is a well-constructed, quality program run by a very strong team with relevant experience in other IND submissions.

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

- The project plan and timeline are aggressively paced and demonstrate an urgency that is commensurate with CIRM's mission.

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**Is the project feasible?**

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

- In the initial review of the application, reviewers were concerned about the feasibility of the novel vector manufacturing methods proposed by the applicant. In the revised submission, the applicant provided additional manufacturing details and a backup plan. Reviewers found the manufacturing and backup plans to be reasonable.
- Reviewers noted that if the FDA disagreed with the applicant's study modification it would likely extend the project timeline by a few months.

**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 composed of scientific and clinical leaders in the field of gene correction for blood disorders.

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

- The team has identified appropriate project risks and has a viable contingency plan.

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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).