CLINICAL

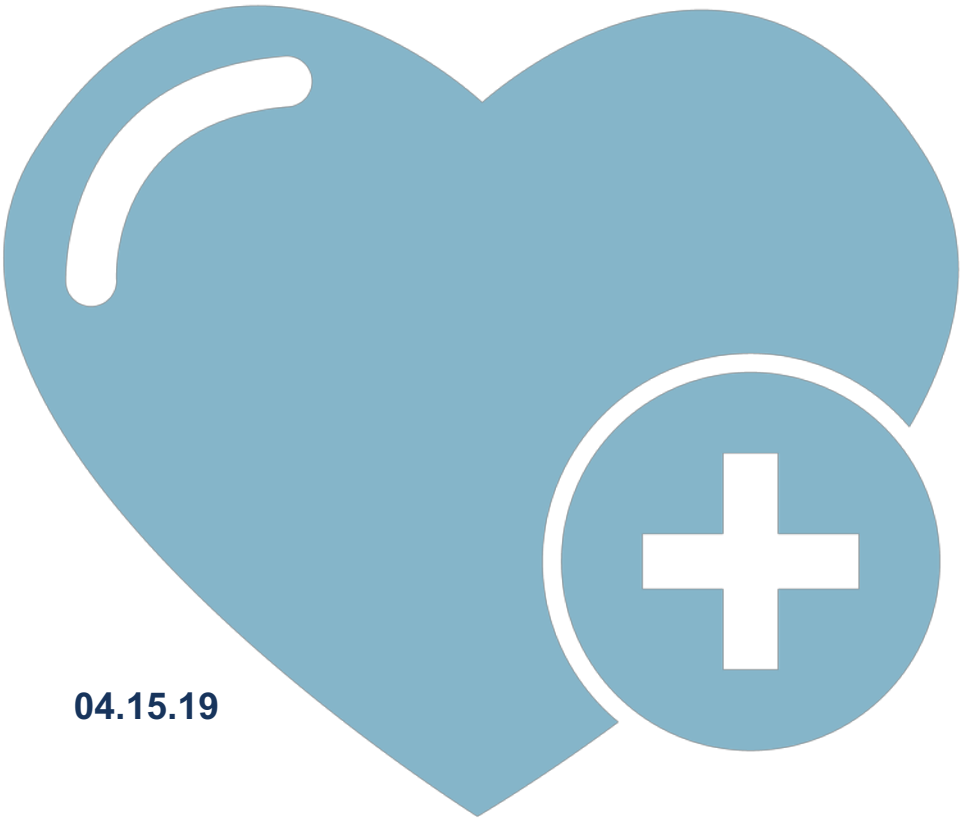
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

Ex-Vivo Autologous Gene Therapy for Leukocyte Adhesion Deficiency-I

Application Number: CLIN2-11480 (Revised Application)	Review Date: 04 April 2019

Clinical Trial Stage Project Proposal (CLIN2)



04.15.19

Ex-Vivo Autologous Gene Therapy for Leukocyte Adhesion Deficiency-I

APPLICATION NUMBER: CLIN2-11480 (Revised application)

REVIEW DATE: 04 April 2019

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

The therapeutic candidate is an ex-vivo autologous gene therapy approach for Leukocyte Adhesion Deficiency-I.

Indication

The target clinical indication is Leukocyte Adhesion Deficiency-I (LAD-I), a pediatric hematological and immunological rare disease.

Therapeutic Mechanism

The therapeutic is based in an ex-vivo, lentiviral-based, patient-specific approach by genetically engineering the patient's own CD34 positively selected cells with the corrected genetic sequence of *ITGB2* (aka *CD18*) gene and subsequently infusing the corrected cells to deliver a potential cure.

Unmet Medical Need

Infants with severe LAD-I present with recurrent, life-threatening infections resulting in ~60-75% mortality prior to reaching the age of 2 years in the absence of a successful allogeneic HSCT (due to extensive bacterial or fungal infection). The proposed gene therapy will treat the underlying gene defect.

Project Objective

Phase 2 trial completed

Major Proposed Activities

Patient recruitment, screening, and support (by various CMOs) on their clinical journey

Enrollment of patients

Cell processing

Funds Requested

$6,567,085 ($5,594,183 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 13 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". While severe leukocyte adhesion deficiency-1 (LAD-1) is very rare, the disease's lethality combined with the limitations of allogeneic hematopoietic stem cell transplants (HSCT) make this a significant unmet medical need. In the initial review of the application, reviewers noted the proposed *ex vivo* gene-modified autologous HSC therapy was based on sound rationale and was supported by the preclinical data. Initial promising results from clinical studies of the same gene therapy technology in other immunodeficiencies was also strongly supportive of the project.

Reviewers had, however, questioned the rationale for using a myeloid specific promoter and for not including a concurrent historical control arm in the trial and had expressed minor concerns over the manufacturing and risk mitigation plans. The applicant adequately addressed the concerns in the revised submission and thus the project was recommended for funding by the GWG.

Review Summary

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

YES	13	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:

- Given that severe LAD-1 is usually lethal in infants and most patients don't have suitable donors for a curative hematopoietic stem cell transplantation (HSCT), this is an unmet medical need.
- The proposed gene-modified autologous hematopoietic stem cell therapy has the potential to be a curative treatment option for infants who are not candidates for allogeneic HSCT. The proposed treatment would also avoid the risk of graft-vs-host disease and need for immunosuppression that are associated with allogeneic HSCT.
- The treatment, if shown to result in immune reconstitution similarly or superior to HSCT, will reduce costs incurred by frequent hospitalizations of LAD-1 patients.

2. Is the rationale sound?

YES	13	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 proposed approach of genetically modifying autologous HSC with the CD18 gene in LAD-1 patients is based on sound scientific and clinical rationale. The preclinical data are supportive of the efficacy of the approach.
- Both the concept of gene-modified HSC and the lentiviral vector technology have shown promising initial results in clinical trials for related immunodeficiencies.
- In the initial review of the application, reviewers questioned the use of a myeloid specific chimeric promoter sequence in the lentiviral vector.
    - Reviewers thought that the applicant's response in the revised submission, which justified their main focus of correction of the myeloid deficit in LAD-1 and described the potential of some expression of CD18 on lymphocytes, adequately addressed their concerns.

3. Is the project well planned and designed?

YES	13	NO	0

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:

- Reviewers had minor concerns with the clinical trial design but noted that it was agreed upon with the FDA.
- In the initial review of the application, some reviewers recommended that the applicant incorporate a concurrent natural history control arm in the trial design as initially suggested by the FDA.

- On the whole, reviewers thought that the applicant's response in the revised resubmission, which noted that the FDA allowed the trial to proceed without such a control, argued that the rare patient population would make such a control arm unfeasible and provided additional information on its published retrospective nature history study, was adequate.
- However, some reviewers remained convinced that the project would benefit from a concurrent natural history arm that could be composed of patients who didn't meet the study entry criteria.

- In the initial review of the application, reviewers recommended that the applicant incorporate phone calls between patient follow up visits in the clinical trial design.
  - The applicant incorporated the GWG recommendation in the revised submission.
- In the initial review of the application, reviewers asked for additional information regarding the product lot release criteria and suggested the incorporation of identity and potency assays.
  - The applicant provided additional information on the product testing plan and adequately justified the release criteria in the revised submission.
- In the initial review of the application, reviewers had questioned the need for producing 3 vector lots to supply the small number of patients in the proposed trial.
  - The revised submission addressed the reviewers' concerns by clarifying the FDA requirements for vector manufacturing and removing manufacture of the third lot from the proposal.

4. Is the project feasible?

YES	13	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:

- In the initial review of the application, reviewers noted discrepancies and errors in the project timeline that called into doubt the feasibility of the projected patient enrollment rate.
  - In the revised submission, the applicant clarified the enrollment rate and corrected the project timeline discrepancies.
- In the initial review of the application, reviewers noted that the contingency plan lacked sufficient detail to address failures in product manufacturing and apheresis procedures in infants.
  - The revised contingency plan, which detailed contingency plans for both risks, adequately addressed the reviewers' concerns.
- The major project risk is patient enrollment but reviewers noted that the applicant has partnered with patient advocacy groups to improve recruitment.

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).