CLINICAL

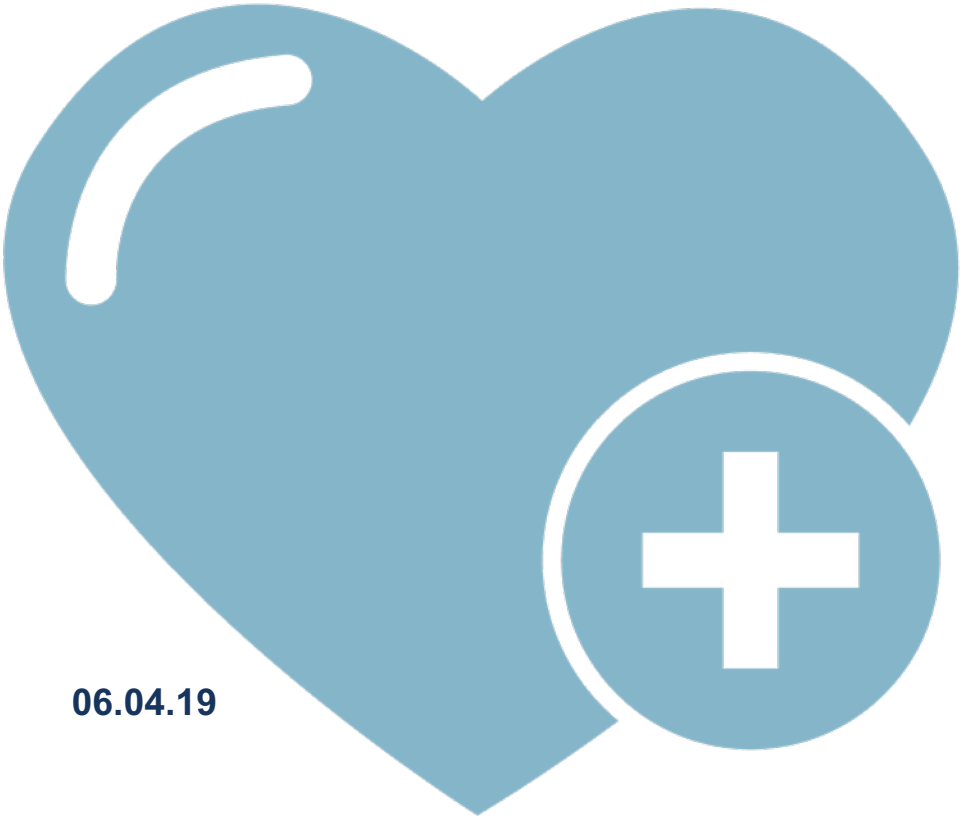
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

Phase 1/2 study for autologous human CD34+ hematopoietic stem cells ex vivo transduced with pCCL-CTNS lentiviral vector for treatment of Cystinosis.

Application Number: CLIN2-11478 (Revised Application)	Review Date: 30 May 2019

Clinical Trial Stage Project Proposal (CLIN2)



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Phase 1/2 study for autologous human CD34+ hematopoietic stem cells ex vivo transduced with pCCL-CTNS lentiviral vector for treatment of Cystinosis.

APPLICATION NUMBER: CLIN2-11478 (Revised application)

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Autologous Human CD34+ HSC from Mobilized PBSC of Patients with Cystinosis Modified by Ex Vivo Transduction using the pCCL-CTNS Lentiviral Vector

Indication

Cystinosis - An autosomal metabolic disease that belongs to the family of the lysosomal storage disorders. Gene involved is CTNS (encodes cystinosin).

Therapeutic Mechanism

The proposed therapy intervention is intended to impact the target indication of Cystinosis via autologous tranplantation of CD34+ HSC-mediated transfer of a functional cDNA using pCCL-CTNS lentivirus vector. The gene-corrected HSC progeny will differentiate into macrophages in injured tissues and transfer cystinosin-bearing lysosomes via Tunneling Nanotubes (TNTs) to disease cells. This transfer of functional cystinosin to endogenous tissue cells leads to long-term tissue preservation.

Unmet Medical Need

The only treatment available for cystinosis is a lifetime oral cysteamine, with severe side effects and compliance challenges, that only delays the disease complications. This approach may represent a one-time life-long therapy that may prevent kidney transplantation and improve the quality of life of patients.

Project Objective

Phase 1/2 trial completed

Major Proposed Activities

Conduct the phase 1/2 clinical trial

Manufacture clinical product for the proposed trial

Funds Requested

$11,999,944 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 15 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

Reviewers were enthusiastic about this resubmission for a phase 1/2 clinical trial for an autologous gene therapy treatment for cystinosis, a rare genetic disease. The applicant was responsive to questions and concerns raised in the initial review, making changes to the patient consent form, providing justification for the dose and release criteria, as well as strengthening immune monitoring plans. Reviewers thought the highly-qualified team would likely achieve the objectives of the proposal within the proposed timeline and thus voted unanimously to recommend the application for funding.

Review Summary

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

YES	**14**	**NO**	**1**

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:

- Cystinosis & Fanconi Syndrome is a progressive multi-organ degenerative disease. Current treatment can delay but not prevent the ultimate consequences, including organ failure and premature death. If successful, this would be a significant improvement on the current standard of care.
- The treatment is likely to be expensive, but given the high costs, difficulty with compliance, and morbidity of the current treatment, the value proposition is likely to be favorable. If successful, this treatment could be curative if delivered early enough.
- The proposed therapeutic approach and mechanism of action, if shown to be effective in cystinosis, will have broader implications for other diseases.

2. Is the rationale sound?

YES	**14**	**NO**	**1**

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 investigators present data from mouse models showing that animals receiving gene-modified cells retained the cells in all organs and had a decrease in cystine levels. A plausible mechanism of action is presented.
- The data support the continued development of this treatment. The outcome of the trial will help determine the right conditioning regimen and correct dose of cells for this therapy.
- In response to reviewer comments the applicants have:
    - included a statement in the consent form that allogeneic transplantation could provide superior results to the proposed therapy.
    - justified the busulfan dose to be used and have agreed to measure real-time pharmacokinetics to verify the correct dosage. They have also added the risks of receiving busulfan to the consent form.
    - provided information on the total number of integration sites. They have also satisfactorily addressed the issue of possible differences in response in men versus women and the question of viability post-thaw and longer-term stability.
    - added relative CTNS expression and cystine measurement on test vs control articles as part of the product release criteria.
    - justified the release criterion for vector copies/cell and have indicated that they will further clarify this value as clinical trial data become available.
    - indicated that, as stated in the original application, they plan to perform complete eye examinations. They also address the issue raised about monitoring renal tubular function in patients who received a kidney transplant. They plan to continue this monitoring to detect potential injury or improvement in function.

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:

- This study is well-designed to assess safety of the procedure and the most important issues regarding effectiveness. The patients are staggered to ensure safety and adequate follow-up before the next is enrolled.
- The investigators have successfully performed three small-scale and one large-scale manufacturing runs, with vector copy numbers at the recommended levels.
- In response to reviewer comments the investigators have:
    - strengthened the plans for immune monitoring.
    - responded to the issue of possible immune sensitization to new lysosomal antigens by providing data from mouse experiments, indicating that this has not been an issue.
    - provided some preliminary data on secondary mice indicating that gene marking was lower, but that CTNS and VCN could still be detected.
    - agreed to encourage female patients to cryopreserve eggs given the busulfan will cause sterility.
    - modified the statistical analysis plan for a 6-patient study.

4. Is the project feasible?

YES	14	NO	1

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 intended objectives are likely to be achieved within the proposed timeline.
- The proposed team is well-qualified and includes international experts in the disease, in pathophysiology, and in gene therapy.

- The project has the appropriate scientific and clinical environment and resources.
- If the study is successful, the applicant has a license agreement for development and commercialization of the product.

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).