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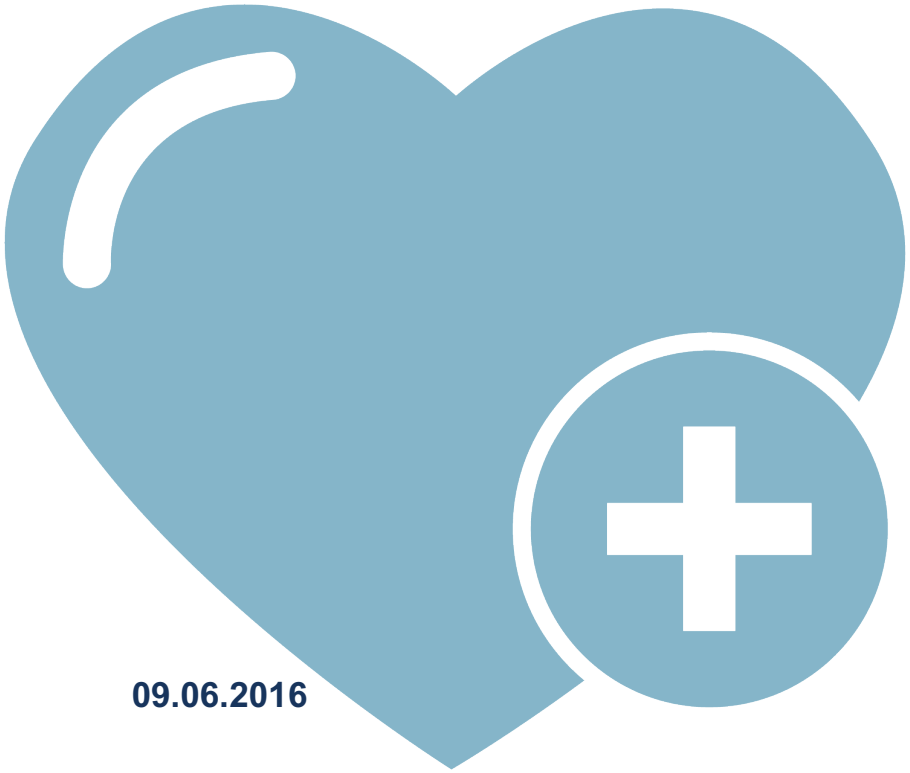
Grants Working Group Public Review Summary

Ex Vivo Transduced Autologous Human CD34+ Hematopoietic Stem Cells for Treatment of Cystinosis

Application Number: CLIN1-09230	Review Date: 30 August 2016

Late Stage Preclinical Project Proposal (CLIN1)



09.06.2016

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Ex Vivo Transduced Autologous Human CD34+ Hematopoietic Stem Cells for Treatment of Cystinosis

APPLICATION NUMBER: CLIN1-09230

REVIEW DATE: 30 August 2016

PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate

Transduced hematopoietic stem cells (HSCs) from peripheral blood stem cells of adults and pediatric patients with cystinosis

Indication

Cystinosis

Unmet Medical Need

Standard of care is cysteamine therapy, which has severe side effects. Patients still require kidney transplants, develop hypothyroidism, diabetes, and neuromuscular disorders. A successful gene-modified HSC therapy would provide a safe and effective one-time life-long therapy for children and adults with cystinosis.

Major Proposed Activities

Support and implement a preclinical study of cysteamine in the mouse model

Develop the CMC necessary for supporting the gene-modified HSCs for autologous transplantation clinical trial for patients with cystinosis

Prepare and submit documents for regulatory approvals

Funds Requested

$ 5,273,189 ($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.

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Review Overview

This is a well written application and clearly described project that addresses an unmet medical need and could improve the standard of care for patients with cystinosis. Further, the preliminary data supports the proposed mechanism of action (MOA) and preclinical proof of concept; the project is well designed and feasible; and the team is of high quality. Reviewers therefore recommend this project for funding.

Review Summary

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

a) Consider whether the proposed therapy fulfills an unmet medical need.

- The proposed therapy holds the promise to fulfill an unmet medical need in an orphan disease indication.

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

- The current standard of care for this patient population is expensive and only partially effective. If successfully developed, this approach would provide an improvement to the standard of care.

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

- A curative therapy would offer a sufficient, impactful, and practical value proposition for both patients and health care providers.

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 MOA is intriguing and supported by sufficient mechanistic data. Reviewers noted that the proposed mechanism is significant and could explain results achieved in other studies using similar approaches.
- The preclinical data supports the efficacy of this approach and suggests that the approach could benefit patients with pre-existing disease, which will be required for treatment of this disease. However, the success of this approach relies entirely on achievement of high levels of transduction efficiency and long-term engraftment.
- The success of this product lies in the ability to achieve high transduction and engraftment rates and to identify appropriate conditioning regimens that will allow high engraftment rates and be tolerated by patients.
    - Some reviewers would like to see additional data in humanized mouse models that support the proposed dosing and that correlate transduction and engraftment rates with efficacy. These reviewers would also like to see additional preclinical data to guide decisions regarding the conditioning regimen for the clinical trial.
    - Other reviewers thought the current data package is appropriate for this stage of research. These reviewers noted that additional data would be collected during the award term to support the phase 1 clinical trial design, and that dose is difficult to address preclinically.

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Human data will likely be necessary to define the required transduction and engraftment levels and determine the best conditioning regimen.

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

- The data strongly supports the continued development of the product.
- Reviewers noted that clinical data within the gene therapy field suggests that vector copy number declines over time. This will need to be monitored and addressed during clinical development of this product if a curative therapy is to be developed.
- Reviewers noted that good natural history of the disease will be required later in development of this therapy in order to get this therapy approved and encouraged the applicant to work proactively with patient advocate foundations to get a good registry well in advance of initiating clinical trials.

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 project is well planned and designed to achieve filing of an IND within the proposed timeframe.
- Reviewers encouraged the team to attempt to enroll as ethnically diverse a population for the eventual clinical trial as possible given the demographics of the prevalence and incidence of this disease.
- Reviewers noted some inconsistencies in describing if and how CROs will be utilized.

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

- The project is well-constructed and of high quality.
- Reviewers encouraged the applicant to carefully calculate a feasible and efficacious dose for the eventual clinical trial and relate that dose to achieving what is necessary for an efficacious and/or curative therapy (which should be described in the TPP).

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

- The project plan and timeline demonstrate an urgency commensurate with CIRM's mission.
- This project is aligned with CIRM's mission.

Is the project feasible?

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

- The FDA has requested a preclinical study that the team has been unable to accomplish due to the technical difficulties of carrying out the study. The team has proposed a reasonable argument to FDA that the study is impractical to perform. However, acceptance of this argument by FDA is the biggest risk to the project as the team has already attempted most strategies to accomplish the study and it is not likely that there is anything else they can reasonably do

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to successfully execute the study.

- Reviewers noted that the proposed dose range for the eventual clinical trial might not be reasonable based upon how well these patients mobilize and collection limits. Dose range will need to be carefully calculated in the final clinical protocol submitted to FDA.

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.

- This group is very well established in performing clinical trials with similar technology and approaches in other areas.
- The principal investigator is a thought leader in the area and has recruited experienced and respected members of the gene therapy community to the team.

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

- A number of issues could delay this project, but the team has proposed good mitigation strategies.

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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).