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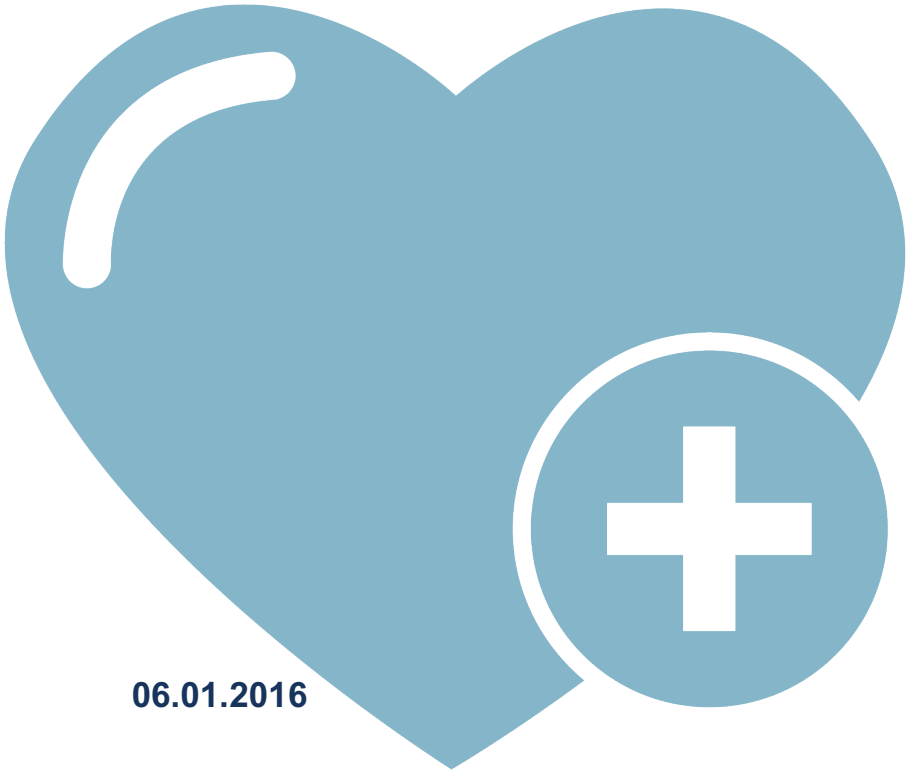
Grants Working Group Public Review Summary

Regeneration of a Normal Corneal Surface by Limbal Stem Cell Therapy

Application Number: CLIN1-08686 (Revised Application 2)	Review Date: May 23, 2016

Late Stage Preclinical Project Proposal (CLIN1)



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Regeneration of a Normal Corneal Surface by Limbal Stem Cell Therapy

APPLICATION NUMBER: CLIN1-08686 (Revised application 2)

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PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate

Cultivated patient-specific corneal epithelial stem cells (limbal stem cells, LSC)

Indication

Corneal blindness from inability to heal due to corneal epithelial stem cell deficiency as a result of injury

Unmet Medical Need

Cultivated LSCs has been shown to be effective and a safer treatment than direct transplantation for LSCD since 1997 in Europe. This stem cell therapy is not available in the United States. The proposed therapy will be the first patient-specific stem cell therapy in the US to treat both unilateral and bilateral LSCD.

Major Proposed Activities

LSC manufacture development and certification

Establishment of manufacture process in GMP facility

Biomarker development

Funds Requested

$4,244,211 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 9 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

Based on the original application, reviewers were concerned that the applicant might not have sufficient high quality proof of concept (POC) data to support moving forward with IND-enabling studies; might not be able to demonstrate to the Food and Drug Administration (FDA) comparability of their product to those the applicant intends to reference in the eventual IND application; and did not have a sufficient plan for clinical and commercial development to support the potential impact of the product. The applicant was given the opportunity to revise the application twice in response to reviewer concerns. While some concerns regarding the quality of the POC data remain after the review of the second revised applicaiton, reviewers recommended this project for funding as the product is highly promising and the project plan and objectives are likely to be achieved. Reviewers thought the applicant had sufficient proof of concept data to justify moving forward with the proposed IND-enabling work; would be able to carry out the proposed project and accelerate this product toward clinical development; and would use the award term to develop an appropriate clinical and commercial development plan.

Review Summary

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

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

- There is a clear unmet medical need that the proposed therapy holds potential to fulfill.

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

- If successfully developed, this approach is likely to provide an improvement over the standard of care for the intended patient population in the United States.

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

- This is a highly competitive area with a large number of groups attempting to develop similar treatments.
    - The investigator asserts that the xeno-free approach provides a significant advantage to this product over other, similar products and reviewers did think it provides somewhat of an advantage.
    - Reviewers noted that this is only an advantage if the product demonstrates comparable clinical benefit, something that has not yet been determined.
- While not critical at this stage of research or for the execution of the proposed project, reviewers noted that the commercialization plan is underdeveloped given this product's potential. During the first and second review of this project, reviewers sought and received assurances from the applicant that the team would seek guidance in this area.
    - The team should target a minimum stability of 24 hours, and preferably 48, for commercial use.
    - Product characterization should be improved and become more quantitative.
    - Precise and sophisticated release testing should be developed.

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- An efficient, commercially viable manufacturing strategy and distribution network should be developed as this will be a key to commercial success and a possible avenue for differentiation of this product from other academic and commercial competitors.

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.

- Reviewers were uncertain if the data presented in the original application adequately support the scientific and clinical rationale necessary for an Investigational New Drug (IND) application. However, the applicant's responses to reviewer questions alleviated many of these concerns.
  - Reviewers were concerned with the rigor and sufficiency of the proof of concept (POC) data. Applicant responses to reviewer questions alleviated concerns regarding the sufficiency of the data to support the IND application, though concerns regarding rigor remain.
  - It is likely that the applicant will able to demonstrate to FDA's satisfaction comparability of the final product to other products available outside the US and to products used by the applicant to generate preclinical data and, therefore, reference such data in the IND application.
  - FDA communications suggest that while reviewers considered the POC data minimal, the existing POC data combined with clinical data referenced from other products will be sufficient to support the safety and efficacy of the final product.
- In the original application, reviewers were concerned by the crudity of the product characterization measures. However, the applicant's responses to these concerns convinced reviewers that the product was sufficiently characterized to support this stage of research.
- The preliminary data suggests that the product is not highly variable, which will support development of a reproducible manufacturing process and demonstration of comparability.

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

- Reviewers thought the project to be highly promising and encouraged continued developed of the product.

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 applicant modified the original project plan based upon reviewer concerns. Reviewers thought the revised project plan to manufacture and characterize the product to be appropriate and likely to achieve meaningful outcomes and further development of the product.
- Based on the final revised application and applicant responses to reviewer questions, reviewers thought it likely that the IND package will be sufficient to support the subsequent clinical trial.

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- The ability of the applicant to demonstrate to FDA's satisfaction the comparability of this product to products that will be referenced in the IND package is crucial. If the applicant is not successful in establishing comparability, the sufficiency of the proposed project plan will be jeopardized. However, based on the applicant's response to reviewer questions, reviewers thought it likely the applicant will be able to establish comparability.
- Reviewers suggested the inclusion of a visual acuity measurement endpoint in the eventual clinical trial. In both the original and the revised applications, the applicant provided a rationale for exclusion of this endpoint, but reviewers were not convinced by the argument and continued to recommend inclusion of such an endpoint.

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

- Reviewers thought this to be a high quality project with an efficient and appropriate plan to move the product toward clinical development.
- Reviewers found the applicant response to concerns regarding the rigor of the POC data unsatisfying, particularly regarding statistical analysis, which impacts the overall evaluation of project quality. However, the applicant will include biostatistician in executing the proposed project, which allayed some concerns regarding experimental rigor and project quality moving forward.

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.

Is the project feasible?

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

- The project objectives are achievable within the proposed timelines.
- During the review of the original application, reviewers were concerned that the applicant did not fully understand what is necessary for product characterization. However, the applicant's responses to these concerns reassured reviewers that the applicant could execute the project plan and develop appropriate assays and properly characterization the product.

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 primary team includes excellent scientists, but reviewers were concerned by responses to questions that the team was not sufficiently experienced to undertake preclinical and clinical development of this product. For example, the team had a tendency to confuse terminology in their responses to reviewer concerns (e.g. product activity testing, potency assays, biomarker, product release assays, etc). However, the applicant recruited additional team members with experience in clinical trials, product development, and regulatory expertise and is continually improving the team, which alleviated these concerns.
- The applicant's expressed willingness to work with CIRM to develop an appropriate clinical and commercial development plan reassured reviewers that the team can be successful in developing this product.
- The addition of an eye banking consortium to the team that occurred between

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the submission of the original application and review of the final revised application strengthened the team and the proposal.

- A biostatistician is critical for the success of this project, and reviewers appreciated the inclusion of a team member with such expertise.

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

- Reviewers did not express concerns with the 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).