CLINICAL

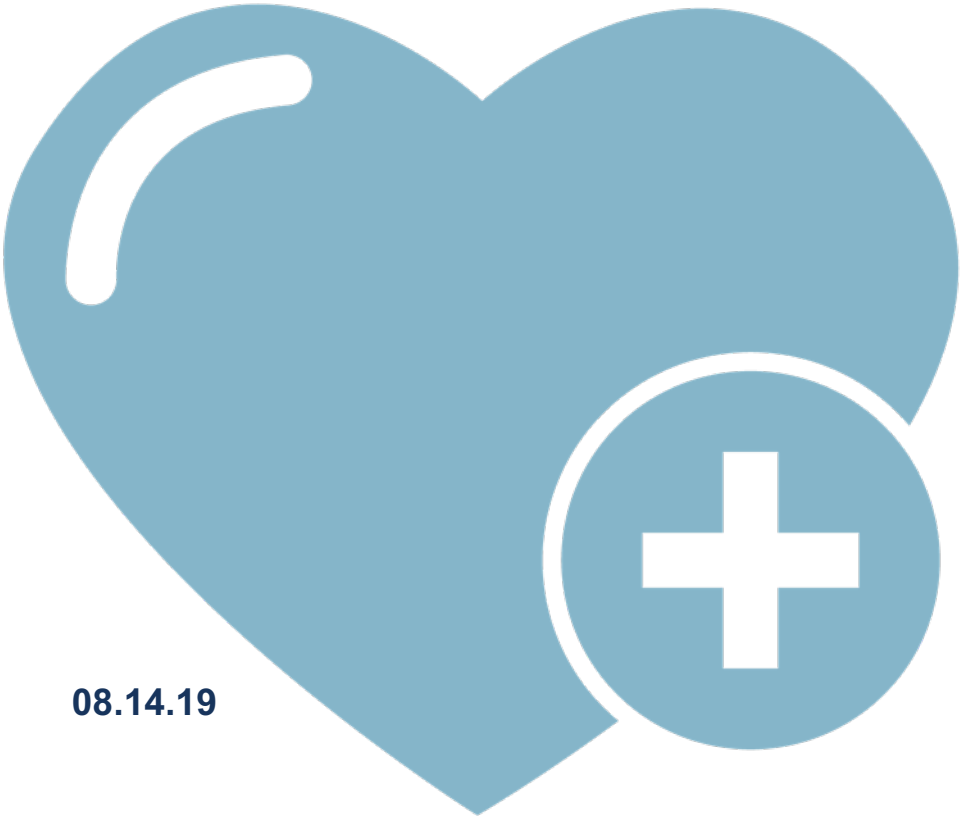
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

Safety and Feasibility of Cultivated Autologous Limbal Stem Cells for Limbal Stem Cell Deficiency

Application Number: CLIN2-11650	Review Date: 25 July 2019

Clinical Trial Stage Project Proposal (CLIN2)



08.14.19

Safety and Feasibility of Cultivated Autologous Limbal Stem Cells for Limbal Stem Cell Deficiency

APPLICATION NUMBER: CLIN2-11650

REVIEW DATE: 25 July 2019

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Autologous cultivated limbal stem cells (cLSC)

Indication

Limbal stem cell deficiency (LSCD)

Therapeutic Mechanism

Restoration of a normal corneal surface using cLSC might be achieved by replenishing the LSC population and/or providing trophic factors to stimulate residual LSCs.

Unmet Medical Need

Therapy using cultivated LSC, which achieves the best clinical outcomes, is a standard of care in Europe. The lack of this therapy in the US is an unmet medical need. Our therapy has the potential to safely, adequately and successfully treat LSCD and become the standard of care in the US.

Project Objective

Complete a phase 1 clinical trial.

Major Proposed Activities

Manufacture and transplant 15 patient-specific cLSC in 15 subjects with LSCD and provide scleral lens treatment to 5 control subjects.

Refine and validate the new diagnostic assays for LSCD and quantify LSC function after transplantation.

Complete the 1 year follow-up in patients treated with the cLSC to assess clinical safety of the cLSC and scleral lens.

Funds Requested

$10,301,486 ($650,000 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 12 GWG members

Votes for Score 2 = 3 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 supportive of the proposed phase 1 clinical trial for an autologous limbal stem cell-based product for corneal disease. The extensive preclinical data and manufacturing development completed by the group under prior CIRM awards provided a strong rationale for continuing the project into the clinic. There were concerns regarding the future scale up of manufacturing, viability of the product over time, and limited intellectual property (IP) that will need to be resolved in the long-term if the therapy is to be commercially successful. Concerns were also raised regarding the overall impact of this project and whether CIRM (given its current stage) should support such a project, which can and has previously garnered funds from other sources. However, the reviewers agreed the proposed trial by an experienced team is straightforward and the overall risk of the project is low.

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:

- This clinical trial addresses the treatment of corneal limbal stem cell deficiency (LSCD), a condition causing severe discomfort and vision loss. Although it is not a common condition, there is no good medical treatment and surgical treatments are difficult, have limited success, and are expensive.
- LSCD is rare and would be considered an orphan condition by FDA and likely to get Orphan Drug Designation or Regenerative Medicine Advanced Therapy (RMAT) designation.
- If successful, this approach would provide improvement over current standard of care which is only supportive in nature and does not impact progression of LSCD.
- The proposed treatment does appear to provide a sufficient value proposition that would support adoption. In the US there is no approved treatment for LSCD. In the EU transplantation of an autologous product has been approved, however this product uses xenogenic reagents. The current proposal will grow LSCs in xeno-free conditions and appears to be superior to the EU approved treatment. Other approaches use allogenic transplantation with subsequent lifelong immunosuppression. The use of an autologous approach would appear to be superior and more cost effective given that immunosuppression would not be required.
- It is unclear whether the return on investment (ROI) for this product will be compelling given the cost to scale this up and to have the capability to manufacture it on a commercial level. In

addition, the IP is limited to specific aspects of the manufacturing process: the xenobiotic-free and feeder-free system.

2. Is the rationale sound?

YES	15	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 project is based on sound rationale and is supported by the scientific data. There is a lot of available data and a history of ophthalmologists using limbal stem cells to repair and restore corneal limbal stem cell loss and deficiency. The applicant has developed extensive data on the culture of limbal stem cells, has developed GMP manufacturing processes, and has developed storage/transport methodology.
- This proposed project is based on current technology but applies a standardized and improved method where the overarching improvement is using less stem cell tissue in an already damaged eye. Using a healthy eye also raises the risk of causing LSCD in unilateral cases.
- The data support the continued development of treatment. This is the next step in a long-standing clinical and laboratory program, supported by CIRM, which has had positive laboratory results.
- The team has also extensively developed non-invasive means of diagnosing LSCD and examining the health of the tissue. These will allow the non-invasive assessment of treatment outcomes and be important in following the progress of patients in the trial.

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:

- The studies completed in the prior CIRM award support advancement to human clinical trials. The current proposal is carefully designed to efficiently assess clinical application.
- The clinical design makes sense and does not pose any extensive risks and/or challenges. The team will be able to conduct the study in the timeframe they propose. The number of experiments is limited to those necessary to address the hypothesis of safety and pilot efficacy.
- While the current manufacturing process is GMP, reviewers raised several manufacturing process concerns that could impact future clinical development and commercialization.
    - The manufacturing process is still very much academic with respect to scale. Scale up of this manufacturing process is going to be difficult. A clear and credible path for long-term scale up of the approach will be needed.
    - Drug product shelf life is a concern. The established 48-hour shelf life at 17 degrees celsius will suffice for clinical development. However, exploration of other methods to extend shelf life will be needed for future multi-center trials and product commercialization.
- Some reviewers thought that the external support indicates the project could be funded through other agencies, and therefore should not be prioritized for CIRM funding. Other reviewers thought that the external, non-CIRM funding indicated favorable and extensive peer review.

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 pre-clinical studies and process development are mature enough to begin this initial clinical study. The manufacturing processes have been developed and tested. This preparation should allow accomplishment of the trial well within the proposed timeline.
- The study team has proven their laboratory and clinical expertise and management by successful completion of the CIRM CLIN1 project. The PI is an acknowledged expert in LSCD. The PI and Co-PI are experts in the treatment of corneal disease and in corneal transplantation and corneal surface surgery. The GMP facility has an outstanding record.
- The team has a well-thought-out risk and mitigation plan in place. The risks for the project are low overall. The CMC activities such as development of the assays, sterility and extended stability assays may present the most significant project risks.

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).