CLINICAL

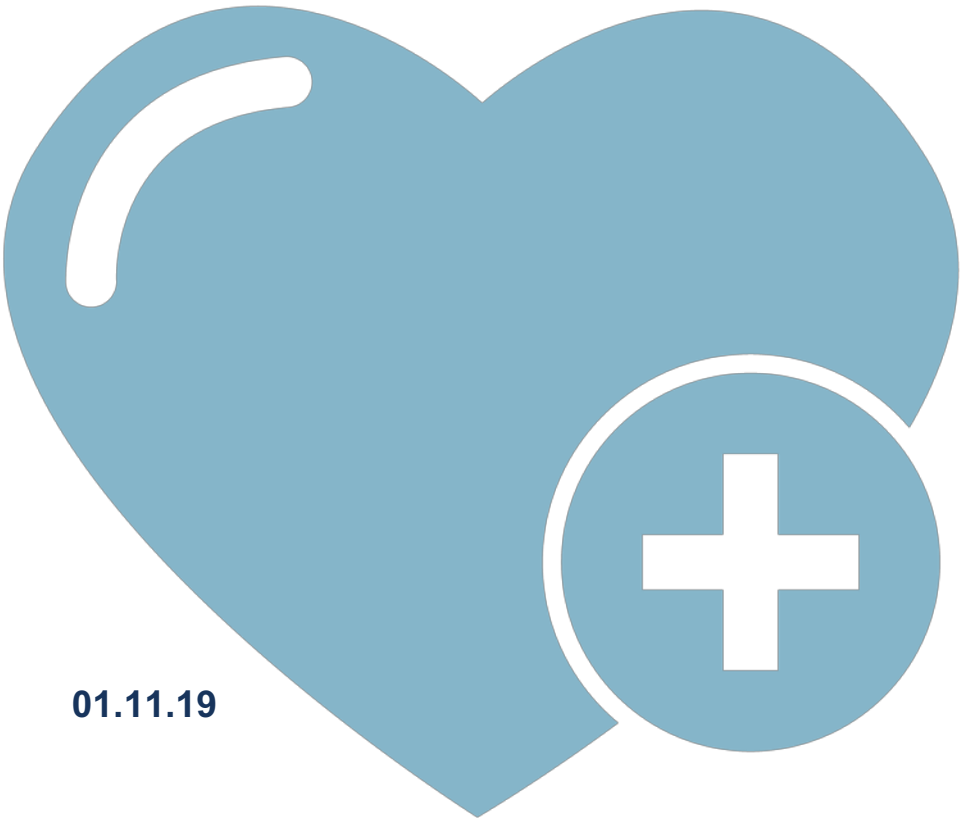
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

A monoclonal antibody that depletes blood stem cells and enables chemotherapy free transplants

Application Number: CLIN2-11431	Review Date: 20 December 2018

Clinical Trial Stage Project Proposal (CLIN2)



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A monoclonal antibody that depletes blood stem cells and enables chemotherapy free transplants

APPLICATION NUMBER: CLIN2-11431

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

CD34+CD90+ hematopoietic stem cells (HSC) in combination with a humanized anti-CD117 monoclonal antibody

Indication

Severe Combined Immunodeficiency (SCID)

Therapeutic Mechanism

This antibody is being utilized as a conditioning agent for selectively eliminating endogenous stem cells in pediatric SCID patients prior to CD34+CD90+ hematopoietic stem cell transplantation for repopulation of the bone marrow. Hematopoietic stem cell (HSC) transplantation possesses the ability to provide a life-long cure for all of these diverse diseases, as it allows for the replacement of defective HSC.

Unmet Medical Need

Although transplant is the proven curative treatment for SCID, this therapy has the risk of life-threatening complications and inadequate efficacy. SCID recipients are uniquely susceptible to the negative consequences of DNA-damaging chemo radiation and risk of both short and long-term side effects.

Project Objective

Phase 1 trial completed

Major Proposed Activities

Complete Phase 1 Clinical Trial
- Enroll, treat, monitor patients
- Determine optimal dose
- Assess clinical safety and efficacy

Funds Requested

$5,999,984 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 9 GWG members

Votes for Score 2 = 6 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 proposal seeking additional funding to complete an ongoing CIRM-funded phase 1 clinical trial for an antibody treatment for HSC transplantation in SCID received mixed support from the GWG. Reviewers agreed the project has a sound rationale and the current data on previously treated patients shows promise. The proposed treatment could potentially be applied to other indications and reduce toxicity for patients, or potentially allow HSC transplantation for patients who are currently not able to tolerate them due to toxicity. However, reviewers disagreed on the feasibility of the project. There were concerns regarding the ability of the applicant to meet the proposed enrollment timeline due to competing trials and a limited number of clinical sites, as well as concern the treatment may not be commercially viable due to the manufacturing process. In addition, funding has not been fully secured in the event of having to manufacture more antibody if the current lot does not remain stable in the long term. Overall, reviewers thought the preliminary positive results of the treatment and potential for application in other indications warrant continued funding of the project despite the feasibility concerns and voted to recommend the project for funding.

Review Summary

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

YES	15	NO	0

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

- SCID is uniformly fatal without an allogeneic stem cell transplant or autologous transplant with genetically modified stem cells in which the underlying defect has been corrected.
- Any method that reduces the toxicity of chemotherapeutic conditioning for HSC transplantation without adversely impacting engraftment will be welcome in several clinical indications. The proposed anti-CD117 treatment could be particularly useful in conditioning autologous gene therapy and SCID patients.

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

- SCID is curable by allogeneic stem cell transplantation, but the standard allogeneic transplant has significant risk due to toxicity of the conditioning regimen and the potential for graft versus host disease.
- If the safety and engraftment data from this trial remains positive, anti-CD117 treatment would certainly be an improvement over busulfan and related conditioning agents because of the potentially lower toxicity. It could be used broadly for other immunodeficiences as well. However, it is not clear whether the treatment would be superior to unconditioned transplants for SCID. The outcome of the ongoing trial will be important in determining this.

c) Consider 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.

- The toxicity of conditioning with this treatment and subsequent HSC infusion appears to be low and could potentially be administered on an out-patient basis. If shown to result in immune reconstitution equal or superior to current approaches, the proposed treatment would reduce toxicity and result in a significant cost reduction.
- In addition to cost reduction, the proposed approach would make HSC transplantation available to many immunodeficient patients who are currently not candidates because their physical condition is too frail to risk chemotherapeutic conditioning.
- The manufacturing of the cells may limit adoption and use of this cell product unless a central business model is put in place.

Is the rationale sound?

YES	15	NO	0

a) Consider 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.

- The rationale is clear and sound. The project plan is supported by the available data from their extensive pre-clinical studies and the early results from the ongoing clinical trial.
- The advantage of sorting CD34+ cells for expression of CD90 is to achieve a 6-7 log reduction of T cells in the graft to reduce the risk of GVHD from allogeneic donor T cells. The disadvantage is that the process of sorting is slower and less amendable to broad dissemination within the transplant community.
- The proposal is significantly strengthened by leveraging prior work done related to GMP manufacturing, stability, PK and safety of the treatment.

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

- The body of available data on the first few patients treated is sufficient to warrant continuing this project. Initial results from the phase 1 clinical trial of SCID patients undergoing a second allogeneic transplant are promising and demonstrate feasibility of the approach as well as some early signs of efficacy.
- It is unclear yet whether this approach will provide full immune reconstitution. One of their outcome goals is to be able to discontinue immunoglobulin therapy (IVIG) in these patients. At the time of review, none of the patients have yet discontinued IVIG.

Is the project well planned and designed?

YES	15	NO	0

a) Consider 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.

- Overall, the plan is appropriate and well-planned. The initial cohorts could provide safety and activity signals supporting moving forward to develop other indications.
- Even though the primary objective of this study is safety and tolerability assessment, the investigators are monitoring efficacy. However, several tests for B and T cell function are less expensive than many of the ones they plan to perform and could provide functional confirmatory data that their approach is able to affect or improve immune reconstitution. The studies would also provide information about when they may be able to discontinue immunoglobulin replacement and help their recruitment efforts.
- A concern is whether enough antibody will persist to impact the engraftment potential of the donor CD34+ HSC leading to deleterious effects on the new donor cells.

b) Consider whether the proposed experiments are essential and whether they create value that advances CIRM's mission.

- Allogeneic transplantation of purified stem cells in the SCID population is a perfect "proof of principle" of the potential utility of this approach. Positive results from the proposed studies will lay the ground work for allogeneic transplantation of purified donor HSC in other conditions such as severe sickle cell disease.
- Successful use of this treatment will support future clinical trials of autologous gene therapy.

c) Consider whether the project timeline is appropriate to complete the essential work and whether it demonstrates an urgency that is commensurate with CIRM's mission.

- The timeline developed by the applicant is appropriate. Given that patients are currently being treated on the initial phase 1 clinical trial, the project meets the urgency for translation that is commensurate with CIRM's mission.

Is the project feasible?

YES	12	NO	3

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

- Enrollment is a major concern. It is not clear if the predicted uptick in referrals anticipated on the basis of the early results has materialized. There are several competing trials trying to enroll rare SCID patients, including two trials at the same applicant institution.
- Timely completion of trial may depend on being able to extend antibody stability.

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 proposed team has ample qualifications to perform these studies. They have the experience and resources to successfully complete this trial.
- A major issue may be the availability of sufficient antibody. The applicant is in the process of securing private entity funding to backstop manufacturing, but it has not yet been completed.

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

- The applicant enumerates several risks and articulates reasonable approaches for each. However, enrollment and antibody availability remain concerns.

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).