CLINICAL

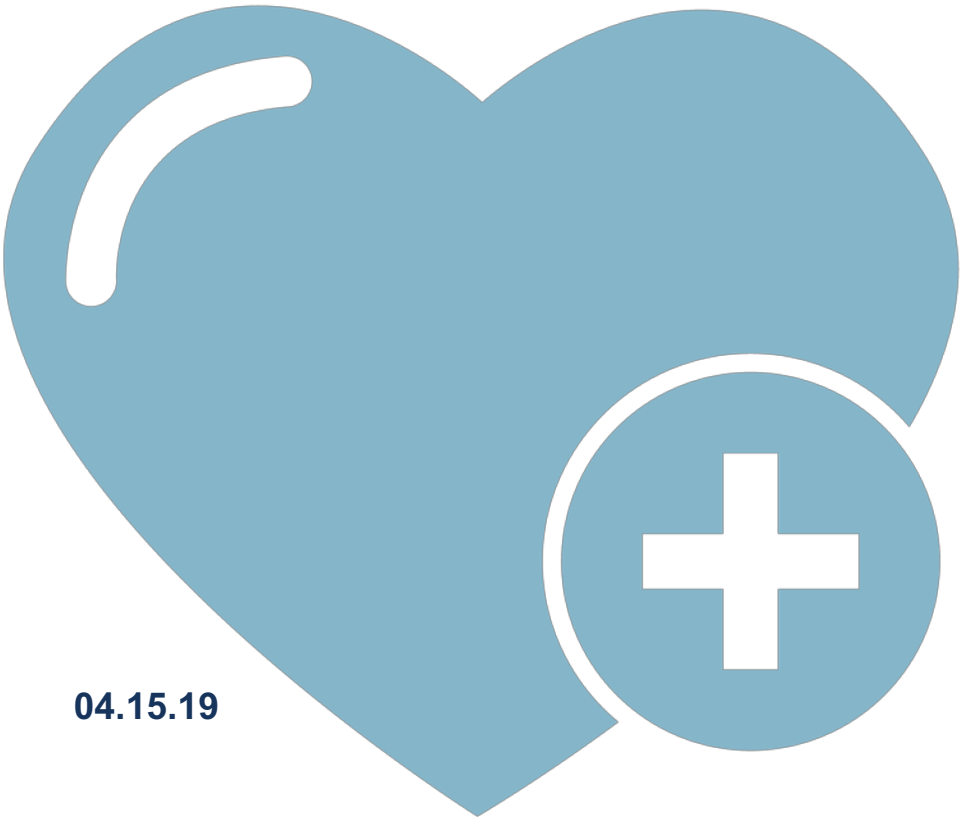
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

Genetic Modification of Stem Cells and T cells to Activate the Immune System to Target Solid Tumors

Application Number: CLIN2-11380 (Revised Application)	Review Date: 04 April 2019

Clinical Trial Stage Project Proposal (CLIN2)



04.15.19

Genetic Modification of Stem Cells and T cells to Activate the Immune System to Target Solid Tumors

APPLICATION NUMBER: CLIN2-11380 (Revised application)

REVIEW DATE: 04 April 2019

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Autologous Peripheral Blood Stem Cells expressing the NY-ESO-1 TCR and a suicide/reporter gene combined with T cells expressing the same TCR

Indication

Locally advanced (unresectable stage IIIc) or metastatic malignancies (stage IV) that are HLA A2.1 +, NY-ESO-1 +, solid tumors, including sarcomas

Therapeutic Mechanism

The administration of TCR transduced mature lymphocytes will expand in vivo and provide a first wave of transient antitumor activity. This will provide a bridge until the genetically modified CD34+ cells expressing a transgenic NY-ESO-1 TCR give rise to T cells recognizing the NY-ESO-1 antigen presented by HLA-A2*0201 in NY-ESO-1 positive malignant cells generating a renewable source of TCR transduced cells for sustained antitumor activity.

Unmet Medical Need

The rarity of sarcomas limits funding and available treatments. This trial will constitute one of the very few options for patients with relapsed or recurrent sarcoma, who have a high prevalence of NY-ESO-1 tumor expression, as well as other types of solid tumors with high NY-ESO-1 expression.

Project Objective

Phase 1 trial completed

Major Proposed Activities

Vectors production and assess feasibility of cell product manufacturing

Assess clinical safety, T cell persistence and anti-tumor response of the combination of the cell products administered

Assess biodistribution of the modified stem cells and progeny

Funds Requested

$4,693,839 ($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.

Review Overview

This is a revised application that previously received a score of ”2”. Reviewers agreed that the lack of effective treatments for advanced sarcomas represents a significant unmet medical need. They expressed strong enthusiasm for the project, which they thought could broadly inform the field on whether engineered stem cell-based immunotherapy would maintain an effective and durable attack on tumors. The reviewers agreed with the rationale for engineering both T cells and stem cells with NY-ESO-1 T cell receptors and thought that it was supported by preclinical and clinical data.

In the initial review of the application, reviewers expressed concerns about the payment structure for the procedures and made several recommendations for correlative studies to improve the quality of data generated from this trial. They also expressed concerns over the feasibility of patient enrollment based on the applicant team’s performance on a current CIRM award for a related trial with the same approach. In the revised submission, the applicant assured the reviewers that patients would not bear the cost of any trial related procedures, incorporated recommendations for all of the correlative studies and provided additional information on the patient enrollment plans. Reviewers were satisfied with the applicant’s revisions and recommended the application for funding.

Review Summary

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

YES	15	NO	0

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:

- Synovial sarcoma and myxoid/round cell liposarcoma are terrible diseases that usually affect young adults. Given the lack of effective treatments for patients with the most advanced forms of these cancers, typical patient survival is less than 2 years.
- The proposed immunotherapy would address this unmet medical need by utilizing both engineered T cells and engineered CD34 to mount a targeted, persistent immune response against the NY-ESO-1 expressing tumor cells.
- The outcome of this project has broader implications for the immunotherapy field. It will inform on the feasibility and safety of stem cell-based immunotherapies. The technology may also be translatable to other NY-ESO-1 positive tumors.
- While the treatment is likely to be expensive, complicated to manufacture and may not be suitable for all patients it will have a very strong value proposition if shown to be effective at improving patient survival.

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:

- Given that sarcoma tumors strongly and uniformly express NY-ESO-1, the rationale for engineering cells with NY-ESO-1 T cell receptors is sound.
- The concept of a dual cell product composed of engineered T cells and engineered CD34 cells to mount both an immediate and persistent immune response against NY-ESO-1 positive sarcomas is based on sound scientific and clinical rationale. The preclinical data and clinical data from 1 treated patient are supportive of the approach.
- There were concerns that the cell persistence may not equate to efficacy and that the engineered cells will be inhibited by the same resistance mechanisms in the tumor microenvironment as natural NY-ESO-1 targeting T cells. However, reviewers noted that only clinical data, such as from this trial, would answer these important questions.

3. Is the project well planned and designed?

YES	15	NO	0

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:

- In the initial review of the application, reviewers noted that the proposed treatment requires stem cell transplantation procedures that are not a part of the standard-of-care for sarcoma patients. Thus, they were concerned that the costs for these procedures may be borne by the trial participants.
    - The applicant adequately addressed this concern in the resubmission by confirming that insurance approval for the procedures had already been secured and that no such costs

would be borne by the patients.

- In the initial review of the application, reviewers thought that the trial was adequately designed to inform on safety and feasibility of the proposed immunotherapy. However, they made several recommendations for correlative studies to better inform trial outcomes. These recommendations included a more extensive immune monitoring plan to monitor functionality and safety of the infused cell products and more rigorous tumor biopsy and imaging assays to monitor tumor progression and relapse.
    - Reviewers strongly commended the applicant for incorporating the recommended correlative studies in the revised clinical protocol and project proposal.
- In the initial review of the application, reviewers asked the applicant to provide a plan for supporting the continued clinical development of this expensive and complex cell therapy.
    - In the revised submission, some reviewers thought that the letter of support from a potential commercial partner was adequate while other reviewers didn't think it conveyed firm commercial interest in, and support of, the project.
- Some reviewers noted that an adaptive trial design would be more efficient and also questioned the inconsistency of the stopping rules associated with dose limiting toxicities.

4. Is the project feasible?

YES	15	NO	0

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:

- In the initial review of the application, reviewers were concerned about timely patient enrollment given the enrollment delays experienced by the applicant team in a related CIRM-funded project studying the same cell product in a hematological cancer setting.
    - The applicant adequately addressed the reviewers' concerns by explaining the nature of the delays on the related CIRM-funded project and by clarifying the patient recruitment plans for the proposed project.
- In the initial review of the application, reviewers noted that the contingency plan didn't account for risk of product manufacturing failures or the risk of disruption of the vector supply.
    - The applicant adequately addressed the reviewers' concerns by providing additional details on contingency plans for these 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).