CLINICAL

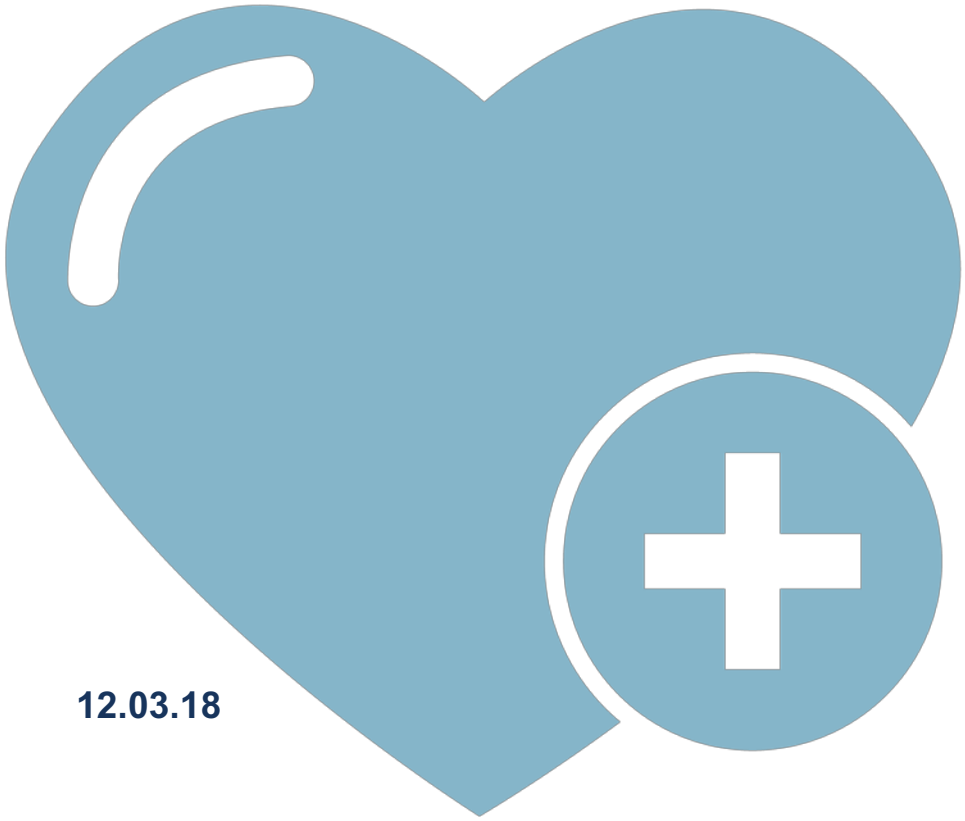
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

Phase 1b Trial and Related Activities to Support Clinical Development of Engineered CD31+ Cells

Application Number: CLIN2-11371	Review Date: 29 November 2018

Clinical Trial Stage Project Proposal (CLIN2)



12.03.18

Phase 1b Trial and Related Activities to Support Clinical Development of Engineered CD31+ Cells

APPLICATION NUMBER: CLIN2-11371

REVIEW DATE: 29 November 2018

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Genetically engineered CD31+ cells derived from Human Umbilical Vein tissue (engineered HUVEC).

Indication

To ameliorate or accelerate recovery from toxicities related to high-dose chemotherapy followed by HDT-ASCT for the treatment of lymphoma and other cancers.

Therapeutic Mechanism

The engineered HUVEC work both via the secretion of angiocrine factors and via direct cell contact signaling with in vivo resident stem and progenitor cells, as well as capillary endothelial cells that comprise the vascular niche which are distributed throughout the body. Infused engineered HUVEC cells interact with injured or damaged vascular niche cells, aiding in their recovery, which subsequently leads to improved tissue regeneration following chemo/radiation regimes.

Unmet Medical Need

There are currently only a few moderately effective treatments available to reduce the toxic side effects associated with aggressive cancer treatments – hence a high unmet medical need. New approaches are urgently needed to both improve quality of life and reduce the risks of high dose therapy.

Project Objective

Phase 1 trial completed

Major Proposed Activities

Production of engineered cell product.

Initiation of patient recruitment

Completion of Phase 1 trial and submission of Final Study Report to FDA

Funds Requested

$6,192,579 ($2,653,963 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 8 GWG members

Votes for Score 2 = 4 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

It is common for lymphoma patients to experience toxicities in multiple organ systems as a result of high-dose chemotherapy treatment. Reviewers agreed that more effective therapies to limit or prevent organ toxicities are sorely needed. They thought that the scientific rationale for the proposed administration of engineered human umbilical vein endothelial cells (HUVEC) to activate the stem cell niche in affected organs was good. They also noted that, if successful, the proposed therapy would be compelling for patients and health care providers.

Reviewers had concerns regarding limited preclinical efficacy data, lack of strong rationale for genetic engineering of the HUVEC product and lack of strong rationale for some of the trial endpoints. Reviewers also noted that similar approaches with mesenchymal stem cells failed to show clinical benefit. However, on the whole, they thought that the data supported clinical testing of the proposed engineered HUVEC therapy. Reviewers recommended the application for funding.

Review Summary

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

YES	**12**	**NO**	**0**

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

- Despite recent advances there are still considerable morbidities associated with high-dose chemotherapy for lymphoma including mucositis, bone marrow toxicity, infections and pneumonitis. The proposed treatment with engineered HUVEC could lower the severity or incidence of these morbidities.

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

- There are supportive therapies such as granulocyte colony stimulating factor (G-CSF) for lowering the duration of neutropenia and recombinant human keratinocyte growth factor (KGF) for lowering incidence of mucositis. However, high-dose chemotherapy still results in toxicities impacting multiple organ systems.
- The proposed approach, if shown to be successful, would improve on the standard of care by reducing toxicity in multiple organ systems.

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.

- If shown to be successful, the proposed treatment would be compelling to both patients and health care providers.
    - The off-the-shelf cell therapy would be easy to administer in the transplant setting.
    - It would reduce hospital stays and lower overall healthcare costs.
    - It would improve patient recovery and patient quality of life.

c) 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?

- N/A

Is the rationale sound?

YES	11	NO	1

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.

- There is scientific rationale for accelerating recovery of organ systems by activating or rescuing the stem cell niches.
- Some reviewers noted that similar approaches to rescue the stem cell niche with systemic delivery of mesenchymal stem cells showed promise in preclinical studies but did not demonstrate clinical benefits in clinical trials.
- Reviewers thought that the preclinical studies generally supported the scientific rationale for the engineered HUVEC. However, they noted several limitations of the provided data.
    - The preclinical data on organ recovery only showed histological data and did not measure organ function.
    - The preclinical data did not demonstrate activation and proliferation of niche stem cells.
    - No data was provided to demonstrate that engineered HUVEC did not act on cancer stem cells.
- Reviewers did not think there was strong scientific rationale or supporting data that the genetic engineering resulted in improved functionality of the HUVEC aside from an increase in proliferative capacity during *in vitro* culture expansion.

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

- While reviewers expressed concerns regarding the preclinical data and the rationale for genetic engineering of HUVEC they acknowledged the limitations of preclinical models and thought that the product should be tested in a clinical transplant setting.

Is the project well planned and designed?

YES	10	NO	2

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.

- Reviewers acknowledged that the phase 1 trial was of a standard design to demonstrate safety of the cell product but expressed several minor concerns.
    - It was unclear how safety of the product will be clearly distinguished from toxicities normally associated with HDT-ASCT.
    - The use of multiple conditioning regimens will likely confound toxicity evaluation. It was unclear how organ toxicities would be objectively measured.
    - It was unclear if the exploratory endpoints would be meaningful given the small sample size and differences in conditioning regimens.
- Reviewers thought that the efficacy endpoints described in the target product profile were modest and may not be clinically significant.

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

- The proposed manufacturing and clinical trial activities are essential for demonstrating safety of the product and enabling further clinical development.

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 project timeline demonstrates appropriate urgency.

Is the project feasible?

YES	12	NO	0

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

- Some cell banks have already been generated but it was not clear if these have been released for production of the final cell product to supply treatment of the initial patient cohorts.
- It was unclear if GMP-grade vector is available for generation of the additional cell banks.
- The trial activities are likely to be achieved in the proposed timeline.

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 team is highly qualified and has access to the necessary facilities to manufacture the product and conduct the clinical trial.
- There is an experienced contract research organization (CRO) in place to manage the trial.

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

- The applicant identified appropriate manufacturing and trial enrollment risks and proposed a viable contingency plan.

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).