CLINICAL

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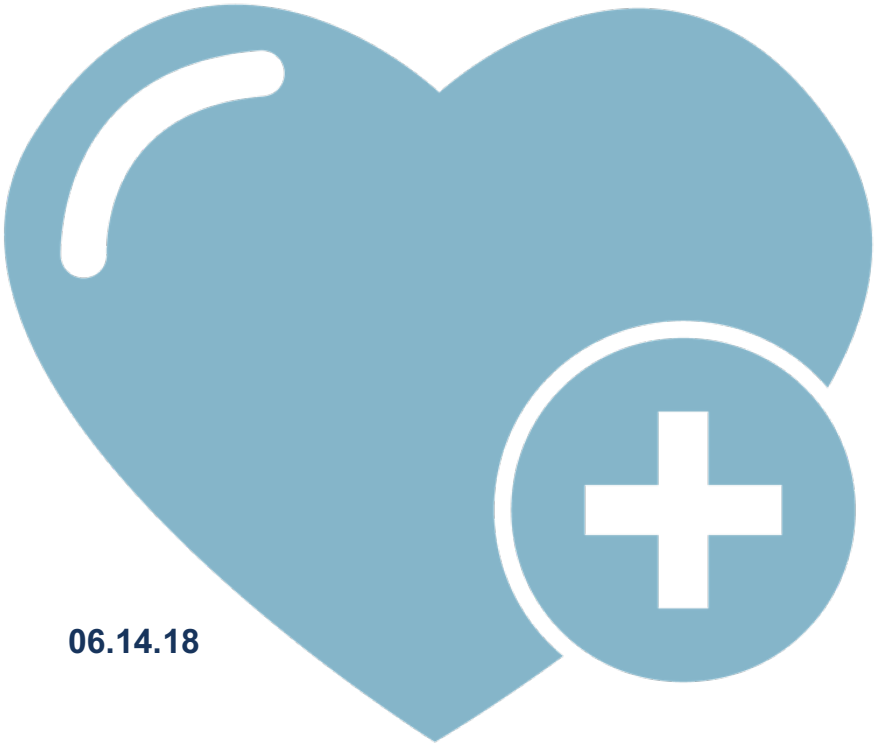
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

Ex Vivo Gene Engineering of Blood Stem Cells for Enhanced Chemotherapy Efficacy in Glioblastoma Patients

Application Number: CLIN1-10967	Review Date: 31 May 2018

Late Stage Preclinical Project Proposal (CLIN1)



06.14.18

Ex Vivo Gene Engineering of Blood Stem Cells for Enhanced Chemotherapy Efficacy in Glioblastoma Patients

APPLICATION NUMBER: CLIN1-10967

REVIEW DATE: 31 May 2018

PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate or Device

Blood stem cells will be genetically engineered to protect them from chemotherapy in glioblastoma patients, producing better patient survival.

Indication

Patients with newly diagnosed glioblastoma (GBM) multiforme, or any grade IV newly diagnosed glioma, will be eligible to receive this therapy.

Therapeutic Mechanism

Chemotherapy is the first-line treatment for GBM, but it is associated with toxic side effects in the blood, limiting the amount of drug a patient can tolerate. Our therapeutic candidate, genetically protected blood stem cells, will decrease the side-effects of the chemotherapy, allowing higher doses of this chemotherapy to be given. This should increase the amount of tumor killing , produce better quality of life, and improved overall survival in these GBM patients.

Unmet Medical Need

There is no cure for glioblastoma. Patient's survival remains ~15 months and treatment involves a type of chemotherapy limited by its toxicity. Our strategy will improve the quality of life and overall survival by reducing these side-effects and allowing more anti-tumor treatment to be given.

Project Objective

IND filing and initiation of Phase 1 trial sites

Major Proposed Activities

Optimize the manufacturing of the therapeutic product. This phase of the project will lead to 3 production runs under clinical trial conditions.

Characterize the efficacy and safety profiles of the therapeutic product.

Prepare the IND application and multi-site clinical trial initiation. This will describe the manufacturing, safety, and clinical trial details.

Funds Requested

$3,684,259 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 10 GWG members

Votes for Score 2 = 2 GWG members

Votes for Score 3 = 2 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

Glioblastoma is a major unmet medical need. Reviewers thought that the proposed treatment, which simultaneously sensitizes tumor cells to chemotherapy while protecting hematopoietic stem cells from its side effects, is based on sound scientific rationale and is supported by preliminary clinical data from two previous studies. Reviewers noted several minor concerns including an aggressive project timeline, lack of preclinical data with patient derived glioblastoma cells, lack of preclinical data supporting the improved vector design, potential impact of the treatment on patient quality of life, and uncertainty whether higher doses of temozolomide chemotherapy would be clinically effective. Ultimately, reviewers thought that the proposed treatment should be progressed to clinical development and recommended it for funding.

Review Summary

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

YES	**13**	**NO**	**1**

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

- Median glioblastoma patient survival is only 18 months with the current treatment regimen that includes surgery followed by radiation and temozolomide chemotherapy. There are currently no curative treatment options for glioblastoma patients.
- The proposed approach will simultaneously sensitize tumor cells to, and protect hematopoietic stem cells from, temozolomide chemotherapy thereby enabling higher dosing and potentially greater anti-tumor efficacy.

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

- If successful, the current approach will allow for a more aggressive chemotherapy regimen while limiting the major side effect of hematopoietic stem cell toxicity.

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 proposed treatment will offer significant value to patients if it is shown to improve overall survival and quality of life over standard of care.
- Some reviewers expressed concern whether the stem cell mobilization procedure would be tolerated by glioblastoma patients.
- The complexity of the proposed treatment requires coordination between hematology and oncology units at the treatment centers. Thus, reviewers were unclear whether it would be readily adopted by health care providers or whether it would be cost effective.

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	**14**	**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 scientific rationale for protecting hematopoietic stem cells to enable higher temozolomide dosing is sound and is supported by clinical data.
- The proposed treatment is informed by two previous preliminary clinical studies.
- Some reviewers noted that no preclinical studies were performed to compare the improved vector design against the vector used in the previous related clinical study.
- Reviewers noted that higher temozolomide dosing was not shown to be effective in other phase 3 clinical studies but acknowledged that the current approach will enable study of even higher doses.

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

- The preliminary clinical data with the proposed approach supports continued preclinical and clinical development of the treatment.

Is the project well planned and designed?

YES	**11**	**NO**	**3**

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.

- The proposed studies, which will optimize genetic engineering of HSC and GMP manufacturing of the engineered HSC product, are appropriately planned and designed to enable filing of an IND.
- Reviewers thought that the applicant's plan for addressing the FDA's pre-IND meeting feedback appeared reasonable. However, some reviewers noted the risk that the FDA may not agree with the applicant's responses.
- Some reviewers expressed concern that patient enrollment in the eventual phase 1 trial may be challenging. They noted that additional preclinical studies on patient derived glioblastoma cells should be conducted to demonstrate increased sensitization and toxicity with the proposed treatment.

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

- The proposed preclinical experiments are adequate and will verify whether the modified vector design will improve expression of the construct and the overall safety profile of the engineered HSC.
- The proposed vector and cell manufacturing studies will support IND filing and conduct of the eventual phase 1 trial.
- Reviewers thought that the cell characterization studies should be conducted post-thaw given that the cell product will be cryopreserved prior to clinical use.

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 is aggressively designed to meet the requirements outlined in the CLIN1 PA.

Is the project feasible?

YES	**13**	**NO**	**1**

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

- Some reviewers found the timeline for vector manufacturing to be unrealistic and expected the activities to take considerably more time to complete.

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 very well qualified to execute the proposed project.
- The team has access to well-qualified manufacturing facilities to conduct the proposed studies.

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

- Reviewers thought that the proposal did not thoroughly identify projects risks and contingency plans. However, they acknowledged that the proposed team has the expertise and experience to adequately address project risks.

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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).