CLINICAL

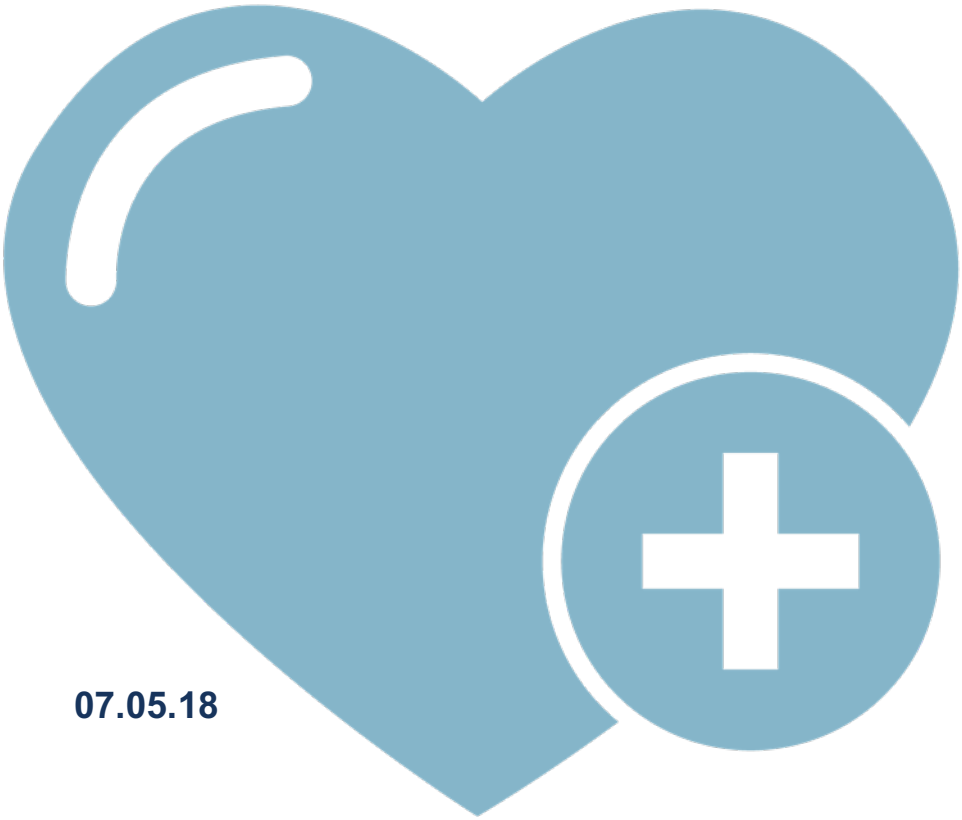
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

Late-Stage Preclinical Study of CAR-T Memory Stem Cells Targeting PSMA for the Treatment of Castrate-Resistant Metastatic Prostate Cancer

Application Number: CLIN1-10999 (Revised Application)	Review Date: 25 June 2018

Late Stage Preclinical Project Proposal (CLIN1)



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PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate or Device

Genetically engineered CAR-T memory stem cells

Indication

Castrate-resistant metastatic prostate cancer

Therapeutic Mechanism

The chimeric antigen receptor T cells (CAR-T) are cells that are removed from a patient's body and genetically engineered to express a receptor that binds to PSMA that is selectively found on prostate cancer cells, triggering the CAR-T cells to specifically kill the prostate cancer cells. Because the CAR-T cells are stem cell memory, they can give rise to many CAR-T effector cells and persist for long periods and kill residual PSMA+ cancer cells or recurrences.

Unmet Medical Need

Other than skin cancer, prostate cancer is the most common cancer among men in the US. In the US, 172,258 men were diagnosed in 2014. Early stage prostate cancer is often managed by surgery, radiation and/or hormone suppression, however, metastatic CRPC is eventually fatal despite current treatments

Project Objective

IND submission and clinical trial start-up

Major Proposed Activities

Manufacturing for IND-enabling study

Completion of nonclinical IND-enabling studies

Preparation and submission of IND

Funds Requested

$3,992,090 ($998,023 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 12 GWG members

Votes for Score 2 = 0 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

Overall, reviewers were strongly supportive of this novel CAR-T therapy approach to address the poor prognosis for patients with castrate-resistant prostate cancer (CRPC). In the initial review of the application, reviewers agreed that there was strong scientific rationale for the applicant's novel improvements to CAR-T cell technology. They also agreed that the improvements could potentially overcome the limitations of current CAR-T approaches for solid tumors. They also agreed that the proposed pre-clinical studies would lead to successful filing of an IND for this therapy.

However, reviewers thought that the initial application lacked strong supporting data to support the scientific rationale and claims of superior CAR-T technology. In particular, there weren't adequate details on the completed preclinical studies in the initial application to allow thorough assessment of the proposed CAR-T technology improvements. Furthermore, reviewers noted that healthy donor cells used to produce CAR-T cells for all previous and proposed preclinical studies. They raised concerns whether the CAR-T cells generated from CRPC patients would have similar characteristics and functionality.

In the revised submission, the applicant provided additional information and data on the previously conducted preclinical *in vitro* and *in vivo* studies. The applicant also performed preliminary studies with patient-derived cells in response to the reviewers' concerns. Reviewers thought that the revised submission thoroughly addressed their initial concerns and it provided strong preclinical data in support of the therapeutic approach. Thus, the reviewers unanimously recommended the application for funding.

Review Summary

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

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

- Given the high prevalence of prostate cancer and the poor prognosis for CRPC, this is a major unmet medical need. The proposed treatment would extend promising CAR-T technology to this solid tumor.

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

- The proposed treatment has the potential to improve survival in this patient group, which faces a poor and fatal prognosis.

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 safe and effective in inducing long-term remission the proposed therapy would be very attractive to CRPC patients and health care providers.
- Widespread adoption by health care providers of CAR-T therapy for blood cancers may aid in accelerating adoption of this therapy as well.

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?

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 strong scientific and clinical rationale for targeting prostate-specific membrane antigen (PSMA), which is over-expressed in prostate cancer cells. Some reviewers noted the potential for off-target toxicity with a PSMA CAR-T product, which should be carefully assessed in the clinical studies.
- Initial CAR-T approaches to solid tumors, including prostate cancer, have shown little success. The applicant provided strong scientific rationale for their proposed technological improvements aimed at enhancing safety and efficacy of CAR-T therapy.
    - Reviewers agreed that the proposed CAR-T technology with non-viral genetic engineering, fully human CAR, and a high proportion of stem memory T cells could improve safety, persistence and efficacy of these cells.
- In the initial review of the application reviewers noted that the applicant provided limited data from the completed preclinical studies to support the scientific and clinical rationale for the proposed treatment. Overall, reviewers were satisfied with the applicant's response to their concerns in this revised submission.
    - Reviewers thought that the preclinical *in vitro* and *in vivo* efficacy data provided in the original application lacked details and justification for controls, doses and study timelines. The applicant provided additional experimental design information and datasets from the previously conducted preclinical efficacy studies. Reviewers thought that the data in the revised submission strongly supported the approach.
    - Reviewers noted that the preclinical studies were performed with healthy donor cells as the source for the CAR-T cells. Reviewers were concerned whether CAR-T cells produced from patient cells would have similar characteristics and activity. The applicant performed preliminary *in vitro* studies with patient cells in the revised submission, reviewers thought that the data adequately demonstrated feasibility of the approach.
    - The original application lacked data to support the claims of enhanced proliferation, persistence, reduced exhaustion and long-term efficacy for the proposed CAR-T product. The applicant provided details and data from the previously conducted studies in the revised submission to support the proposed CAR-T technology enhancements. Reviewers thought that the provided data pointed toward a more potent and persistent CAR-T product, which would be important for achieving efficacy in this indication.

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

- The data strongly supports clinical development of the proposed CAR-T therapy for CRPC.

Is the project well planned and designed?

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 thought that the IND-enabling studies were appropriately designed to achieve timely submission of the IND.
- In the initial review of the application it was unclear how the manufacturing process resulted in

enrichment of stem memory T cells. Reviewers thought that the additional data and information provided in the revised submission was adequate but noted that the exact mechanism of stem cell enrichment is not well understood.

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

- The proposed experiments are essential to achieving IND submission and progressing to clinical study of the proposed CAR-T 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 project timeline meets the 18-month to IND requirement of the CLIN1 PA.

Is the project feasible?

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

- Reviewers noted the applicant's successful experience translating similar CAR-T cell technology to clinical study for a different indication as a particular strength of this application.
- In the initial review of the application some reviewers were concerned that the complex manufacturing process could adversely impact timely completion of project activities. Reviewers were satisfied with the applicant's response in this revised submission, which highlighted successful and timely manufacturing of the related CAR-T product that is currently in clinical trials.

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 is highly qualified and has previously demonstrated successful IND-enabling preclinical development of a similar CAR-T product.

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

- The applicant identified manufacturing risks and described appropriate contingency plans.

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).