City of Hope

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Independent Citizens' Oversight Committee (ICOC)
California Institute for Regenerative Medicine (CIRM)
1999 Harrison Street, Suite 1650
Oakland, CA 94612

Application: DISC2-11107

Title: Chimeric Antigen Receptor-Engineered Stem/Memory T Cells for the Treatment of Recurrent Ovarian Cancer

Principal Investigator: Saul J Priceman, Ph.D.

Dear Members of the ICOC,

Immunotherapy is one of the most promising approaches in the war against cancer; in the last ten years, the use of Chimeric Antigen Receptor (CAR)-engineered T cells has revolutionized the treatment of blood cancers. Unfortunately, the CAR T cell approach has not yet shown equal success in eradicating solid tumors. The major challenges hampering the clinical success of CAR T cells in solid tumors are limited CAR T persistence and poor T cell infiltration into tumors, both of which are specifically addressed in this proposal. City of Hope was the first institution to treat solid tumor (neuroblastoma) patients using CAR T cells, as well as the first to demonstrate a durable clinical response with CAR T cells in a glioblastoma patient. For over a decade, City of Hope has invested significant resources in developing new CAR approaches for treating the most incurable and deadly solid tumors.

Our proposal (DISC2-11107) specifically focuses on developing ovarian cancer-specific immunotherapy, particularly for patients who have no effective treatment options. In California alone, five women will be diagnosed with ovarian cancer today, and every day this year. Four of these women will be diagnosed with late-stage aggressive and incurable disease, and only one will survive. While CIRM funding supports a broad cancer portfolio, ovarian cancer is notably under-represented. Only one DISC1 grant (for $172,000) specifically focuses on the treatment of ovarian cancer.

We address several barriers to the development of effective cellular immunotherapy strategies for this disease. First, our unique CAR approach builds on our recent findings that regional delivery of CAR-engineered T cells (infused into the abdominal space rather than in the bloodstream) kills ovarian tumors and increases survival in preclinical models. Next, specifically programming the CAR therapeutic using a stem/progenitor T cell population maximizes their ability to persist longer in the body and potently kill tumor cells in patients. Last but not least, we will also endow these stem/memory CAR T cells with the ability to produce cytokines that further promote stem T cell maintenance and persistence leading to durable anti-tumor responses.

We greatly appreciate the GWG's favorable review of our proposal, and are pleased with their recommendation for funding. We believe two minor concerns reduced their enthusiasm, and would like to address them below.

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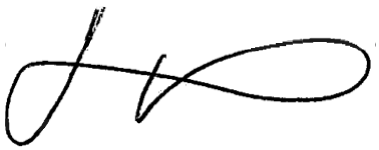
The reviewers questioned "*the stem cell targeting aspect of the proposal.*" Our proposed therapy focuses on re-engineering human blood stem/progenitor cells to produce a stem/memory-derived CAR T cell therapeutic candidate. In addition, the target of our CAR is expressed on ovarian cancer cells including stem-like cells. This specific targeting of ovarian cancer stem cells has been validated by new studies published since the submission of this proposal. Therefore, we firmly believe our CAR T cells will effectively target both stem-like ovarian cancer cells as well as more differentiated cancer cells, making it a powerful and broad therapeutic approach for treating advanced disease.

The second concern was that "*the inducible approach is not novel and could have limited efficacy.*" Several lines of evidence have demonstrated that intrinsic cytokine production promotes T cell persistence, improves anti-tumor activity, and drives the infiltration of T cells into solid tumors. We have extensive data with one of these cytokines that promotes T cell "stemness" and generates a long-lived stem/memory CAR T cell therapeutic product, and will be novel to the treatment of ovarian cancer. These approaches will be developed in parallel and compared to identify the most optimal CAR design for further clinical development.

Our therapeutic strategy aims to eradicate metastatic ovarian cancers. We have already generated promising preclinical data, and will be able to develop this approach further with funding of this CIRM DISC2 award. Our goal is to submit a pre-IND application at the completion of the funding period. With City of Hope's extensive experience, expertise, and infrastructure in CAR T cell immunotherapy, we aim to move rapidly toward clinical development of an effective CAR T cell therapy that could greatly improve survival of patients with advanced ovarian cancer.

Sincerely,



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