Ansuman Satpathy, M.D., Ph.D.
Assistant Professor
Department of Pathology
Parker Institute for Cancer Immunotherapy
Stanford University School of Medicine
300 Pasteur Drive, L-235
Stanford, CA 94305-5324
(650) 723-5252 Fax: (650) 725-6902

Stanford MEDICINE
PARKER INSTITUTE for CANCER IMMUNOTHERAPY

August 19, 2021

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

Application: **DISC2-12694**
Project Title: **Preclinical development of an exhaustion-resistant CAR-T stem cell for cancer immunotherapy**
PI Name: Ansuman Satpathy M.D., Ph.D.

Dear Members of the ICOC and CIRM Board,

We are respectfully writing to you regarding our application titled, "Preclinical development of an exhaustion-resistant CAR-T stem cell for cancer immunotherapy," which will be reviewed at the meeting of the Application Review Subcommittee (ARS) on August 24, 2021.

We would like to thank the Grants Working Group (GWG) for their constructive review and recommendations to improve the proposal. **Our application received a median score of 84, which is one point lower than the fundable score of 85.** The GWG voted that the proposal has high significance and potential for impact (Yes/No: 10/0), sound rationale (Yes/No: 9/1), is well planned and designed (Yes/No: 7/3), and importantly, has the potential to serve the needs of underserved communities (Yes/No: 10/0).

A few highlights of the GWG Reviewer Comments include:

- "Novel and cutting-edge technology addressing the important problem of CAR-T exhaustion."
- "The development of better CAR-T strategies would be clinically useful."
- "The previous clinical development of gene edited CAR-T products that have entered clinical testing is a positive."
- "The investigators are a major strength of the proposal."
- "Phenomenal team."

Indeed, 6/14 GWG Reviewers voted to fund the proposal, and their Minority Report states:

- "This application for exhaustion resistant CAR-T cells for immunotherapy had an extremely strong team and if the problem of cell persistence in immunotherapies could be solved, it would be an important advance for the field."
- "The technology, if successful, **would have a significant impact on the field as well as being a good fit for CIRM funding as a strong stem cell-focused project**."

While we understand that our proposal is slightly below the fundable score, we would like to take this opportunity to emphasize a few key aspects of our proposal, and modifications that we have made in response to the GWG's recommendations, and respectfully ask for the ICOC's consideration to fund this project.

1. GWG recommendations and changes to the proposal.

We thank the GWG for their critical review and recommendations for improving the proposal. The primary weakness identified by the GWG was that the proposal was too ambitious for a 2-year award. In particular, the GWG recommended that we limit the number of cancer model systems used in the study and suggested that we focus on sarcoma, given the clinical need for novel therapies for this cancer type. Indeed, our group and collaborators have demonstrated that CAR-T cell exhaustion is a significant limitation to CAR-T therapy in sarcoma, and to date, effective cell therapies for this clinical indication and patient population are severely lacking (Lynn et al, *Nature*, 2020; Majzner et al, *Nat Med*, 2019; Gennert et al, *PNAS*, 2021). **Thus, we fully agree with the GWG's recommendation and have adapted the proposal to focus on a single *in vivo* cancer model for sarcoma, which we believe improves the overall feasibility of this study, while maintaining its high clinical significance.**

2. Synergy with 22 existing CIRM Awards.

The ability to genetically program and administer living cellular therapies is rapidly becoming a mainstay of clinical medicine, and CAR-T cells represent a promising therapeutic strategy for many cancer types, as well as non-malignant diseases, such as autoimmune and infectious diseases. Accordingly, in our estimation, CIRM has funded a total of 22 CAR-T or T cell therapy-focused studies (6 Discovery, 6 Translational, 10 Clinical) over the past 5 years with a total of ~$122M. We believe that our technology, which aims to fundamentally improve the longevity and function of CAR-T cells in patients, will broadly synergize with and could be applied to each of these previously funded studies, including CIRM-funded CAR-T therapies that are currently in clinical use. **Therefore, we hope that the development of this technology will not only benefit patients with sarcoma but also many patient populations that have previously been targeted by CIRM's funding and institutional resources.**

3. Funding opportunity/gap for junior faculty.

Our laboratory is relatively new; we began our group in July 2019, just a few months prior to the COVID-19 pandemic. For junior faculty, this early funding window can be a critical gap, since funding timelines and cycles from more traditional avenues, such as the NIH, can take much longer to successfully complete. Therefore, this application will support a critical window of opportunity and funding gap for our laboratory, and it will allow us to rapidly pursue the clinical translation and development of a highly promising therapy that we have recently discovered. The studies proposed here are not currently supported by any other funding sources, and thus, they will be solely driven forward by CIRM funding.

Thank you for your consideration, and for the tremendous support that you offer to patients, clinicians, and researchers in California. We are fortunate to have CIRM as a granting agency in our state, and we look forward to our future collaborations together.

Sincerely,

Ansuman Satpathy M.D., Ph.D.