Preclinical development of an exhaustion-resistant CAR-T stem cell for cancer immunotherapy

Grant Award Details

Preclinical development of an exhaustion-resistant CAR-T stem cell for cancer immunotherapy

Grant Type: Quest - Discovery Stage Research Projects

Grant Number: DISC2-13212

Project Objective: Establish proof-of-concept that GD2-CAR-T cells and NY-ESO-1 TCR-T cells (both referred to as "CAR T cells"), engineered to resist T cell exhaustion (TEx) through INO80 complex deletion, achieve improved persistence and tumor (osteosarcoma) clearance, and maintain a highly functional progenitor TEx phenotype, as compared to equivalent conventional CAR-T cells (INO80 intact). Robustness (autologous T cell product) assessed by testing CAR-T cell products from 5 or more T cell donors from diverse ethnic/racial backgrounds, both sexes, old and young individuals.

Investigator:

Name:	Ansuman Satpathy
Institution:	Stanford University
Type:	PI

Disease Focus: Cancer, Sarcoma, Solid Tumors

Human Stem Cell Use: Adult Stem Cell

Award Value: $1,420,200

Status: Active

Grant Application Details

Application Title: Preclinical development of an exhaustion-resistant CAR-T stem cell for cancer immunotherapy

Public Abstract:

Research Objective

The expected outcome is an exhaustion-resistant CAR-T cell, which persists long-term in a functional progenitor T cell state in the tumor microenvironment and can be used for cancer immunotherapy.

Impact

CAR-T cells are effective in B cell cancer, but less than 50% of patients experience long-term disease control. Exhaustion-resistant CARs may provide long-term benefit that extends to solid tumors.

Major Proposed Activities

- Establish and optimize a CRISPR-engineered CAR-T stem cell therapy that resists T cell exhaustion.
- Perform in vitro evaluation of TEx-resistant CAR-T cell tumor recognition and cytolysis, and progenitor cell state characterization, compared to conventional CAR-T cells.
- Perform in vivo evaluation of TEx-resistant CAR-T cell function and persistence in xenograft tumor models, compared to conventional CAR-T cells.
- Perform epigenomic characterization of T cell exhaustion in TEx-resistant CAR-T cell in tumor models, compared to conventional CAR-T cells.

Statement of Benefit to California:

A significant barrier to long-term efficacy of cancer immunotherapy is the development of T cell exhaustion, which limits T function in the tumor microenvironment. The proposed exhaustion-resistant CAR-T stem cell therapy candidate has the potential to benefit a large population of patients in California who suffer from a broad range of cancers that may be targeted by CAR-T cells, including solid tumors (lung, prostate, sarcoma, and skin) and blood cancers (leukemia, multiple myeloma, lymphoma).
