Weill Cornell Medicine

Platform for Endogenous Protein Knockout for Enhanced CAR-T Therapy

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Background & Unmet Need

- Chimeric Antigen Receptor (CAR)-T cell therapy is an immunotherapy wherein T cells are collected from patients and engineered to express CARs, which recognize and target specific tumor antigens
- This type of therapy has shown promising results for blood cancers, with seven therapies approved since the first CAR-T approval in 2017 (for Acute Lymphoblastic Leukemia)
- However, CAR-T therapies lack efficacy in solid tumors in part due to interactions with the tumor microenvironment (TME), which rapidly suppresses and eliminates T cell anti-tumoral activity
- For example, binding of PD-L1 to PD-1 on CAR-Ts can suppress T-cell functions, including proliferation, cytokine production, and cytolytic activity, leading to immune escape
- **Unmet Need:** Enhanced methods of CAR-T therapy that facilitate T cell expansion and function in the presence of the immunosuppressive TME

Technology Overview

- **The Technology:** Integration of Protein Knockout (PKO) technology with cell therapy, such as CAR-T therapy, to enhance expansion and efficacy
- **The Discovery:** PKO is a method that reduces or inactivates a target protein by genetically linking a small targeting peptide to E3 ubiquitin ligase β-TrCP
- PKO can be integrated into the same vector as therapeutic proteins, such as CARs, in cell therapy to selectively eliminate endogenous proteins which hinder therapeutic efficacy
- **PoC Data:** As a proof of concept, PKO was used to selectively degrade endogenous PD-1 in CAR T-cells, which is known to suppress T cell function
- Transduction of primary human T-cells with the experimental vectors effectively reduced PD-1 expression and intensity and improved CAR-T expansion even in the presence of PD-L1
- CAR expression on the cell surface was not affected by PKO integration

Inventors:
Pengbo Zhou
Weiwei Gao

Patents:
PCT Application Filed

Publications:
Zhang et al. *Prot Natl Acad Sci USA*. 2003.

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CAR: Chimeric Antigen Receptor; **CAR-T Therapy:** Chimeric Antigen Receptor T-Cell Therapy
TME: Tumor Microenvironment; **PKO:** Protein Knockout

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Technology Applications

- Method for improving CAR-T expansion and function for cancer immunotherapy
- Beyond cancer, PKO can be integrated into CAR-Ts for other indications, such as autoimmune diseases
- PKO can be integrated into additional cell therapy modalities to inhibit other endogenous protein activity which hinders therapeutic efficacy

Technology Advantages

- PKO reduces but does not completely eliminate target genes, allowing for baseline expression in cases where complete knockout can be detrimental
- PKO and therapeutic genes can be incorporated into the same vector, allowing for streamlined delivery
- May reduce costs, side effects, and patient burden by eliminating the need for anti-PD-1 medications in addition to CAR T-cell therapy

Supporting Data / Figures

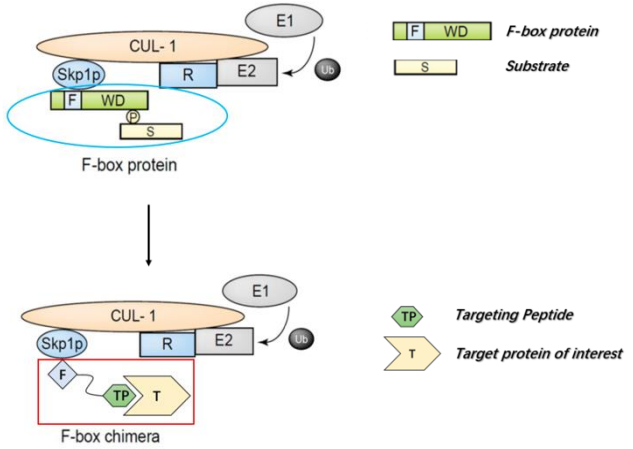

Figure 1: Schematic diagram of Protein Knockout Technology (PKO). F-box protein in SCF E3 ubiquitin ligase complex (top) is substituted by the β-TrCP chimera (bottom) containing the targeting peptide (TP)specific for substrates of interest

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PKO: Protein Knockout

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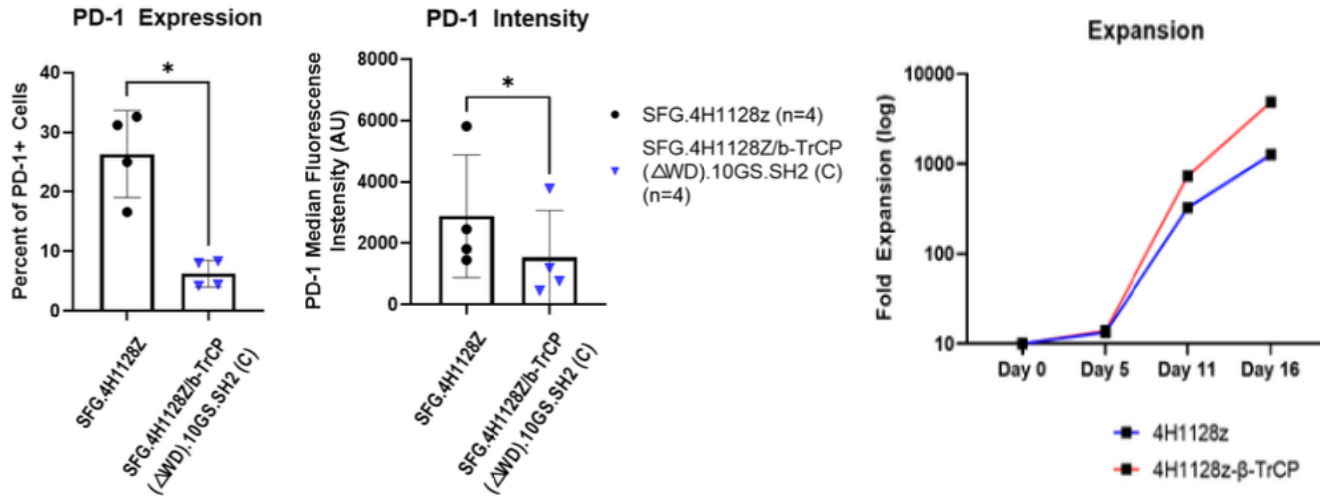

Figure 2: Left: CAR T-cells co-expressing the β-TrCP chimera dramatically decreased PD-1 expression and intensity *in vitro* when compared to unmodified CAR T-cells **Right:** β-TrCP chimera-containing CAR T-cells *in vitro* show substantial proliferation compared to unmodified cells.

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