Optimization of Safe and Effective PSCA-CAR/IL12 Engineered T cell Combinatorial Treatment Strategies Against Metastatic Prostate Cancer

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Background
Prostate stem cell antigen (PSCA)-targeted CAR T cells have shown promise in prostate cancer models, but their efficacy is constrained by the immunosuppressive tumor microenvironment and the need for lymphodepleting chemotherapy with additional cytokine support. Both strategies, however, can increase off-target toxicities and limit therapeutic benefit. Engineering CAR T cells to deliver immuno-cytokines locally, such as IL-12, may enhance anti-tumor activity while reducing systemic exposure. Here, we evaluated PSCA-CAR T cells engineered with either an aPDL1-IL12 fusion construct or membrane-bound IL-12 (mbIL12) to assess efficacy, safety, and dependence on different lymphodepleting regimens.

Methods
A murine PTEN/Kras-driven prostate cancer cell line was implanted subcutaneously or in an aggressive intratibial metastatic model. Mice were treated with PSCA-CAR/aPDL1-IL12, PSCA-CAR/mbIL12, or conventional PSCA-CAR T cells, with or without cyclophosphamide (Cy) preconditioning. The addition of fludarabine (Flu) to Cy was tested to evaluate synergistic conditioning effects. Outcomes included tumor control, systemic toxicity, and dose dependency.

Results
Cy/Flu conditioning was superior to Cy alone in supporting CAR T cell therapy. In subcutaneous models, PSCA-CAR/aPDL1-IL12 achieved enhanced tumor control compared to conventional CARs and, unlike PSCA-CAR/mbIL12, retained activity without Cy preconditioning. In the intratibial metastatic model, PSCA-CAR/aPDL1-IL12 elicited potent anti-tumor responses but induced dose-dependent systemic toxicity when combined with Cy. Omitting Cy reduced toxicity but also limited therapeutic efficacy.

Conclusions
PSCA-CAR/aPDL1-IL12 improves CAR T cell efficacy in prostate cancer models, including metastatic disease, and may overcome the preconditioning requirement of mbIL12 CARs. Nonetheless, dose-dependent toxicities emphasize the need to optimize CAR T cell dosing and lymphodepleting strategies. Future studies should refine Cy/Flu conditioning regimens, optimize timing, and explore additional engineering approaches to restrict aPDL1-IL12 activity, with the goal of maximizing therapeutic benefit while maintaining safety for clinical translation.

Funding Acknowledgements
PCF Young Investigator Award 2021 (PI: Murad), PCF Tactical Award (PI: Pricman), Department of Defence Idea/Expansion Awards (PI: Priceman), Tower Cancer Research Foundation Career Development Award 2025 (PI: Murad)

Conflict of Interest Statement
There are no conflicts to report for data presented.