High-affinity PRAME TCRs synergize with tailored CD8 co-receptor to generate potential best-in-class PRAME-targeting TCR-T therapy
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Background
PRAME is a promising target for immunotherapy due to both its high expression and prevalence in multiple tumor indications with high unmet medical need, and its limited expression in healthy tissues. T cell receptor-engineered T cell (TCR-T) therapy targeting PRAME has shown promising early clinical validation. Accumulating clinical evidence suggests that deep and durable clinical responses require additional T-cell engineering, such as incorporating a CD8 co-receptor (CoR) to enable redirection of CD8+ T cells to peptide-MHC class I complexes. Since CD8 T cells play a pivotal role in the anti-tumor response (e.g., secretion, CD8 T cell cross-activation, memory formation), these next-generation approaches have the potential to improve the efficacy of TCR-based therapeutics.

Methods
We identified highly reactive PRAME-directed TCRs from T-knife’s MyT™ platform – a murine-based human TCR discovery engine with the ability to overcome central tolerance. Using the MyT platform, we were able to generate TCRs of high affinity when benchmarked to TCRs from human donors, where tolerance to self-presentation of endogenous ligands by conventional methods is a limiting factor. Our novel high-throughput approach of screening TCRs, combined with withility (wt) CD8 CoR or enhanced single-chain (esc) CD8 CoRs (for details on CD8 co-receptor design and constructs please visit poster #375).

1) MyT platform immunization
2) TCR identification and screening
3) Next-generation TCR characterization

PRAME is highly immunogenic in the MyT platform with a dominant T-cell response against the epitope SLL

85 TCRs directed against the PRAME epitope SLL were identified across a broad reactivity range

Combining PRAME TCRs with escCD8 CoR further increases the competitive advantage of MyT TCRs

Outlook: T-knife’s add-on toolbox to enhance TCR-T function and protect from PRAME-targeting immunosuppression

Conclusions
• T-knife’s MyT platform delivered high-affinity, potentially best-in-class PRAME TCR candidates for further clinical evaluation.
• Combining such high-affinity PRAME TCRs with CD8 CoRs and switch receptors tailored to indications highly expressing PRAME has the potential to induce deep and durable clinical responses.

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