Product characteristics and clinical trial design for T-Plex: Multiplexed, enhanced T cell receptor-engineered T cell therapy for solid tumors

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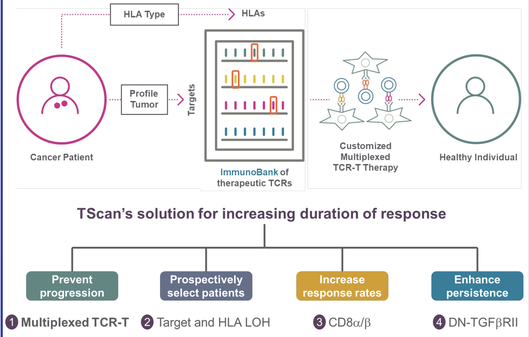
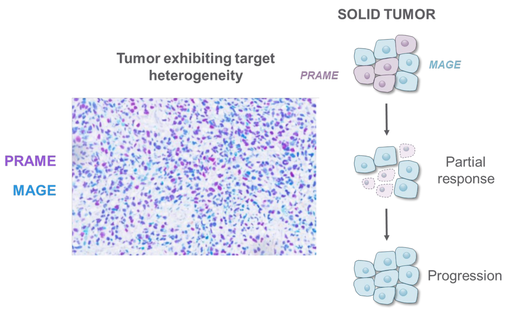
Background and Rationale

- Most patients fail checkpoint immunotherapy due to lack of sufficient endogenous anti-tumor T cells
- A potential solution is to engineer T cells with exogenous T cell receptors (TCRs) that target tumor antigens
- However solid tumors are notoriously heterogenous with heterogenous target antigen expression
- Solid tumors have also been recently recognized to have HLA loss of heterozygosity (LOH) in up to 40% of tumors
- First generation TCR-Ts targeting single antigens had limited response rates (30-50%) and short durations of response (3-4 months)
- TScan's solution is to develop multiplexed TCR-Ts targeting different antigens on different HLA types
- TCR-T cells also have genetic enhancements to enable potent tumor killing and long-term persistence.

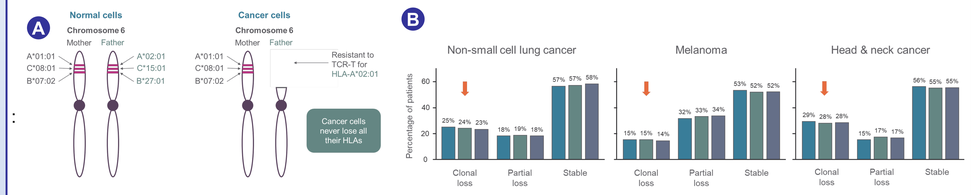


Target heterogeneity in solid tumors



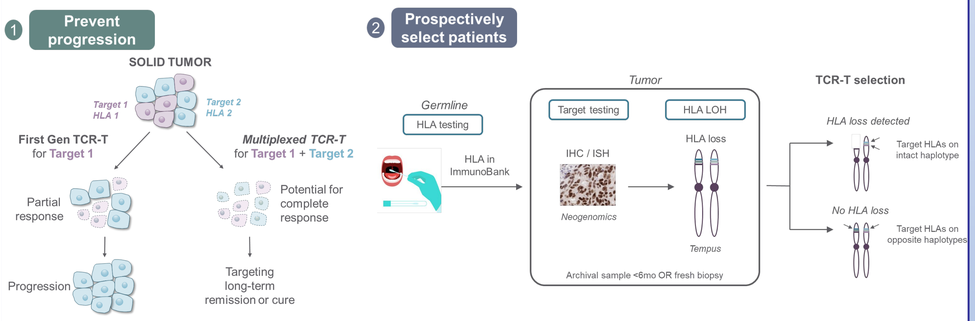
- Melanoma samples were stained with PRAME (purple) and MAGE-C2 antibodies (blue).
- Tumor cells were noted to be positive for either PRAME or MAGE-C2 or both
- Targeting single antigens is expected to result in partial responses in these tumors with rapid progression

HLA loss of heterozygosity (LOH) is prevalent and overlooked in solid tumors



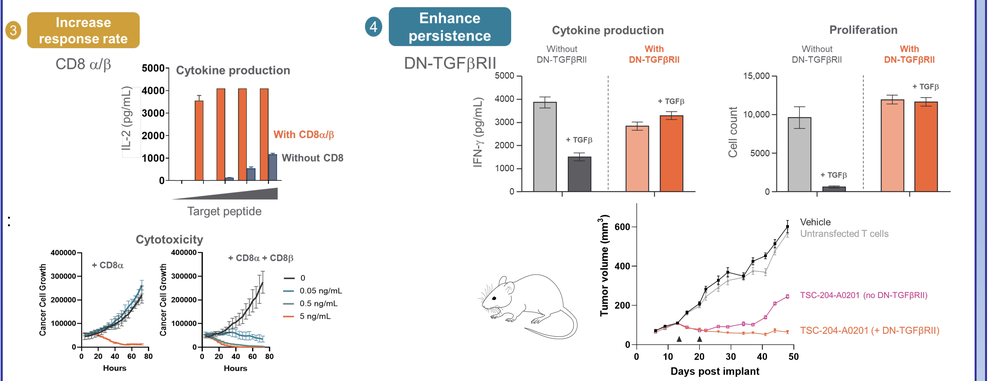
(**A**) HLA loss of heterozygosity (LOH) generally occurs through loss of one HLA haplotype on chromosome 6. (**B**) Novel HLA LOH detection algorithm using tumor/ normal comparisons of Tempus tumor data identifies HLA clonal loss in 15-30% of common solid tumors. Those tumors cannot respond to single-targeted TCR-Ts.

Multiplexing and TCR-T selection overcome heterogeneity and HLA LOH



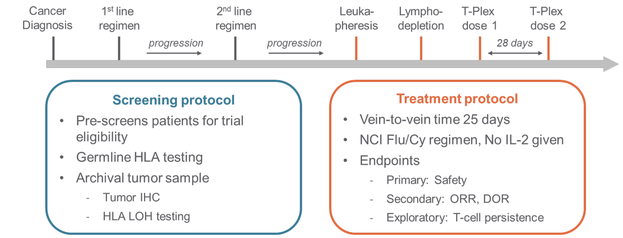
(**1**) **Prevent Progression**: First generation TCR-Ts targeted single antigens on single HLA types in partial responses and rapid progression. Multiplexing TCR-Ts targeting different target antigens on different HLA types has the potential for complete responses and long-term remissions (**2**) **Prospectively select patients**: Germline HLA typing is followed by testing tumors for target antigens and HLA LOH. TCR-T selection can be used to overcome HLA LOH.

TCR-T cell function is enhanced with CD8α/β coreceptors and DN-TGFβRII



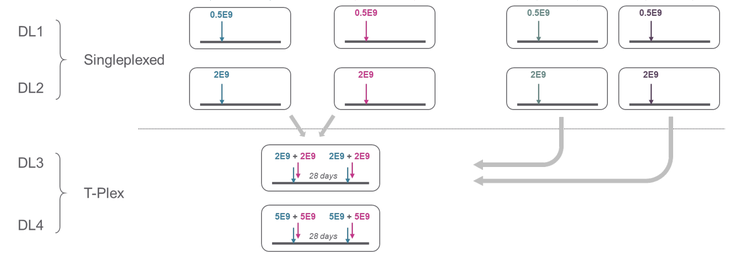
(3) Increase response rate: CD4+ T cells engineered to express TCR+CD8α+CD8β coreceptors had ~100-fold higher cytokine production and cytotoxicity versus CD4+ cells expressing TCR alone or TCR+CD8α. (4) **Enhance persistence**: Expression of dominant-negative TGFβRII (DN-TGFβRII) results in ~2-fold higher cytokine production and ~10-fold higher T-cell expansion in the presence of TGFβ *in vitro* and durable responses of tumors *in vivo*.

Screening protocol pre-identifies patients eligible for treatment protocol



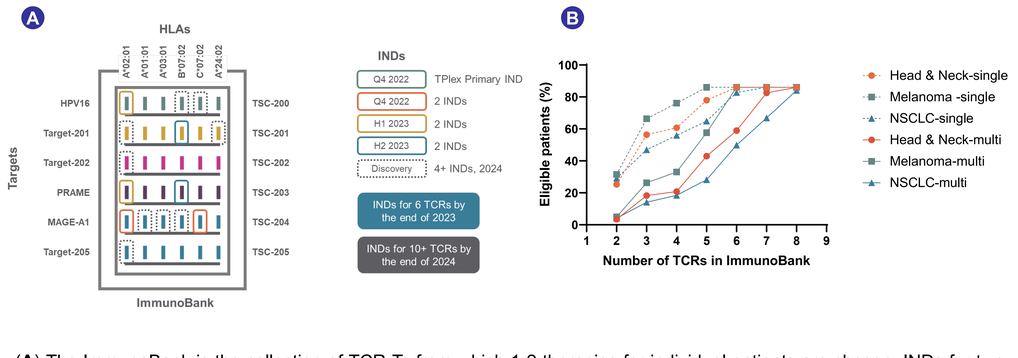
Patients with melanoma, non-small cell lung cancer, head and neck cancer, cervical cancer, ovarian cancer or anogenital cancers are eligible. Screening includes germline HLA typing then archival tumor testing for antigens and HLA LOH any time during standard cancer treatment. Treatment involves 1-2 doses of TCR-T cell therapy after lymphodepletion.

Dose escalation scheme provides rapid path to multiplexing from dose level 3



INDs have been cleared for TCR-Ts targeting MAGE-A1 on HLA-A*02:01 (TSC-204-A0201), HLA-C*07:02 (TSC-204-C0702) and their combination. The FDA cleared protocol allows multiplexing and repeat dosing from dose level 3. As additional INDs for TCR-Ts targeting HPV16 and PRAME are cleared, they will follow the same dose escalation scheme.

Eligibility for multiplexed therapy increases with growing collection of TCR-Ts



(**A**) The ImmunoBank is the collection of TCR-Ts from which 1-2 therapies for individual patients are chosen. INDs for two TCR-Ts and the TPlex combination have been cleared. Two additional INDs are on track to be cleared by mid-2023 and 6 TCR-Ts are expected to be available by end of 2023. **(B)** As the number of TCR-T choices grows, the number of solid tumor patients eligible for singleplexed therapy (dotted lines) or multiplexed therapy (solid lines) increases.