Trial in progress: A phase 1, first-in-human clinical trial for T-Plex, a multiplex, enhanced T cell receptor-engineered T cell therapy (TCR-T) for solid tumors

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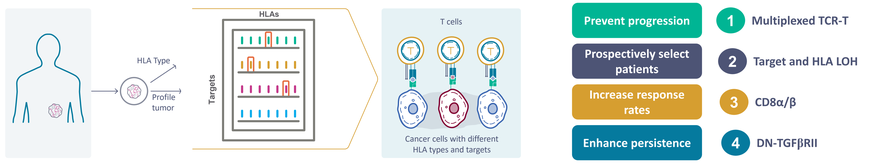
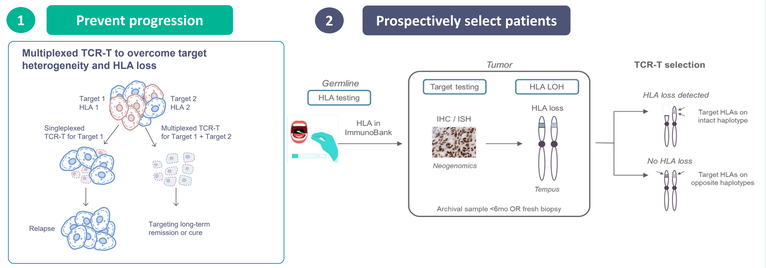
Abstract # CT170

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 specific antigens
- However, solid tumors are notoriously heterogenous with variable 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 (T-Plex)
- TScan's TCR-Ts also have genetic enhancements to enable potent tumor killing and long-term persistence

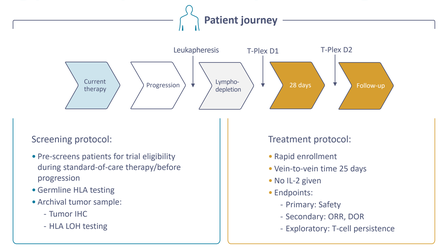


T-Plex can effectively address tumor heterogeneity and HLA LOH



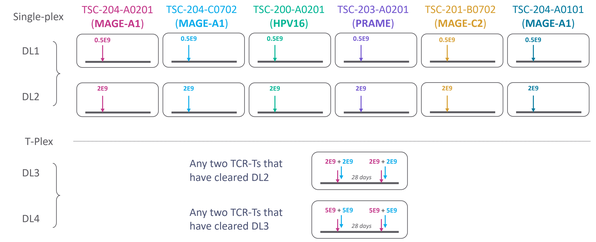
(1) Prevent Relapse: First-generation TCR-Ts targeting single antigens on single HLA types often result in partial responses and rapid progression. Multiplexed TCR-T targeting different target antigens on different HLA types has the potential to induce more durable or even complete responses.
(2) Prospectively 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.

Screening protocol pre-identifies patients eligible for treatment



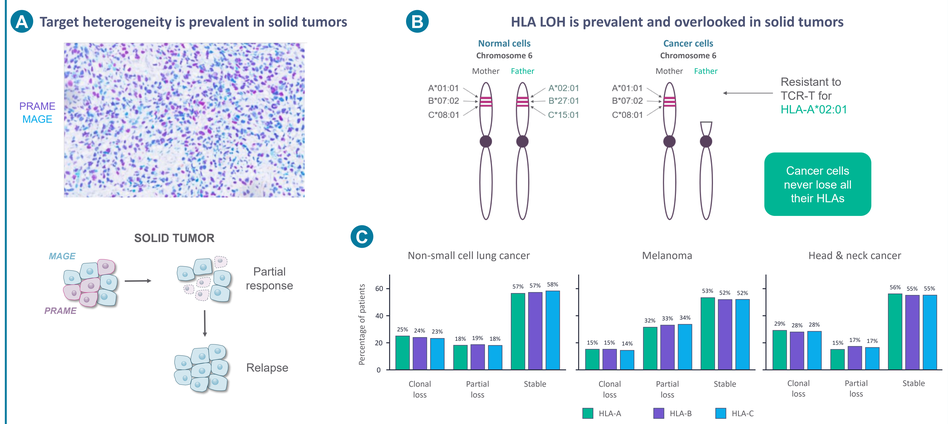
Patients with melanoma, NSCLC, head and neck cancer, cervical cancer, ovarian cancer, anogenital cancers or other solid tumors with a reasonable likelihood of target expression are eligible. Screening includes germline HLA typing then archival tumor testing for antigens and HLA LOH any time during standard anticancer treatment. Treatment involves 1-2 doses of TCR-T therapy after lymphodepletion.

Rapid dose escalation path to multiplexing at dose level 3



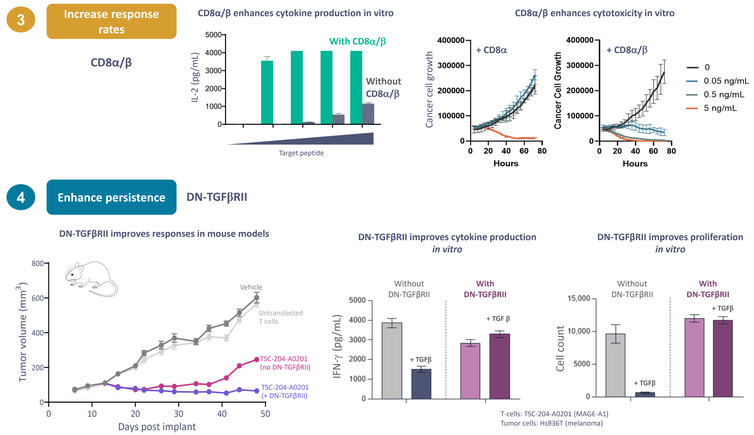
INDs have been cleared for 6 TCR-Ts: targeting MAGE-A1 on HLA-A*02:01 (TSC-204-A0201), HLA-C*07:02 (TSC-204-C0702), and HLA-A*01:01 (TSC-204-A0101); HPV16 on HLA-A*02:01 (TSC-200-A0201); PRAME on HLA-A*02:01 (TSC-203-A0201); and MAGE-C2 on HLA-B*07:02 (TSC-201-B0702) as well as their combinations (T-Plex). As additional INDs are cleared, they will be incorporated into the same study and follow the same dose escalation scheme.

Heterogeneity in Solid Tumors



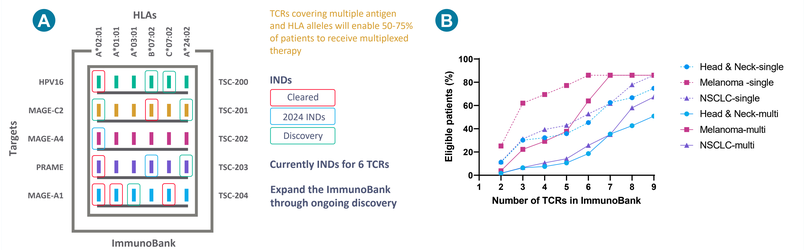
(A) Melanoma samples were stained with PRAME (purple) and MAGE-C2 antibodies (blue). Tumor cells were noted to be positive for either PRAME or MAGE-C2 or both. Targeting single antigens is expected to result in partial responses in these tumors with rapid progression.
(B) HLA LOH generally occurs through loss of an HLA haplotype on chromosome 6.
(C) Novel pan-HLA LOH detection algorithm using tumor/ normal comparisons of Tempus tumor data indicate that clonal and sub-clonal loss of HLA occurs in ~15-30% of common solid tumors. Tumors that have lost the target HLA cannot respond to single-targeted TCR-Ts.

TCR-T 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 (left) and cytotoxicity (right) versus CD4+ cells expressing TCR alone or TCR+CD8α.
(4) Enhance persistence: Expression of dominant-negative TGFβRII (DN-TGFβRII) results in durable responses of tumors in vivo (left), and ~2-fold higher cytokine production and ~10-fold higher T-cell expansion in the presence of TGFβ in vitro (right).

Eligibility for multiplex 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 6 TCR-Ts and the T-Plex combination have been cleared. Two additional INDs are on track to be submitted by end-2024. (B) As the number of TCR-T choices grows, the number of solid tumor patients eligible for singleplex therapy (dotted lines) or multiplex therapy (solid lines) increases.