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 heterogeneous with heterogeneous 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.

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

- (3) Increase response rate: CD4+ T cells engineered to express TCR-CD8αβ+CD8αβ heterodimer had ~100-fold higher cytokine production (top) and cytotoxicity (bottom) versus CD4+ cells expressing TCR alone or TCR-CD8a.
- (4) Enhance persistence: Expression of dominant-negative TGFβRII (DN-TGFβRII) results in durable responses of tumors in vivo (top), and ~5-fold higher cytokine production and ~15-fold higher T-cell expansion in the presence of TNF-α in vitro (bottom).

Screening protocol pre-identifies patients eligible for treatment

- Screening protocol:
  - Pre-screen patients for trial eligibility
  - Germline HLA testing
  - Archival tumor sample
  - Tscan HCR
  - Expression T-cell persistence

- Treatment protocol:
  - Veno-to-vein time 25 days
  - NCI Flu/Cy regimens, No IL-2 given
  - Endpoints: Safety

Rapid dose escalation path to multiplexing from dose level 3

- INDs have been cleared for 4 TCR-Ts: targeting MAGE-A1 on HLA-A*02:01 (TSC-204-A0201) and on HLA-C*07:02 (TSC-204-C0702); HPV 16 on HLA-A*02:01 (TSC-205-A0201), and PRAME on HLA-A*01:01 (TSC-203-A0101), as well as their combination (T-Plex). As additional INDs for new TCR-Ts are cleared, they will be incorporated into the same clinical study and 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 TCR-Ts and the T-Plex combination have been cleared. Two additional INDs are on track to be submitted by end-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.

For more information on TScan’s ImmunoBank, see abstracts:

# 357: Discovery of a novel MAGE2 epitope for TCR-T adoptive cell therapy from expanded T cell clones of TIL therapy products
# 364: Non-clinical development of T-Plex component TSC-200-A0201: A natural HPV16 E7-specific TCR-T cell therapy for the treatment of HPV16 positive solid tumors
# 376: Overcoming tumor heterogeneity - Clinical trial assay to prospectively assign patients customized multiplexed TCR T-cell therapy in Phase 1
# 390: Discovery of MAGE-A1 specific TCR-T cell therapy candidates to expand multiplex therapy of solid tumors