DISCOVERY OF TSC-203-A02: A PRAME-SPECIFIC TCR-T CELL THERAPY CANDIDATE FOR THE TREATMENT OF SOLID TUMORS

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Background The cancer/testis antigen PRAME exemplifies an ideal TCR-T cell therapy target due to its high expression in multiple malignancies and its absence in normal tissues. Initially identified in metastatic cutaneous melanoma, PRAME is highly expressed in various additional solid tumors including lung, head & neck, and ovarian cancers. PRAME plays a pivotal role in multiple cellular processes and has been demonstrated to exhibit protumorigenic function primarily through inhibition of retinoic acid receptor signaling. Targeting of PRAME in solid tumors, particularly when performed as part of a TCR-T multiplexing strategy, represents a promising therapeutic approach in the treatment of many cancer indications.

Methods We discovered TCRs specific for 5 different A*02:01-restricted PRAME-derived epitopes using TScan’s proprietary ReceptorScan platform. Using an activation-based screening technology termed ActivScan, we identified the most functional TCRs from a library of 1300 PRAME-specific TCRs to select for TCRs with greatest avidity and expression. These highly active TCRs were examined for their cytotoxic function using a panel of PRAME-expressing A*02:01-positive cell lines. Lead TCRs were assessed for potential off-target reactivity using our proprietary SafetyScan platform, in which off-target recognition of antigens derived from all proteins that comprise the human proteome is evaluated. Safety was further confirmed by examining alloreactivity to high-frequency class I HLAs and by testing TCR reactivity to a panel of normal primary human cells. Lastly, we tested TCR-T cells for their ability to control tumor growth in vivo using PRAME-expressing xenograft mouse models.

Results We screened 871 million naïve CD8+ T cells from 16 unique healthy donors in ReceptorScan to identify 5706 TCRs specific for 5 PRAME epitopes. PRAME425–434-specific TCRs demonstrated superior recognition of a PRAME-expressing cell line compared to all other PRAME epitopes tested. Following selection of high-expressing and high avidity PRAME425–434-specific TCRs in ActivScan, TCRs were evaluated for their cytotoxic function, and two TCRs compared favorably to a clinical-stage benchmark TCR with respect to cytotoxicity, cytokine release, and T cell proliferation. Safety assessment demonstrated that few off-target peptides were recognized by lead TCRs, minimal alloreactivity was observed to 110 allootypes tested, and no reactivity to normal primary human cells was found. PRAME425–434-specific TCR-T cells were also able to control tumor growth in vivo following infusion into immunodeficient mice implanted with PRAME-expressing xenografts.

Conclusions Based on its demonstrated activity in vitro and in vivo, this autologous TCR-T cell therapy candidate, TSC-203-A02, has been advanced to IND-enabling studies.

REFERENCES
