Discovery of TSC-200-A02: A natural HPV16 E7-specific TCR-T cell candidate for the treatment of HPV-positive solid tumors

Human papillomavirus (HPV) is an oncogenic virus responsible for over 90% of cervical and anal cancers and over 25% of head and neck cancers, which are typically incurable upon metastasis. HPV E7 oncoprotein is a competing target for TCR-engineered T cell therapy as it is homogeneously expressed in every tumor cell, essential for tumor cell survival, and not expressed by healthy tissues. Notably, a recent clinical trial of an E7-directed TCR-T cell therapy conducted at the National Cancer Institute (NCI) showed a 50% objective response rate in heavily pre-treated patients with HPV+ cancers (1).

Using Tsc’s proprietary ReceptorScan platform, we discovered 453 putative HPV16 E7\textsubscript{425–440} TCRs by screening 681 naïve naïve human T cells from 15 unique healthy donors. We tested each TCR for expression in primary T cells and for its ability to kill 22 cell lines pulsed with the E7\textsubscript{425–440} peptide, using the NCI TCR as a benchmark for these studies (2). The top 3 TCRs from this screen were evaluated in depth for cytotoxicity, cytokine production, and T cell proliferation in response to a panel of HPV16+ cancer cell lines expressing varying levels of HLA-A2.02 and E7. A lead TCR was identified that showed comparable activity relative to the NCI TCR. The lead TCR was evaluated for its reactivity using an array-based screen and for off-target activity using our proprietary SafetyScan platform, which is a highly sensitive screen for off-target recognition based on supranormal expression of protein fragments that span the entire human proteome. No off-targets were observed in 108/110 non-E7 expressing cell lines (2). The TCRs showed no reactivity to a panel of normal primary human cells, including cells that naturally express the putative off-target identified in the SafetyScan screen. In vivo studies in immunocompromised mice showed efficient control of xenograft tumor growth by TCR-200-A02 cells in two independent tumor models.

To further enhance the activity of our T cells, we designed a transposon-based vector that delivers the TCR gene, along with the genes for CD8\textsuperscript{c} and a dominant, negative form of TGF\textbeta\textsubscript{2}, into both CD4\textsuperscript{+} and CD8\textsuperscript{+} T cells. We have advanced the resulting autologous TCR-T therapy candidate, TSC-200-A02, to IND-enabling studies. These results validate the use of ReceptorScan in conjunction with SafetyScan, as a way to rapidly identify naturally occurring, high affinity TCRs that are suitable for clinical development.

**TSGF\textbeta\textsubscript{2}**

**Introductions**

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