TGFβ-ARMORING BOOSTS POTENCY AND PERSISTENCE OF ENGINEERED TCR T CELLS, UNLOCKING SUPERIOR EFFICACY AGAINST HPV-POSITIVE SOLID TUMORS

Gail Turner, Gabriela Diaz, Andreia Costa, Yeonjoo Oh, Jianguo Huang, Jenna Bailey, Cyr De Imus, Stephanie Busch, Teresa Foy, Pallavur Sivakumar, Ruth Salmon, Cédric Cleyrat*. *Bristol Myers Squibb, Seattle, WA, USA*

Background Adoptive transfer of chimeric antigen receptor (CAR)-expressing T cells targeting cell surface antigens has shown remarkable success in hematological malignancies. However, only limited success has been achieved to date with CAR T cells, or their engineered T cell receptor (eTCR) counterparts, in the context of solid tumors. This is largely due to: 1) challenges in identifying highly expressed, tumor-specific antigens and; 2) the immune-suppressive tumor microenvironment mediated by cellular and secreted factors such as TGFβ, known to suppress intra-tumoral immunity and notably elevated in many human cancers, including in human papilloma virus (HPV)-associated cancers (e.g. head and neck squamous cell carcinoma and cervical cancers). Here, we describe the generation of highly potent, TGFβ-armored, engineered T cells expressing a novel fully human, natural TCRαβ sequence that is HLA-A*02:01-restricted, CD8 coreceptor-independent and targets the tumor-restricted HPV-16 E7(11–19) onco-peptide.

Methods Donor-derived T cells were genetically engineered using high efficiency CRISPR-Cas9 editing as follows: 1) TRAC domain knock-out (KO) to prevent endogenous TCR expression; 2) knock-in of an HPV-specific eTCR at the TRAC locus; and 3) KO of TGFBR2 to prevent TGFβ signaling. Functional evaluation of edited T cells was performed in vitro using 3D serial spheroid stimulation as well as in vivo using NSG mouse tumor xenografts and against two cancer lines, SCC-152 and CasKi.

Results Under chronic antigen stimulation and in the presence of high TGFβ at optimal effector-to-target (E:T) ratio, HPV eTCR WT (control) and HPV eTCR TGFBR2 KO cells demonstrated robust and comparable cytotoxic functions in vitro. However, when tested at suboptimal E:T ratio, HPV eTCR TGFBR2 KO cells demonstrated superior expansion (>5-fold difference), cytotoxicity and an improved functional phenotype, suggesting that TGFβ-Armoring may decouple T cell expansion and the onset of exhaustion. In vivo studies demonstrated significant inhibition of tumor growth ($p < 0.0001$) and survival advantage ($p < 0.05$) in HPV eTCR TGFBR2 KO treated NSG mice when compared to HPV eTCR WT treated animals at a suboptimal dose of eTCR-positive cells. Additionally, in all conditions tested, T cell expression of CD103 (a pharmacodynamic marker of TGFβ-induced signaling) was ablated in TGFBR2 KO groups. Both in vitro and in vivo data robustly reproduced across donors and tumor models.

Conclusions Pharmacology studies demonstrate that the HPV eTCR armoring strategy aimed at overcoming TGFβ-mediated immune-suppression is highly effective in suboptimal conditions. Additionally, TGFβ-armored eTCR cells presented with improved pharmacodynamic and phenotypic characteristics, paving the way for effective clinical applications in solid tumors.

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