RAPID IDENTIFICATION OF A TCR LIBRARY TARGETING THE HPV E6/E7 ONCOPROTEINS TO ENABLE MULTI-TCR T-CELL THERAPIES FOR PATIENTS WITH HPV16+ EPITHELIAL CANCERS

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Background In the United States, the HPV16 strain is responsible for nearly 60% of newly diagnosed HPV-driven cancers. HPV16 drives oncogenesis through persistent expression of the E6 and E7 oncoproteins.1 The viral antigens E6 and E7 are absent from healthy tissues, making them attractive targets for TCR T-cell therapy. Both oncoproteins are validated targets for TCR T-cell therapies based on clinical trials with objective clinical responses in 50% (6 of 12) of patients for an E7-directed TCR, however, durability of response and coverage of the patient population were limited.2,3 Both issues can be addressed by a larger TCR library that allows treatment of patients of all ethnicities with a multi-TCR product. Here we describe a suite of TCR discovery and validation platforms for the rapid generation of an off-the-shelf TCR library targeting the HPV16 E6 and E7 oncoproteins presented by the 16 most prevalent HLA alleles across all ethnicities in the US. This library of TCRs provides social equity for patients with HPV16-driven cancer, since it will enable more than 80% of the US population to receive a multi-TCR T-cell therapy product with the potential to mitigate tumor escape mechanisms, such as HLA mutation or loss of heterozygosity, for durable anti-tumor responses.

Methods E6- and E7-specific TCRs were identified using the rapid and highly sensitive imPACT Isolation Technology® (capable of capturing T cells at a frequency of 1 in 300,000 CD8+ T cells) and barcoded libraries of peptide-HLA proteins predicted to derive from the HPV16 E6 or E7 oncoproteins. Every identified TCR undergoes functional validation as well as safety and specificity testing using primary human T cells non-virally edited to express the TCR of interest.

Results We have identified potent TCRs specific for HPV16 E6 or E7 from both HPV+ cancer patients and healthy donors (+/- HPV infection). In one example, circulating T cells from an HPV+ cancer patient yielded three novel TCRs against related E6 peptides restricted by A*11:01 that exhibit clinically relevant T-cell functionality. Interestingly, in this patient, the A*11:01 allele in the tumor had a deleterious mutation allowing the tumor to escape killing by these TCRs further validating their biological relevance. However, as part of an off-the-shelf HPV library for use in a multi-TCR T-cell therapy product, these TCRs have the potential to be highly effective in patients with intact A*11:01 expression.

REFERENCES