Abstract

Human papillomavirus (HPV) infection causes at least 650,000 anogenital and oropharyngeal cancers (OPC) worldwide annually. A prophylactic vaccine against high-risk HPV types was approved in 2006 by the FDA, but still, the burden of HPV-related cancers is constantly increasing. Thus, therapies that directly target HPV-antigens represent an attractive alternative therapeutic approach. However, current research’ focus is on epitopes in E6 and E7 proteins despite a high expression of other HPV-related proteins in tumors. Large efforts in targeting HPV antigens with cellular therapy or therapeutic vaccines has focused on E6 and E7 epitopes presented by HLA-A*02:01. However, most patients with HPV16+ cancer do not express this allele, indicating a large unmet clinical need in non-HLA-A*02:01 patients. In addition, although HLA-A*02:01 is common among Caucasians, only 9% and 12% of people of Asian or African American decent, respectively, express it – demonstrating an inequality that should be corrected. Here, we introduce a high-throughput and epitope-agnostic pipeline for HPV16-reactive T cell discovery and validation. The basis of the pipeline is the functional expansion of antigen-specific T cells after stimulation with peptide-pulsed antigen-presenting cells, and with it we can evaluate T cell responses against any epitope within each individual HPV16 protein. Our goal is to build a library of TCRs that will meet the unmet need in terms of HLA-restriction and that targets any expressed HPV16 epitope.

Clinical translation

**Cellular therapy**

**GOAL:** Build a suite of TCRs against different HPV specificities / multiple HLA-alleles

**HPV16 vaccine**

**GOAL:** Construct a multi-valent HPV16 vaccine against persistent HPV16 infection

**Immune checkpoint**

**GOAL:** Identify actionable targets on CD8 T cells in the tumor microenvironment (e.g., TIGIT)