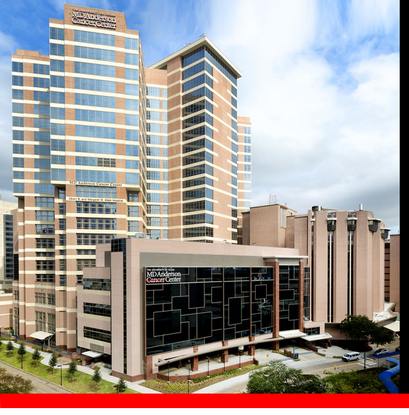

Determine the relevance of HPV-specific T-cells in the immune response against the HPV-positive cancers

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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 2. 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.

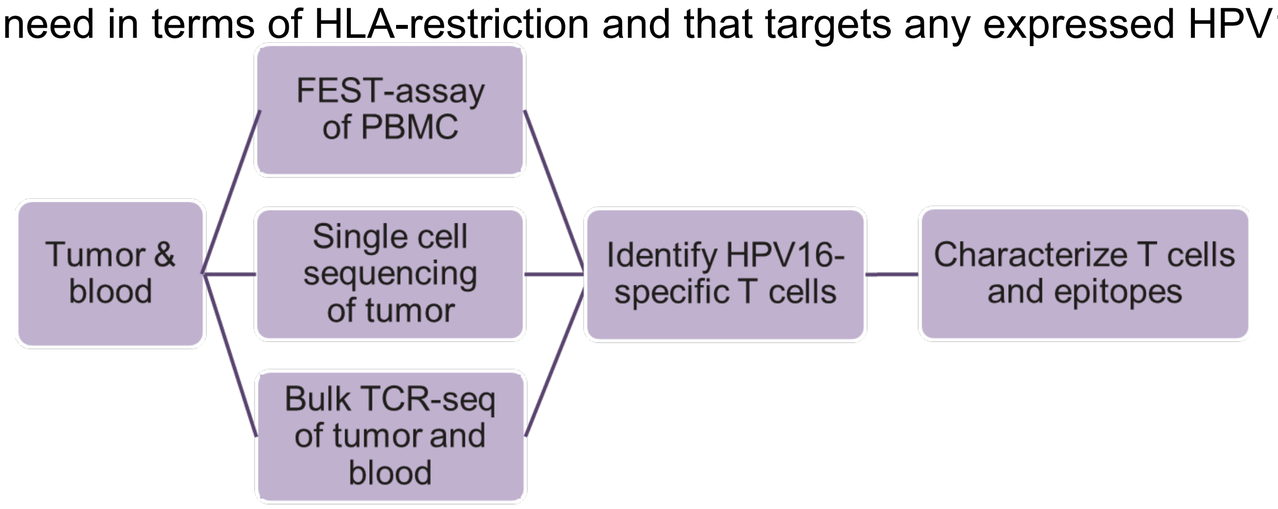

Fig. 1: Pipeline for comprehensive TCR and cognate epitope discovery and validation

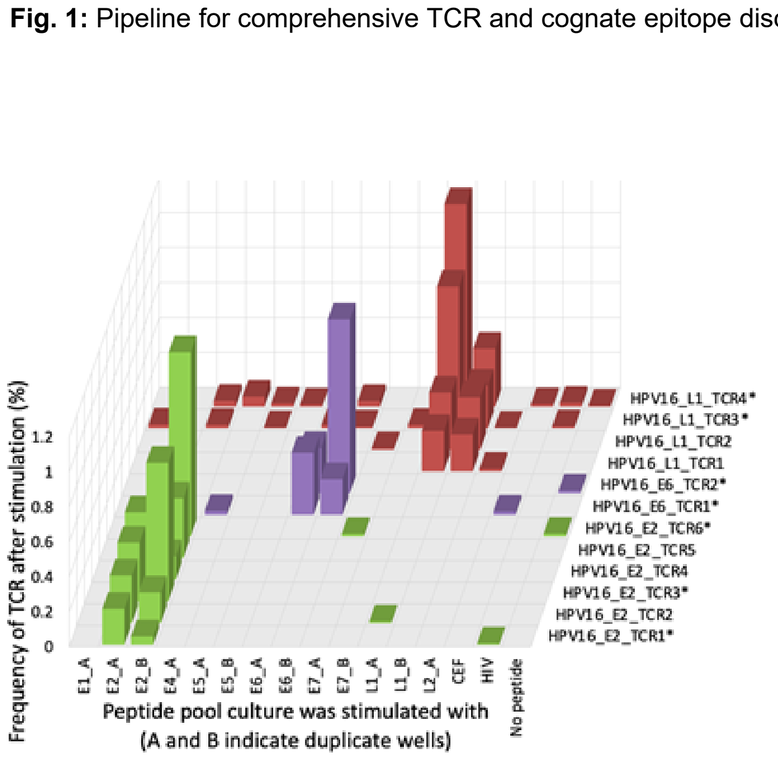

Fig. 2:HPV16-reactive T cell clones were identified in HPV16-positive HNSCC patients (one patient shown here) using the FEST assay that allows expansion of antigen-specific T cells.

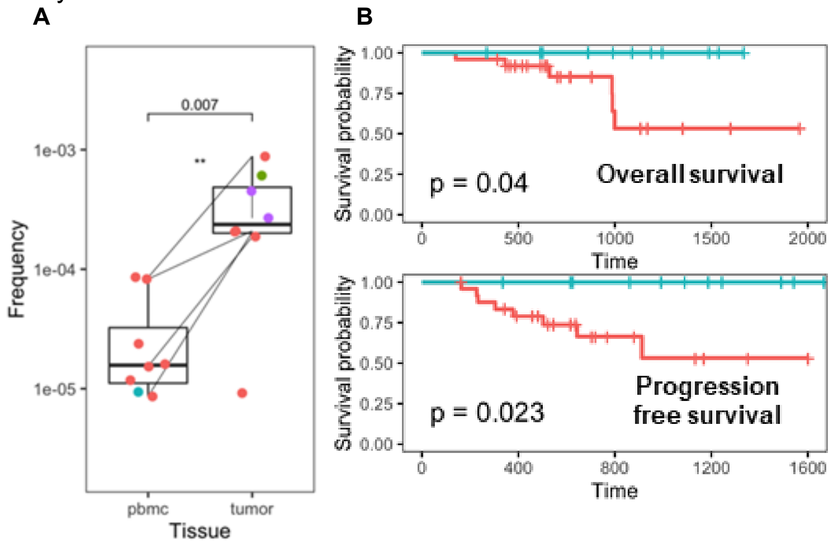

Fig. 3: (**A**) Using GLPH2, TCR motifs were constructed, and a HPV16-E6-TCR1 motif was found enriched in tumors vs PBMC in patients with HPV16-positive HNSCC. (**B**) Association between natural presence of the HPV16-E6-TCR1 motif and survival in patients with HPV16-positive HNSCC.

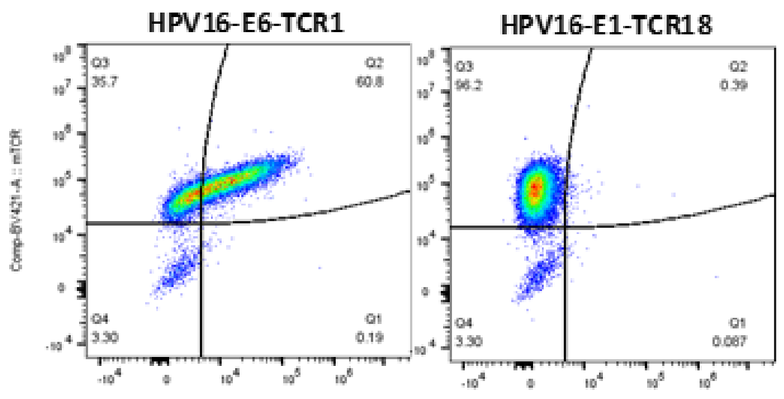

Fig. 4: Validation of target candidate on Jurkatluc TCR KO cells transduced with HPV16-E6-TCR1 or HPV16-E1-TCR18 (negative ctr) using a dextramer staining.

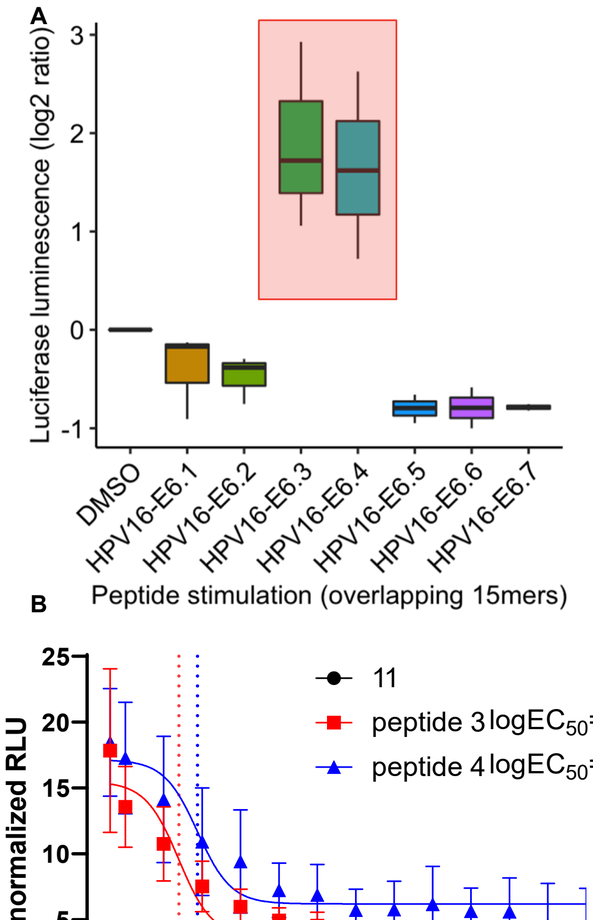

Fig. 5: (**A**) HPV16-TCR engaged 2 peptides (HPV16-E6.3 and HPV16-E6.4) overlapping within 11mer. Signal measured by luciferase assay using transduced Jurkatluc TCR KO cells. (**B**) Concentration-dependent response of HPV16-E6-TCR1 to compatible peptides (3,4) and non-compatible peptide (11) determined by luciferase assay with Jurkatluc TCR KO cells transduced with HPV16-E6-TCR1 and HLA-specific donor PBMC

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)