Scientific Abstract

SU2C-Farrah Fawcett Foundation Human Papillomavirus (HPV) Research Team:

"Therapeutic CD8 Vaccines Against Conserved E7 HPV Epitopes Identified by MS"

[This abstract was provided by the scientists when their application was accepted.]

Globally, human papillomaviruses (HPV) cause more cancers than any other virus. The incidence of HPV-associated cancers in sites for which no screening algorithms exist, including the oropharynx and anus, is increasing steadily. FDA-approved vaccines have no therapeutic effect. Because HPV proteins E6 and E7 are functionally required for disease initiation and persistence, they offer compelling targets for immune-based therapies.

Our multi-institutional, highly integrated translational research program merges expertise in T cell biology, ion physics/mass spectrometry, molecular immunology, computer science, genomics, tumor immunology, and clinical expertise in head & neck, cervical and anal cancer. Here we shall use our recently established physical tumor antigen identification methods in conjunction with understanding of the molecular features of HPV-driven cancers and T cell receptor (TCR) function to develop transformative immunotherapeutic approaches for HPV-associated disease. Our Poisson detection mass spectrometry (MS3) analysis of peptides eluted from MHC complexes from HPV-16+ tumor biopsy samples in HLA-A*0201 cervical cancer subjects identified a strain-invariant epitope, HPV-16 E711-19 on the majority of patient's tumors.

In Aim 1, we shall perform a phase 1b/2 trial of adjuvant E711-19 nanomer vaccine DPX-E7 in 40 HLA-A*0201 positive patients with HPV16+ squamous cancers of the cervix, anus, or oropharynx. In addition to standard primary and secondary clinical endpoints, we will identify biomarkers of response, by examining blood and tumor tissue before and after intervention, by genomic, transcriptomic and proteomic analysis as well as flow cytometry and immunohistology.

In Aim 2, we will perform a comprehensive analysis of HPV-driven cancers to identify HLA-bound HPV tumor antigens using MS3. We will isolate HLA-bound peptides for each allele or class, focusing on those epitopes that are detected broadly on HPV-16 or HPV-18 tumors.

In Aim 3, we shall identify TCRs specific for the vaccine epitope in tissues of HPV tumor-bearing responder patients. Given that the TCR is a mechanosensor, optical tweezers will be used to identify those TCRs with catch bond characteristics linked to high functional avidity for design of TCR gene transfer/adoptive therapies at NCI. In view of the sparse display of HPV epitopes on tumor cells and limited CTL access to tumors, we hypothesize that focusing of relevant T cell responses is a prerequisite for effective immunotherapy.

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There are currently few therapeutic options for patients with HPV-driven cancers who relapse following initial therapy. This program will impact these high-risk patients, providing a novel approach to iterative improvements. Our definitive tumor antigen detection methodology for identification and subsequent monitoring during immunotherapy is relevant to HPV-induced tumors and other virally induced cancers.