CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180349

Project Title:
Therapeutics Targeting Cancer-Associated HPV Replication

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Human papillomavirus (HPV)-induced cervical cancer is a leading cause of death in women. In addition, HPV is causally associated with some oral cancers developed via sexual contact and found mostly in men. Among >200 types of HPVs, only a dozen or so HPVs classified as “high-risk” are linked to cancer. Many “low-risk” HPVs only induce benign warts that rarely, if ever, progress to cancer. Recently, prophylactic vaccines that prevent up to nine major types of genital HPV infection (HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58) have become available and are recommended for vaccination of adolescent girls and boys. However, therapeutic agents that can “cure” HPV infection in the majority of populations already infected by HPVs are not yet available. In our decade-long effort to identify cellular targets potentiating HPV-associated cancer, we found a cellular protein, named BRD4, is crucial for viral gene expression and HPV replication. Intriguingly, we discovered several small compounds targeting a small surface in this BRD4 protein could block HPV replication in cultured human cervical and oral epithelial cells. This finding raises the possibility that these small compounds may inhibit HPV propagation in infected individuals and thus cure HPV-associated cancer. To test this hypothesis, we will first improve the potency and specificity of these hit compounds via chemical modification and analog analysis. In addition, we will employ biochemical and structural approaches to provide more detailed contact information between BRD4 and its interacting proteins and compounds to provide a better guidance for compound design and then examine the efficacy of these inhibitors in suppressing HPV replication in skin-like epithelial cell differentiation systems that mimic the natural HPV life cycle. Collectively, these studies will provide a lead for developing therapeutics targeting HPV-associated cancer and thus eliminate HPV infection in human populations in the near future.