Pilot Project 2: DEVELOPMENT OF TRIP13 INHIBITORS FOR TREATMENT OF HPV+ CANCERS
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The project's overall goal is to determine an underlying mechanism for HPV-driven cancer cell survival and exploit this pathway for therapeutic benefit.

Inputs	Specific Aims & planned initiatives			Outcomes -- Impact	
	Aims	***Activities***	***Outputs***	***Short-term/ Intermediate***	***Long-term***
• UPR-MSC • MDACC • UPR/MADCC Cores • IAC • PSC • Molecular Sciences Research Center • U54 Pilot Project Award	1. To test the hypothesis that HPV+ cancer cells rely on both TRIP13 and Aurora kinase activity for mitotic exit and survival, such that their combined inhibition will lead to irreversible mitotic arrest and cell death. 2. To synthesize a potent and selective small molecule inhibitor of TRIP13 using molecular design, docking and structural optimization.	**Aim1** • Determine the protein and mRNA expression levels of Rb, p16, Mad2 and TRIP13 in PSCC and HNSCC PDX models, Determine whether the combination of TRIP13 depletion and Aurora kinase inhibition leads to selective cell death in HPV+ cancer cells via in vitro assays. • Determine the feasibility of small-interference RNA (siRNA)-containing liposomes to knockdown TRIP13 in vivo in HPV+ PSCC PDX models. **Aim 2** • Use iterative optimization to develop a novel TRIP13 inhibitor. • Test the effect of the TRIP13 inhibitor candidates on TRIP13 activity in vitro in cancer cell lines.	**AIM 1** • Protein and mRNA expression in PDX models • Test if the combination of TRIP13 depletion and Aurora kinase inhibition lead to selective cell death in HPV+ cancer cells via in-vitro flow based assays. • The feasibility of TRIP13-KD in vivo in PDX **AIM 2** • Develop synthesis procedures and assay setup • Measure the inhibition of TRIP13 ATPase activity of all new compounds • Iteration 1: Identify Structure Activity Relationships on the eastern part of the molecule • Iteration 2: Identify Structure Activity Relationships on the western part of the molecule • Iteration 3: Combine the features of optimized activities *Standardized outputs* • # publications • # high-impact journals • # grants and supplements • # students trained • # collaborations established • # patents	**AIM 1** • Demonstrate that HPV+ cancer cells undergo more apoptosis when exposed to combined TRIP13 depletion and Aurora kinase inhibition than when exposed to single pathway inhibition. • Determine if this combination would be promising clinically, we need to demonstrate that it is selectively toxic to cancer cells with low Rb expression. **Aim 2** • A novel more potent and selective TRIP13 inhibitor will be developed. • The activity of the novel TRIP13 inhibitor will be tested *in vitro* in cancer cell lines.	• We expect to prove that the efficacy of dual TRIP13 and Aurora kinase inhibition in HPV+ driven HNSCC, cervical, and PSCC animal models will shift current clinical practice paradigms for HPV+ cancers. • It is expected that a novel TRIP13 inhibitor will be developed that potentially can be used clinically for treatment of susceptible cancers.
	Process Evaluation			**Outcome Evaluation**	