**Effective Combinatorial Immunotherapy for Penile Squamous Cell Carcinoma in Genetically Engineered Mouse Model**

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**Summary**

Penile squamous cell carcinoma (PSCC) accounts for over 90% of penile malignancies and causes significant mortality and morbidity in developing countries. Molecular mechanisms and therapies of PSCC are understudied, owing to scarcity of laboratory models. Here, we describe a genetically engineered mouse model of PSCC, by co-deletion of Smad4 and Apc in the mouse penis. Penile cancer is rare disease in the United States. Men in some other regions have a higher incidence and mortality. In a genetically engineered mouse model, more than half of the 8 cases were cancer relative to normal human penis as compared with mouse penile cancer (SA, SAP). Numbers KL2 TR002530 and UL1 TR002529 (A. Shekhar, PI) from NIH, NCATS and Indiana University were used in this study. We performedorks.

**Wnt/β-catenin signaling and inflammatory pathways**

**Combined targeted therapy and immunotherapy for PSCC**

**Pten deletion confers chemoresistance**

**Conclusions**

- Our studies have established the essential resources for studying PSCC biology and developing new therapies.
- PSCC GEM models harbor massive MDSC infiltration to cause strong immunosuppression.
- Combinatorial therapy of IC8 and MDSC-targeted agent is promising in eradicating PSCC.

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