

## **Targeting cytidine deaminase-induced chromosomal instability as a driver of metastasis in bladder cancer**

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**Abstract:** Metastatic urothelial cancer (UC) is incurable and often leads to cancer death. Understanding drivers of metastasis is critical for developing curative therapeutic strategies. The APOBEC3 family of single-stranded DNA cytosine-to-uracil deaminases is the dominant source of mutations in UC, where it causes driver mutations and therapeutic resistance. However, the role of APOBEC3-induced mutagenesis in driving genomic heterogeneity and distant dissemination of primary UC cells is currently unknown. In this proposal, we will investigate the mechanisms linking APOBEC3-induced CIN to cGAS-STING driven metastasis. We will identify targetable signaling hubs linking APOBEC3-induced CIN-cGAS-STING to epithelial-mesenchymal transition (EMT) with the goal of preventing metastasis and improving clinical outcomes for patients with metastatic UC. We pursue these objectives through multidisciplinary approach that integrates metastasis models established from patient-derived UC tumors, transgenic animal models of APOBEC3 expression and techniques that pair lineage tracing with single-cell DNA and RNA sequencing. Our team brings together physician-scientists and metastasis experts with complementary expertise in bladder cancer, APOBEC3 biology, chromosomal instability, and the biology of metastasis. Our team is uniquely positioned to successfully achieve our goals and translate this knowledge into therapeutic advances for patients with urothelial carcinoma.