

## **Defining the Functional Impact of Composite Mutations in Oncogene-driven Urothelial Cancer using Circulating-tumor DNA and Single-cell Sequencing**

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**Abstract:** Cancer evolution requires the accumulation of serial genetic changes that confer a fitness advantage. Composite mutations (CMs) occurring in the same oncogene were recently discovered to be frequently occurring genetic events. Several observations suggest that the occurrence of these composite mutations is not stochastic and not explained solely by the mutational load in cancer. We posit that the accumulation of CMs confers fitness advantage on UC cells. Our proposal will define the functional effects of these CMs on cancer fitness and whether they create a state of oncogenic hyper-addiction that represents therapeutic vulnerabilities to targeted agents. We will show that CMs are key serial genetic changes required for the evolution of urothelial cancer and that they emerge from deterministic processes where the first mutational event determines the serial change in a gene-specific pattern. Using both a longitudinal analysis of patient samples and robust experimental models, the proposed work will be the first systematic evaluation of the functional consequences of CMs. By merging single base editing and single-cell sequencing, we apply novel high throughput tools to study the effects of CMs that will transform the field of functional genomics. We will define the distinct therapeutic vulnerabilities that occur as a consequence of acquired CMs. Finally, we will establish the clinical rationale targeting serial genetic change instead of making targeted therapy based on a snapshot genomic profile from a single biopsy of tumor tissues. These results will open the door for dynamic precision medicine for patients with urothelial cancer and other cancers.