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We are using next-generation sequencing methods to define the spectrum of co-mutational events in muscle-invasive bladder cancers. Our focus is on defining the prevalence and prognostic relevance of mutations in the PI3 kinase/AKT/mTOR pathway. To avoid selection bias, we are performing this analysis using a large, prospectively collected, sequential cohort of patients with muscle-invasive disease undergoing radical cystectomy and curative intent radiation therapy.

In the clinic, we have observed that patients with bladder cancer develop multiple primary tumors within the urinary tract. To explore the genetic basis for this phenomenon, we will extend our analysis by comparing the genomic profile of normal-appearing bladder tissue to primary tumors to matched metastatic lymph nodes and distant metastatic sites. One goal of these studies will be to determine the temporal sequence of mutational events in bladder cancer, with a focus on the timing of PI3 kinase alterations in disease progression.

Functional studies will focus on genes that are commonly co-mutated with PI3 kinase pathway alterations so that we can identify aberrations that enhance or abrogate tumor invasion and/or PI3 kinase and mTORC1-dependence. To directly compare the functional consequences of *PTEN* and *TSC1* loss in

bladder cancer in depth, we are comparing the phenotype of genetically engineered mouse (GEM) models with conditional inactivation of the *PTEN* and *TSC1* genes in the bladder epithelium. The long-term objective will be to develop GEM mice that model the pattern of co-mutations identified in human bladder cancer, with the goal of using these mice to understand the contribution of specific genomic alterations to bladder cancer progression and as models to study novel therapeutic strategies. This work is being support by R01-CA182587 (PI: David Solit).

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