

Determining and Targeting Evolutionary Trajectories Driving Bladder Cancer

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Abstract: Bladder Cancer (BCa) is heterogeneous disease classified into non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). Compared to NMIBC, MIBC is associated with higher mortality rates partially due to higher incidence of distant metastasis. The study of MIBC is hampered by the lack of relevant models with an intact immune system, particularly models that recapitulate metastasis with a capacity for gene perturbation-based testing of potential MIBC drivers and therapies.

Thus, we developed a mouse model of BCa — *EvoCaB* (“Evolution in Cancer of the Bladder”) where a specific MIBC signature is introduced in somatic cells of the bladder postnatally. Our platform faithfully replicates human BCa spread from focally induced primary disease to lymph nodes in animals with intact immune systems. *EvoCaB* includes luminescence/fluorescence markers and lineage tracing with a Cas9-marked, heritable barcode. Our platform enables simultaneous analysis of clonal architecture and disrupting genetic signatures associated with MIBC.

Our objective is to track BCa in our model via Cas9-generated heritable barcode edits to reconstruct disease progression using phylogenetic tree construction, and to then identify drivers of MIBC, which we will perturb functionally to establish causative relationships between gene dysregulation and evolutionary progression of BCa.

The expected outcomes of this proposal are: (1) validating the *EvoCaB* mouse model for interventions-based testing to interrupt BCa progression and metastasis, and (2) integrating the cross-species discovery of genes and pathways by using genomic-based human BCa datasets to functionally test drivers of MIBC.