Effective combinatorial immunotherapy for penile cancer demonstrated in the first GEM model of penile squamous cell carcinoma

Background: Penile cancer is a rare but highly morbid disease, with penile squamous cell carcinoma (PSCC) accounting for over 95% of all cases. Compared with other urological malignancies, PSCC is among the least understood with very limited treatment options.

Methods: We developed of the first genetically engineered mouse model (GEM) of PSCC by co-deletion of *Smad4* and *Apc* in penile epithelia. Transcriptomics of the penile tumor and normal penile epithelium was profiled by RNA-seq for mechanistic investigation and comparison to human penile cancer transcriptomics. Immunophenotyping of the model was performed by CyTOF. Targeted proteomics by RPPA on the model informed inhibitor screening for finding novel drugs against PSCC. Targeted therapeutics and immune checkpoint blockade antibodies (PD1, CTLA4) were combined as key preclinical evidence of new treatment strategy.

Results: The GEM model is highly relevant to the human disease by virtue of sharing up- and down-regulated genes and pathways. Both cancer cell-intrinsic (β-catenin and SOX2 transcription activation) and extrinsic (COX2-dependent inflammatory microenvironment) mechanisms drive the progression of PSCC. Mouse PSCC fosters an immunosuppressive microenvironment with myeloid-derived suppressor cells (MDSCs) as the dominant population. Preclinical trials in the model demonstrate synergistic efficacy of immune checkpoint blockade with the MDSC-debilitating drugs cabozantinib or celecoxib. Drug screen studies informed by targeted proteomics identified potential drugs (e.g. mubritinib).

Conclusion: Our studies have established the essential resources for studying PSCC biology and therapy (Figure 1). The combinatorial immunotherapy approach illuminates a promising clinical path for treating aggressive PSCC.

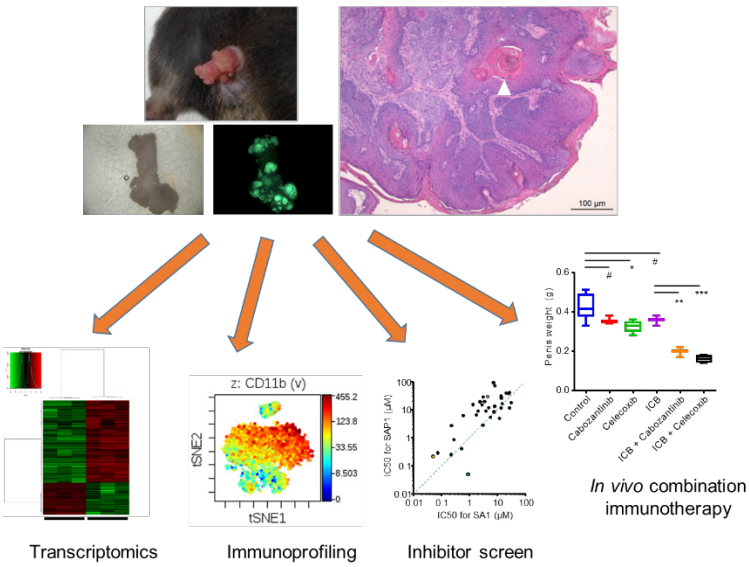

Figure 1. First genetically engineered mouse model of penile cancer and its application in preclinical studies