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Inhibition of a G9a/DNMT network as a novel therapeutic strategy in bladder cancer

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Background: Bladder cancer (BC) is a common neoplasm lethal in its advanced metastatic stage with few therapeutic options. Relevant BC mouse models for investigating the disease progression or therapeutic approaches have been lacking. Recently, molecular characterization of BC has defined new genetic and epigenetic drivers governing chromatin organization and histone modifications. G9A (EHMT2), a H3K9 methyltransferase, in human BC was associated with a poor clinical outcome indicating possible therapeutic options for patients.

Objectives: Our aim was to validate G9A as a suitable target for BC therapy using a genetically engineered mouse model of metastatic BC.

Methodology: We tested the effect of a novel G9A/DNMT dual inhibitor (CM272) *in vivo,* in an immunocompetent quadruple ($Pten^{F/F}$; $Trp53^{F/F}$; $Rb1^{F/F}$; $Rbl1^{-/-}$) bladder-specific knockout transgenic mouse model of highly aggressive metastatic muscle-invasive BC. Biochemical, immunohistochemical and whole transcriptome analyses were performed to analyze the response.

Results: CM272 alone and in particularly in combination with cisplatin improves survival *in vivo*. Transcriptomic analyses show similarities between specific human bladder cancer groups and our BC mouse model. We observed a potent antitumoral effect of the combination through immune microenvironment leading to immune tumor debulking.

Conclusions: Our data support that epigenetic inhibitor may induce immune eradication of metastatic BC, in particular in basal-squamous subtypes. These data also support the combined use of these epigenetic inhibitors with immunotherapies.

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