cancer vaccination opportunity when combined in heterolo-
gous prime-boost regimen.

Materials and Methods Mice were vaccinated with subcutane-
ous (s.c.) injection of KISIMA-TAA vaccine and/or with intrave-
nous injection of VSV-GPTAA in different settings. Immunogenicity was assessed by measuring the peripheral anti-
gen-specific response. Anti-tumoral efficacy as well as in depth monitoring of TILs and tumor microenvironment modulation were assessed following therapeutic vaccination in different tumor models. Additionally, transcriptome and immunohisto-
chemistry analyses of the TC-1 tumor have been performed. Combination of heterologous prime-boost with checkpoint blockade PD-1 therapy has been assessed.

Results Priming with KISIMA-TAA followed by VSV-GPTAA boost induced a large pool of polyfunctional and persistent antigen-specific cytotoxic T cells in the periphery as well as within the tumor in several tumor models. Frequencies of antigen specific T cells are significantly higher than the respective homologous vaccinations. Additionally, transcriptome analysis of a cold tumor model revealed profound changes in the tumor microenvironment upon heterologous vaccination, including a strong upregulation of gene signatures of several pro-inflammatory cytokines and chemokines required for anti-tumor immunity along with dendritic and T cell trafficking and activation. This was corroborated by flow-cytometric analy-

sis of tumor-infiltrating leukocytes showing massive CD8+ and CD4+ T cell infiltration as well as repolarization of M2-
like macrophages towards M1-phenotype. The presence of the CD8+ T cells within the tumor core was confirmed by immu-

n histochemistry analysis. Moreover, combining heterologous vaccination with checkpoint blockade further improved its therapeutic efficacy and the number of long-term survivors.

Conclusions The KISIMA/VSV-GP heterologous prime-boost approach holds great promise for patients with primary or acquired resistance to checkpoint blockade due to its ability to induce tumor-specific T cell, improve T cell infiltration and increase tumor inflammation, even in tumors with limited per-

missivity for the oncolytic virus.

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References


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