

## DIFFERENTIAL EFFECT OF NKG2A BLOCKADE ON PERIPHERAL AND INTRA-TUMORAL CD8 T CELL RESPONSE INDUCED BY KISIMA – VSV-GP-TAG HETEROLOGOUS PRIME-BOOST VACCINATION

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**Background** KISIMA™ platform-derived recombinant chimeric protein vaccines were shown to elicit both CD8 and CD4 T cell responses against model or tumor associated antigens, resulting in control of tumor growth in different preclinical models.<sup>1</sup> Vesicular stomatitis virus (VSV)-GP is a chimeric variant of VSV modified to avoid neurotoxicity, which is exploited for cancer therapy thanks to its oncolytic activity and also as a potent vaccine vector for delivering of tumor associated antigen. Previously, we have shown that therapeutic heterologous prime-boost vaccination with KISIMA protein vaccine and a tumor-antigen armed VSV-GP (VSV-GP-TAg) oncolytic virus elicits a potent CD8 T cell response, enhances the infiltration and functionality of antigen-specific CD8 T cells, and inflames the tumor microenvironment in different mouse models, resulting in increased anti-tumoral efficacy.<sup>2</sup> However, the efficacy of tumor-specific immune responses could be limited by intratumoral T cell exhaustion which can result in tumor escape and disease relapse. Immune checkpoint inhibitors changed the landscape of cancer therapy, but their efficacy is often restricted to highly T cell infiltrated tumor, making them attractive for combination therapy with cancer vaccines.

**Methods** In this study, we evaluate the combination of NKG2A blockade and KISIMA – VSV-GP-TAg heterologous prime-boost vaccination focusing on modulation of T cell phenotype and antitumoral efficacy in TC-1 tumor model, a lung epithelial cell line transfected with HPV16 E6/E7 and c-H ras oncogene.

**Results** KISIMA – VSV-GP-TAg prime-boost vaccination strongly increased the expression of NKG2A on both circulating and tumor infiltrating antigen-specific CD8 T cells. Vaccination of TC-1 tumor-bearing mice in combination with NKG2A blocking antibody resulted in inhibition of tumor growth, induced complete tumor remission and prolonged survival. Mechanistically, NKG2A blockade did not enhance the infiltration nor the ability to secrete cytokine of antigen-specific CD8 T cells induced by heterologous prime-boost vaccination, but it significantly reduced exhaustion. Surprisingly, NKG2A blockade reduced the expansion and activation of circulating antigen-specific CD8 T cells elicited by KISIMA – VSV-GP-TAg vaccination. Consistently, combination treatment resulted in decreased number of long-lasting antigen-specific effector memory CD8 T cells in secondary lymphoid organs, while complete responders were only partially protected against homologous tumor rechallenge, highlighting a negative impact of NKG2A blockade on immune memory.

**Conclusions** Taken together, these data suggest a dual role of NKG2A blockade on cancer vaccine-induced T cells, increasing early antitumoral efficacy by reducing intratumoral T cell exhaustion but impairing the establishment of long-term immunity.

### REFERENCES

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**Ethics Approval** This study has been approved by the Cantonal veterinary authority of Geneva, under the authorization number GE193.

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