

**P04.02 A NOVEL CANCER IMMUNOTHERAPY COMBINES RMVA-CD40L WITH TUMOR TARGETING ANTIBODIES**

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**Background** Virus-based vaccines and appropriate costimulation potently enhance antigen-specific T cell immunity against cancer. In the present study, we exploit both innate and adaptive immune responses triggered by a novel recombinant modified vaccinia virus Ankara (rMVA) encoding a Tumor-Associated Antigen (TAA) and the costimulatory CD40L against solid tumors in combination regimes to overcome tumor-induced resistance to immunotherapy.

**Material and Methods** Subcutaneous murine tumors were induced in C57BL/6 or Balb/c mice using syngeneic tumor cell lines. When tumors were established (60–80 mm<sup>3</sup>) mice were intravenously injected with rMVA-CD40L. Tumor growth monitoring and immune cell analysis was performed.

**Results** Therapeutic treatment with rMVA-CD40L resulted in the control of established tumors in several independent tumor models. This antitumor effect was based on the generation of non-exhausted, systemic tumor-specific cytotoxic CD8<sup>+</sup> T cells that was essential for therapeutic efficacy. Strikingly, rMVA-CD40L also induced strong NK cell activation and enhanced cytotoxicity. Moreover, the combination of rMVA-CD40L and tumor targeting antibodies resulted in increased therapeutic antitumor efficacy. This therapeutic combination relied on Fcγ receptor-expressing immune cells as well as on NK cells.

**Conclusion** We describe a novel and translationally relevant therapeutic synergy between viral vaccination and CD40L costimulation. We show strengthened antitumor immune responses when both rMVA-CD40L-induced innate and adaptive immune mechanisms are exploited by combining immunotherapeutic regimes, such as TAA targeting antibodies. This finding could have a direct positive impact in therapeutic regimens where TAA targeting antibodies could be employed.

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**P04.03 IMMUNE MODULATORY VACCINE DIRECTED AGAINST IDO1-EXPRESSING IMMUNE CELLS ELICITS T CELL-MEDIATED ANTI-TUMOR IMMUNITY AND ENHANCES ANTI-PD1 RESPONSES**

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**Background** Indoleamine 2,3-dioxygenase 1 (IDO1) is a tryptophan-catabolizing enzyme that contributes to immunoregulation at many levels, including suppressing effector T cells and inducing/activating regulatory T cells. Thus far, several therapeutic approaches to target IDO1 enzymatic activity have shown promise in preclinical models, however, results from the first major clinical trial were disappointing. The present study seeks to provide preclinical PoC data for the conceptually unique idea of developing an IDO1-targeted vaccine based on our earlier findings that humans exhibit intrinsic T cell reactivity against IDO1 epitopes<sup>1</sup> suggesting the existence of a T cell-mediated, counter-regulatory mechanism directed against cells that express IDO1.

**Materials and Methods** IDO1-derived peptide vaccines were identified by measurement of vaccine-induced *ex vivo* response (IFNγ ELISpot) and demonstration of anti-tumor responses in CT26 tumor-bearing mice. To understand the vaccine's mode of action, resected tumors were analyzed by immunofluorescence microscopy and flow cytometry.

**Results** The CT26 colon carcinoma model was selected for these studies based on evidence of high levels of IDO1 expression and responsiveness to IDO1 inhibition reported for these tumors. *In silico*-predicted H2<sup>d</sup> MHC class I and II-restricted IDO1 peptide sequences were tested and vaccine candidates were chosen after confirming *ex vivo* response and anti-tumor response in CT26. Therapeutic treatment of established CT26 tumors with MHC class I- and II-directed, IDO1-derived peptide vaccines elicited anti-tumor responses when administered alone, and the effect was further pronounced when combined, suggesting distinct mechanisms of action. In addition, a combination of IDO1 vaccine with anti-PD-1 antibody produced a combinatorial anti-tumor response beyond what was achieved with either agent alone. Consistent with this observation, adoptive transfer of isolated CD8<sup>+</sup> T cells from class I and CD4<sup>+</sup> T cells from class II peptide-vaccinated responder mice delayed tumor growth in treatment naïve mice. The class II-directed response was completely IDO1-dependent while the class I-directed response included an IDO1-independent component indicative of antigen spread. Examination into the tumors in vaccinated mice indicated that IDO1 vaccine treatment exerts its effect by selective reduction of IDO1 expression in the tumor microenvironment and concomitant expansion of activated CD4<sup>+</sup> and CD8<sup>+</sup> T cells.

**Conclusions** As noted in humans, our data demonstrate that IDO1 is immunogenic in mice confirming that this endogenous protein is excluded from normal tolerance mechanisms. The observed immunotherapeutic efficacy of IDO1 peptide vaccines on their own and in combination with anti-PD-1 antibody support the rationale for ongoing clinical development of IDO1 peptide vaccine-based therapy. Future studies include further differentiation of the vaccine platform against