VECTORIZED TREG-DEPLETING ANTI-CTLA-4 ELICITS ANTIGEN CROSS-PRESENTATION AND CD8+ T CELL IMMUNITY TO REJECT “COLD” TUMORS

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Background Immune checkpoint blockade (ICB) is a clinically proven concept to treat cancer. Still, a majority of cancer patients including those with poorly immune infiltrated “cold” tumors are resistant to currently available ICB therapies. CTLA-4 is one of few clinically validated targets for ICB, but toxicities linked to efficacy in approved anti-CTLA-4 regimens have restricted their use and precluded full therapeutic dosing. At a mechanistic level, accumulating preclinical and clinical data indicate dual mechanisms for anti-CTLA-4; immune checkpoint blockade and Treg depletion are both thought to contribute efficacy and toxicity in available, systemic, anti-CTLA-4 regimens. Accordingly, strategies to deliver highly effective, yet safe, anti-CTLA-4 therapies have been lacking. Here, BioInvent and Transgene present and preclinically characterize a highly efficacious and potentially safe strategy to target CTLA-4 in the context of oncolytic virotherapy.

Methods A novel human IgG1 CTLA-4 antibody (4-E03) was identified using function-first screening for mAbs and targets associated with superior Treg depleting activity. A tumor-selective oncolytic Vaccinia vector was then engineered to encode this novel, strongly Treg-depleting, checkpoint-blocking, anti-CTLA-4 antibody and GM-CSF (VV_{GM}-ahCTLA4, BT-001). Viruses encoding a matching Treg-depleting mouse surrogate antibody were additionally generated, enabling proof-of-concept studies in syngeneic immune competent mouse tumor models.

Results Our studies demonstrate that intratumoral (i.t.) administration of VV_{GM}-aCTLA4 achieved tumor-restricted CTLA-4 receptor saturation and Treg-depletion, which elicited antigen cross-presentation and stronger systemic expansion of tumor-specific CD8+ T cells and antitumor immunity compared with systemic anti-CTLA-4 antibody therapy. Efficacy correlated with FcγR-mediated intratumoral Treg-depletion and the reduction of exhausted CD8+ T cells. Remarkably, in a clinically relevant mouse model resistant to systemic immune checkpoint blockade, i.t. VV_{GM}-aCTLA4 synergized with anti-PD-1 to reject “cold” tumors.

Conclusions Our findings demonstrate in vivo proof-of-concept for spatial restriction of strongly Treg-depleting, immune checkpoint blocking, vectorized anti-CTLA-4 as a highly effective and safe strategy to target CTLA-4 which is able to overcome current limitations of approved anti-CTLA-4 regimens. A clinical trial evaluating i.t. VV_{GM}-ahCTLA4 (BT-001) alone and in combination with anti-PD-1 in metastatic or advanced solid tumors has commenced.

Ethics Approval All mouse experiments were approved by the local ethical committee for experimental animals (Malmö/Lunds djurförsöksetiska nämnd); at BioInvent under permit numbers 17196/2018 or 2934/2020; or at Transgene APAFIS Nr21622 project 2019072414343465 and performed in accordance with local ethical guidelines.

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