OVERCOME SOLID TUMOR IMMUNOSUPPRESSION FOR T CELLS-MEDIATED CANCER ELIMINATION


Background In solid tumors, intratumoral myeloid leukocytes including macrophages (i.e. tumor-associated macrophage or TAM) and myeloid-derived suppressive cells (MDSC) play critical roles in controlling the tumor microenvironment (TME) immunosuppression that supports tumor growth and also confers tumor resistance to immunotherapeutic treatments. Through a proprietary process, we have identified a unique reagent, termed KX147, of which treatment of tumor potently repolarizes the TME, resulting in abrogation of multi-axes immunosuppressive signal transduction pathways reprogram the TME for innate and adaptive immunity against cancer.

Methods In vitro and in vivo testing the effect of KX147 on TAM antigen-presentation and proinflammation; preclinical testing KX147 to treat pancreatic ductal adenocarcinoma (KPC) or colorectal carcinoma (MC38).

Results We found that immunotherapy-refractory solid tumors under therapies generally fail to induce intratumoral macrophages for proinflammatory phenotypic change, nor did they reprogram the TME towards anti-tumor immunogenicity. Rather, these tumors arbitrate strong resistance through increasing IL-10 production, TGFβ signaling (TGFBR1 and TGFBR2), and CCL2 chemokine that attracts MDSC, leading to wound healing and reinforcement of tumor immunosuppression. In stark contrast, tumors treated with KX147 exhibit completely different TME responses to checkpoint blockade, RT and other immune-modulatory therapies, and reshape intratumoral macrophages from immunosuppression to potent proinflammation, featuring high expressions of TNFα, IFNγ, IL-1β, IL-6, IL-12, IL-17, IL-18, etc., while abating IL-10 and TGFβ. Moreover, KX147 also induces a prominent immunogenic antigen presentation machinery with elevated cell surface MHC-I, MHC-II, and costimulatory molecules CD80, CD86, CD40, OX40L on macrophages, which through antigen presentation induces large expansion of tumor-specific T cells for tumor elimination.

Conclusions Our studies demonstrate a novel immunotherapy strategy with KX147 combination, which holds promises for rapid and systemic elimination of solid tumors and metastases to achieve cure.

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