Bifunctional Immunotherapeutic HCW9218 Facilitates Recruitment of Immune Cells from Tumor-draining Lymph Nodes to Promote Antitumor Activity and Enhance Checkpoint Blockade Efficacy in Solid Tumors

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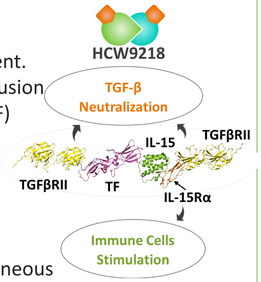
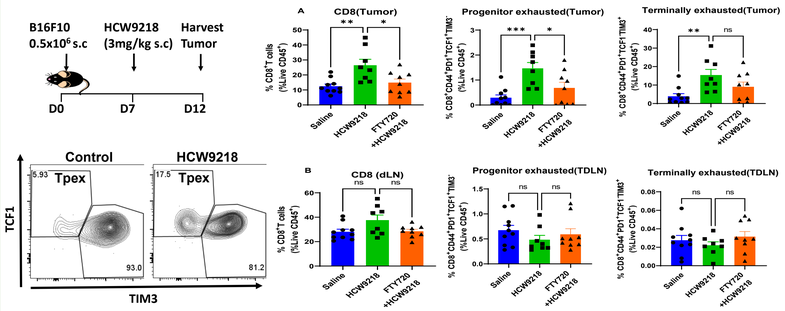
Abstract

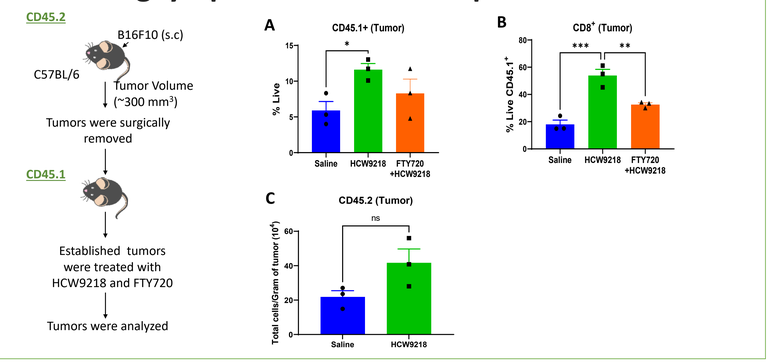
Immunotherapeutics that aid in boosting natural immune defenses against cancers have revolutionized cancer treatment. Previously, we reported a novel heterodimeric bifunctional fusion molecule, HCW9218, designed using soluble tissue factor (TF) -based scaffold technology comprising extracellular domains of the human transforming growth factor-β (TGF-β) receptor II and a human interleukin (IL)-15/IL-15 receptor α complex which exhibited both immune cell stimulatory and TGF-β neutralizing properties. Herein, we showed in two different syngeneic murine tumor models (B16F10&4T1) that subcutaneous injection of HCW9218 induces a proliferative burst of CD8$^+$ T cells and NK cells in blood and a subsequent infiltration of these cells into established tumors. In vivo imaging of 4T1 tumor-bearing mice treated with HCW9218 showed that HCW9218 was present both in lymph nodes and established tumors up to 24hrs following treatment. Comprehensive analysis of tumor-infiltrating lymphocytes (TILs) showed that HCW9218 mediated antitumor activity by expanding TCF$^+$TIM3$^-$ 'progenitor exhausted' (Tpex) CD8$^+$ T cells in tumors. Sphingosine-1-phosphate receptor blockade resulted in decreased tumor infiltration of CD8$^+$ Tpex in B16F10 and 4T1 tumor-bearing mice indicating that these cells originate from tumor draining lymph nodes (TDLNs). Increased 'terminally exhausted' TCF-1$^-$TIM3$^+$ (Tex) CD8$^+$ TILs were also observed in tumors of HCW9218-treated mice indicating increased antitumor activity. Tumor transplantation experiments further confirmed the mechanism of HCW9218 antitumor activity by increasing influx of CD45.1$^+$ CD8$^+$ T cells into transplanted tumors from CD45.2$^+$ mice. Additionally, HCW9218 enhanced the therapeutic efficacy of PD-L1 treatment by increasing the infiltration of activated/memory CD8$^+$T cells into B16F10 tumors in mice, leading to significant reduction in tumor volume. Collectively, this study demonstrated that treating mice bearing solid tumors with HCW9218 resulted in modulating the TdLN immune landscape and invigorating T cells for enhanced checkpoint blockade efficacy. HCW9218 are currently in two clinical trials against chemo-resistant/refractory solid tumors and pancreatic cancer (ClinicalTrials.gov: NCT05322408, NCT05304936).



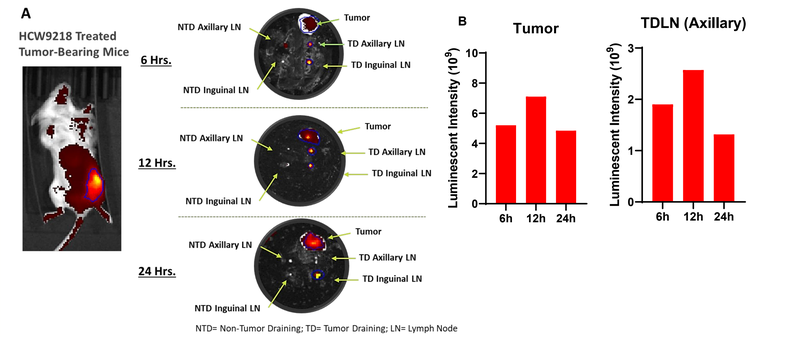
HCW9218 increases CD8$^+$ T cell subset infiltration in melanoma tumor model



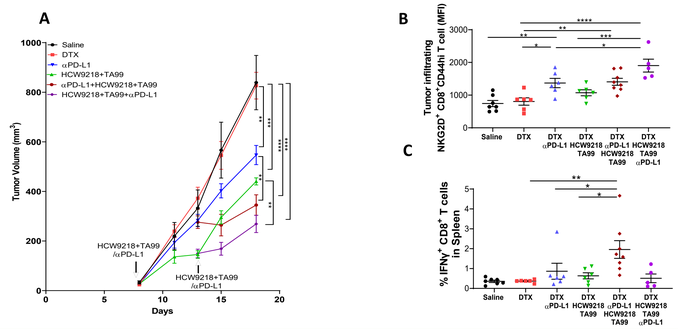
HCW9218 enhances host CD8$^+$ T cell infiltration from draining lymph nodes into transplanted tumors



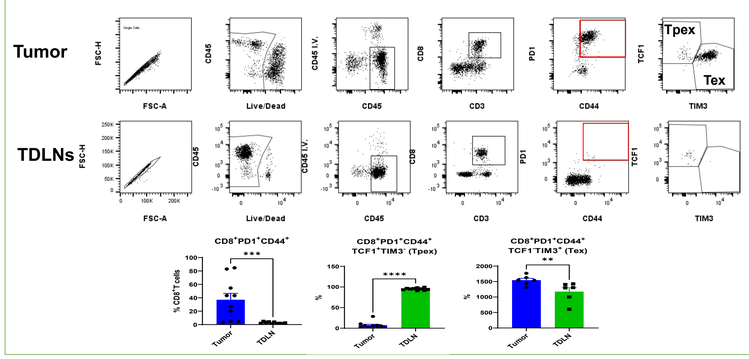
HCW9218 localized to tumor draining LNs and tumor in 4T1 tumor bearing mice



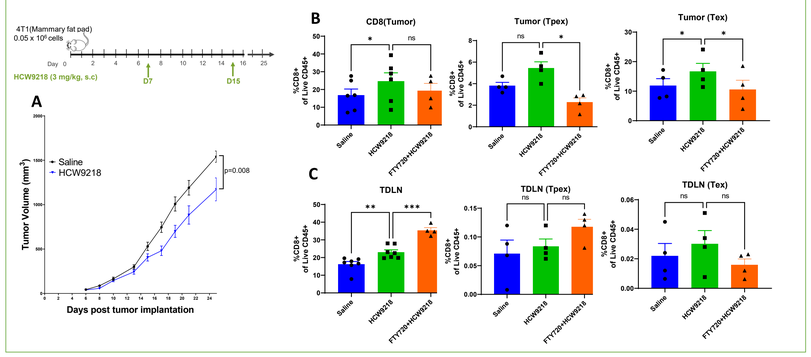
Combination treatment of HCW9218 with ICB enhances anti-tumor activity



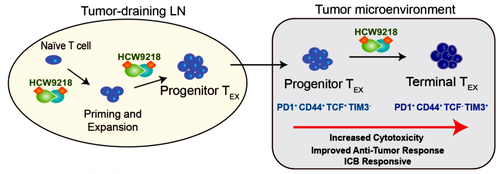
Increased frequencies of antigen specific TIL subsets in tumors of B16F10 tumor-bearing mice



HCW9218 enhances CD8$^+$ T cell infiltration of tumors in triple negative breast cancer model



Summary



- HCW9218 stimulates CD8$^+$ T cells and enhances tumor infiltration in two syngeneic 'cold tumor' mouse models.
- HCW9218 acts by activating antigen experienced CD8 T cells in draining LN followed by trafficking into tumors (maybe change to "HCW9218 activates antigen…")
- HCW9218 can localize in both draining LNs and tumors 24hrs following s.c. administration and therefore can potentially reactivate tumor resident exhausted T cells.
- Combination therapy with HCW9218 and ICB in the background of chemotherapy enhances antitumor efficacy.

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