Anti-VISTA antibody HMBD-002 reprograms tumor associated macrophages and promotes cytotoxic T cell response

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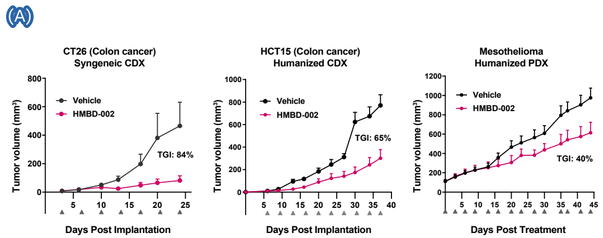
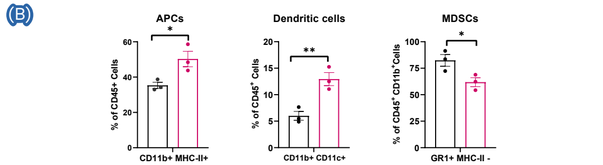
Background and Rationale

- VISTA is an emerging, predominantly myeloid, immune checkpoint, and its blockade has shown benefit in multiple preclinical models of cancer as both a monotherapy and in combination with other immune checkpoint inhibitors such as anti-PD1 and anti-CTLA-4[1].
- In some cancers, such as non-small cell lung cancer, clear renal cell carcinoma and colorectal carcinoma (and in murine models thereof), VISTA is expressed on both T cells and macrophages. Understanding the cell subset specific immunomodulatory functions of VISTA is important to inform patient selection, develop effective combination strategies, and identify biomarkers of response to anti-VISTA therapy.
- Here, we used HMBD-002, an IgG4 anti-VISTA antibody which does not deplete VISTA-expressing cells[2], to assess the functional role of VISTA blockade in the absence of Fc-mediated cytotoxic activity. CT26 tumor-bearing mice were treated with HMBD-002 and/or anti-PD1 and tumors were profiled via multicolor flow cytometry and RNAseq.

HMBD-002 inhibits tumor growth as a single agent by remodeling the tumor microenvironment[2]



CT26 tumor profiling



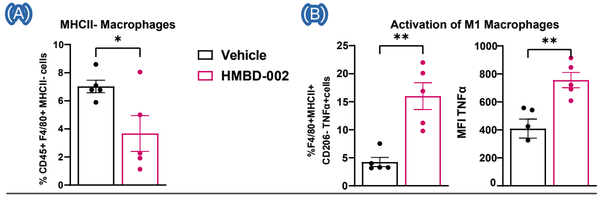
Tumor bearing mice were treated with HMBD-002 and examined for rate of tumor growth and changes in tumor microenvironment. (A) Anti-tumor efficacy of HMBD-002 in syngeneic CDX, humanized CDX and humanized PDX models. (B) Profiling of CT26 tumors via multi-color flow cytometry. (TGI: Tumor growth inhibition)

Tumors from CT26 xenograft mice treated with vehicle or HMBD-002 were harvested. Paired end sequencing of RNA libraries was performed on Illumina's Novaseq platform. Data shown is log2 fold change in HMBD-002 treated tumors with respect to vehicle control.

References

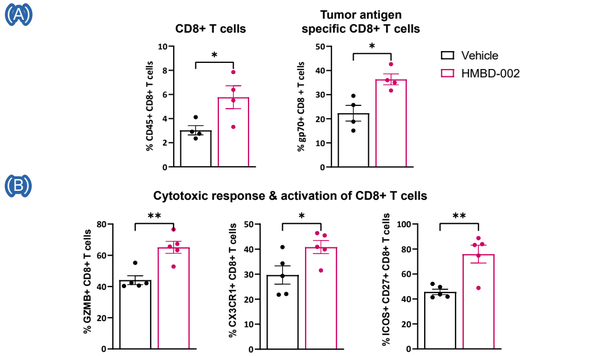
[1]*Yuan L, et al. Trends Immunol 2021 Mar;42(3):209-227*
[2]*Thakkar D, et al. J Immunother Cancer 2022; 10:e003382*

Blocking VISTA reprograms tumor associated macrophages to an activated inflammatory phenotype



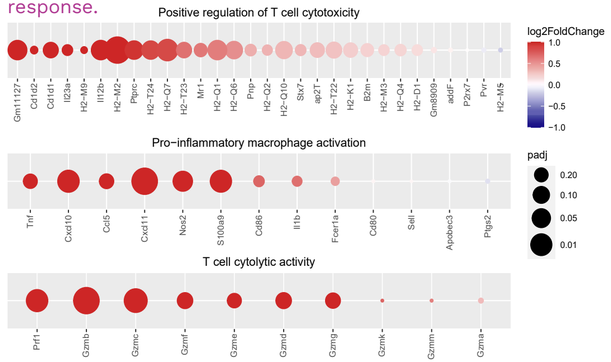
Tumors from CT26 xenograft mice treated with vehicle or HMBD-002 were harvested and profiled via multi-color flow cytometry on Cytek Northen Lights 3000. (A) Frequency of MHCII- macrophages. (B) Frequency of TNFα+ M1 macrophages and expression levels of TNFα.

Blocking VISTA increases tumor antigen specific CD8+ T cells and their cytotoxic activity

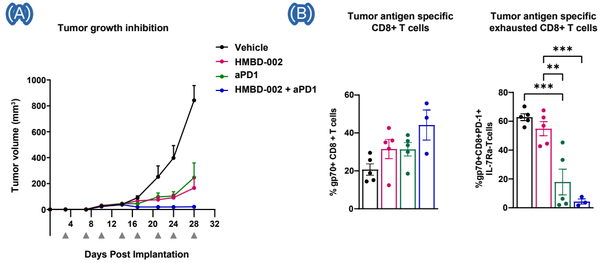


Tumors from CT26 xenograft mice treated with vehicle or HMBD-002 were harvested and profiled via multi-color flow cytometry on Cytek Northen Lights 3000. (A) Frequency of CD8+ T cells and tumor antigen gp70 specific CD8+ T cells. (B) Expression of makers associated with cytotoxicity and activation of CD8+ T cells.

Blocking VISTA leads to upregulation of genes associated with pro-inflammatory macrophage activation and cytotoxic T cell response.

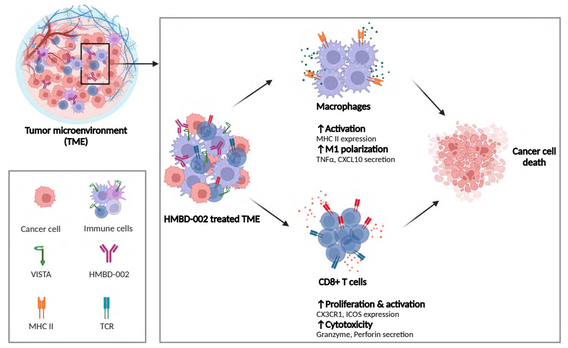


HMBD-002 combined with anti-PD1 results in enhanced efficacy and reduced T cell exhaustion



Tumors from CT26 xenograft mice treated with vehicle or HMBD-002 and/or aPD1 were harvested and profiled via multi-color flow cytometry on Cytek Northen Lights 3000. (A) Tumor growth under the indicated treatment conditions. (B) Frequency and exhaustion levels of tumor antigen gp70 specific CD8+ T cells.

Proposed mechanism of action of HMBD-002



HMBD-002 binds to and blocks VISTA on macrophages and CD8 T cells leading to an anti-tumor immune response. VISTA blockade reverses the immunosuppressive phenotype of tumor associated macrophages to an inflammatory M1 state characterized by upregulation of TNFα, CXCL10 and promotes a cytotoxic T cell response leading to proliferation and release of cytolytic protein Granzyme B by CD8+ T cells.

Conclusion

- Anti-tumor effect due to VISTA blockade via HMBD-002 is driven by polarization of macrophages to an activated pro-inflammatory anti-tumor phenotype and significant increases in tumor antigen specific CD8+ T cells with a concurrent increase in CD8+ T cell activation.
- Combining anti-VISTA with other immune checkpoint inhibitors such as anti-PD1 that can reprogram exhausted T cells has the potential for synergistic activity by further enhancing anti-tumor T cell response.