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Poster #451

Targeting IL-18BP-mediated adaptive resistance with WB01 restores endogenous IL-18 activity and enhances checkpoint inhibitor efficacy

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Background

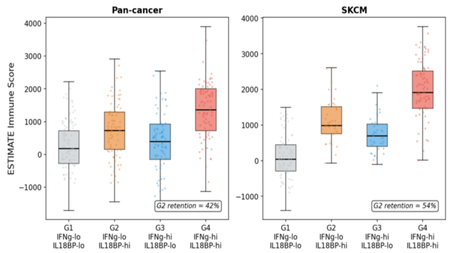
Despite the success of immune checkpoint inhibitors (CPIs), a substantial fraction of patients fails to achieve durable responses. Many non-responding tumors remain immune infiltrated, suggesting the presence of suppressive mechanisms beyond CPIs. IL-18 binding protein (IL-18BP), a high-affinity soluble decoy receptor that neutralizes the anti-tumor cytokine IL-18, has been associated with poor clinical outcomes and resistance to immunotherapy. Previous clinical studies of recombinant IL-18 demonstrated limited efficacy due to IL-18BP-mediated sequestration. To overcome high target abundance and rapid target replenishment, we developed WB01, a pH-sensitive anti-IL-18BP VHH-Fc fusion that combines IL-18BP blockade with enhanced target clearance. We evaluated the translational relevance of IL-18BP and the anti-tumor activity of WB01 in multiple preclinical tumor models.

CPI-mediated IL-18BP Expression Blunts CPI Response

- Classification of 10,345 TCGA tumors across 32 cancer types into four states defined by IFNγ and IL18BP expression
- Definition of 4 states by IFNγ × IL18BP (TCGA)

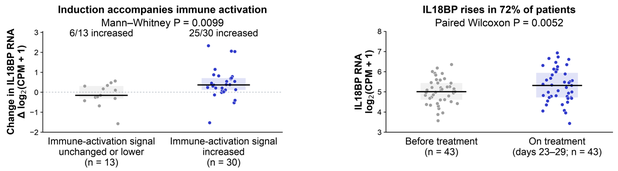
	IL18BP-low	IL18BP-high
IFNγ-high	G3 – Hot **(CPI alone)**	G4 - Hot + Braked **(CPI + anti-IL18BP target)**
IFNγ-low	G1- Cold	G2 - Infiltrated + Braked **(combination entry point)**

- G2 has higher ESTIMATE Immune Score than G1 in pan-cancer and SKCM → not an immune desert



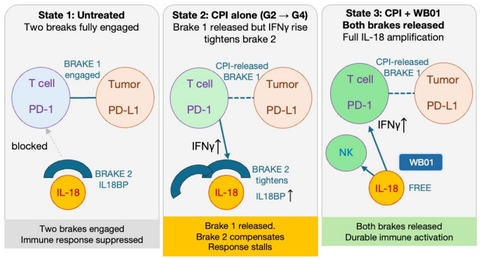
IL-18BP expression in IFNγ-high vs IFNγ-low tumors: Representative examples

IL-18BP increases during checkpoint therapy



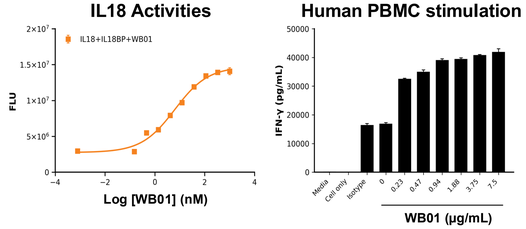
These findings support a rationale for combining IL18BP blockade with checkpoint therapy.
Activation signal: IFNG RNA (change >0 versus ≤0). Change = on treatment minus pretreatment. Tests are two-sided, unadjusted.
Riaz et al., Cell 2017 • GSE91061 • doi:10.1016/j.cell.2017.09.028 • Wrench Bio reanalysis

A prevalent "double-brake" in CPI-active tumors



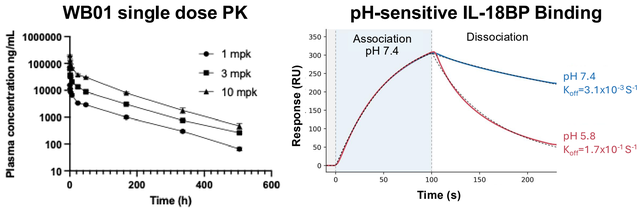
Tumors suppress immunity via two brakes: PD-1/PD-L1 and IL-18BP/IL-18. CPI alone releases Brake 1, but the resulting IFN-γ rise upregulates IL-18BP, tightening Brake 2 and stalling response. WB01 releases Brake 2, enabling full IL-18 amplification and durable immune activation.

WB01 Neutralizes IL-18BP and Restores IL-18 Bioactivity



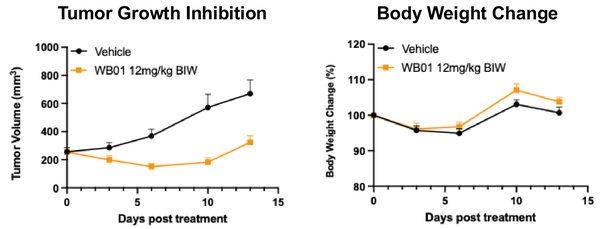
WB01 dose-dependently restored IL-18 signaling blocked by IL-18BP, confirmed in two orthogonal assays: (left) IL-18 reporter cell line, EC50 = 6.3 nM; (right) primary human PBMC.

WB01 Shows Antibody-like PK and pH-Dependent IL-18BP Release



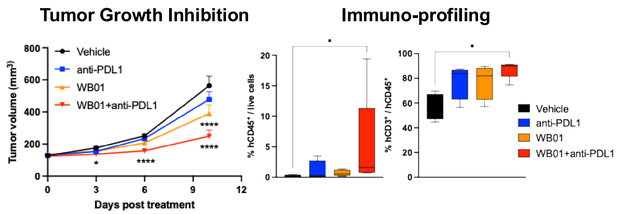
WB01 exhibited dose-proportional, antibody-like PK (1–10 mg/kg). SPR confirmed pH-sensitive IL-18BP binding — stable at neutral pH with ~55-fold faster off-rate at acidic pH (Koff $3.1\times10^{-3} \rightarrow 1.7\times10^{-1}$ s^{-1}) — supporting enhanced target clearance.

WB01 Single-Agent Activity in Humanized JHH6 Model



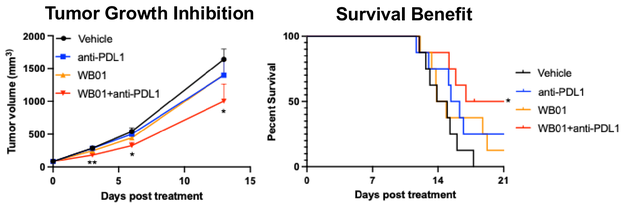
In an HSC-humanized JHH6 tumor model, WB01 monotherapy drove substantial single-agent tumor growth inhibition versus vehicle, with no significant change in body weight — supporting a favorable efficacy/tolerability profile.

WB01 + anti-PD-L1 Enhances Tumor Inhibition and Immune Infiltration in the Humanized Hep3B Model



Combination significantly inhibited tumor growth and increased immune infiltration (%hCD45⁺, %hCD3⁺) versus monotherapy or vehicle.

WB01 improves tumor growth inhibition and survival in the MC38 hIL18BP KI model



WB01 reduced tumor volume versus vehicle and improved survival in the MC38 hIL18BP knock-in model, with added benefit when combined with anti-PD-L1.

Broad combination opportunity across CPI pipeline

Rank	Checkpoint	Mean r	% positive cancers	% Significant (FDR)	Coupled?
1	TIGIT	0.649	100%	100%	Yes
2	TIM-3 (HAVCR2)	0.631	100%	100%	Yes
3	LAG-3 (LAG3)	0.615	100%	94%	Yes
4	PD-1 (PDCD1)	0.593	97%	94%	Yes
5	CTLA-4 (CTLA4)	0.589	100%	100%	Yes
6	BTLA	0.518	100%	97%	Yes
7	PD-L1 (CD274)	0.515	100%	97%	Yes
8	VISTA (VSIR)	0.487	100%	100%	Yes
9	B7-H3 (CD276)	0.163	78%	72%	No

IL-18BP/IL-18 axis is significantly coupled to 8 of 9 checkpoint targets, including TIGIT, TIM-3, LAG-3, PD-1, CTLA-4, BTLA, PD-L1, and VISTA. Only B7-H3 was uncoupled. Supports broad CPI combination potential beyond PD-1/PD-L1.
Partnering opportunities are welcome.

Summary

WB01 is our DC compound
- Preclinical VHH-Fc with antibody-like PK, and developability assessed
- Differentiated MoA: IL18BP inhibition + degradation
- Transcriptomic rationale: 32 cancer types, 5 CPI cohorts
- In vivo proof-of-concept in multiple models: single-agent efficacy with no body weight loss, and significant combination benefit vs CPI
- Quantitative synergy matrix for partner-indication matching
- IND-enabling studies initiated

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