A First-in-Class PD1-IL18 Immunocytokine (BPT567) Targets PD-1^{+} IL18R^{+} CD8^{+} T Effector Cells Enriched in the Tumor Microenvironment and Exhibits Potent Antitumor Efficacy With Excellent Tolerability

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BRIGHT PEAK THERAPEUTICS

ABSTRACT

Immunocytokines (IC) leverage orthogonal mechanisms of action in one molecule to induce potent antitumor immune responses. PD-1-targeting ICs are of particular interest since they harbor the multifunctional ability to selectively target antigen-experienced PD-1^{+} CD8^{+} T cells, enriched in the tumor microenvironment (TME), release them from PD-(L)1 pathway inhibition, be retained within the TME, and simultaneously deliver potent cytokine receptor stimulation to the same T cell in *cis* (*cis*-signaling).

Interleukin (IL-18) is a proinflammatory cytokine that stimulates both innate and adaptive immunity and generates potent antitumor activity mediated by both, T effector and NK cells. Recent evidence indicates that a subset of tumor-infiltrated PD-1^{+} CD8^{+} T effector cells characterized by high expression of IL-18 receptor (IL-18R) exhibits a superior cytotoxic and proliferative phenotype (Codarri Deak et al. (2022) Nature). Hence, we developed a PD1-IL18 IC to specifically target and activate intratumoral IL-18R-expressing PD-1^{+} CD8^{+} T cells.

We engineered a conjugatable variant of human IL-18 with enhanced potency and significant resistance to IL-18 binding protein (IL-18BP), an IFNγ-induced neutralizing factor blocking IL-18 signaling. The enhanced IL-18 payload was used to create a PD1-IL18 IC (BPT567) via site-specific chemical conjugation to a defined lysine residue within the heavy chain of an anti-human PD-1 antibody (Ab), LZM009. Conjugation did not affect the basic properties of the Ab as neither binding to PD-1 nor the interaction with the neonatal Fc receptor (FcRn) or Fcγ receptors were significantly impacted. Of note, the conjugation handle in our enhanced IL-18 variant was inserted at a site distinct from its N- or C-terminus to preserve the full potency and selectivity of the IL-18 payload. As a result, BPT567 exhibits increased potency and marked resistance to IL-18BP inhibition compared to wild-type IL-18.

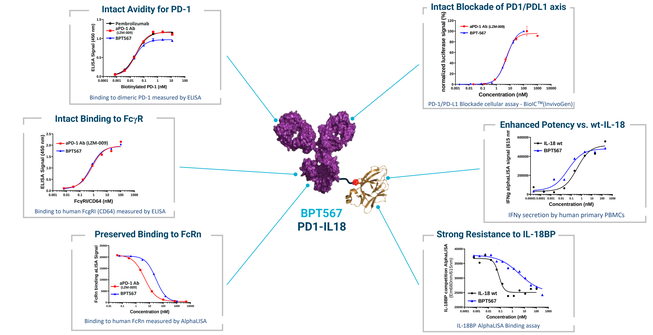
Here we describe the *in vivo* characterization of our first-in-class PD1-IL18 IC focusing on the PK properties of BPT567 and its pharmacodynamic (PD) as well as anti-tumor effects elicited in tumor-bearing mice.

Poster #1850
PO.IM02.17: Immunomodulatory Agents and Interventions 2
Section 24

AACR American Association for Cancer Research

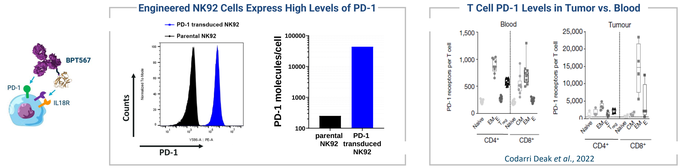
IN VITRO PROFILING

Antibody and IL-18 Payload Properties are Fully Preserved in BPT567



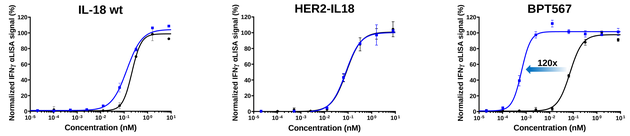
Cis-SIGNALING

Engineered NK Cell Line Expresses PD-1 at Levels Comparable to Tumor-Infiltrating T cells



Codarri Deak *et al.*, 2022

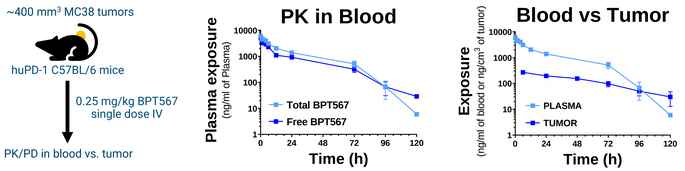
Cis-Signaling Results in Enhanced Potency of BPT567 in PD-1^{high} Cells



IFNγ secretion by either PD-1-negative or PD-1-positive NK92 cells stimulated for 16 h with indicated molecules

PHARMACOKINETICS

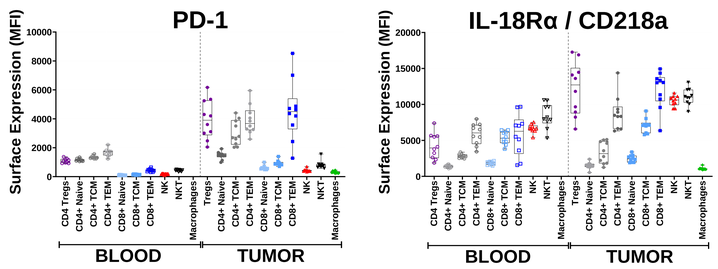
BPT567 is Not Neutralized by IL-18BP and is Retained in the Tumor



Concentration of total and unbound (not complexed to IL-18BP) BPT567 in plasma and tumor of MC38 tumor-bearing huPD-1 C57BL/6 mice injected with single i.v. dose of BPT567 at 0.25 mg/kg

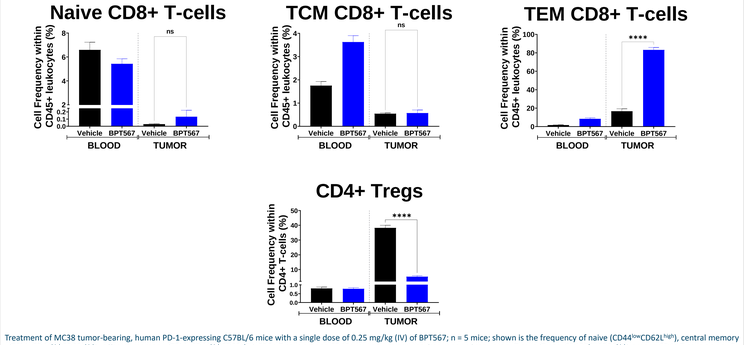
PHARMACODYNAMIC EFFECTS

Both Targets of BPT567 - PD-1 and IL-18Rα - are Found Upregulated in Tumor-Infiltrating T Cells



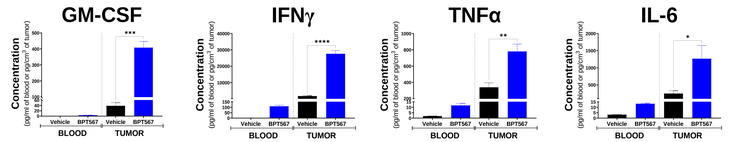
Expression of PD-1 and IL18Rα at surface of indicated immune cell subsets in blood and tumor of MC38-tumor bearing human PD-1-expressing C57BL/6 control mice (n=5 mice)

BPT567 Preferentially Expands Tumor Infiltrating Effector Memory T Cells While Suppressing Intratumoral T$_{regs}$



Treatment of MC38 tumor-bearing, human PD-1-expressing C57BL/6 mice with a single dose of 0.25 mg/kg (IV) of BPT567; n = 5 mice; shown is the frequency of naive (CD44^{low}CD62L^{high}), central memory (TCM: CD44^{high}CD62L^{high}), effector memory (TEM: CD44^{high}CD62L^{low}) CD8+ T cells among CD45+ leukocytes and the frequency of regulatory T cells (Tregs: CD127^{low}CD25^{high}) among CD4+ T cells on day 7 post-treatment; unpaired two-tailed t-test ; ns: non significant, * P<0.05, ** P<0.005; *** P<0.0005; **** P<0.0001

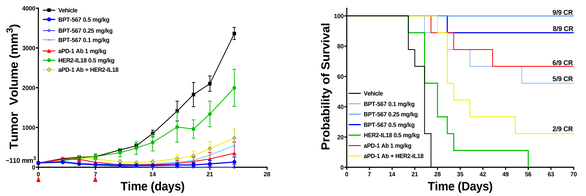
BPT567 Triggers the Release of Pro-Inflammatory Cytokines To A Far Greater Extent In The Tumor Compared to Blood



Treatment of MC38 tumor-bearing, human PD-1-expressing C57BL/6 mice with a single dose of 0.25 mg/kg (IV) of BPT567; n = 5 mice;
shown are cytokine levels in plasma and MC38 tumors at 48h post-treatment ; unpaired two-tailed t-test ; ns: non-significant* P<0.05, ** P<0.01, *** P<0.001; **** P<0.0001

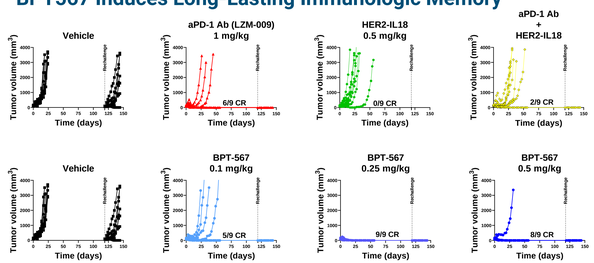
ANTI-TUMOR EFFICACY

Efficacy of BPT567 is Superior to anti-PD-1, Non-Targeted HER2-IL18, and to the Combination of anti-PD-1 + HER2-IL18



MC38 tumor-bearing transgenic huPD-1 C57BL/6 mice treated with two doses of the indicated molecules (QWx2, IV).
Tumor size at start of treatment ~110 mm³ ; n=9 ; mean ± SEM.

BPT567 Induces Long-Lasting Immunologic Memory



Animals showing complete responses were rechallenged with 3x10^{5} MC38 cells injected SC on the opposite flank 112 days after end of treatment.

CONCLUSIONS

- Bright Peak Immunocytokines are generated via an approach that is entirely different from the generation of conventional fusion proteins i.e., via chemical conjugation of engineered cytokines to the Fc domain of existing human Abs in a rapid (2-3 weeks) and cell-free process.
- Conjugation is site-specific and existing antibodies can be used "off-the-shelf" without antibody engineering.
- BPT567 is generated using LZM-009, a clinical stage anti-PD-1 Ab, and Bright Peak's IL-18BP-resistant enhanced IL-18 variant. Following conjugation, BPT567 retains activity of the engineered IL-18 payload as well as full PD-1 affinity and functional PD-1/PD-L1 blockade.
- *In vitro*, BPT567 shows enhanced potency in PD-1^{high} cells due to simultaneous binding to IL18R and PD-1 on the same cell (*cis*-signaling).
- *In vivo*, BPT567 induces a striking and selective expansion of effector memory CD8^{+} T cells within the tumor microenvironment (TME). Binding to PD-1^{high} CD8^{+} T cells residing primarily in the TME leads to sustained tumor retention and triggers substantial remodeling of the TME.
- BPT567 is well tolerated and exhibits remarkable single agent anti-tumor efficacy that is superior to that of single agent anti-PD-1 Ab or non-targeted IL-18 IC as well as to the combination of both single agents.