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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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 because they harbor the multifunctional ability to selectively target antigen-experienced PD1+ CD8+ T cells enriched in the tumor microenvironment (TME), release them from PD-1/L1 pathway inhibition, escape 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 receptors (IL-18R) exhibit superior cytotoxic and proliferative phenotype (Codarri Deak et al., 2023). Hence, we developed a PD1-IL18 IC to specifically target and activate intratumoral IL-18-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 IFN-γ-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), LM209. Conjugation did not affect the properties of the Ab as neither binding to PD-1 nor the interaction with the neonatal Fc receptor (FcγRn). Fcγ receptors were significantly impacted. Of note, the conjugation handle in our enhanced IL-18 variant was inserted into the C-terminus of the IL-18 protein to preserve the full potency and selectivity of the IL-18 payload. As a result, BPT567 exhibited 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.

IN VITRO PROFILING

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

PHARMACODYNAMIC EFFECTS

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

BPT567 Preferentially Expands Tumor Infiltrating Effector Memory T Cells While Suppressing Intratumoral Tregs

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

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 proprietary enhanced IL-18 variant. Following conjugation, BPT567 retains activity of the engineered IL-18 payload as well as IL-18 Ab and functional PD-1/PD-L1 blockade.
- In vivo, BPT567 shows enhanced potency in PD-1+ 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/PD-L1+ 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 the combination of both single agents.