Unleashing natural IL-18 activity using an anti-IL-18BP blocker antibody induces potent immune stimulation and anti-tumor activity


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**Background**

Conventional cytokines have limited anti-cancer efficacy mostly due to narrow therapeutic window and systemic adverse effects. IL-18 is an inflammasome-induced pro-inflammatory cytokine that enhances T and NK cell activity and stimulates IFNγ production. The activity of IL-18 is naturally blocked by high affinity endogenous binding protein (IL-18BP). Traditionally, the expression of IL-18 and IL-18BP is in the tumor, we measured their levels in tumor derived supernatants (TDS) by ELISA assay. To relate endogenous bound IL-18 activity generated COM503, high affinity anti-human IL-18BP antibody (Ab) COM503 activity was examined in T and NK cell-based assays. For mouse in vivo studies, a surrogate Ab was generated and examined in several models either as monotherapy or in combinations with immune checkpoints (ICP) blockers.

**IL-18**

- An effector cytokine
- Secreted upon inflammation activation
- Upregulated in the TME

**IL-18BP**

- Binds IL-18 and blocks its immune stimulatory activity
- IL-18BP secretion is increased via an IL-18-mediated feedback mechanism

**COM503**

- Has the potential to induce potent anti-tumor responses and pronounced TME-constrained immune modulation

**Inflammasome induced cytokines such as IL-18 and IL-1β are abundant in the tumor microenvironment**

**IL-18 is upregulated in cancer patient serum and pathway**

- **Tumor volume** of 120mm3 and 250mm3 for MC38ova and E0771 respectively, on day 4 for B16gp100, and was injected twice a week for 3 weeks.
- **Anti-mouse IL-18BP Ab inhibits tumor growth in E0771 orthotopic mouse breast tumor model (A)**
- **MC38ova mouse CRC tumor model (B)**
- Anti-mouse IL-18BP antibody demonstrates monotherapy activity against murine syngeneic tumor models

**IL-18BP-Bound IL-18 levels in the TME are above amount required for T cell activation in vivo**

**Anti-mouse IL-18BP Ab modulates tumor microenvironment without affecting the periphery**

**IL-18BP is upregulated in tumor associated macrophages in the TME and expressed across multiple human cancer indications**

**Anti-mouse IL-18BP Ab demonstrates monotherapy activity against murine syngeneic tumor models**

**Conclusion**

- IL-18 is upregulated in the TME and is mostly bound by IL-18BP • COM503, a potential first-in-class, high-affinity anti-IL-18BP Ab, induces human T and NK cell responses in vitro • In mouse, anti-IL-18BP Ab induces potent anti-tumor responses and pronounced TME-constrained immune activation, this in contrast to systemically administered therapeutic cytokines, which generate a non-localized inflammatory response • Taken together, blocking IL-18BP is a promising novel approach to harness cytokine biology for the treatment of cancer