Unleashing natural IL18 activity using an anti-IL18BP blocker antibody induces potent immune stimulation and anti-tumor activity

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Conventional cytokines have limited anti-cancer efficacy mostly due to narrow therapeutic window and systemic adverse effects. IL18 is an inflammasome induced proinflammatory cytokine that enhances T and NK cell activity and stimulates IFNγ production. The activity of IL18 is naturally blocked by a high affinity (~440fM) endogenous binding protein (IL18BP). IL18BP is induced in the tumor microenvironment (TME) in response to IFNγ upregulation. We measured the protein expression of IL18 in human tumors. IL18 was highly expressed across 72 individual tumors (median 12.2ng/gr) and was clearly elevated compared to serum (median 0.32ng/ml). By assessing total and free IL-18 we showed that most of TME IL18 is bound by IL18BP (median 10.1ng/gr), and its levels are above the amount required for T cell activation in-vitro (1ng/ml), implying that releasing IL-18 in the TME could lead to T cell immune activation.

To unleash endogenous bound IL18 activity, COM503, a fully human, high affinity anti-IL18BP antibody (Ab), was generated. COM503 blocks the IL18BP-IL18 interaction and displaces pre-complexed IL-18 to enhance T cell activation (increased IFNγ 197%, $p<0.001$; CD137 86%, $p<0.05$) in ex-vivo stimulated human CD8+ tumor infiltrating lymphocytes-tumor cells co-culture assay. Moreover, COM503 induced human NK cell function as evident by increased IFNγ secretion (26-fold, $p<0.001$).

To assess the effect of IL18BP blockade in-vivo, a surrogate anti-IL18BP Ab was generated and administered systemically to mice. In an orthotopic E0771 breast cancer model, anti-IL18BP Ab monotherapy resulted in a significant tumor growth inhibition (91%, $p<0.0001$), and increased survival ($p<0.0001$). Anti-IL18BP Ab induced pronounced multi-parametric TME modulation including an increase in CD3+ T cells infiltration (108.5%, $p=0.015$), and specifically in infiltrating effector IFNγ+GrB+ CD8+ T cells (258.5%, $p=0.02$) and IFNγ+ TNFα+ NK cells (76.9%, $p=0.001$). Similarly, anti-tumor effects were shown in MC38ova model (58% TGI, $p<0.001$), with a robust TME-localized immune modulation including increased CD8+ infiltration (85%, $p=0.009$) and IFNγ secretion (76%, $p=0.052$). In contrast, no increase in inflammatory cytokines and lymphocyte numbers or activation state was observed in serum and spleen.

In summary, we demonstrated that IL18 is upregulated in the TME and is mostly bound by IL18BP. COM503, a potential first-in-class, high-affinity anti-IL18BP Ab, induces human T and NK cell responses in-vitro. A mouse surrogate anti-IL18BP Ab induces potent anti-tumor responses and pronounced TME-constrained immune modulation, this in contrast to systemically administered therapeutic cytokines, which generate a non-localized inflammatory response. Taken together, blocking IL18BP is a promising novel approach to harness cytokine biology for the treatment of cancer.