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

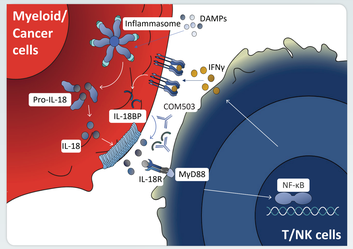
Assaf Menachem, Zoya Alteber, Gady Cojocaru, Tal Fridman Kfir, Dan Blat, Olga Leiderman, Moran Galperin, Lital Sever, Nadav Cohen, Keren Cohen, Roy Granit, Sandra Vols, Masha Frenkel, Lior Faigenbloom, Liron Soffer, Karin Meyer, Keren Menachem, Hadas Galon Tilleman, Michal Perpinial, Evgeny Tatirovsky, Pierre Ferre, Eran Ophir

Compugen Ltd, Holon, Israel

compugen
FROM CODE TO CURE®

Abstract Presentation # 4072

Conventional cytokines have limited anti-cancer efficacy mostly due to narrow therapeutic window and systemic adverse effects. IL-18 is an inflammasome induced proinflammatory cytokine that activates T and NK cells and stimulates IFNγ production. The activity of IL-18 is naturally blocked by a high affinity endogenous binding protein (IL-18BP), which is induced in response to IFNγ upregulation as a negative feedback mechanism. By assessing total and free IL-18 we examined whether bound-IL-18 levels in the tumor are above the level required for in-vitro human T-cell activation. To unleash endogenous bound IL-18 activity, COM503, high affinity anti-human IL-18BP blocker Ab, was generated and examined in T and NK cell-based assays. In-vivo, IL-18BP blockade was evaluated in multiple mouse tumor models.

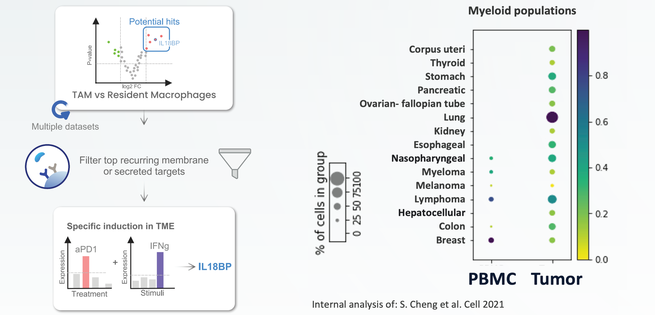


IL-18 is:
- An effector cytokine
- Secreted upon Inflammasome activation
- Upregulated in the TME

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

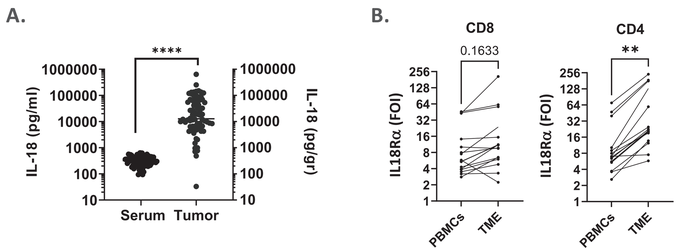
COM503:
- Has the potential to Induce potent anti-tumor responses and pronounced TME-localized immune modulation

IL-18BP was identified computationally while querying for TAM negative feedback immunosuppression mechanism



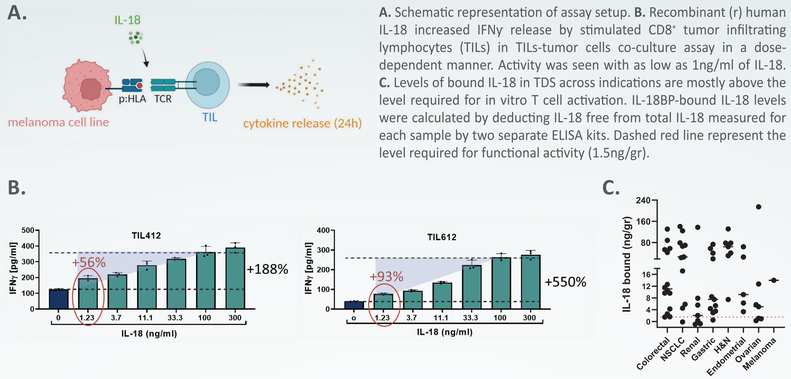
A. A scheme describing the process of IL-18BP identification as a potential soluble immune checkpoint. **B.** scRNA analyses of tumor-infiltrating myeloid cells, across indications show that IL-18BP is up-regulated in myeloid population in the TME compared to the periphery (PBMCs).

IL-18 pathway is elevated in human TME



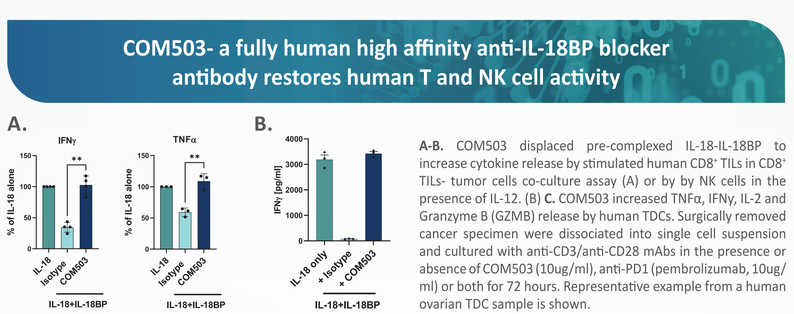
A. IL-18 levels in tumor derived supernatants (TDS) are elevated compared to levels in serum in cancer patients. **B.** IL-18 receptor α subunit (IL-18Rα) expression is induced on tumor infiltrating lymphocytes (TILs) in the tumor microenvironment (TME) compared to periphery. Statistical analysis was preformed using paired t test (two tailed). P ≤ 0.01**, P ≤ 0.0005****

IL-18BP-Bound IL-18 levels in human TME are above amount required for T cell activation in vitro



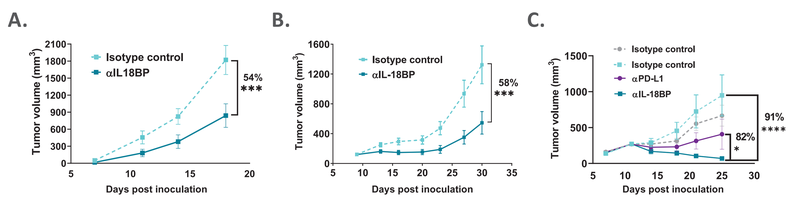
A. Schematic representation of assay setup. **B.** Recombinant (r) human IL-18 increased IFNγ release by stimulated CD8⁺ tumor infiltrating lymphocytes (TILs) in TILs-tumor cells co-culture assay in a dose-dependent manner. Activity was seen with as low as 1ng/ml of IL-18. **C.** Levels of bound IL-18 in TDS across indications are mostly above the level required for in vitro T cell activation. IL-18BP-bound IL-18 levels were calculated by deducting IL-18 free from total IL-18 measured for each sample by two separate ELISA kits. Dashed red line represent the level required for functional activity (1.5ng/gr).

COM503- a fully human high affinity anti-IL-18BP blocker antibody restores human T and NK cell activity



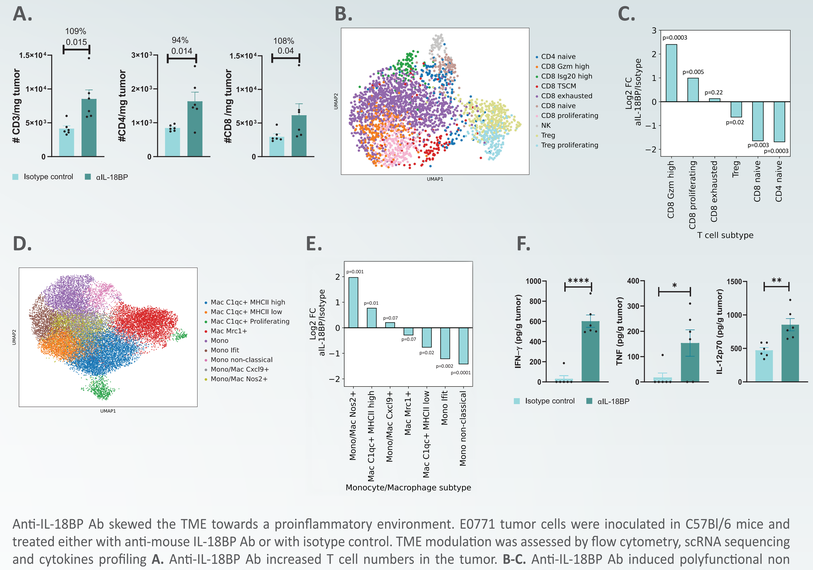
A-B. COM503 displaced pre-complexed IL-18-IL-18BP to increase cytokine release by stimulated human CD8⁺ TILs in CD8⁺ TILs- tumor cells co-culture assay (A) or by by NK cells in the presence of IL-12. (B) **C.** COM503 increased TNFα, IFNγ, IL-2 and Granzyme B (GZMB) release by human TDCs. Surgically removed cancer specimen were dissociated into single cell suspension and cultured with anti-CD3/anti-CD28 mAbs in the presence or absence of COM503 (10ug/ml), anti-PD1 (pembrolizumab, 10ug/ml) or both for 72 hours. Representative example from a human ovarian TDC sample is shown.

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



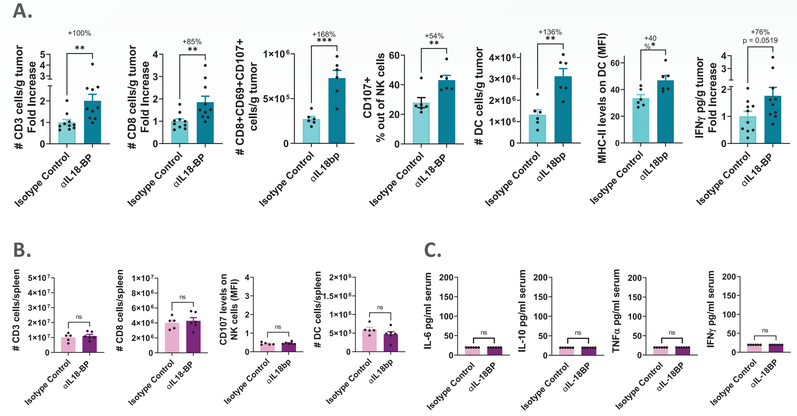
A-C. Anti-mouse IL-18BP Ab inhibited tumor growth in B16F10-hmgp100 mouse melanoma tumor model (A), MC38OVA^{dim} mouse CRC tumor model (B), and led to tumor regression in E0771 orthotopic mouse breast tumor model (C). Tumor volumes are represented as the mean volume + SEM. Treatment initiated on day 4 for B16gp100 and at tumor volume of 120mm³ and 270mm³ for MC38OVA^{dim} and E0771 respectively and was administered twice a week for 6 doses.

Anti-mouse IL-18BP Ab induces proinflammatory environment in the TME



Anti-IL-18BP Ab skewed the TME towards a proinflammatory environment. E0771 tumor cells were inoculated in C57Bl/6 mice and treated either with anti-mouse IL-18BP Ab or with isotype control. TME modulation was assessed by flow cytometry, scRNA sequencing and cytokines profiling **A.** Anti-IL-18BP Ab increased T cell numbers in the tumor. **B-C.** Anti-IL-18BP Ab induced polyfunctional non exhausted T cells in the TME. **B.** UMAP projection showing T and NK cells present in E0771 tumors **C.** Enrichment of major T cell subpopulation frequencies in Ab/ isotype treated groups. **D-E.** Anti-IL-18BP Ab increased pro-inflammatory macrophages in the TME. **D.** UMAP projection showing tumor-associated monocyte and macrophage subpopulations present in E0771 tumors **E.** Enrichment of major tumor-associated monocytes and macrophages frequencies in Ab/ isotype treated. F. Anti-IL-18BP Ab increased pro-inflammatory cytokine secretion in the TME.

Anti-mouse IL-18BP Ab induces TME-localized effects



A-C. Anti-IL-18BP Ab modulated the TME without affecting the periphery. C57BL/6 mice were subcutaneously injected with MC38OVA^{dim} and were treated with anti-mouse IL-18BP Ab or isotype control. Tumors, spleens and serum were harvested, and immune composition and cytokine concentrations were determined in the tumor microenvironment (A), in the spleen (B) and in the serum (C).

CONCLUSION

• IL-18, upregulated in the TME, is inhibited by IL-18BP, which is induced by IFNg in the TME. • Blocking IL-18BP in murine cancer models inhibits tumor growth. • Immune modulation following treatment with anti-IL-18BP Ab is restricted to the TME suggesting favorable therapeutic window, in contrast to recombinant therapeutic cytokines given systemically. • COM503, a human IgG4 high affinity anti-IL-18BP blocker Ab, releases IL-18 to activate T and NK cells. • IND expected in 2024.