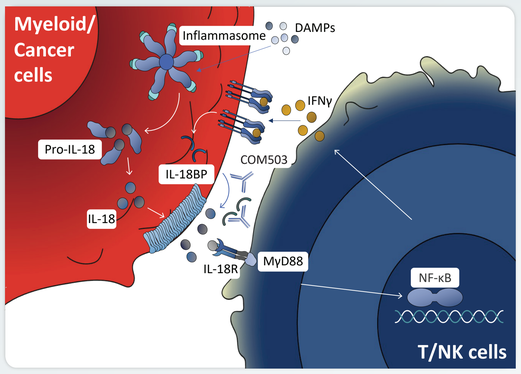
Unleashing natural IL-18 activity using an anti-IL-18BP blocker antibody induces potent immune stimulation and anti-tumor effects

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®

Poster #2042

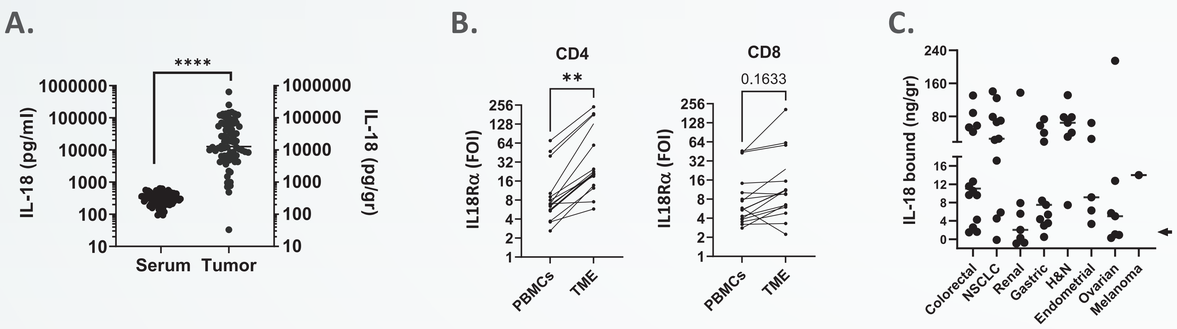


IL-18 is:
- An effector cytokine
- Secreted upon Inflammasome activation
- Upregulated in the TME

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

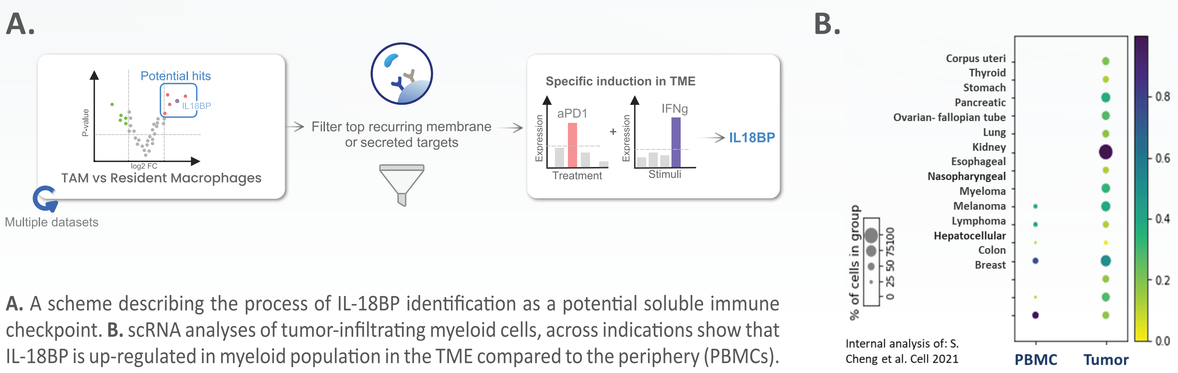
COM503:
- Has the potential to Induce potent anti-tumor responses and pronounced TME-localized immune modulation

IL-18 pathway is elevated in the TME and most of the IL-18 is bound by IL-18BP



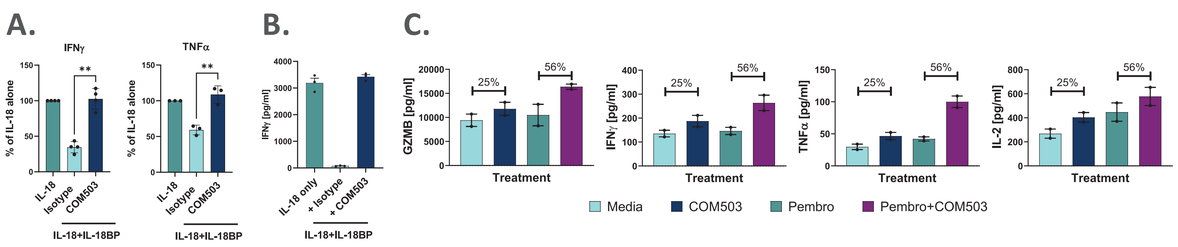
A. IL-18 levels in tumor derived supernatants (TDS) are elevated compared to levels in serum in cancer patients. **B.** IL-18 receptor a subunit (IL-18Ra) expression is induced on tumor infiltrating lymphocytes (TILs) in the tumor microenvironment (TME) compared to periphery. **C.** Most of the IL-18 in the TME is bound by IL-18BP. L-18BP-bound IL-18 levels were calculated by deducting IL-18 free from total IL-18 measured for each sample by two separate ELISA assays. Statistical analysis was preformed using paired t test (two tailed). P ≤ 0.01**, P ≤ 0.0005****

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



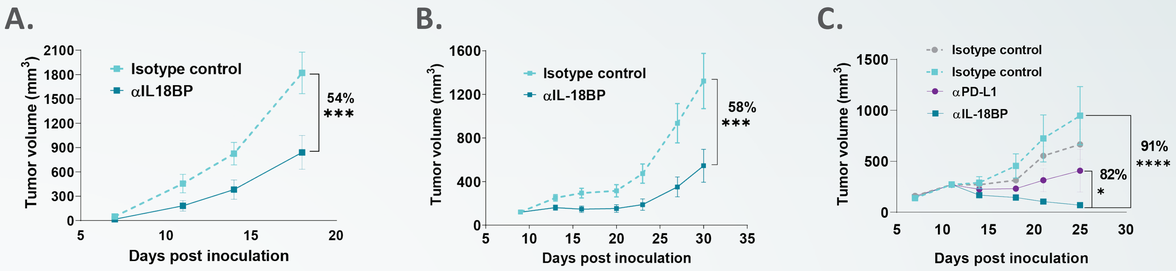
A. A scheme describing the process of IL-18BP identification as a potential soluble immune checkpoint. **B.** scRNA analyses of tumor-infiltrating myeloid cells, across indications show that IL-18BP is up-regulated in myeloid population in the TME compared to the periphery (PBMCs).

COM503- high affinity anti-IL18BP blocker Ab restores human T and NK cell activity



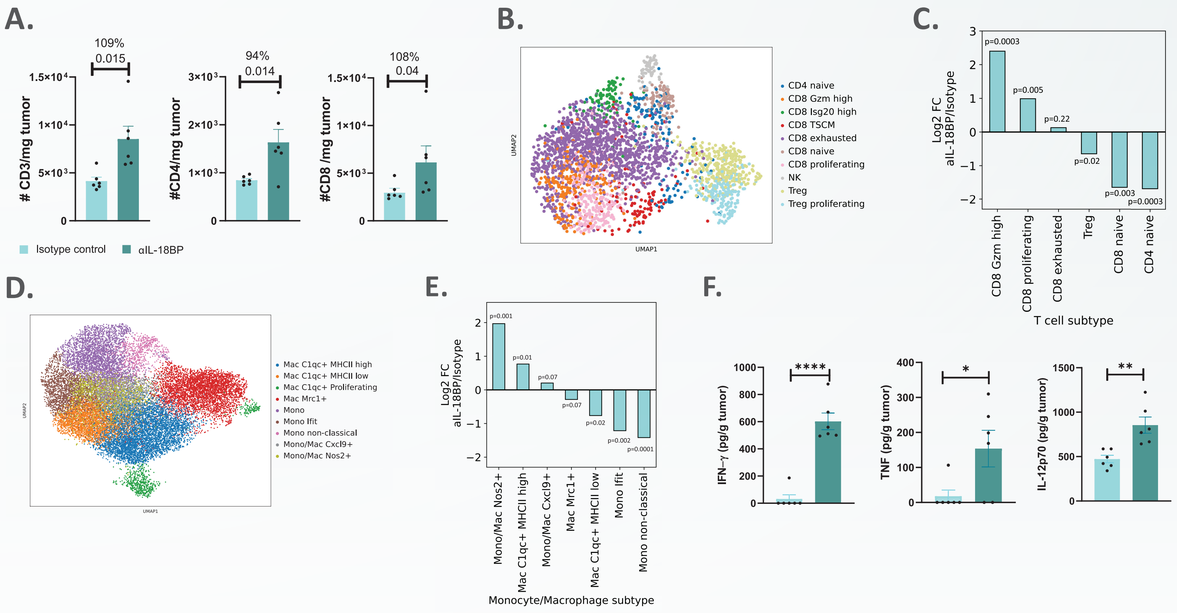
A. COM503 displaced pre-complexed IL-18-IL-18BP to increase IFNg and TNFa release by stimulated human CD8+ TILs in CD8 + TILs- tumor cells co-culture assay in the presence of rIL-18BP and rIL-18. **B.** COM503 displaced pre-complexed IL-18-IL-18BP to increase IFNg release by NK cells in the presence of IL-12. **C.** COM503 increased TNFa, IFNg, 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



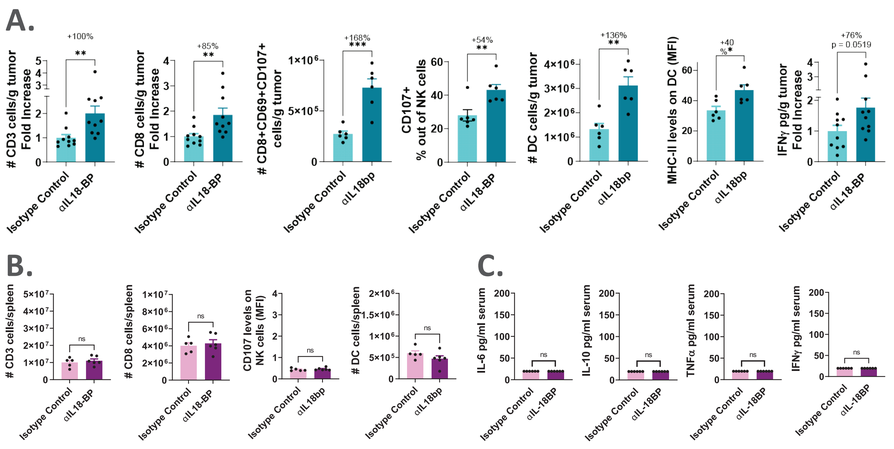
A-C. Anti-mouse IL-18BP Ab inhibited tumor growth in B16F10-hmgp100 mouse melanoma tumor model (A), MC38OVA^{dim} mouse CRC tumor model (B), and led to tumor regression in E0771 orthotopic mouse breast tumor model (C). Tumor volumes are represented as the mean volume + SEM. Treatment initiated at tumor volume of 120mm^3 and 270mm^3 for MC38OVA^{dim} and E0771 respectively, and on day 4 for B16gp100, 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 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 modulates 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 inhibited 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, released IL-18 to activate T and NK cells. • IND expected in 2024