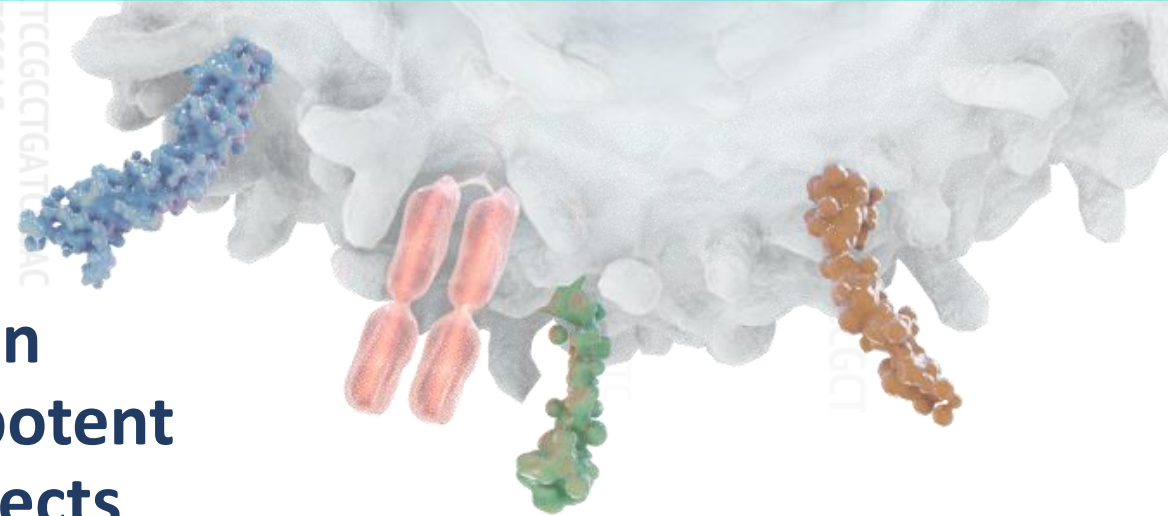




FROM CODE TO CURE®

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

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Preclinical Development, Compugen




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Disclosure

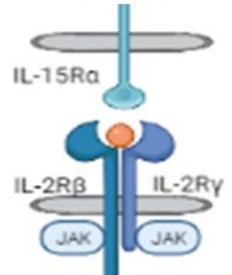
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Cytokines: powerful tools with challenging therapeutic window



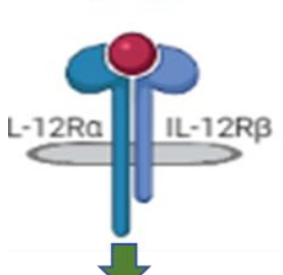
The diagram shows the IL-2 signaling pathway. At the top, a red label 'IL-2' is positioned above a blue receptor complex. The receptor consists of two extracellular domains and a transmembrane domain. Below the transmembrane domain, two JAK proteins are associated. A green arrow points downwards from the JAKs to the label 'STAT5'.

- Short half life
- Pleiotropy
- Vascular leak syndrome
- Cardiotoxicity



The diagram shows the IL-15 signaling pathway. At the top, a red label 'IL-15' is positioned above a blue receptor complex. The receptor consists of an IL-15R α subunit and a heterodimer of IL-2R β and IL-2R γ subunits. Two JAK proteins are associated with the IL-2R β subunit. A green arrow points downwards from the JAKs to the label 'STAT5'.

- Short half life

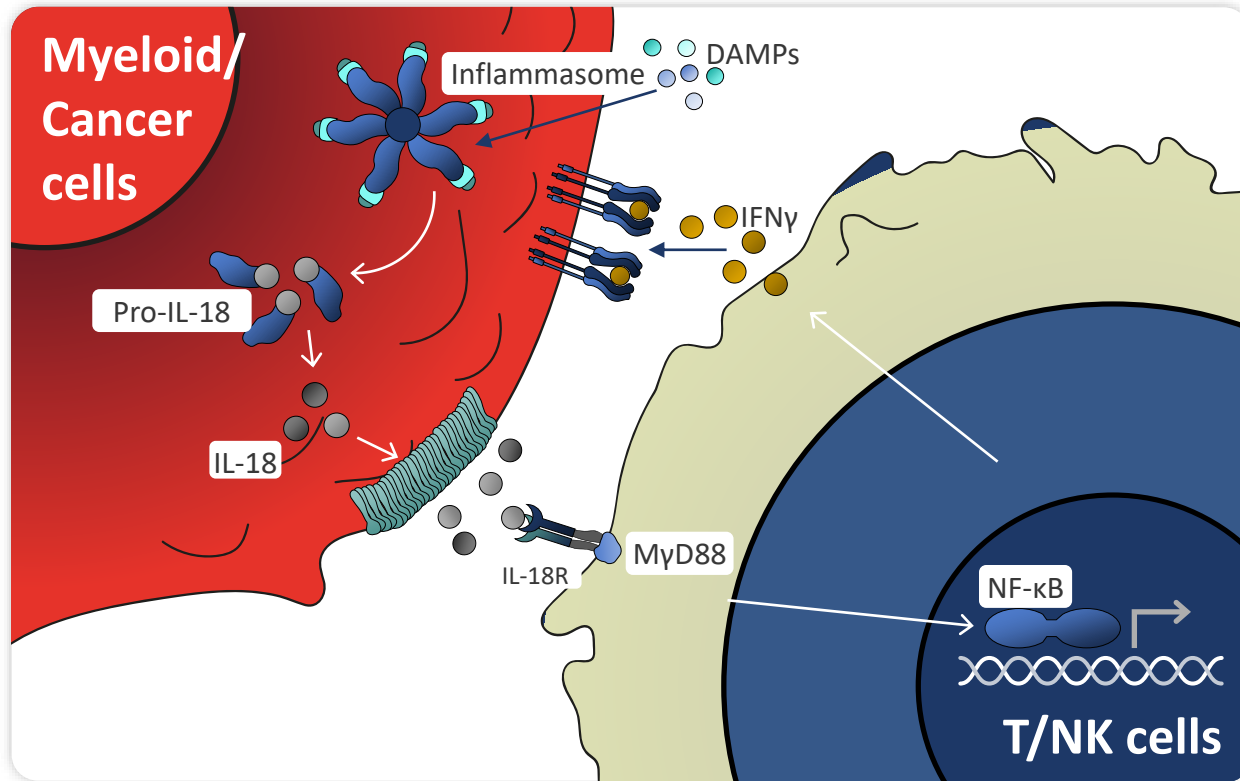


The diagram shows the IL-12 signaling pathway. At the top, a red label 'IL-12' is positioned above a blue receptor complex. The receptor consists of an L-12R α subunit and an IL-12R β subunit. A green arrow points downwards from the receptor to the label 'STAT4'.

- Short half-life
- Systemic inflammation
- Myelotoxicity
- Hepatotoxicity

Pleiotropy, toxicity, short half-life severely limit the therapeutic use of cytokines

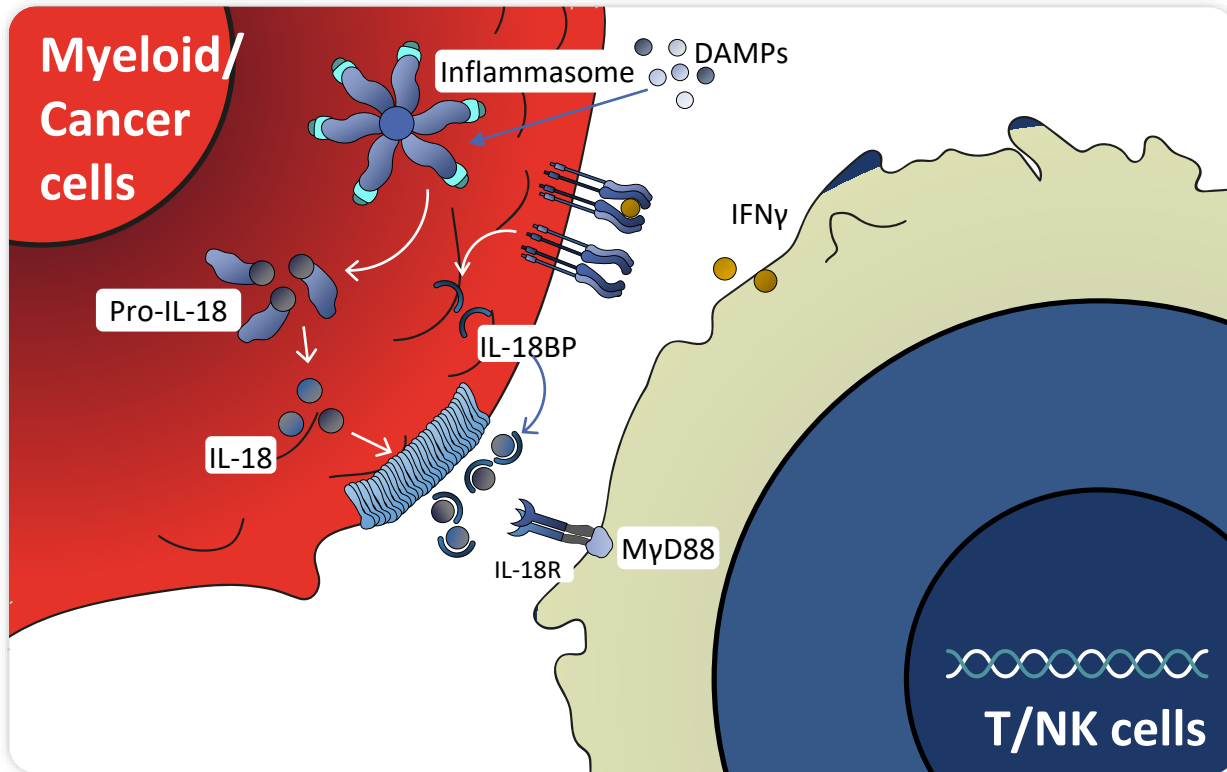
IL-18 stimulates both innate & adaptive immune system



IL-18 is:

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

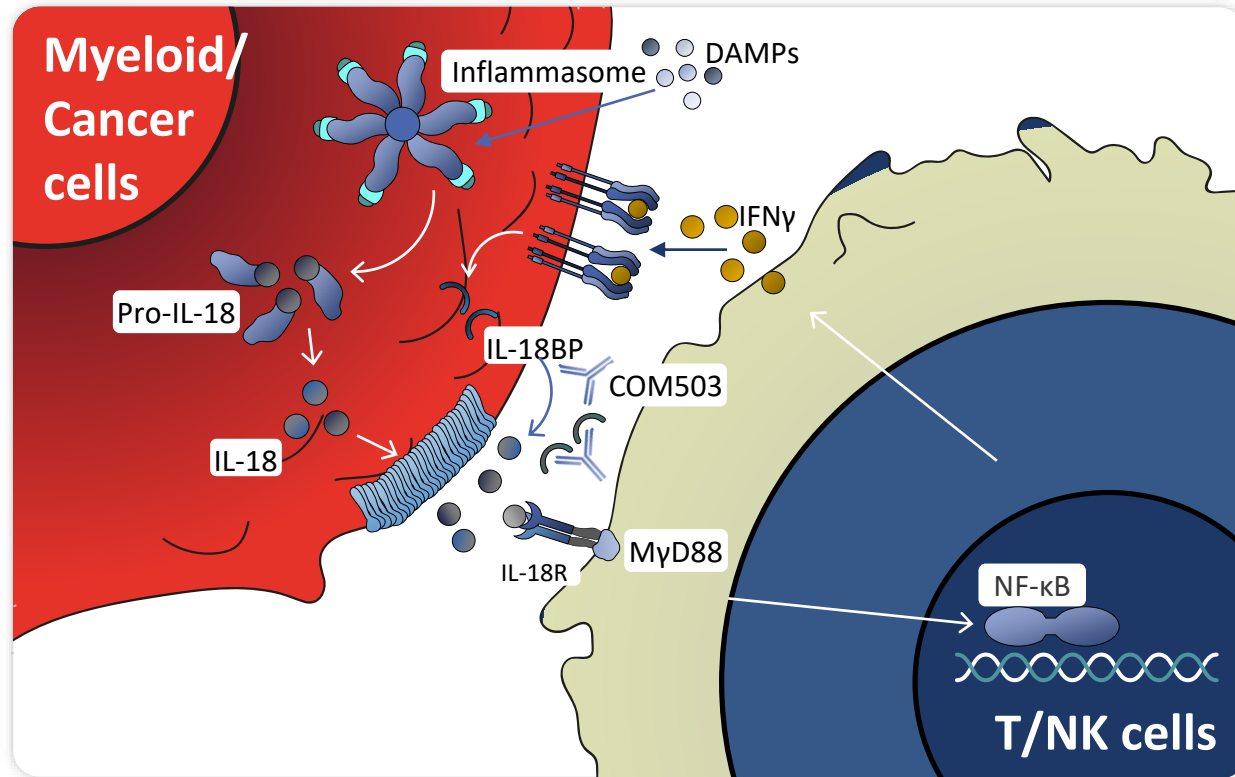
IL-18 binding protein is a natural inhibitor of IL-18



IL-18 binding protein (BP):

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

COM503, a potential first-in-class anti-IL-18BP blocker antibody that unleashes endogenous IL-18 in the TME

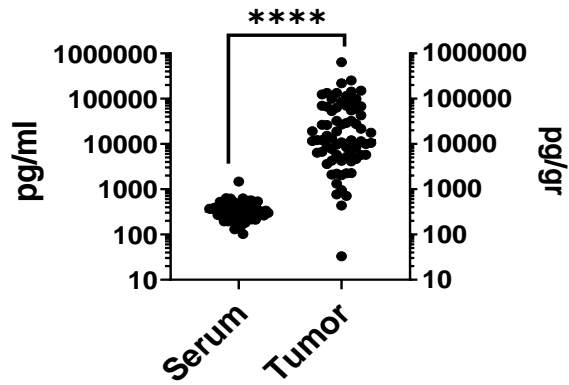


COM503:

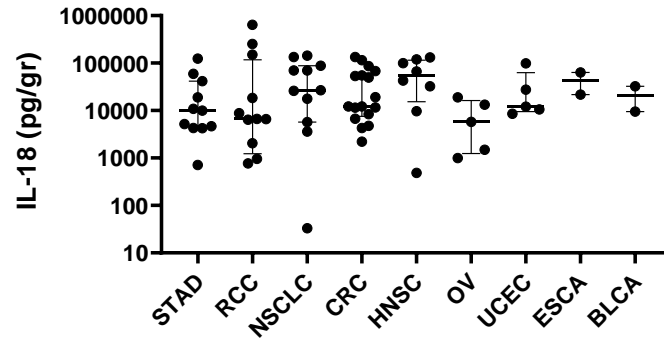
Has the potential to induce potent anti-tumor responses and pronounced TME-localized immune modulation

IL-18 pathway is elevated in human TME across indications

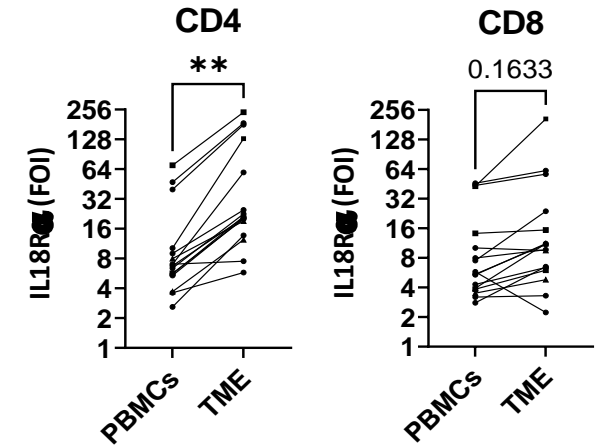
IL-18 levels are elevated in the TME compared to levels in the serum



IL-18 is expressed in the TME across indications



IL-18R α is induced on TILs in the TME

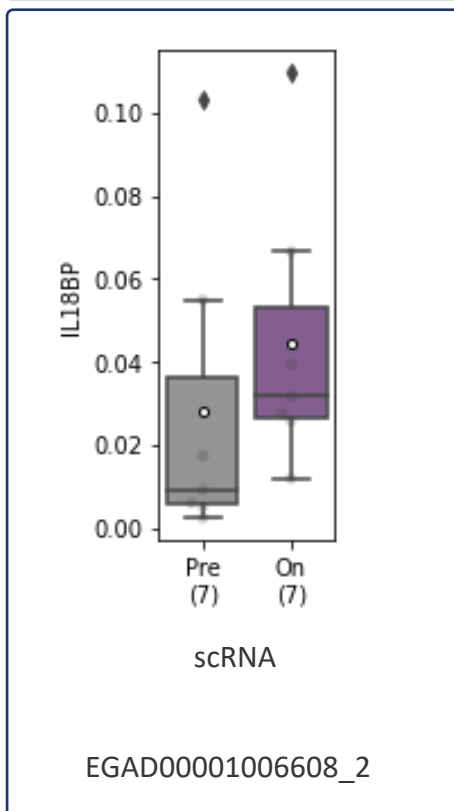


Compugen identified IL-18BP while querying for TAM negative feedback immunosuppression mechanism

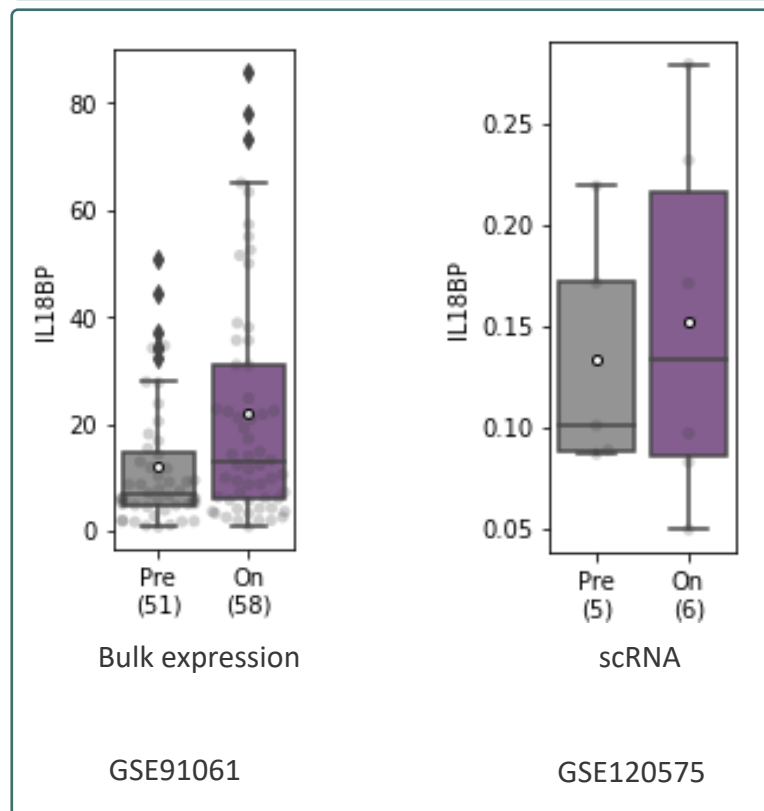


IL-18BP is upregulated following immune checkpoint blockers treatment

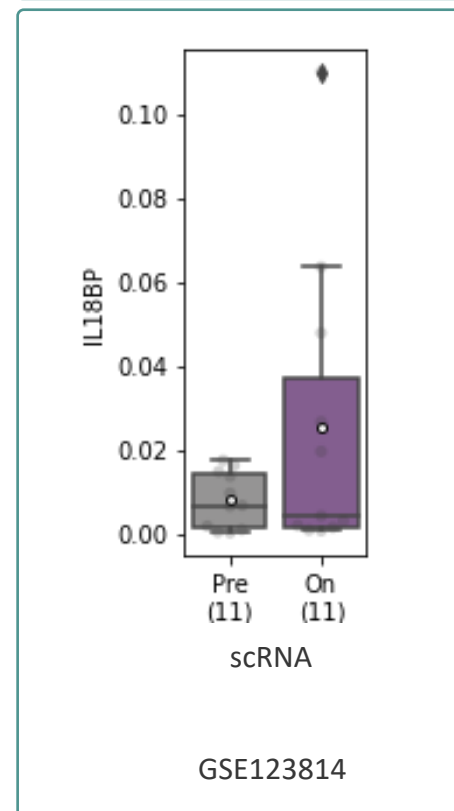
Breast cancer (anti-PD-1)



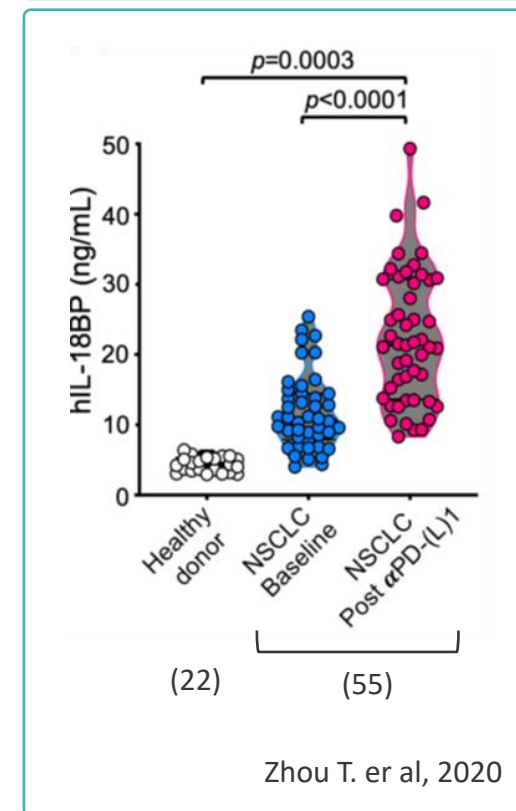
Melanoma (anti-CTLA-4 & anti-PD-1)



Basal cell carcinoma (anti-PD-1)



NSCLC (anti-PD-(L)1)



The concept of anti-IL18BP antibody

1

IL-18 is naturally present in human tumors at high levels sufficient to stimulate T cells

2

High levels of IL-18BP in the tumors block its IL-18 anti-tumor activity

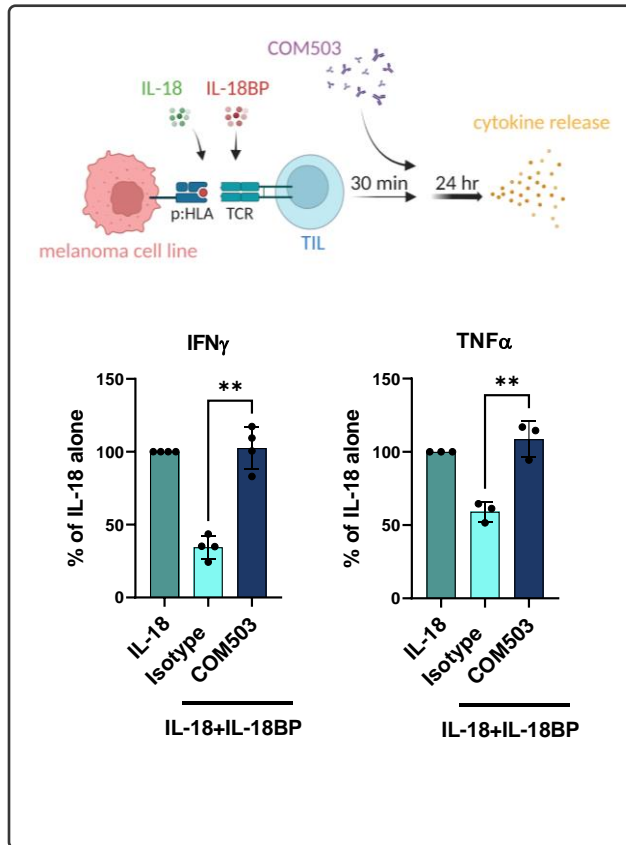
3

IL-18 endogenous levels in blood are low, and the IL-18 receptor is induced in the tumor

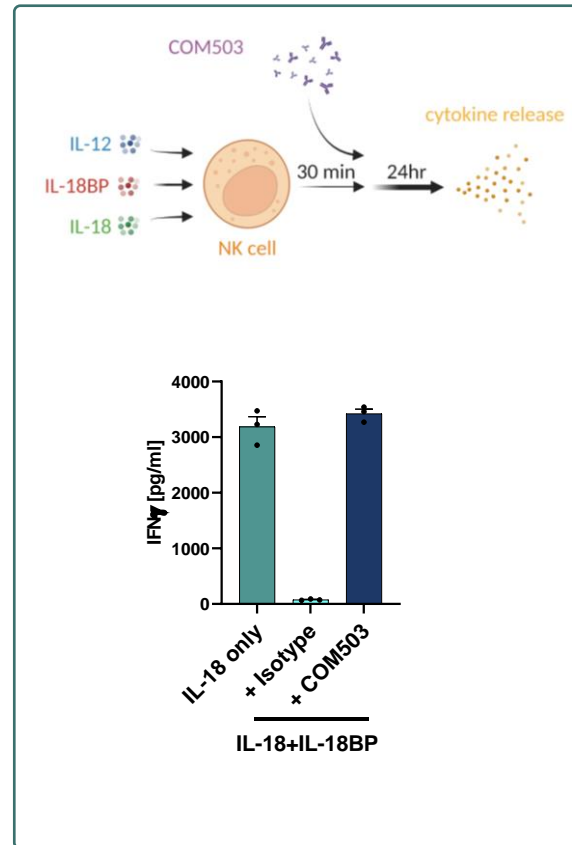
Blocking IL-18BP should unleash IL-18 activity to increase the immune stimulation predominantly in the tumor and not in blood

Compugen developed COM503, a fully human, high affinity anti-IL18BP antibody that restores human TIL and NK cell activity

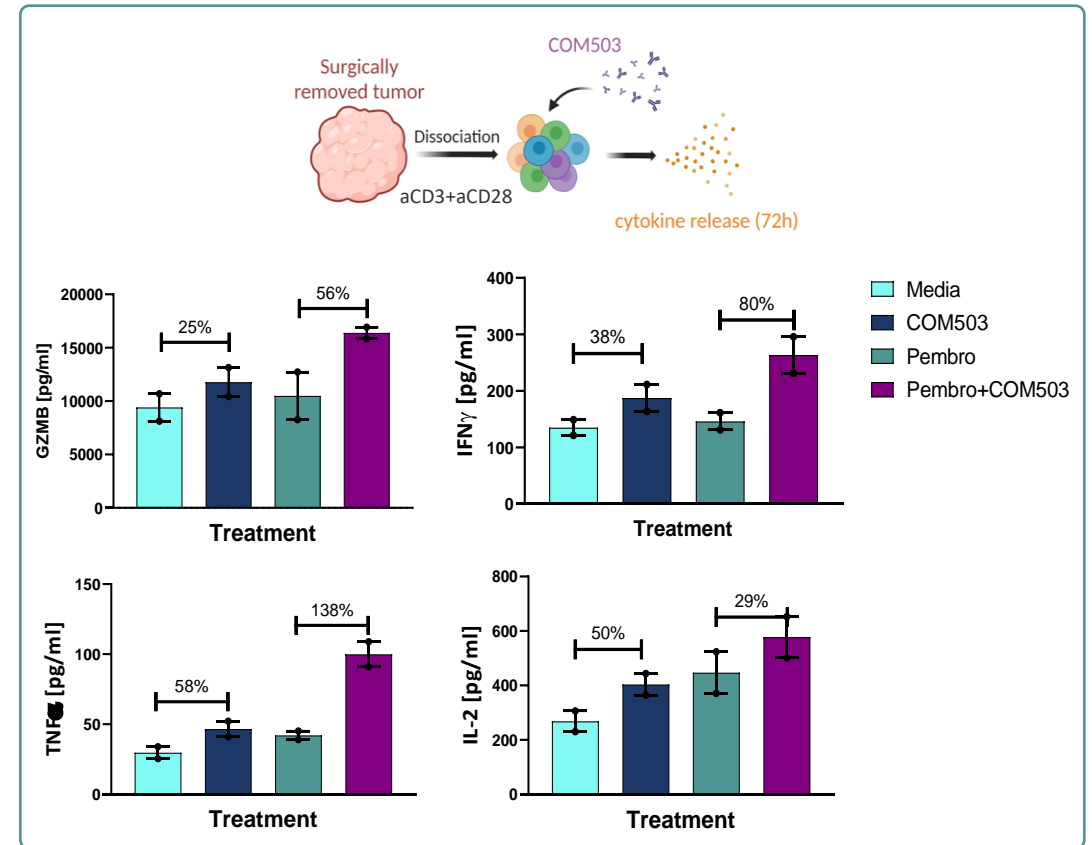
COM503 restored TILs activity



COM503 restored NK cell activity

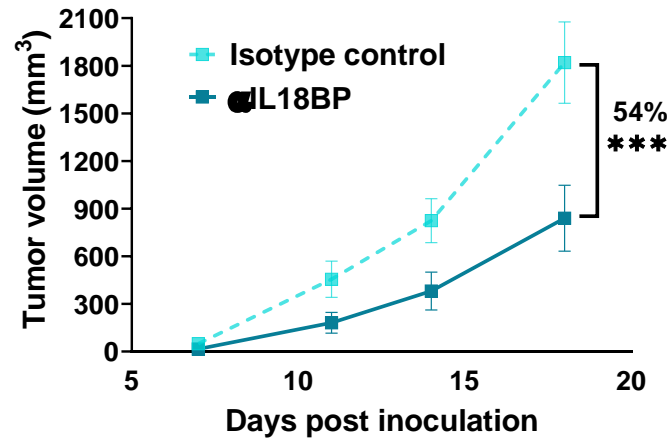


COM503 enhanced T-cell activation in human dissociated tumor cells assay

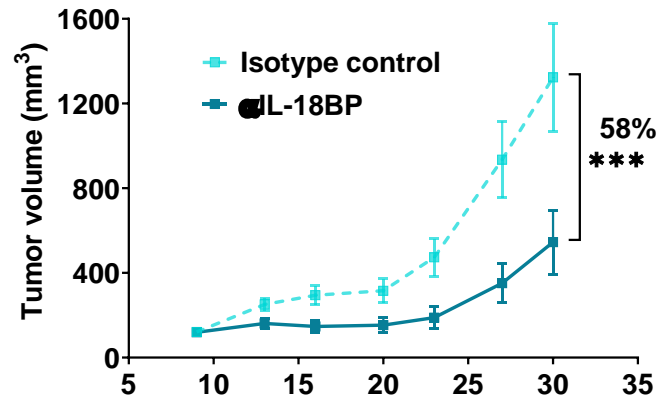


Anti-IL-18BP surrogate antibody demonstrates monotherapy activity across murine syngeneic tumor models

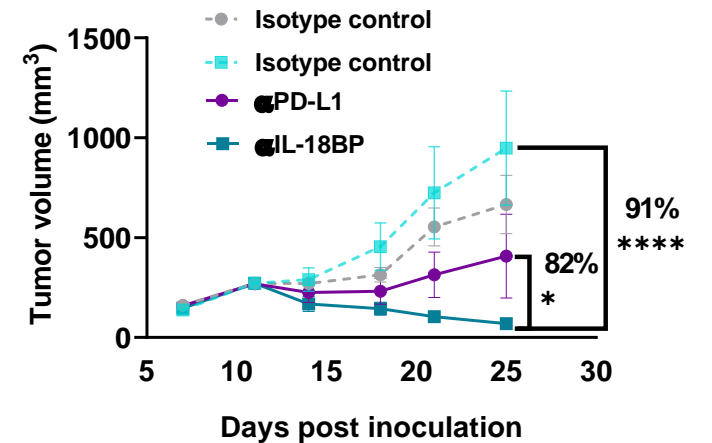
α IL-18BP Ab inhibited tumor growth in B16F10-hmgp100 mouse melanoma model



α IL-18BP Ab inhibited tumor growth in MC38OVA^{dim} mouse CRC tumor model

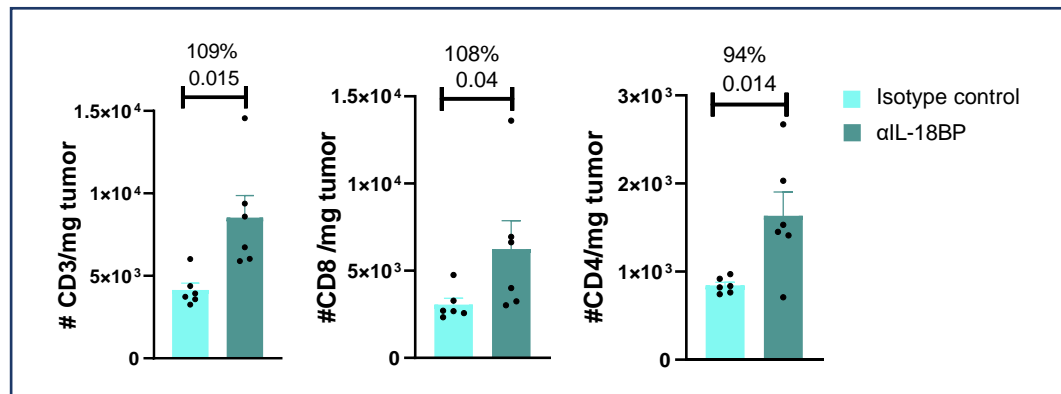


α IL-18BP Ab inhibited tumor growth in E0771 orthotopic mouse breast tumor model

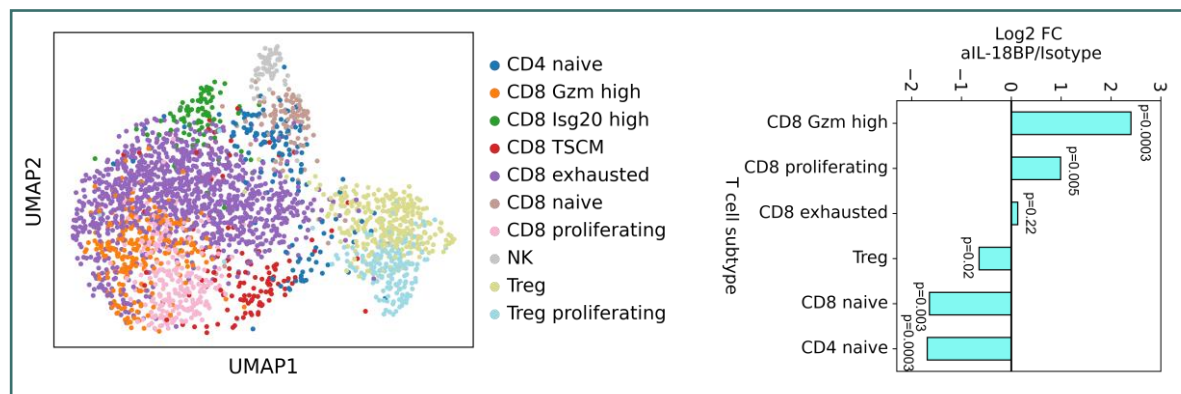


IL-18BP blockade induces a proinflammatory environment in the TME

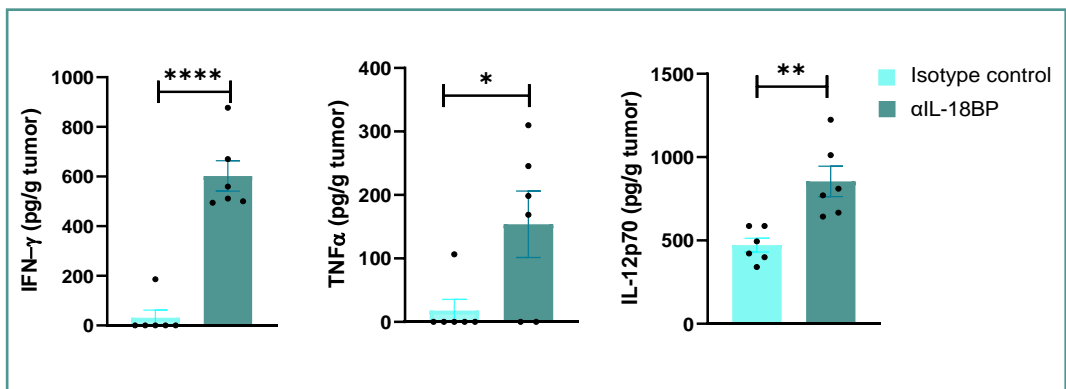
α IL-18BP Ab increased T cells numbers in the TME



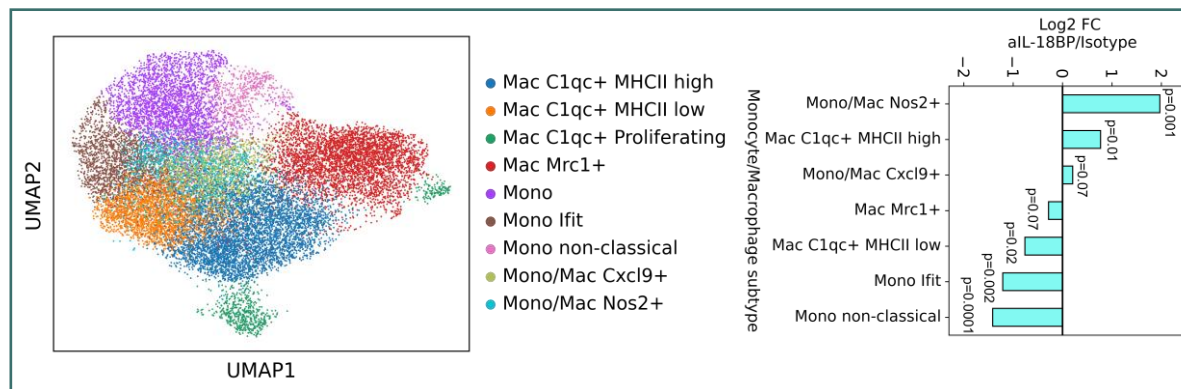
α IL-18BP Ab induced the expansion of polyfunctional non exhausted T cells in the TME



α IL-18BP Ab increased proinflammatory cytokine secretion in the TME

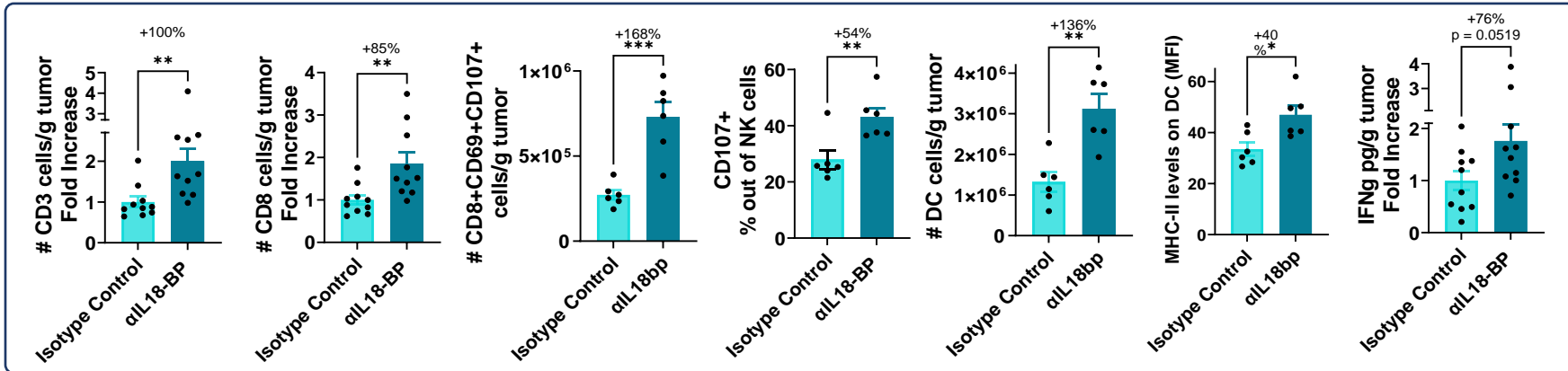


α IL-18BP Ab increased the expansion of proinflammatory macrophages in the TME

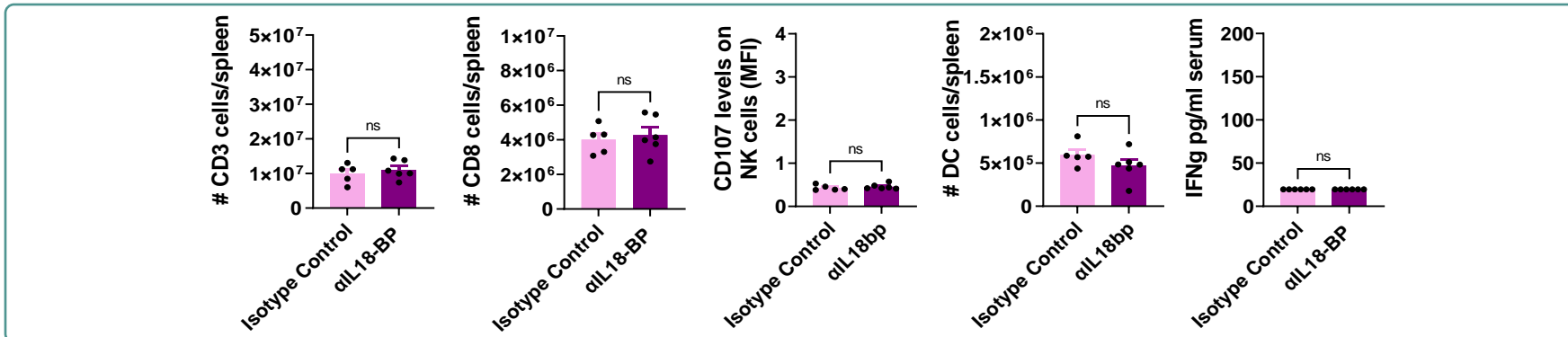


Anti-IL-18BP Ab modulates tumor microenvironment without affecting the periphery in murine tumor model

Monotherapy with anti-IL-18BP Ab immune-modulated TME



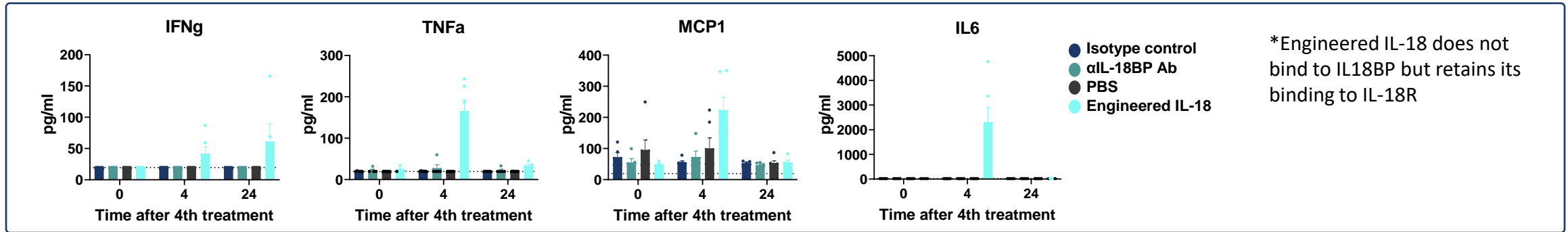
Monotherapy with anti-IL-18BP Ab did not modulate peripheral immunity



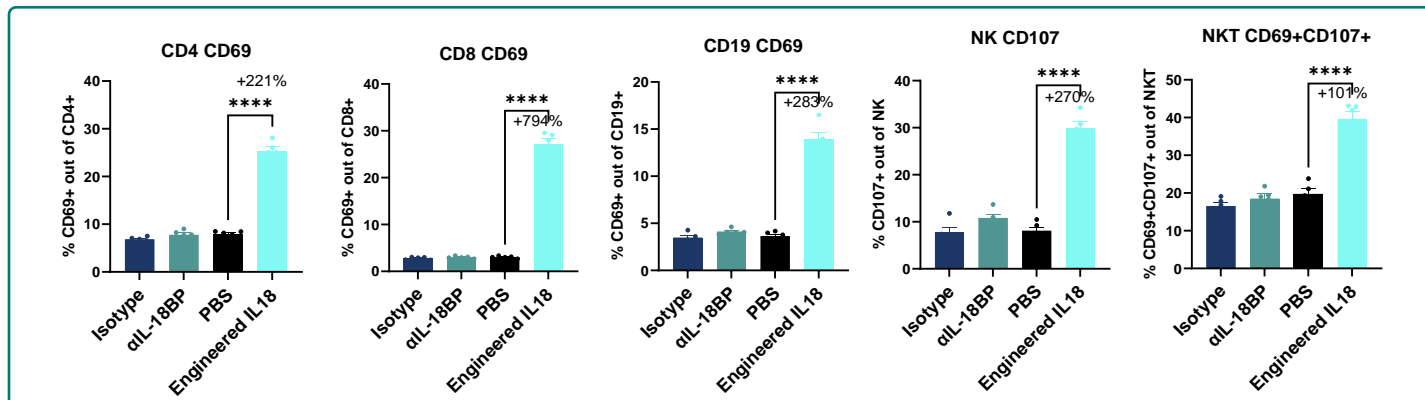
Immune modulation restricted to tumor site in contrast to therapeutic recombinant cytokines given systemically

Anti-IL18BP Ab is expected to have a better therapeutic window than recombinant cytokines

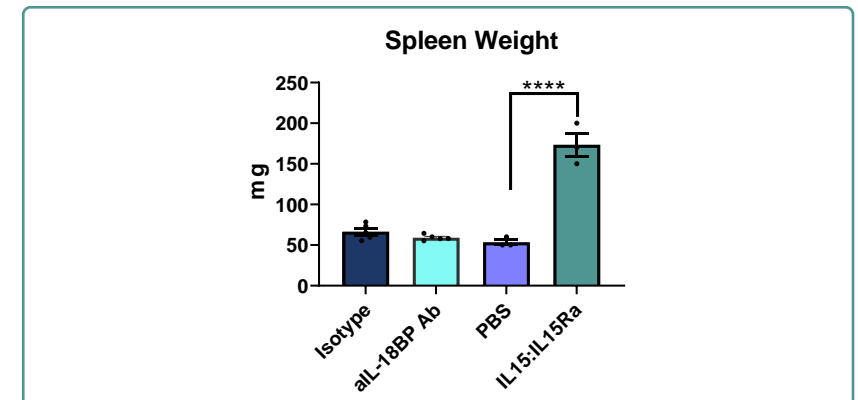
Administration of anti-mIL-18BP Ab to mice did not affect serum cytokines in contrast to engineered mouse IL-18*



Administration of anti-IL-18BP Ab to mice did not affect lymphocytes activation in contrast to engineered mouse IL-18



Administration anti-mIL-18BP Ab to mice did not result in splenomegaly in contrast to rIL-15:IL15Ra



Summary

- IL-18 is upregulated in the TME but is naturally blocked by IL-18BP
- Blocking IL-18BP in vivo inhibits tumor growth as monotherapy
- Immune modulation following treatment with anti-IL-18BP antibody is restricted to the TME suggesting favorable therapeutic window, in contrast to recombinant therapeutic cytokines given systemically
- COM503, human IgG4 high affinity anti-IL-18BP blocker antibody, unleashes IL-18 activating T & NK cells
- IND expected in 2024

Blocking IL-18BP is a novel approach to harness cytokine biology for cancer therapeutics



Thank you!

See our poster #2042

Acknowledgments:

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