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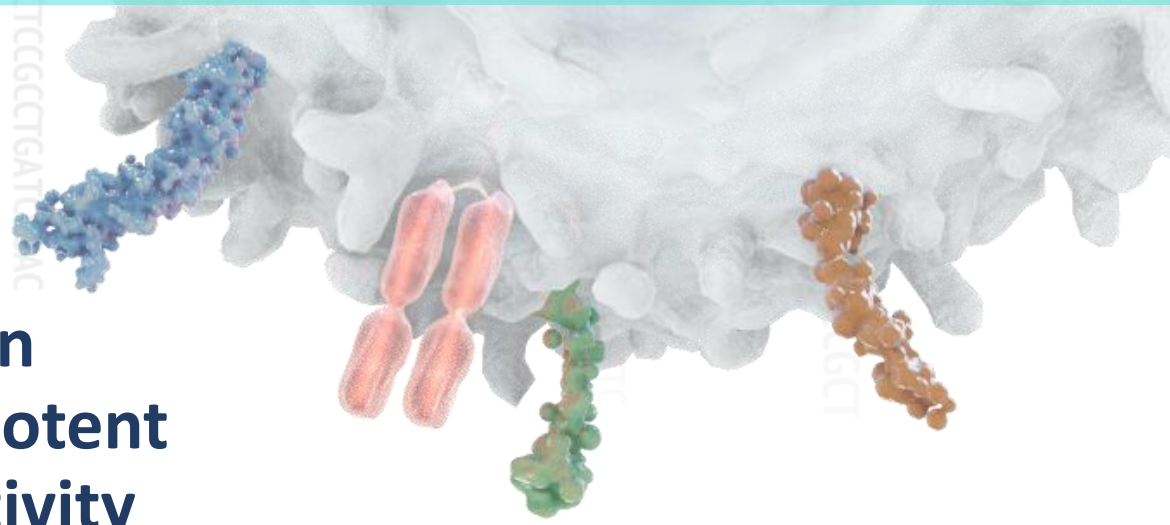

Unleashing natural IL-18 activity using an anti-IL-18BP blocker antibody induces potent immune stimulation and anti-tumor activity

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Pre-Clinical Development, Compugen

SITC 38th annual meeting, 3 Nov, 2023
Abstract 550

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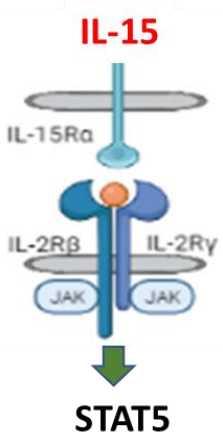
Employee of Compugen LTD.

Cytokines: powerful tools with challenging therapeutic window

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



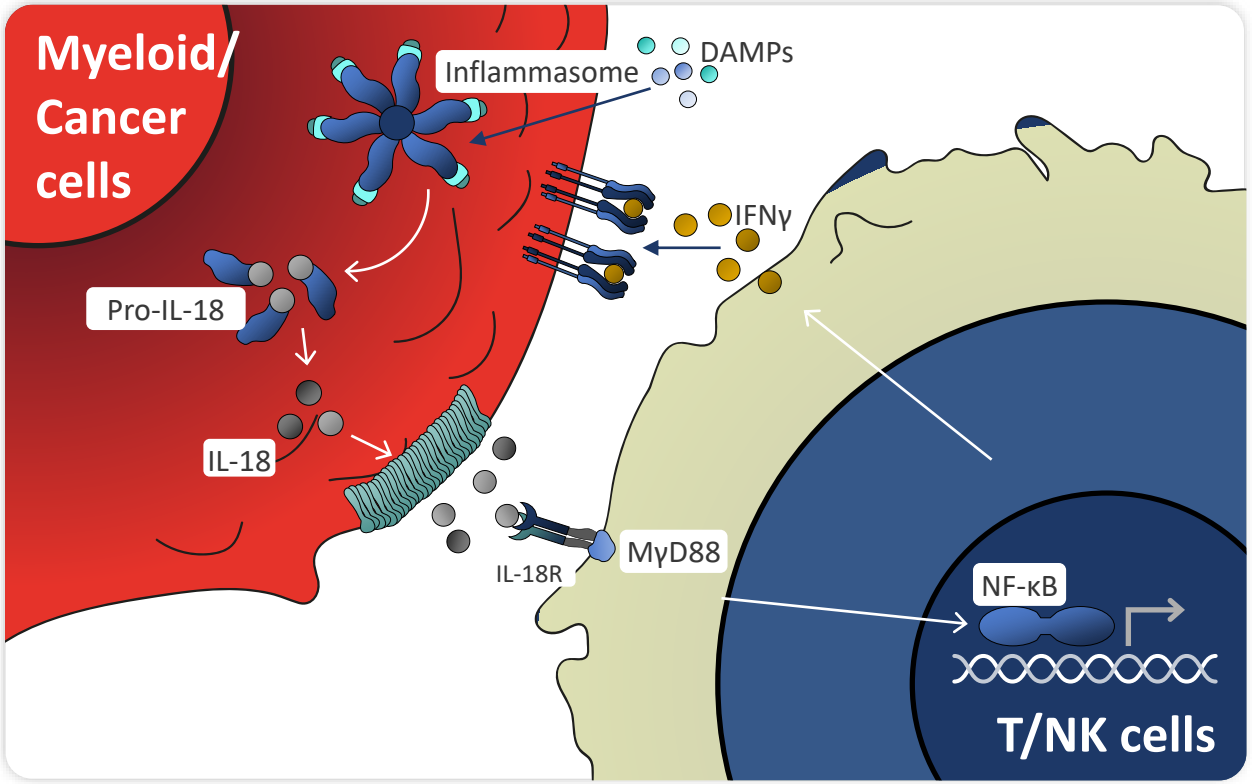
- Short half life

- Short half-life
- Systemic inflammation
- Myelotoxicity
- Hepatoxicity

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

Propper DJ. et al, 2022

IL-18 stimulates both innate & adaptive immune system

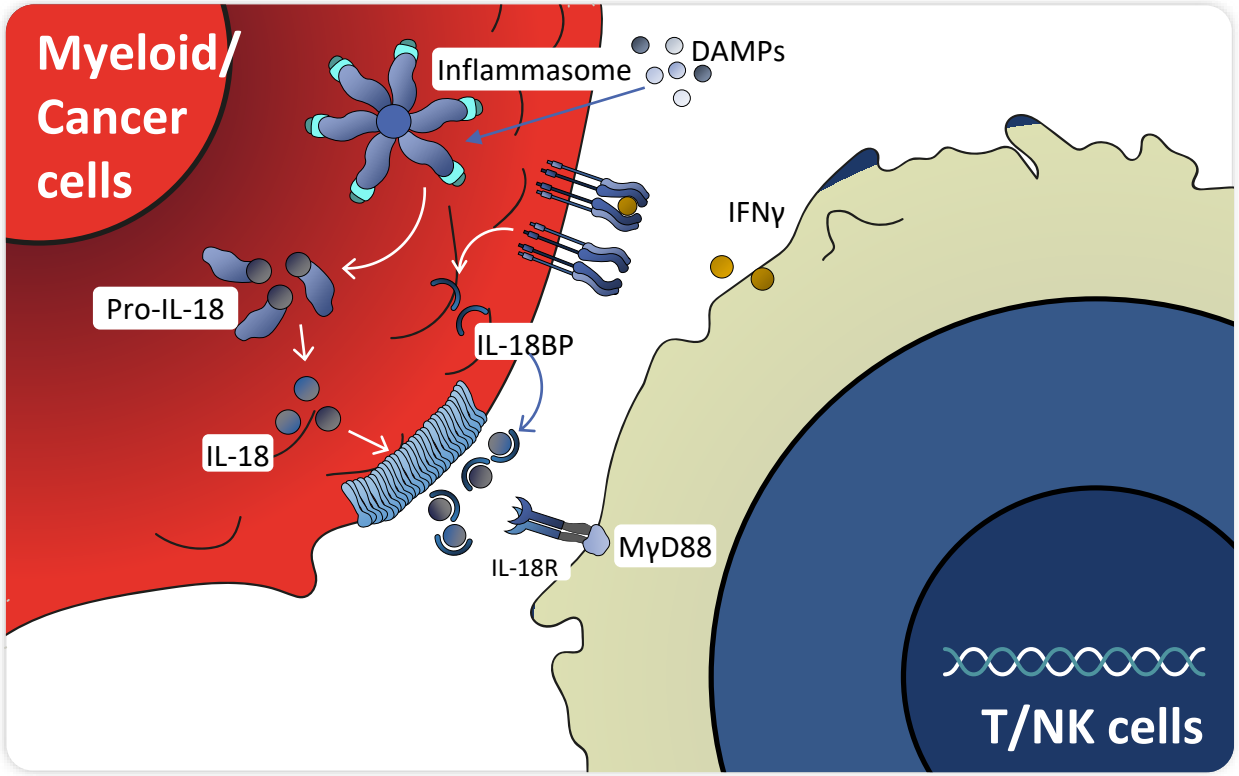


IL-18 is:

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

DAMPs- Damage-associated molecular patterns
TME- tumor microenvironment

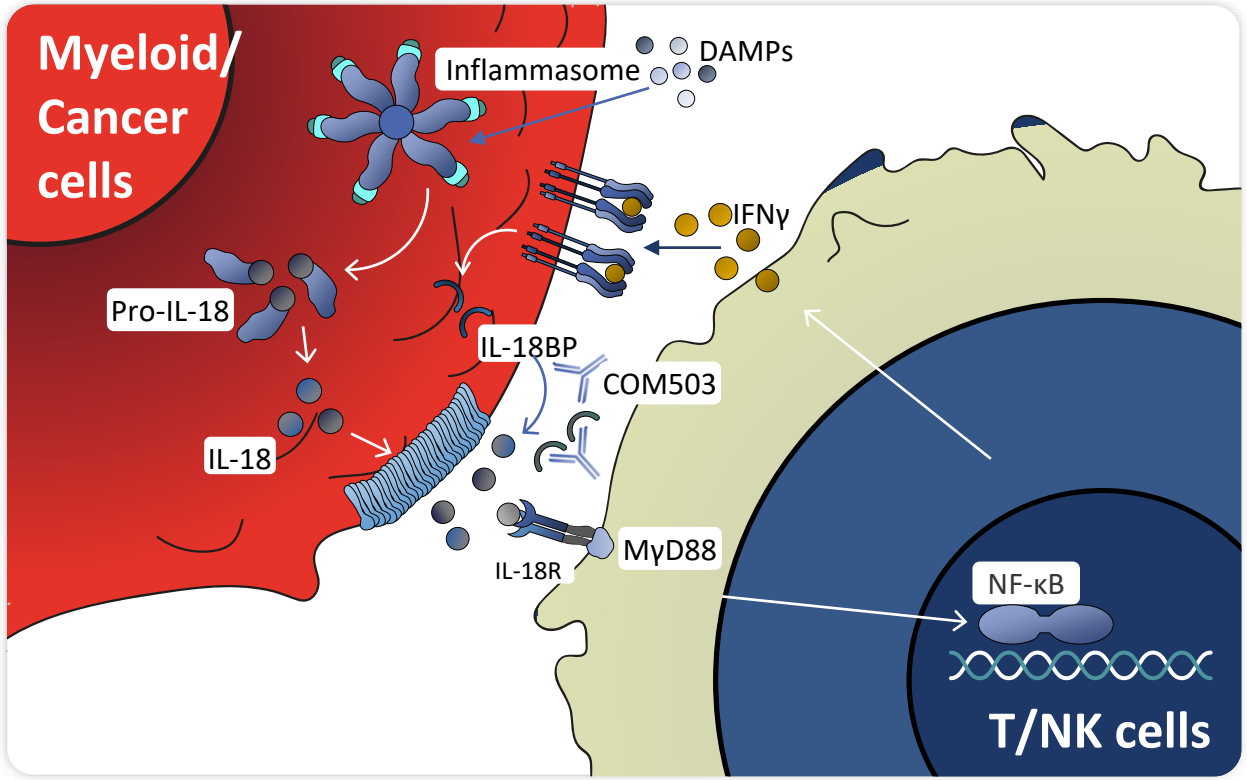
IL-18 binding protein is a natural inhibitor of IL-18



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

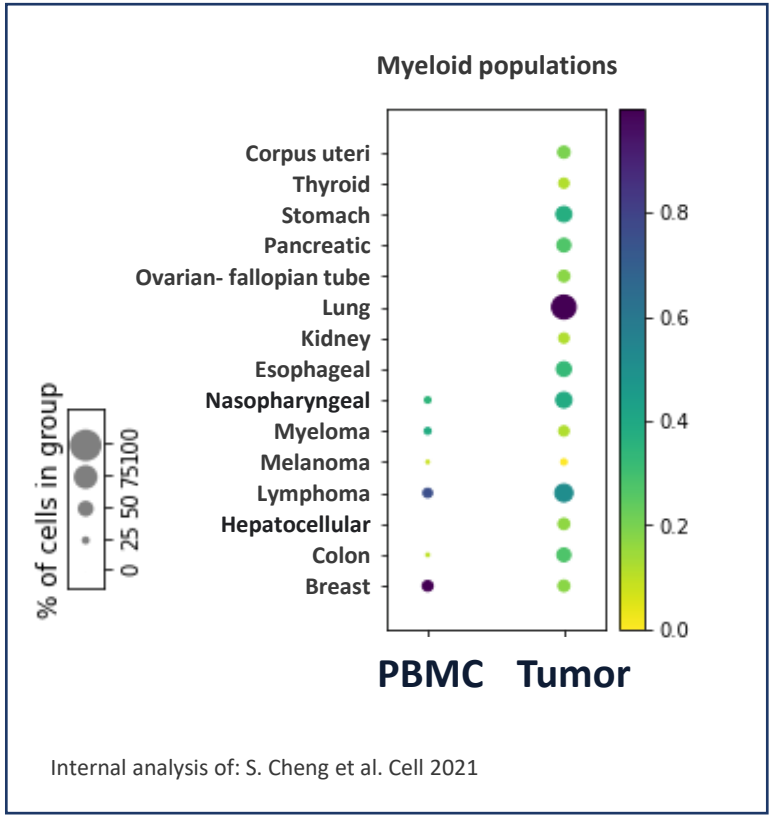


COM503:

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

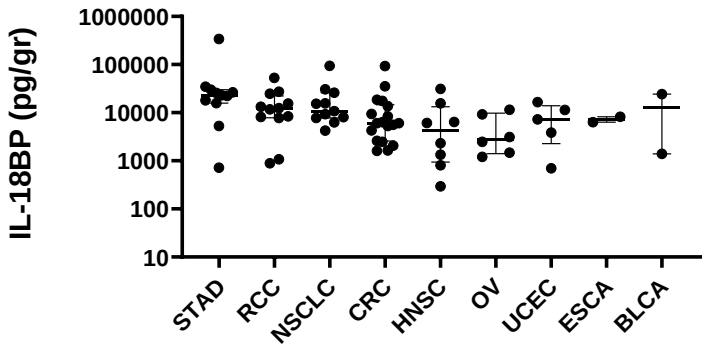
Compugen identified IL-18BP while querying for TAM negative feedback immunosuppression mechanism

IL-18BP is upregulated in myeloid populations in the TME across indications (scRNA data)



Internal analysis of: S. Cheng et al. Cell 2021

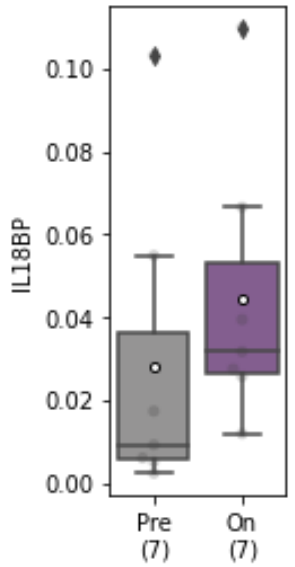
IL-18BP is expressed in the TME across indications (ELISA on tumor supernatants)



TAM- Tumor associated macrophage

IL-18BP is upregulated following immune checkpoint blockers treatment

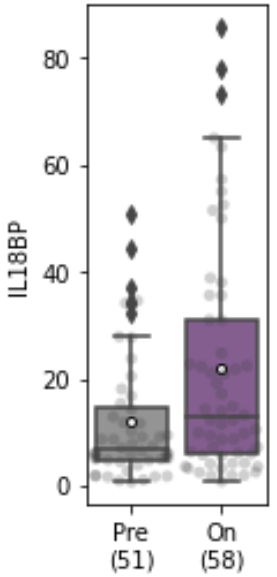
Breast cancer (anti-PD-1)



scRNA

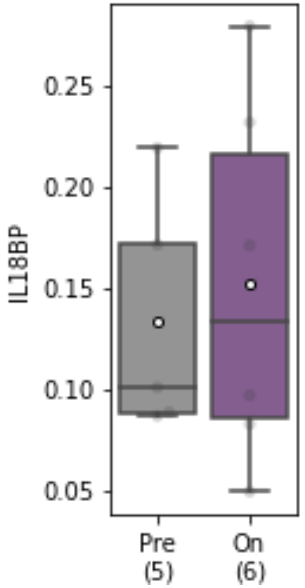
EGAD00001006608_2

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



Bulk expression

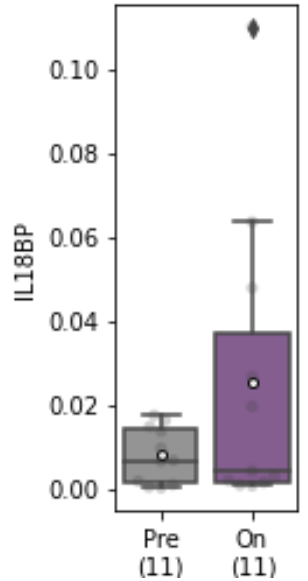
GSE91061



scRNA

GSE120575

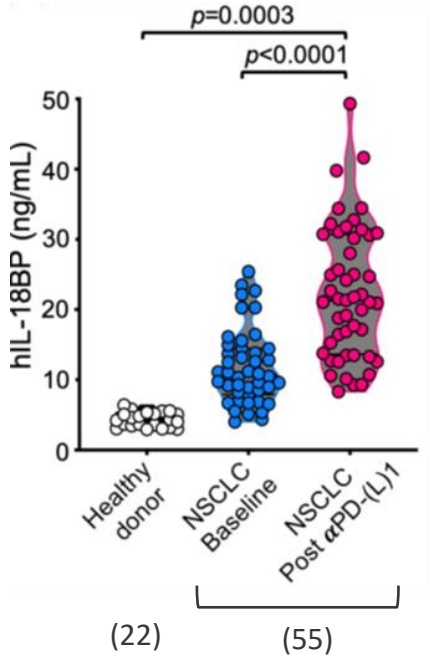
Basal cell carcinoma (anti-PD-1)



scRNA

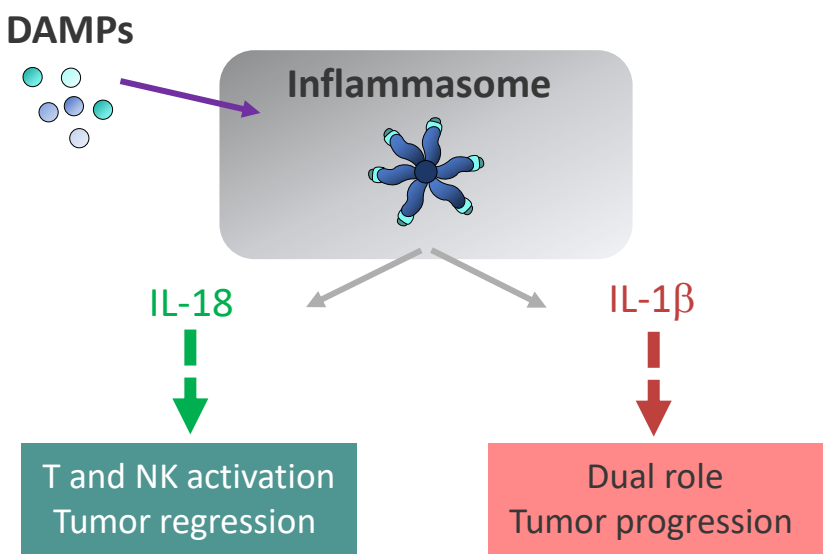
GSE123814

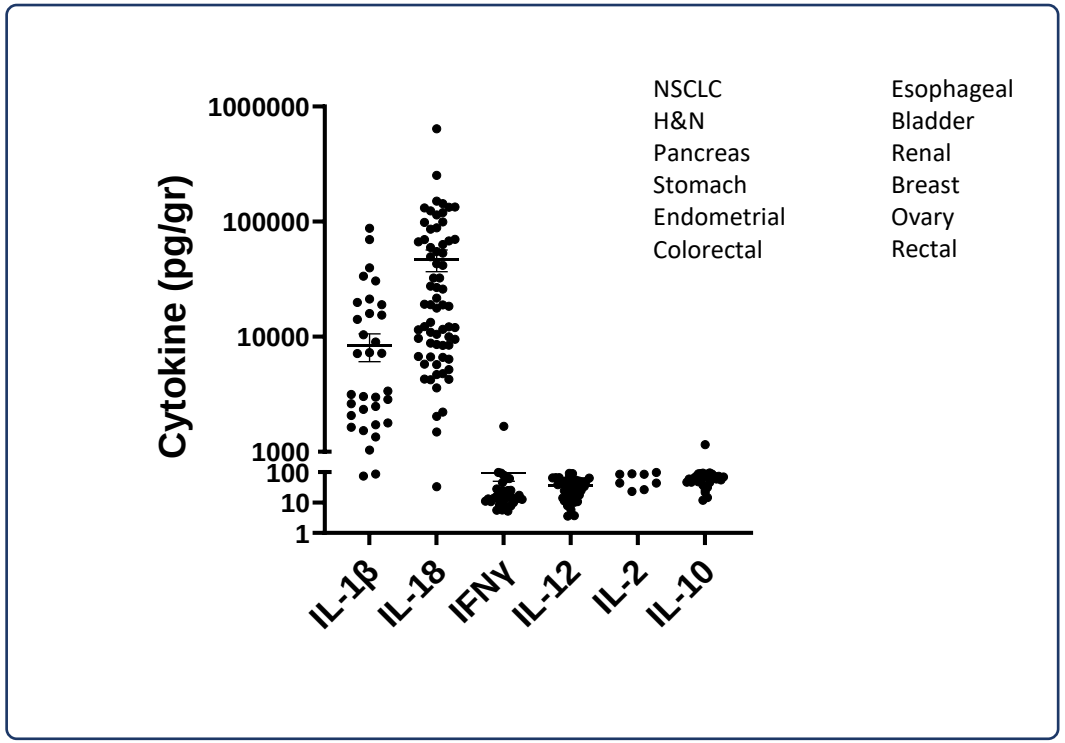
NSCLC (anti-PD-(L)1)



Zhou T. er al, 2020

Unlike other cytokines, inflammasome induced cytokines such as IL-18 and IL-1β are abundant in the TME

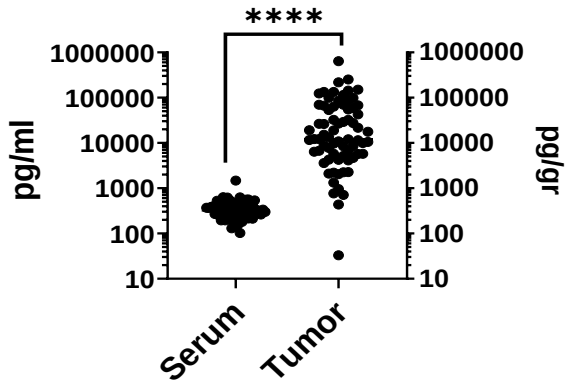




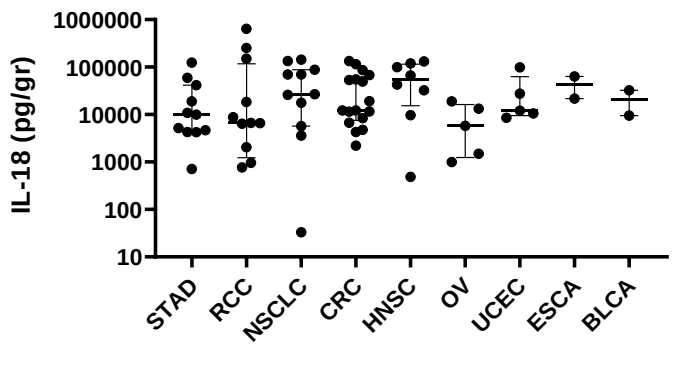
IL-18 is naturally blocked by endogenous IL-18 binding protein

IL-18 pathway is elevated in the TME across indications

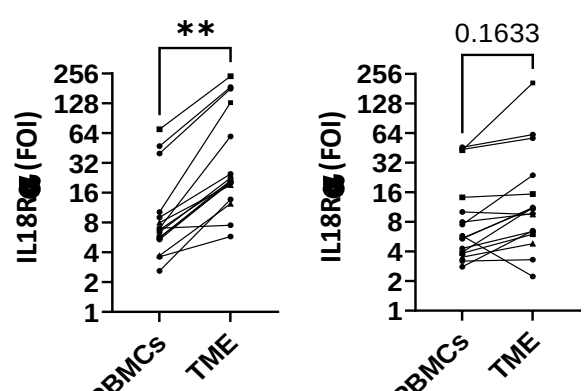
IL-18 levels are elevated in the TME compared to levels in the serum



IL-18 is expressed in the TME across indications



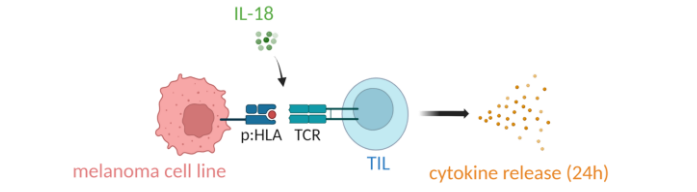
IL-18Rα is induced on TILs in the TME

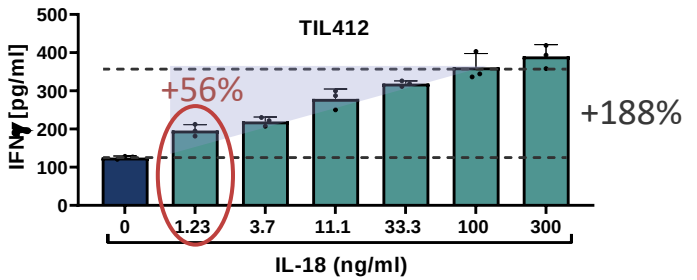


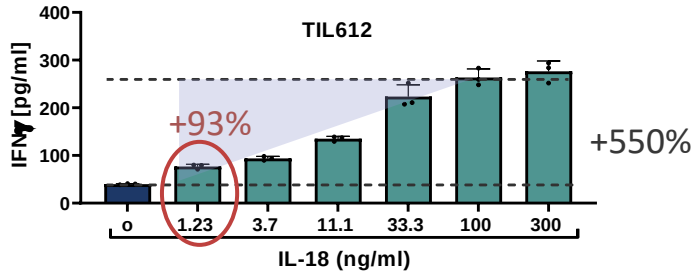
TILs- Tumor infiltrating lymphocytes

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

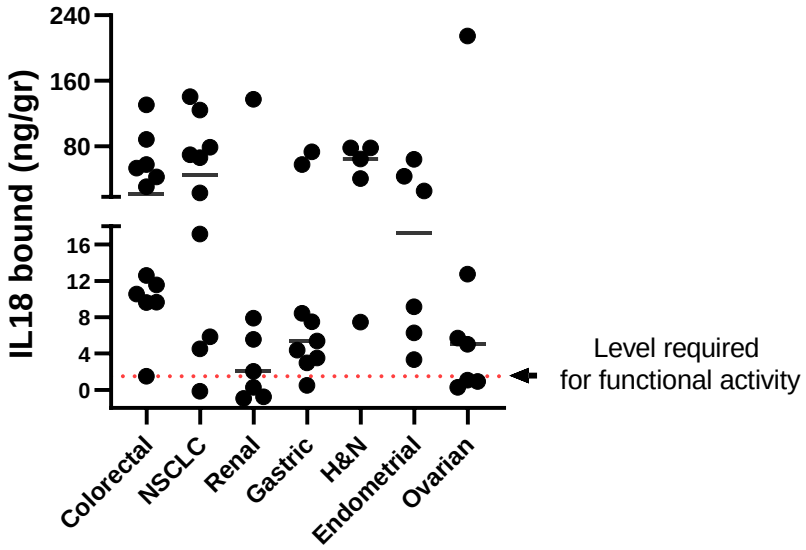
IL-18 activates TILs at concentrations from ~1ng/ml







In most tumors IL-18BP-bound IL-18 level is above ~1ng/ml



IL18 bound= estimated from IL18 total minus IL18 free (measured in 2 ELISA kits)

Total IL18 levels were measured using MBL ELISA kit (R&D #.7620)
Free IL18 levels were measure by in house established ELISA assay

The concept of anti-IL18BP antibody

1. IL-18 is naturally present in human tumors at levels sufficient to stimulate T and NK cells

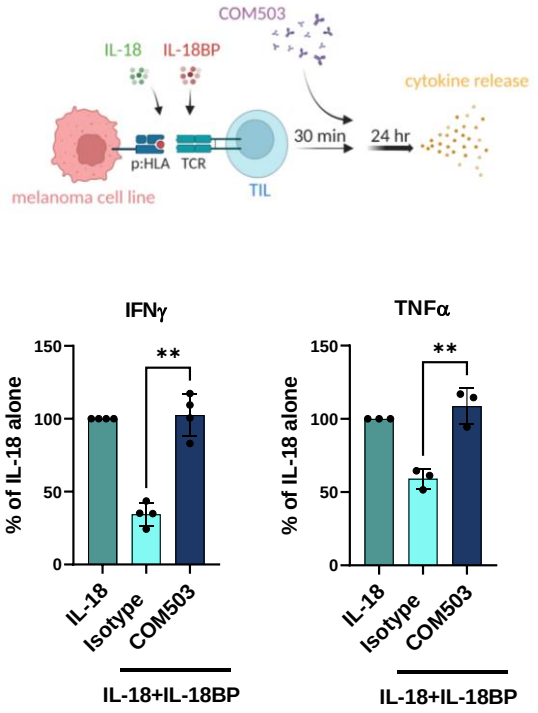
2. High levels of IL-18BP in the tumors block its IL-18 anti-tumor activity

3. IL-18 endogenous levels in blood are low, and the IL18 receptor is induced in the tumor

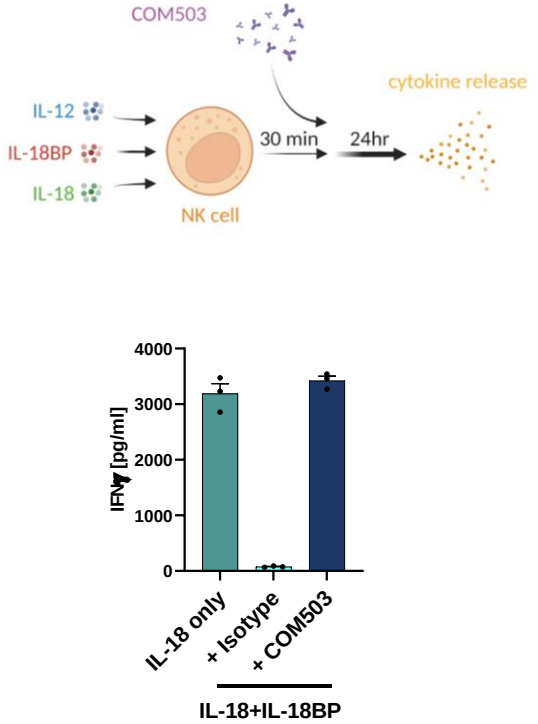
Blocking IL-18BP should unleash IL-18 activity
to increase the immune stimulation predominantly in the tumor and not in blood

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

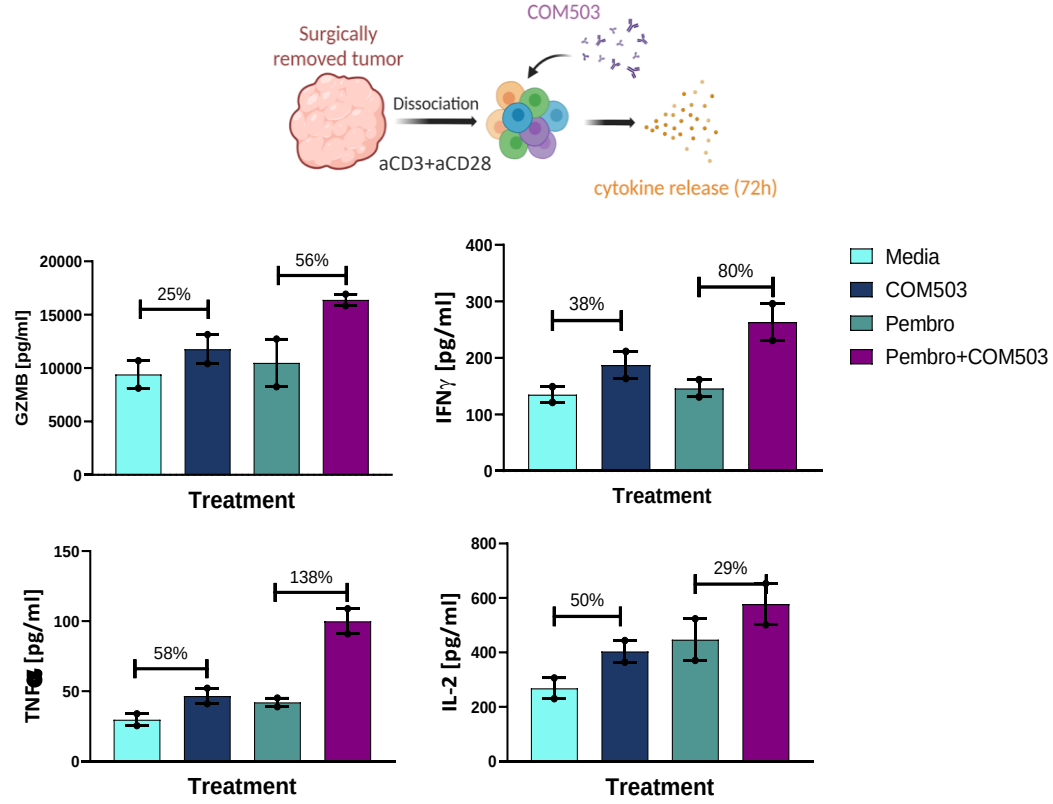
COM503 restored TILs activity



COM503 restored NK cell activity



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



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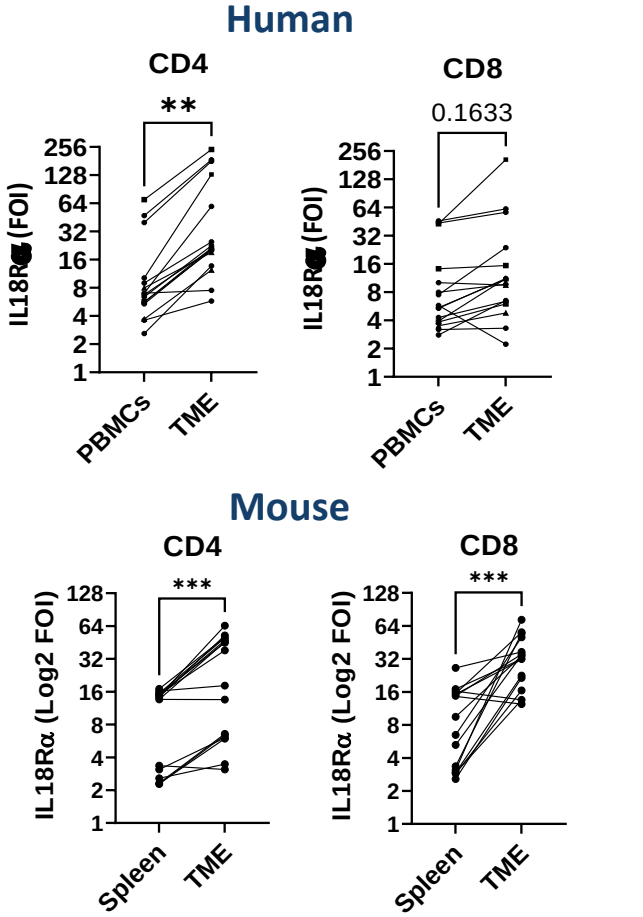
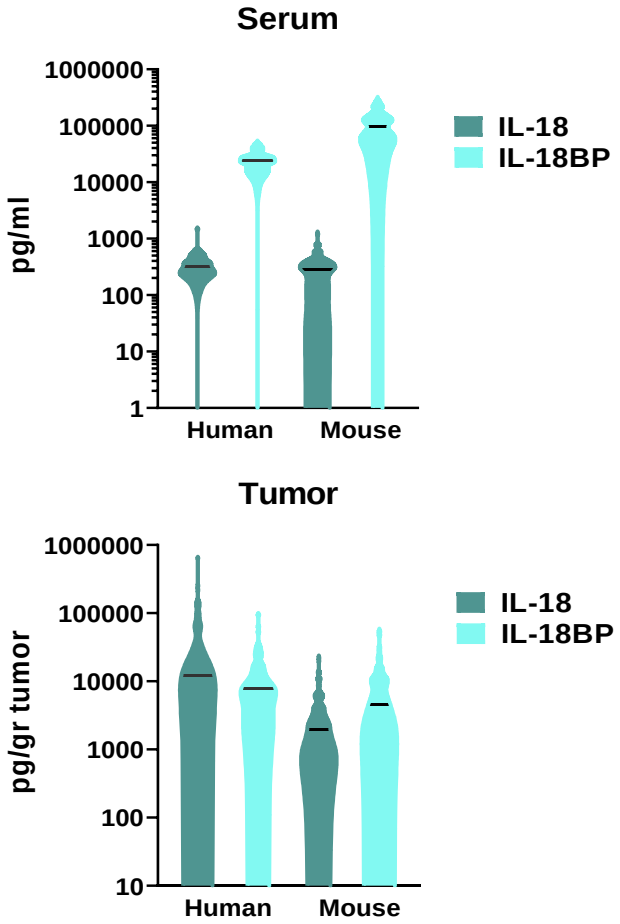
Mouse and human IL-18 pathway share similar biological properties

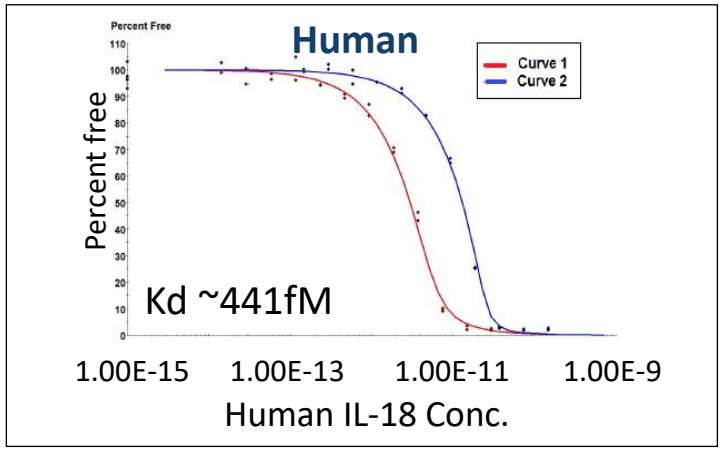
Mouse IL-18Rα is expressed and induced on T cells in mouse TME

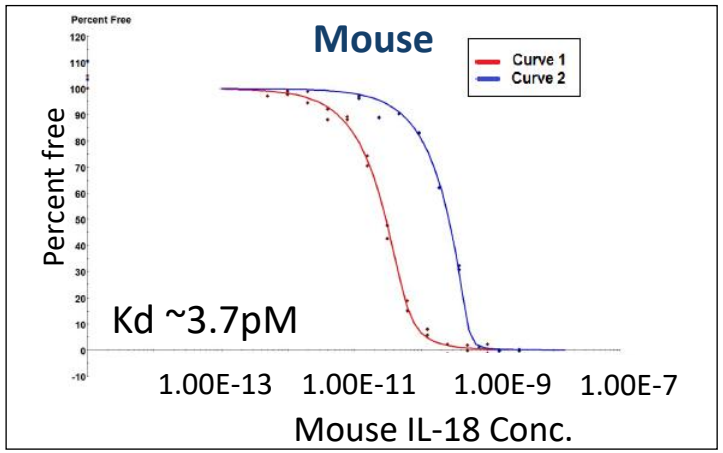


Similar pattern expression of IL-18 and IL-18BP in serum and TME



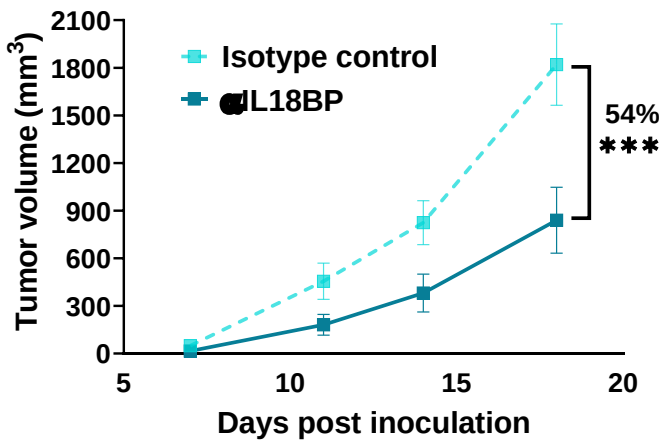
High-affinity interaction between IL-18:IL-18BP



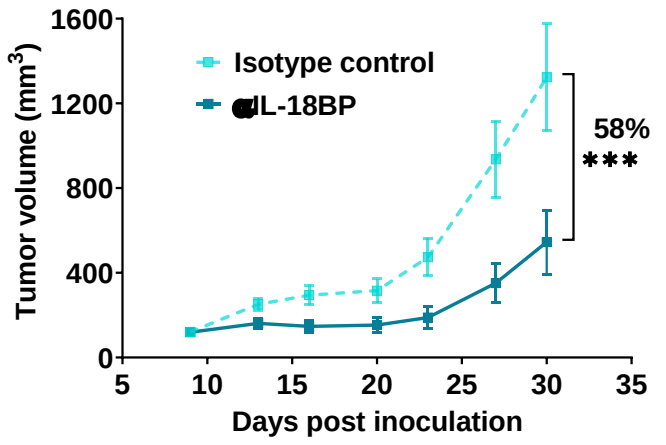


Anti-IL-18BP surrogate Ab demonstrates monotherapy activity across murine syngeneic tumor models

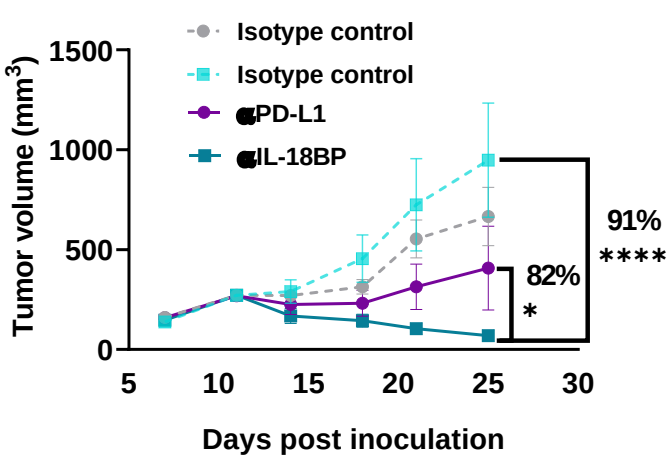
αIL-18BP Ab inhibited tumor growth in B16F10-hmgp100 mouse melanoma model



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

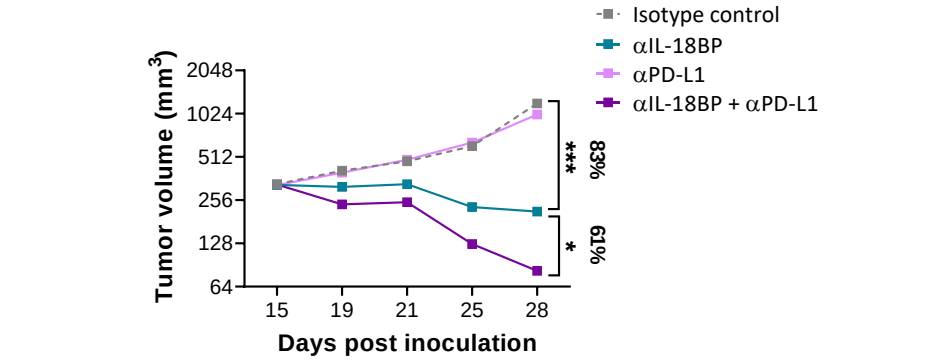


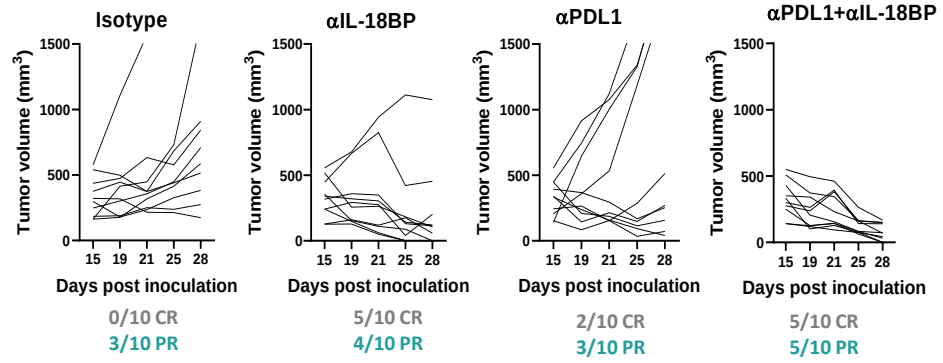
αIL-18BP Ab inhibited tumor growth in E0771 orthotopic mouse breast tumor model



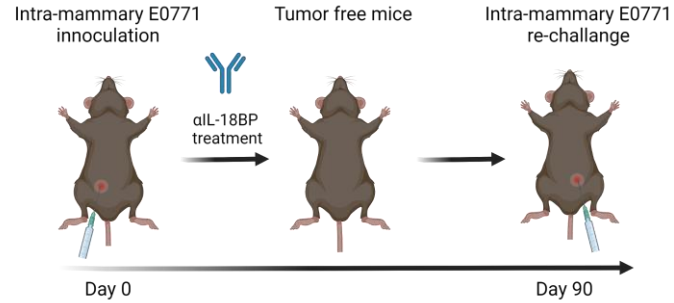
Anti-IL-18BP surrogate Ab demonstrates combo activity with anti-PD-L1 and induces immune memory in E0771

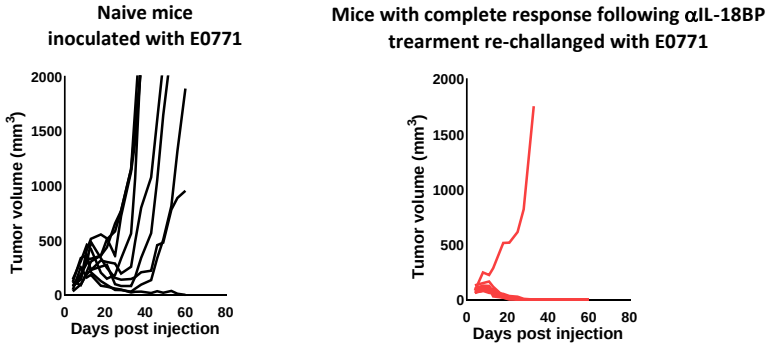
αIL-18BP Ab + αPD-L1 Ab inhibited tumor growth in E0771 orthotopic mouse breast tumor model





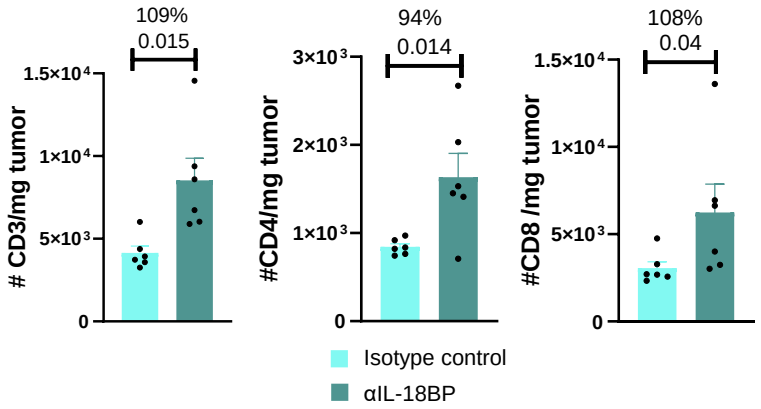
αIL-18BP Ab monotherapy induced immune memory



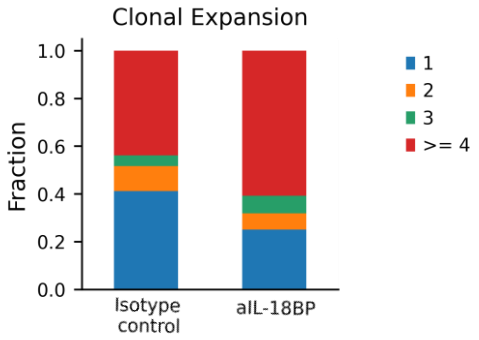


IL-18BP blockade increases T cell numbers, effector state and clonal expansion in the TME in murine tumor model

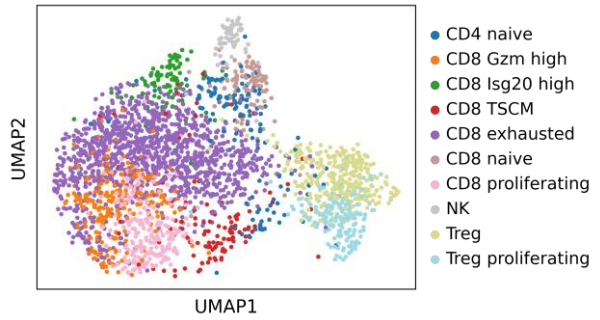
αIL-18BP Ab increased T cells numbers in the TME

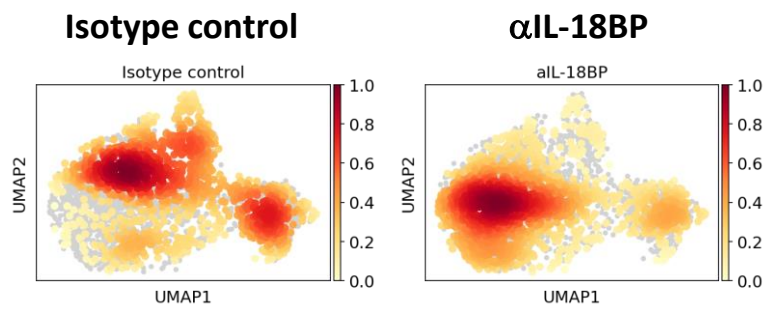


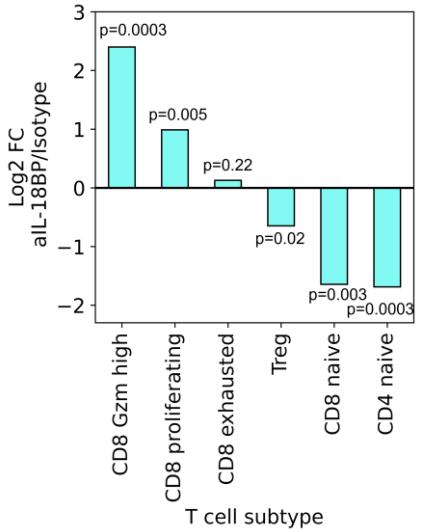
αIL-18BP Ab increased T cell clonal expansion suggesting Ag-specific immune response

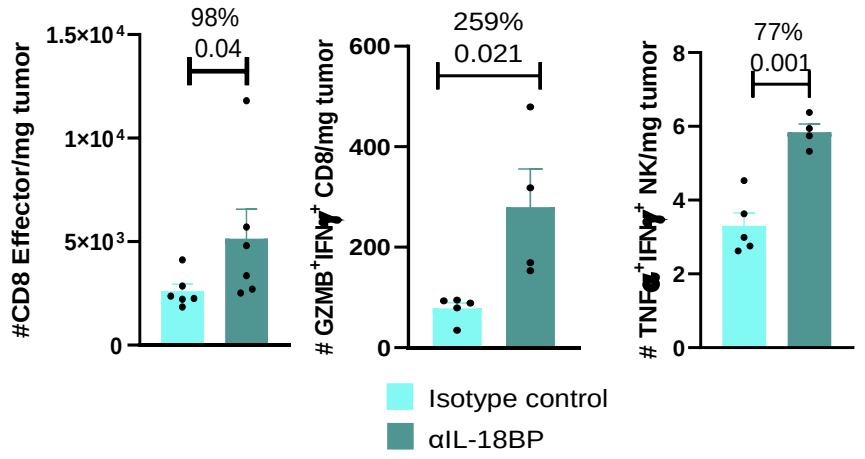


αIL-18BP Ab induced the expansion of polyfunctional non exhausted T cells in the TME



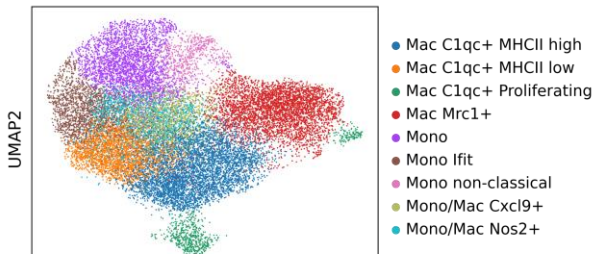


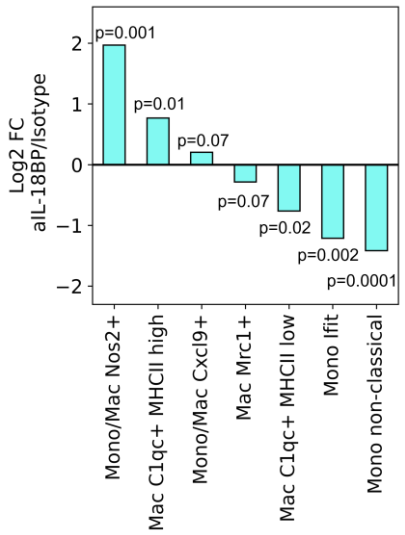




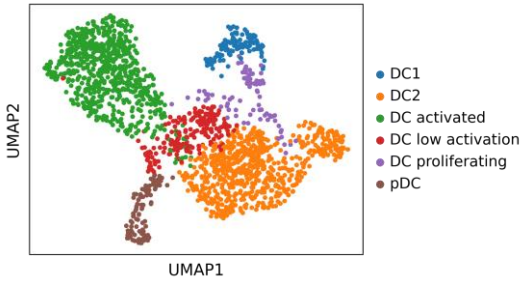
IL-18BP blockade increases proinflammatory myeloid populations and pro-inflammatory cytokine secretion in murine tumor model

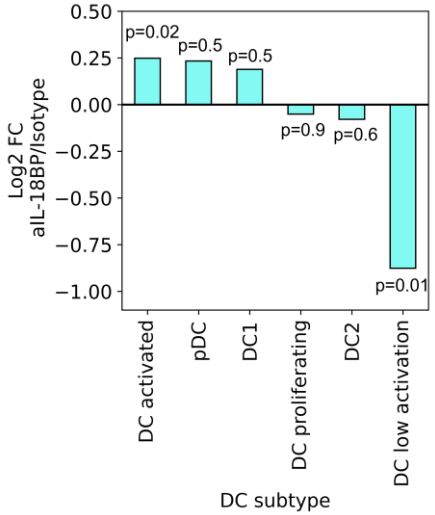
αIL-18BP Ab increased the expansion of proinflammatory macrophages in the TME



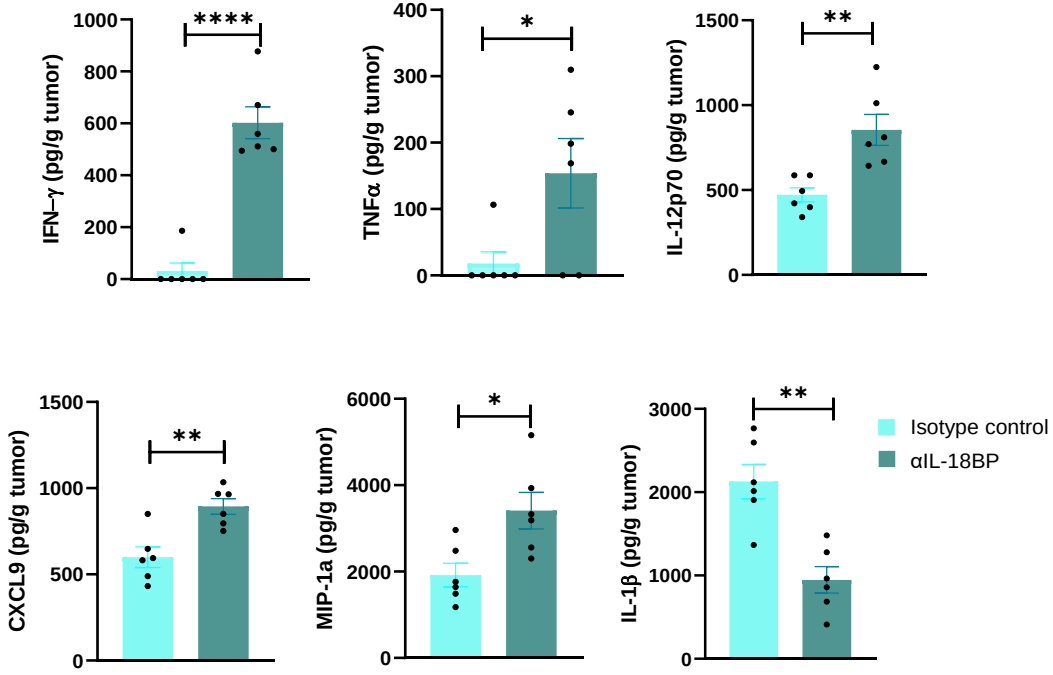


αIL-18BP Ab increased activated DC population in the TME



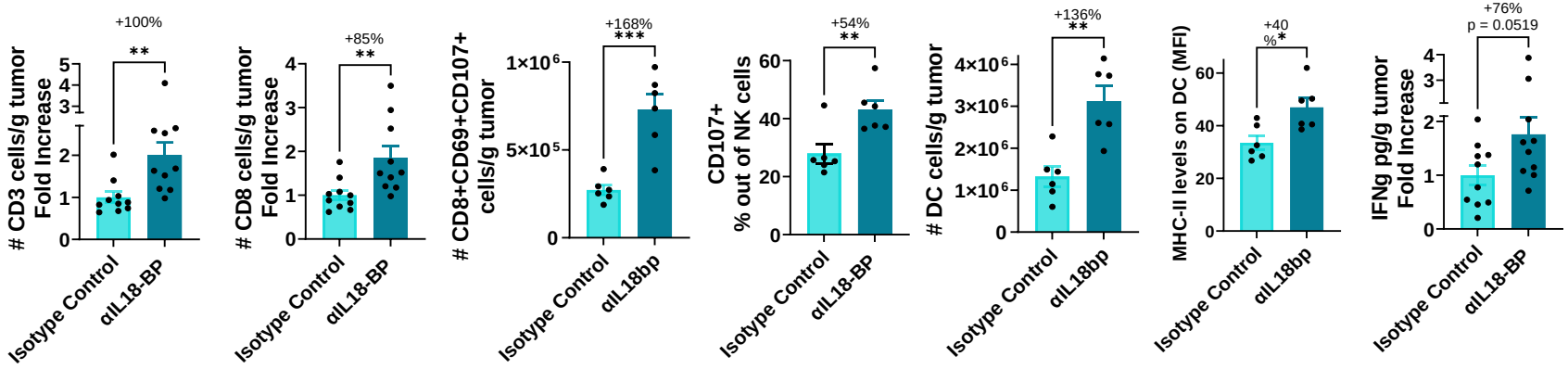


αIL-18BP Ab increased proinflammatory cytokine secretion in the TME

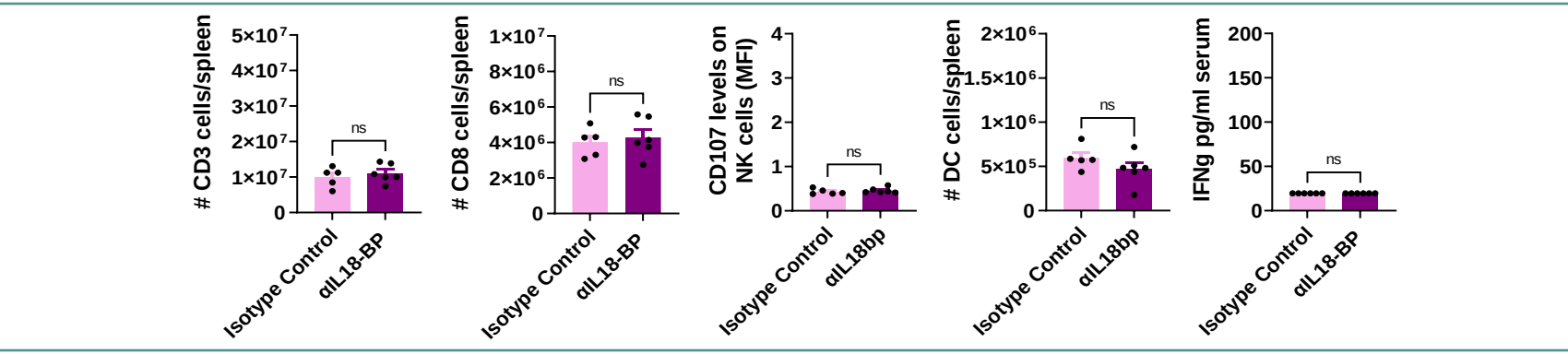


Anti-IL-18BP Ab modulates tumor microenvironment without affecting the periphery in murine tumor model

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



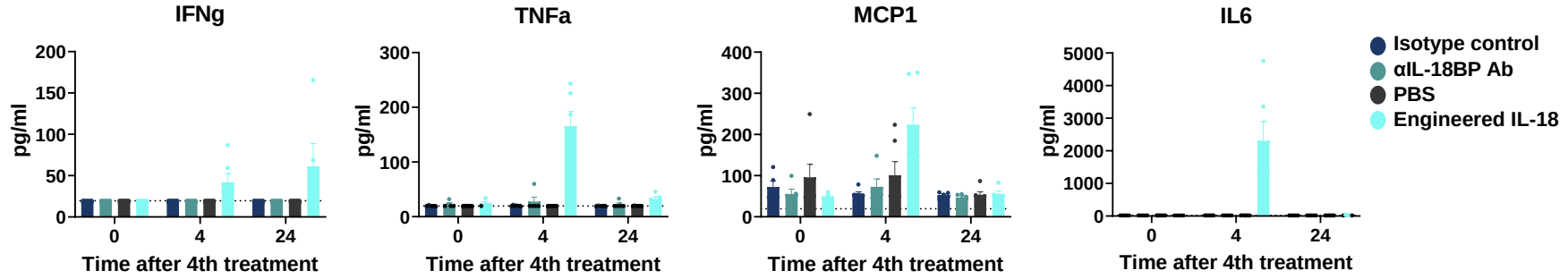
Monotherapy with anti-IL-18BP Ab did not modulate peripheral immunity



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

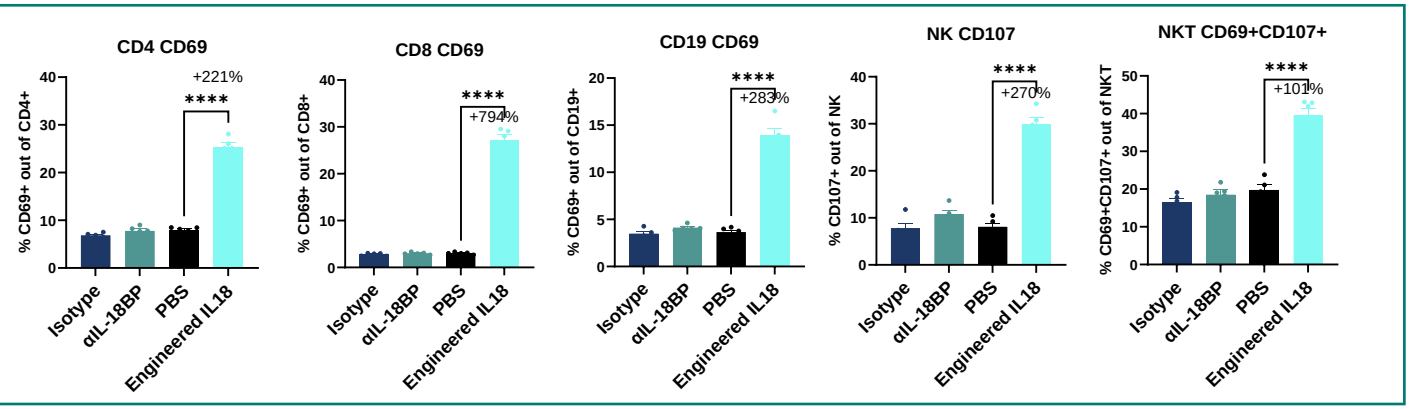
Anti-IL18BP Ab is expected to have a better therapeutic window than recombinant cytokines

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

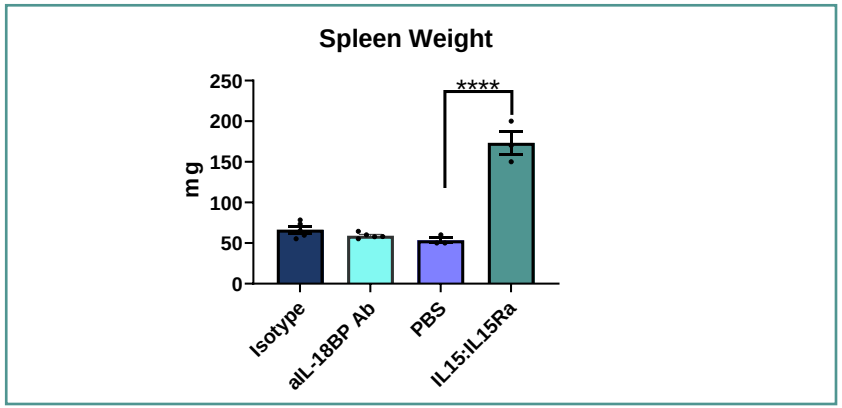


*Engineered IL-18 does not bind to IL18BP but retains its binding to IL-18R

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



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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 and in combination with anti-PD-L1
- 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, unleashes IL-18 to activate T and 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 #550 on Saturday 4

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