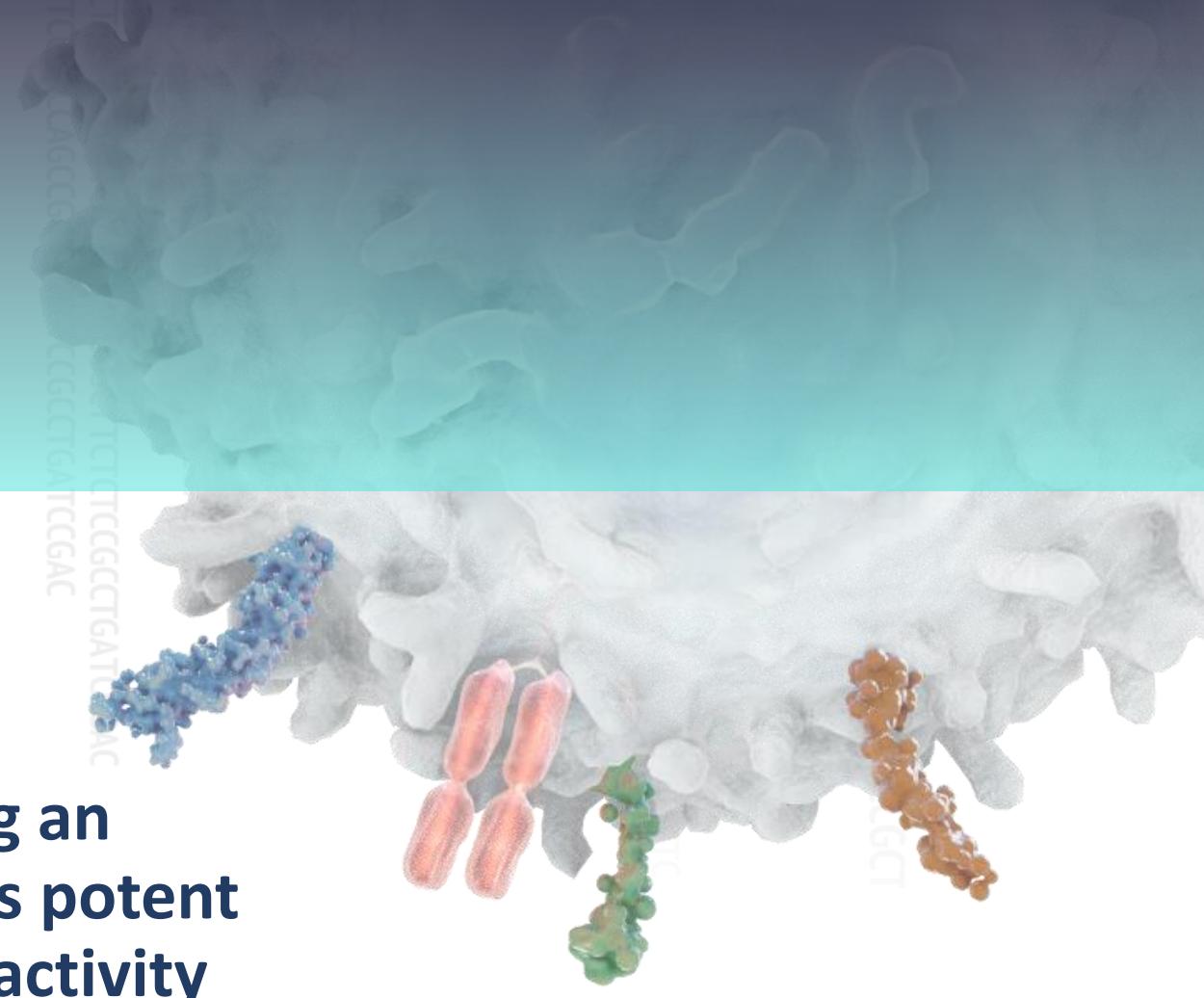




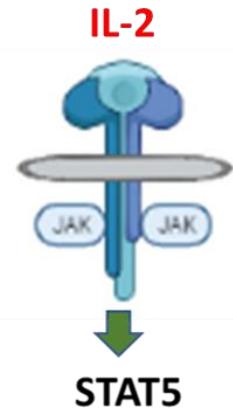
FROM CODE TO CURE®



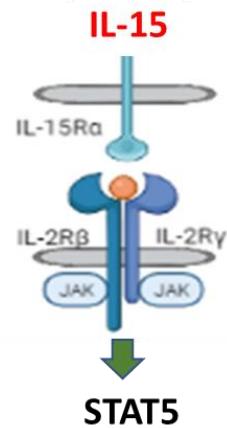
**Unleashing natural IL-18 activity using an
anti-IL-18BP blocker antibody induces potent
immune stimulation and anti-tumor activity**

CIMT Annual Meeting
Dr. Eran Ophir, SVP Research & Drug Discovery
May 5, 2023

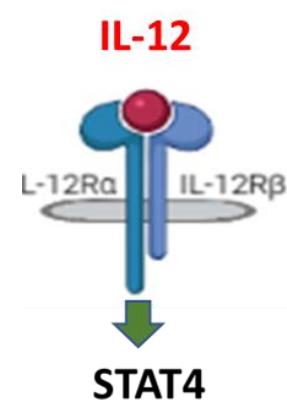
Cytokines: powerful tools with challenging therapeutic window



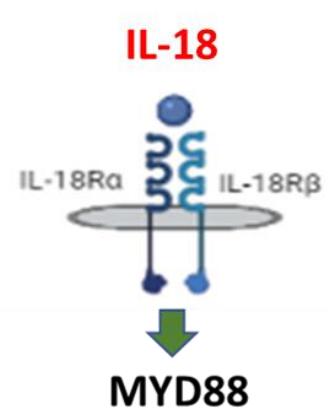
- Short half life
- Pleiotropy
- Vascular leak syndrome
- Cardiotoxicity



- Short half life



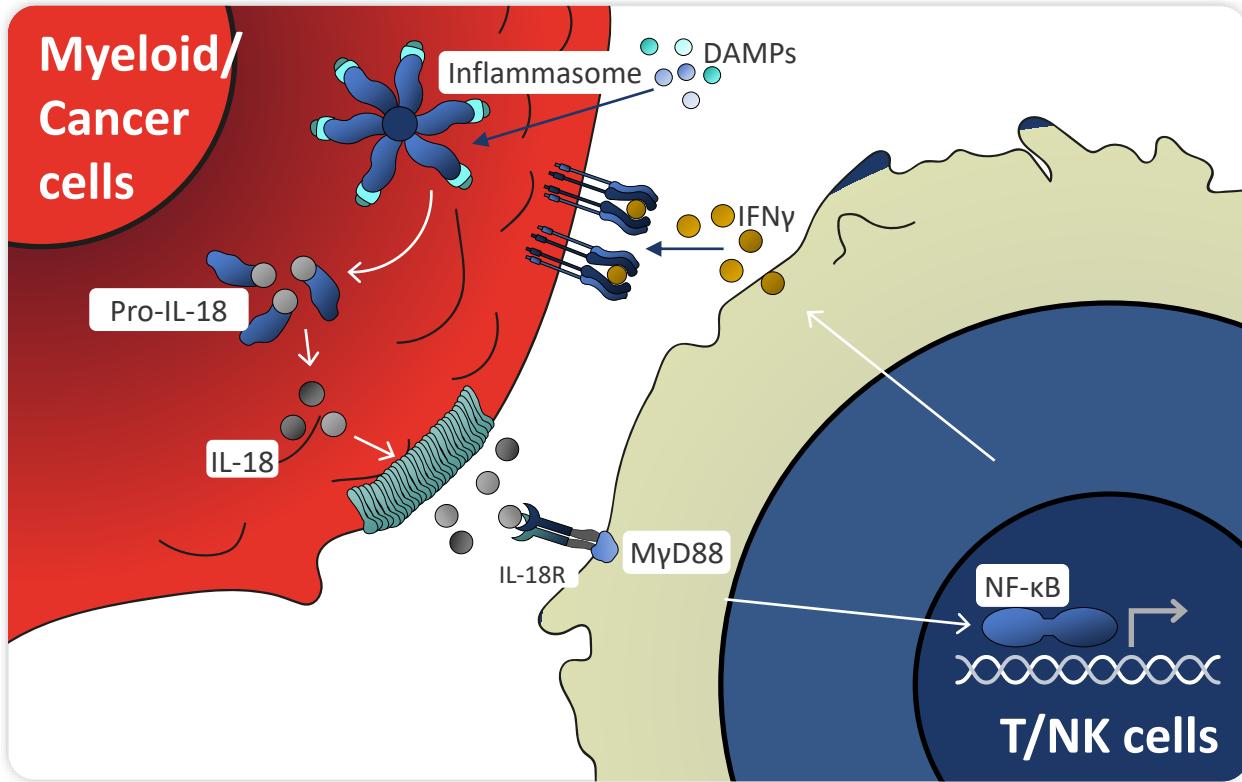
- Short half-life
- Systemic inflammation
- Myelotoxicity
- Hepatotoxicity



- Inhibited by being bound to high affinity binding protein
- Short half-life

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

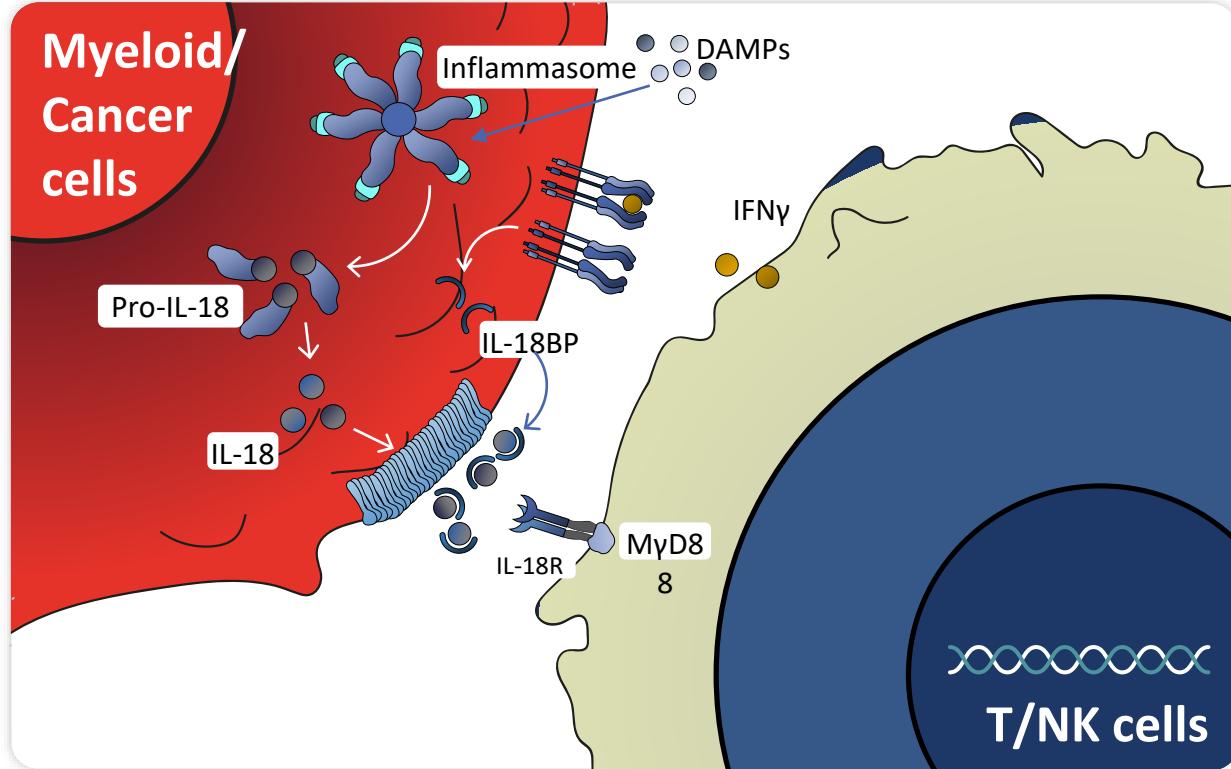
IL-18 stimulates both innate & adaptive immune system



IL-18 is:

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

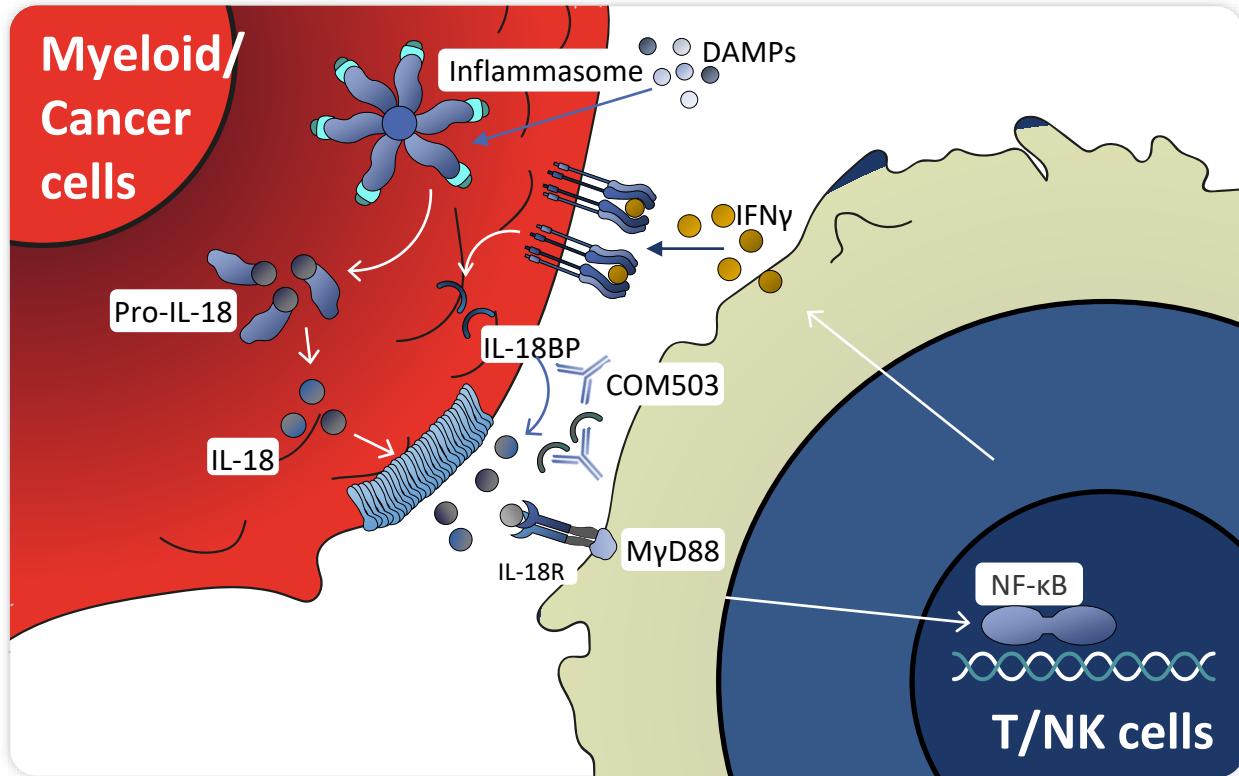
IL-18 binding protein is a natural inhibitor of IL-18



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

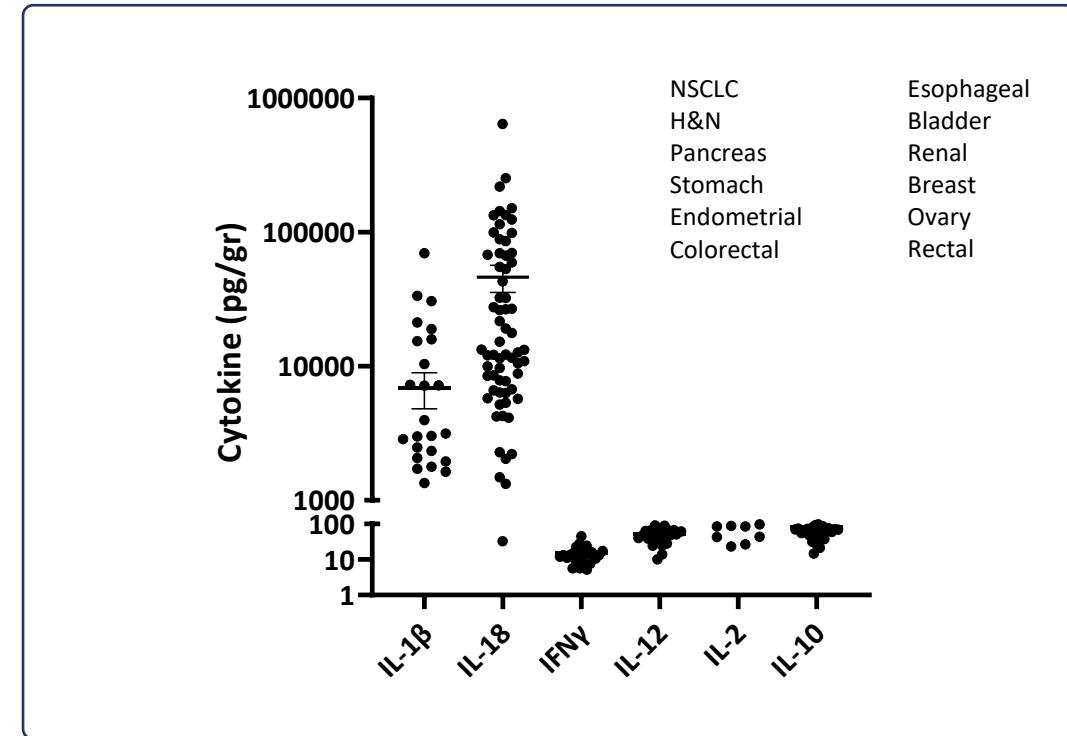
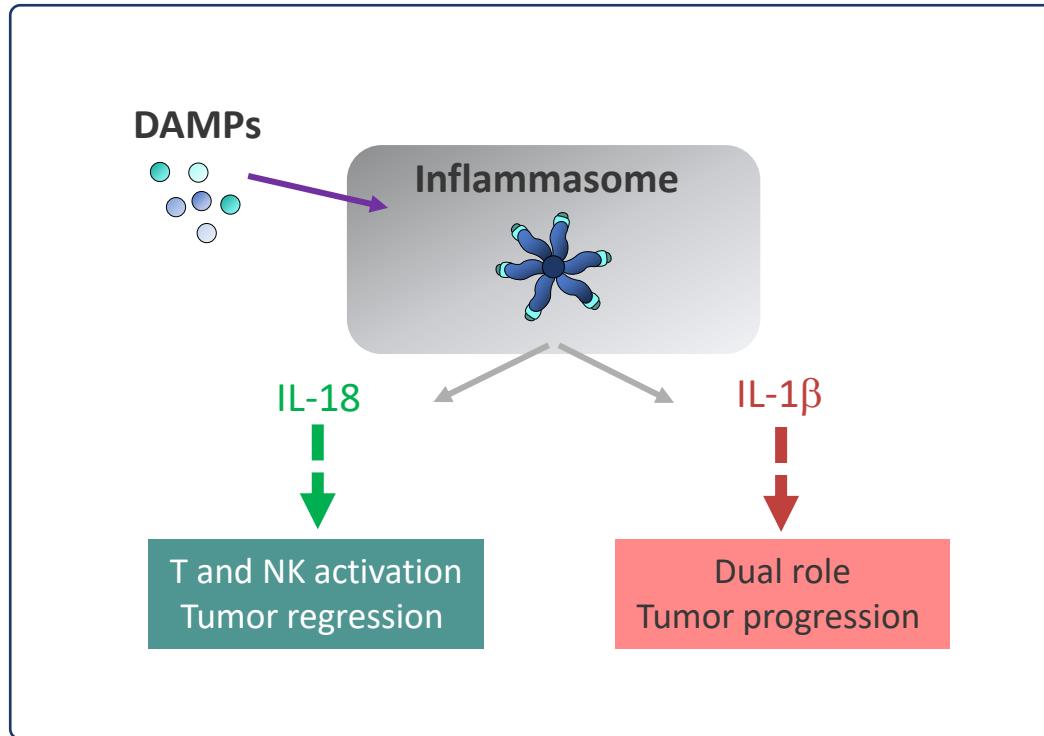
COM503, a potential first-in-class anti-IL-18BP blocker antibody that unleashes endogenous IL-18 in the TME



COM503:

Has the potential to
Induce potent anti-tumor
responses and
pronounced TME-
constrained immune
modulation

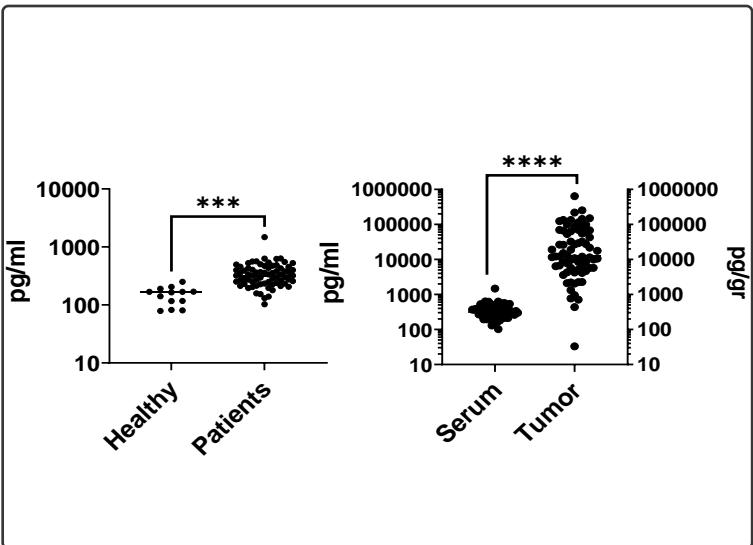
Unlike other cytokines, inflammasome induced cytokines such as IL-18 and IL-1 β are abundant in the TME



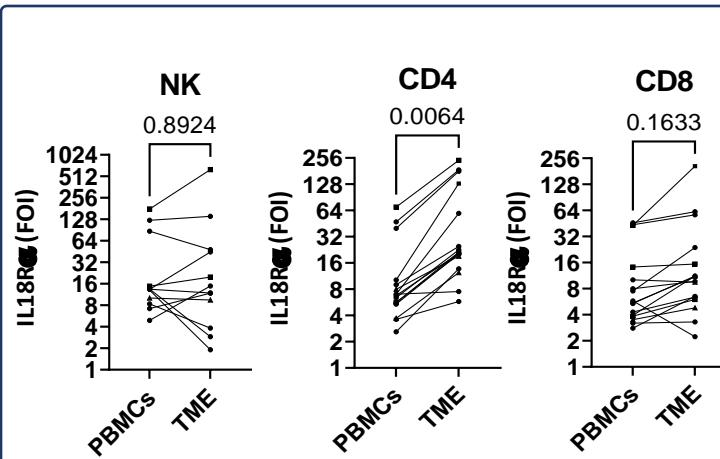
IL-18 is naturally blocked by an endogenous binding protein

IL-18 pathway is upregulated in cancer patients and elevated in the TME across indications

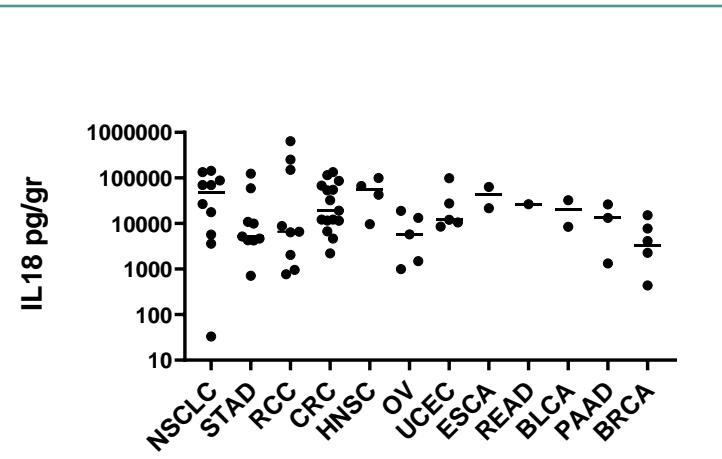
IL-18 is upregulated in serum of cancer patients and elevated in the TME



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

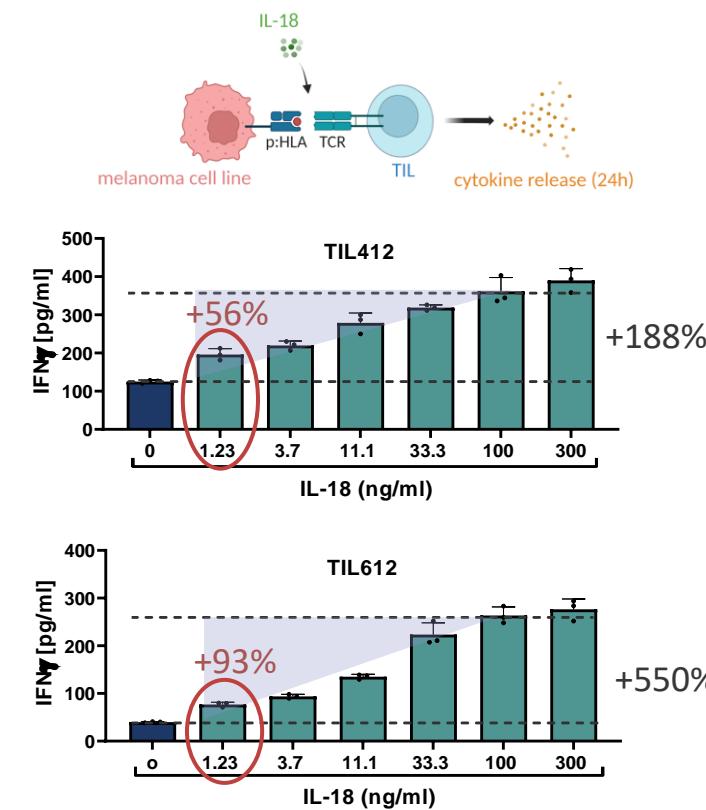


IL-18 is expressed in the TME across indications

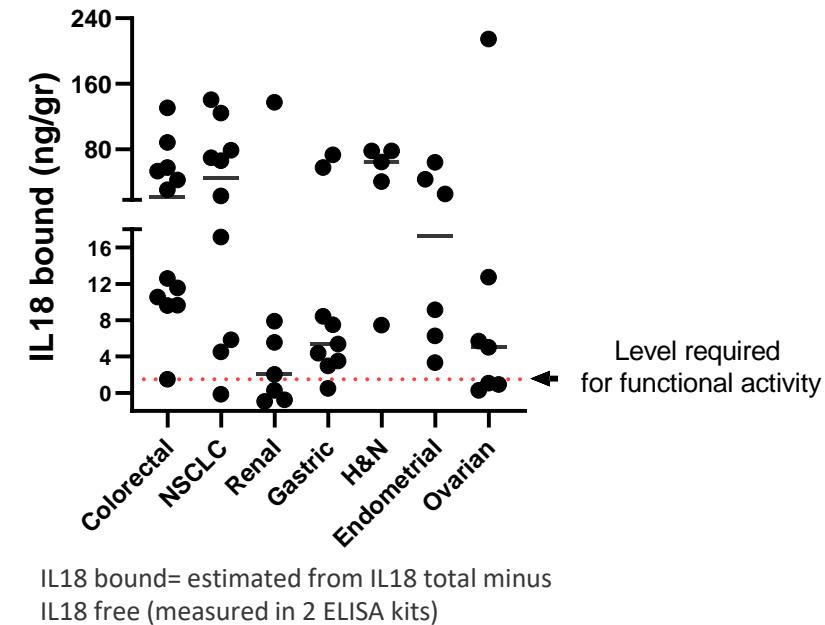


IL-18BP-Bound IL-18 levels in the TME are above the amount required for T cell activation in vitro

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



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

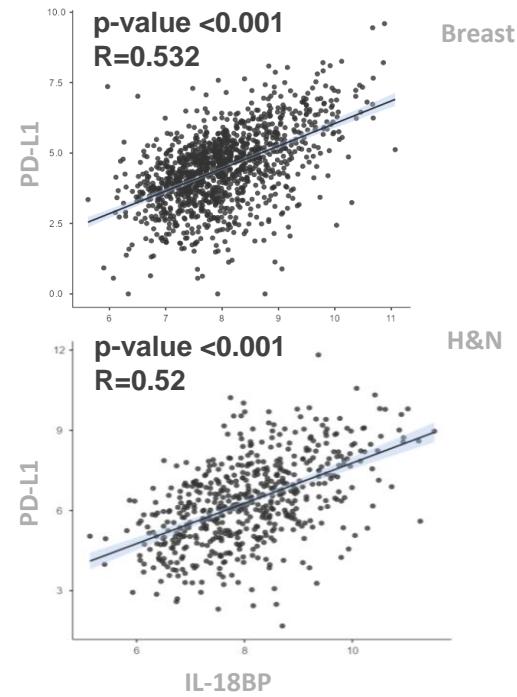


IL18 bound= estimated from IL18 total minus
IL18 free (measured in 2 ELISA kits)

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

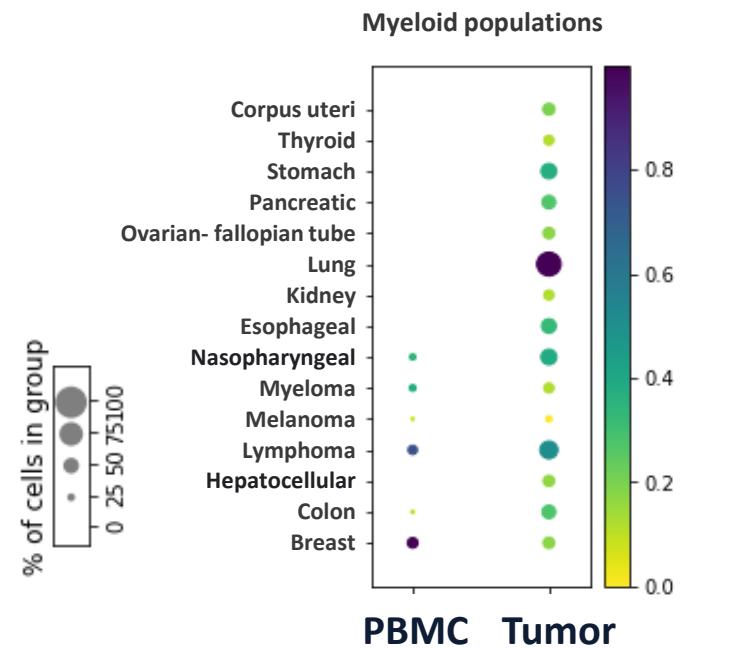
Compugen identified IL-18BP while querying for TAM negative feedback immunosuppression mechanism

Correlation of IL-18BP to PD-L1 in breast and H&N cancer

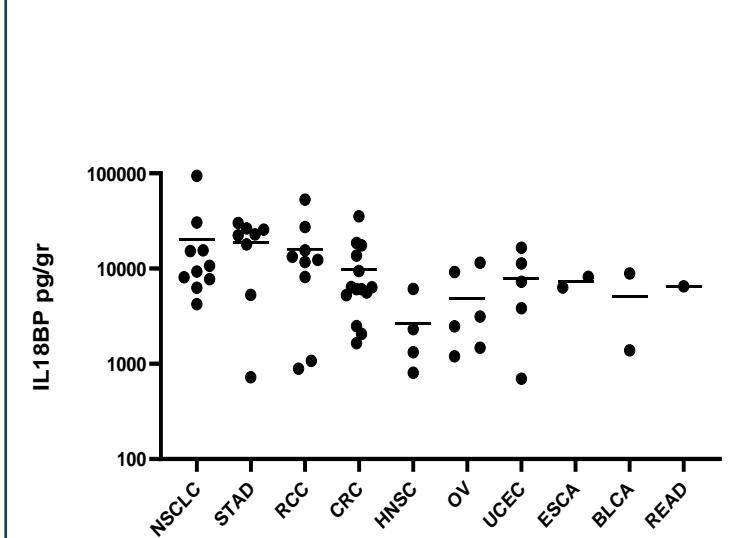


Adjusted from TCGA

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



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

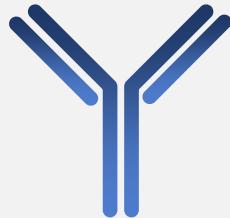


H&N – Head and Neck

TAM- Tumor associated macrophage

COM503 is a fully human, high affinity Anti-IL18BP Ab that restores human TIL and NK cell activity

Antibody characteristics



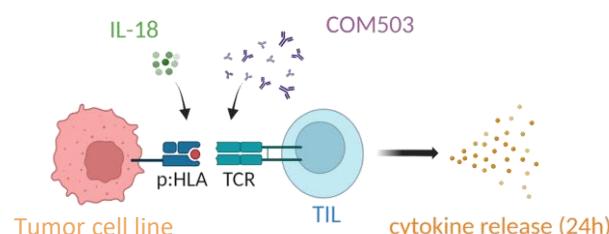
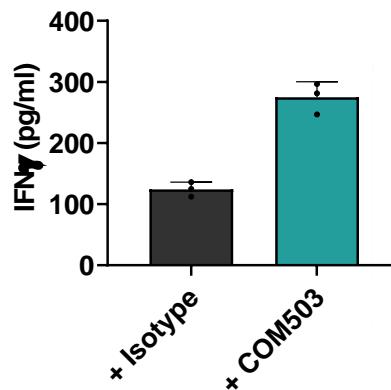
Fully human IgG4 antibody

High affinity (<1pM KD)

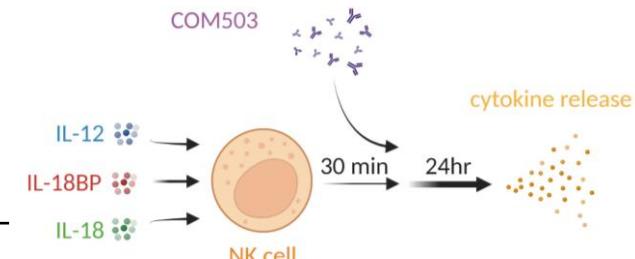
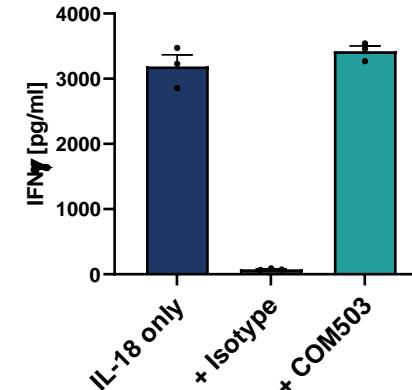
Releases IL-18 from pre-formed IL-18:IL-18BP complex

Enhances T and NK cell activation

COM503 restores TILs activity

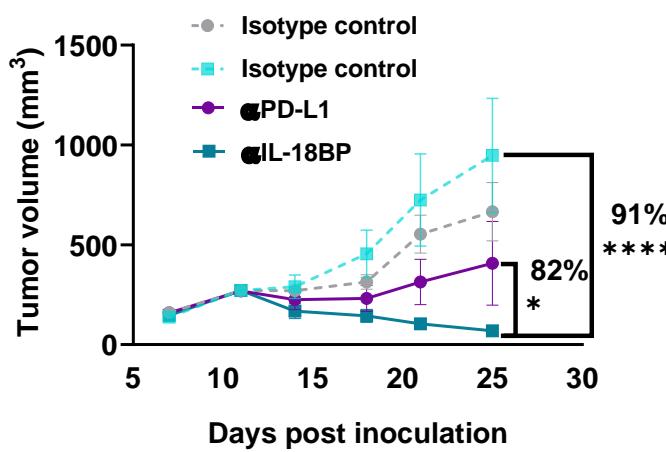


COM503 restores NK cell activity

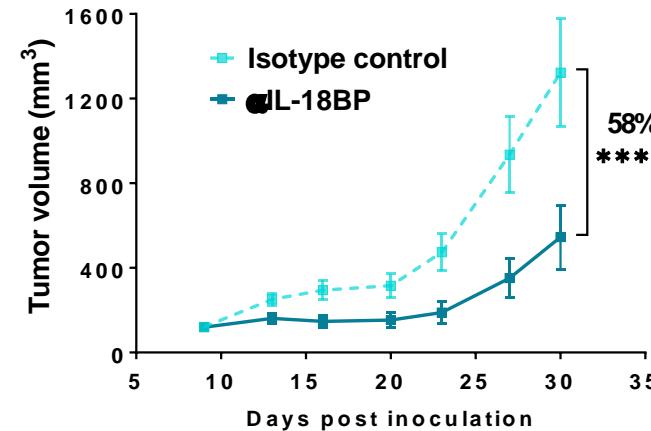


Anti-IL-18BP surrogate Ab demonstrates monotherapy activity across murine syngeneic tumor models

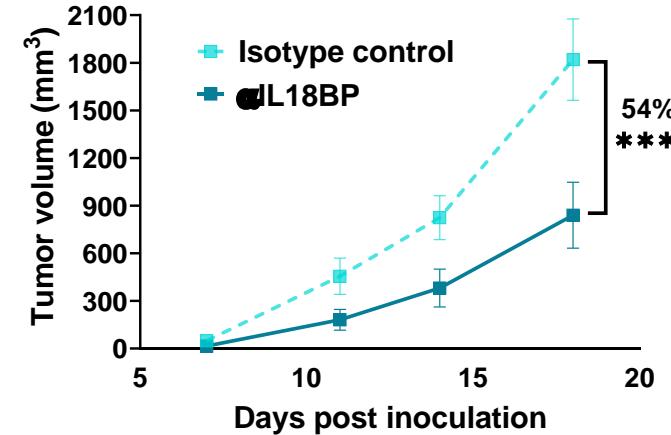
α IL-18BP Ab inhibits tumor growth in E0771 orthotopic mouse breast tumor model



α IL-18BP Ab inhibits tumor growth in MC38ova mouse CRC tumor model

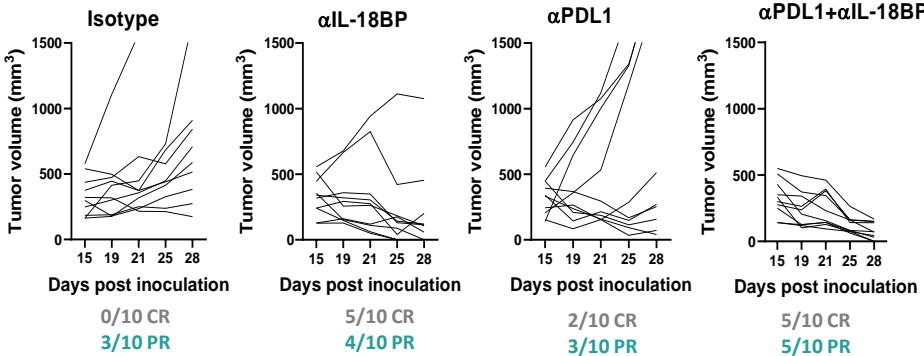
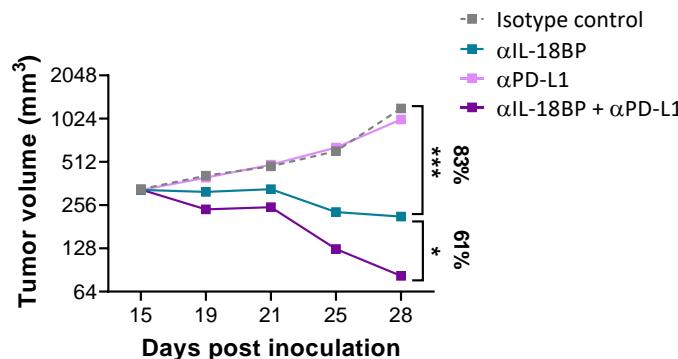


α IL-18BP Ab inhibits tumor growth in B16F10-hmgp100 mouse melanoma model

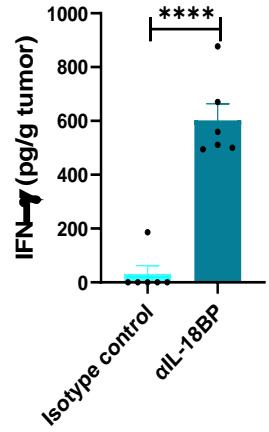
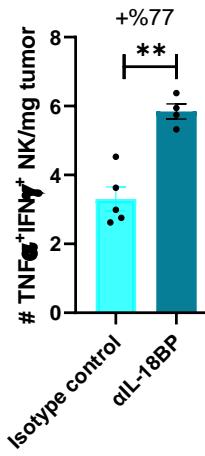
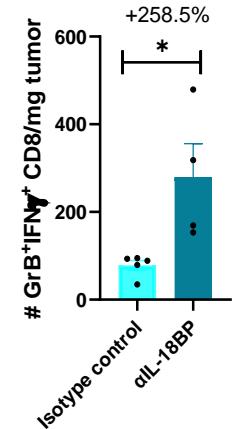


Anti-IL-18BP surrogate Ab demonstrates combo activity with anti-PD-L1, modulate the TME & induces immune memory in E0771

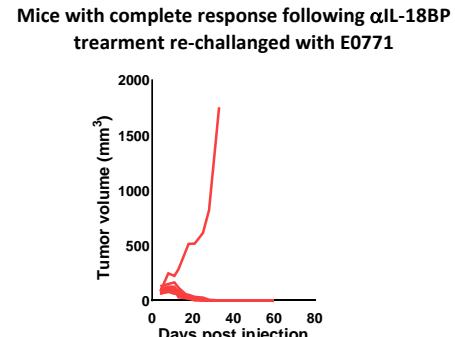
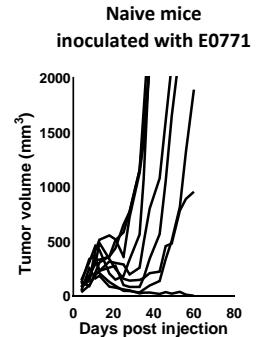
α IL-18BP Ab + α PD-L1 Ab inhibit tumor growth in E0771 orthotopic mouse breast tumor model



α IL-18BP Ab monotherapy immune-modulate the TME

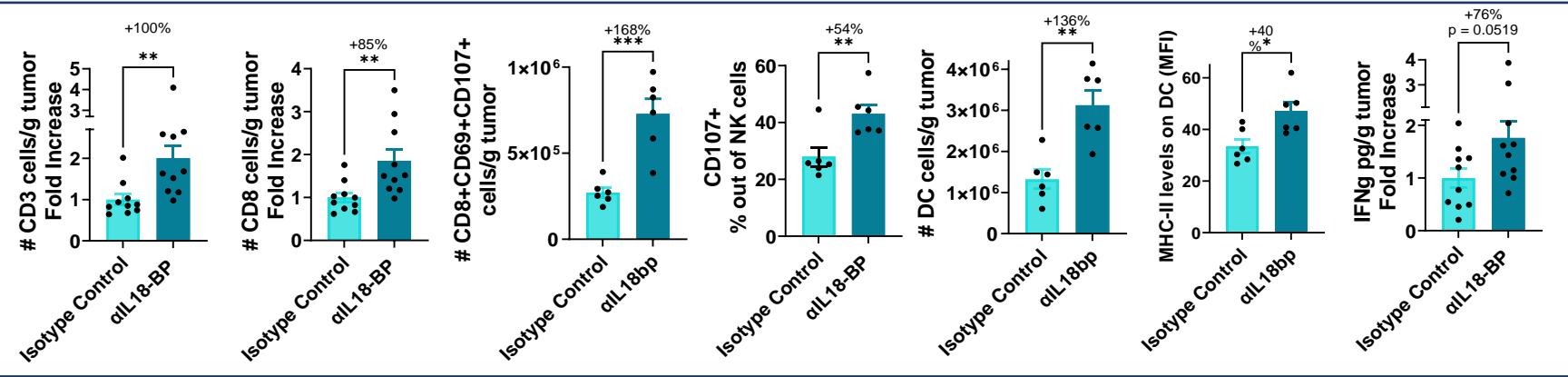


α IL-18BP Ab monotherapy induces immune memory

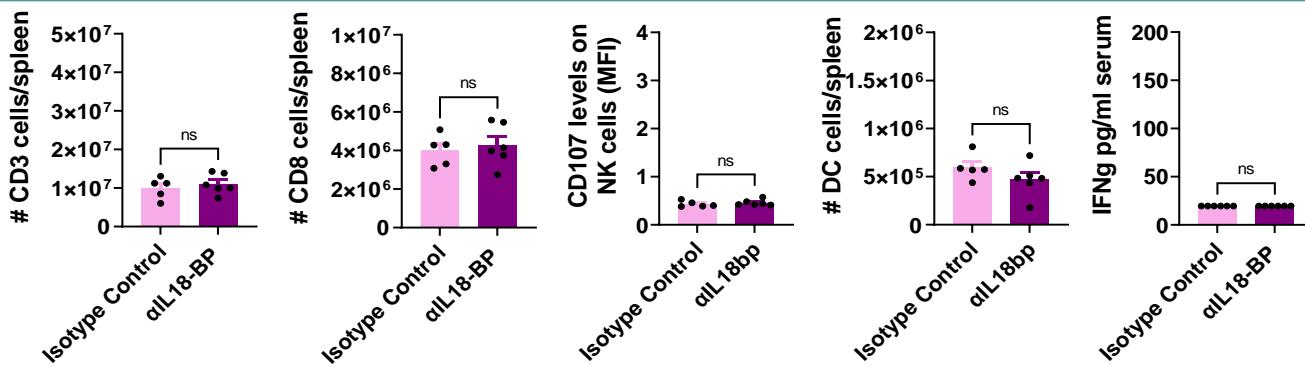


Anti-IL-18BP Ab modulates tumor microenvironment without affecting the periphery in murine tumor model

Monotherapy with anti-IL-18BP Ab immune-modulated TME in MC38ova model



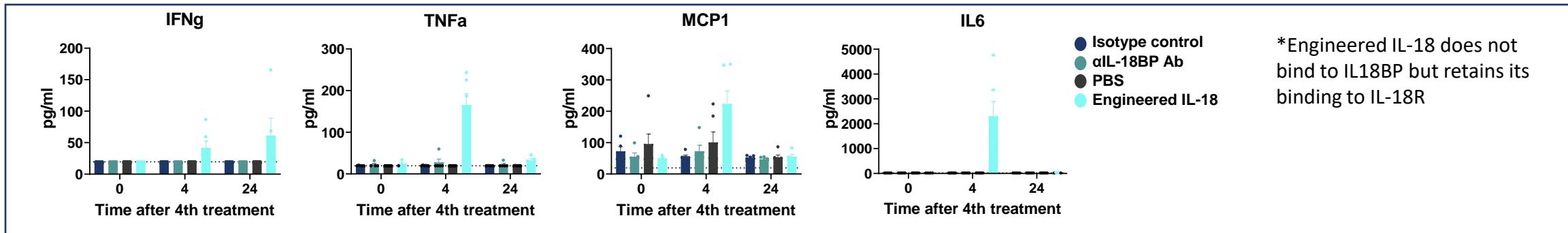
Monotherapy with anti-IL-18BP Ab does not modulate peripheral immunity



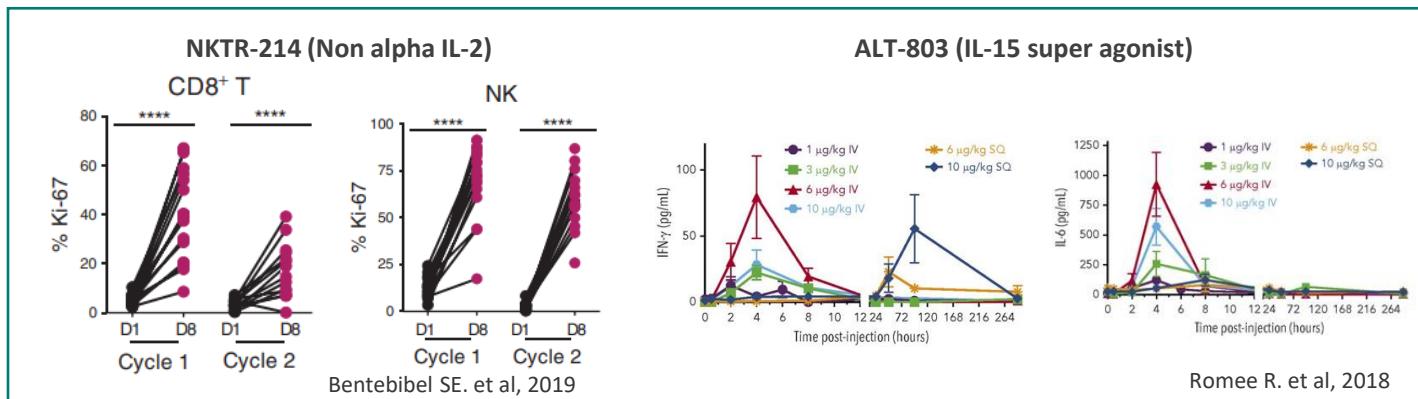
Immune modulation restricted to tumor site in contrast to therapeutic recombinant cytokines given systemically

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

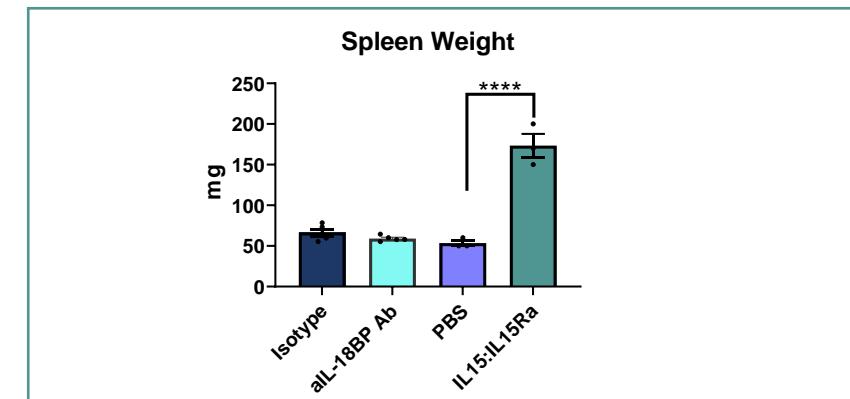
Administration of anti-mIL-18BP Ab to mice did not affect serum cytokines in contrast to engineered mouse IL-18*



Systemic administration of cytokines results in increased serum cytokines and lymphocyte proliferation



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 and is inhibited by IL-18BP, which is induced in the TME in response to IFN γ
- Blocking IL-18BP in murine cancer models inhibit tumor growth as mono and in combo with anti-PD-L1 antibody
- Immune modulation following treatment 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

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



Thank you!

Acknowledgments:

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