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

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-constrained immune modulation
Unlike other cytokines, inflammasome induced cytokines such as IL-18 and IL-1β 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-18Rα 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 measure 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**

- Breast
  - p-value < 0.001
  - R = 0.532
- H&N
  - p-value < 0.001
  - R = 0.52

Adjusted from TCGA

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

- Myeloid populations
  - Corpus uteri
  - Thyroid
  - Stomach
  - Pancreatic
  - Ovarian-fallopian tube
  - Lung
  - Kidney
  - Esophageal
  - Nasopharyngeal
  - Myeloma
  - Melanoma
  - Lymphoma
  - Hepatocellular
  - Colon
  - Breast

% of cells in group

PBMC Tumor

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

**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**
- IL-12
- IL-18
- COM503
- 30 min
- 24hr
- cytokine release

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

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

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

αIL-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

\[ \alpha \text{IL-18BP Ab} + \alpha \text{PD-L1 Ab inhibit tumor growth in E0771 orthotopic mouse breast tumor model} \]

\[ \alpha \text{IL-18BP Ab monotherapy immuno-modulate the TME} \]

\[ \alpha \text{IL-18BP Ab monotherapy induces immune memory} \]
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

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.

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

➢ IL-18 is upregulated in the TME and is inhibited by IL-18BP, which is induced in the TME in response to IFNγ

➢ 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

Block IL-18BP is a novel approach to harness cytokine biology for cancer therapeutics
Thank you!

Acknowledgments:

Compugen Ltd. Holon, Israel