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

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Abstract 550
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Disclosure

Employee of Compugen LTD.
Cytokines: powerful tools with challenging therapeutic window

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

IL-2
- STAT5

IL-15
- STAT5
- Short half life

IL-12
- STAT4
- Short half-life
- Systemic inflammation
- Myelotoxicity
- Hepatotoxicity

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)

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

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

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. et al, 2020
- p=0.0003
- p<0.0001

IL-18BP expression in different types of cancer following immune checkpoint blockers treatment.
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 measured 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**

- **IFNγ**
  - IL-18 only: 100
  - Isotype: 90
  - COM503: 110

- **TNFα**
  - IL-18 only: 100
  - Isotype: 90
  - COM503: 110

- **GZMB**
  - Media: 25%
  - COM503: 56%
  - Pembro: 52%
  - Pembro+COM503: 56%

- **IL-2**
  - Media: 50%
  - COM503: 29%
  - Pembro: 50%
  - Pembro+COM503: 29%

- **IL-12**
  - Media: 58%
  - COM503: 138%

- **IFNγ**
  - Media: 25%
  - COM503: 56%
  - Pembro: 38%
  - Pembro+COM503: 80%

- **TNFα**
  - Media: 58%
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**

<table>
<thead>
<tr>
<th># CD3/mg tumor</th>
<th># CD4/mg tumor</th>
<th># CD8/mg tumor</th>
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<tr>
<td>1.5×10^4</td>
<td>3×10^3</td>
<td>1.5×10^4</td>
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<tr>
<td>109% 0.015</td>
<td>94% 0.014</td>
<td>108% 0.04</td>
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- Isotype control
- αIL-18BP

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

- Isotype control
- αIL-18BP

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

- Isotype control
- αIL-18BP
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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>Mean ± SEM</th>
<th>Fold Increase</th>
<th>p-value</th>
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<tbody>
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<td>IFNg pg/ml serum</td>
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<td>αIL18-BP</td>
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Monotherapy with anti-IL-18BP Ab did not modulate peripheral immunity

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<th>Fold Increase</th>
<th>p-value</th>
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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 anti-mIL-18BP Ab to mice did not result in splenomegaly in contrast to rIL-15:IL15Ra.
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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