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

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Disclosure

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

- 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
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-18Rα is induced on TILs in the TME

TILs- Tumor infiltrating lymphocytes
IL-18BP-bound IL-18 levels in human 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.
IL-18BP is upregulated following immune checkpoint blockers treatment

**Breast cancer (anti-PD-1)**

- Bulk expression: EGAD00001006608
- scRNA: GSE91061

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

- Bulk expression: GSE15126
- scRNA: GSE120575

**Basal cell carcinoma (anti-PD-1)**

- scRNA: GSE123814

**NSCLC (anti-PD-(L)1)**

- GSE123814

Zhou T. et al, 2020
The concept of anti-IL18BP antibody

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td>IL-18 is naturally present in human tumors at high levels sufficient to stimulate T cells</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>High levels of IL-18BP in the tumors block its IL-18 anti-tumor activity</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>IL-18 endogenous levels in blood are low, and the IL-18 receptor is induced in the tumor</td>
</tr>
</tbody>
</table>

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.
Anti-IL-18BP surrogate antibody 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\textsuperscript{dim} mouse CRC tumor model

αIL-18BP Ab inhibited tumor growth in E0771 orthotopic mouse breast tumor model
IL-18BP blockade induces a proinflammatory environment in the TME

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

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

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

αIL-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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Isotype Control</th>
<th>αIL18-BP</th>
<th>Fold Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td># CD8 cells/g tumor</td>
<td>0</td>
<td>1</td>
<td>+100%</td>
</tr>
<tr>
<td># CD8 cells/g tumor</td>
<td>1</td>
<td>4</td>
<td>+85%</td>
</tr>
<tr>
<td>CD8+CD107+ cells/g tumor</td>
<td>1×10⁶</td>
<td>5×10⁶</td>
<td>+168%</td>
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<tr>
<td>CD107+ cells/g tumor</td>
<td>0</td>
<td>20</td>
<td>+54%</td>
</tr>
<tr>
<td># DC cells/g tumor</td>
<td>1</td>
<td>4×10⁶</td>
<td>+136%</td>
</tr>
<tr>
<td>% MHC-I levels on DC (MFI)</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>IFNγ pg/ml serum</td>
<td>ns</td>
<td></td>
<td>p = 0.0519</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Isotype Control</th>
<th>αIL18bp</th>
<th>Fold Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td># CD3 cells/spleen</td>
<td>0</td>
<td>1×10⁶</td>
<td>+100%</td>
</tr>
<tr>
<td># CD8 cells/spleen</td>
<td>0</td>
<td>2×10⁶</td>
<td>+136%</td>
</tr>
<tr>
<td># CD8+CD69+CD107+ cells/g tumor</td>
<td>0</td>
<td>3×10⁶</td>
<td>+168%</td>
</tr>
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<td>0</td>
<td>3×10⁶</td>
<td>+168%</td>
</tr>
<tr>
<td>MHC-II levels on DC (MFI)</td>
<td>0</td>
<td>20</td>
<td>+40%</td>
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<tr>
<td>IFNγ pg/ml tumor</td>
<td>ns</td>
<td></td>
<td>+76%</td>
</tr>
</tbody>
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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

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 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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