BioComo Inc.
Proposal for Private Placement Capital Raise
TAV : T cell-signaling anti-tumor virus

A NEW TNFRSF SIGNAL ENHANCEMENT SYSTEM
Three Antitumor Immune Effects of Antibodies

① Antibodies bind directly to cancer cells

Feature

Fabs of antibodies (Abs) bind to cancer cells. Macrophages, NK cells, etc. bind to Fcs of Abs and these cells attack cancer cells by ADCC.

② Positive immune activation

CD4⁺ T cells

Agonistic Abs activate TNFRSF signals in T cells followed by proliferation of cytotoxic T cells (CTLs) which attacks and kills tumor cells.

③ Negative immune pathway blockade

T cells

Cancer cells express PD-L1, etc., which binds to the PD-1 of T cells and suppresses cancer immunity. Anti PD-1 antibodies, etc. block this pathway, activate anti-tumor immunity, and attack cancer cells.

<table>
<thead>
<tr>
<th>Status</th>
<th>Commercialized</th>
<th>Not Commercialized: difficult to develop</th>
<th>Commercialized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products</td>
<td>Trastumab (Herceptin): HER2</td>
<td>Anti PD-1 antibodies: Opdivo and Kietluda</td>
<td>Anti PD-1 antibodies: BABENTIO/IMIFINDI</td>
</tr>
<tr>
<td></td>
<td>Rituximab (Rituxan): CD20</td>
<td>Anti PD-L1 antibodies: Zevalin</td>
<td>Bevacimazb (Avastin): VEGF</td>
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<tr>
<td></td>
<td>Ibritumomab tiuxetan (Zevalin): CD20</td>
<td>Cancer cells express PD-L1, etc., which binds to the PD-1 of T cells and suppresses cancer immunity. Anti PD-1 antibodies, etc. block this pathway, activate anti-tumor immunity, and attack cancer cells.</td>
<td>The mechanism of action is more complex than ① and ③. Expected very effective however, liver toxicity occurred with the anti-4-1BB antibodies from other company. The toxic mechanism is being elucidated in detail.</td>
</tr>
</tbody>
</table>
Future cancer treatments will be focused on anti-tumor immunotherapy by enhancement of positive immune signals in T cells.

In particular, TNFRSF signal enhancement such as OX40/4-1BB has unmet medical needs.

BC-PIV technology has high affinity for TNFRSF signal enhancement.

Current agonistic antibodies such as anti-4-1BB antibody have severe adverse effects. It is likely that BC-PIV technology will alleviate adverse events surrounding agonistic antibodies for cancer immunotherapy.
Non-toxic Enhancement of Positive Immunity is Key to Next-Generation anti-tumor Immunotherapy Agents

- Binding of OX40 or 4-1BB ligand to OX40 or 4-1BB receptor expressed on T cells will activate TNFRSF signals, induces proliferation of cytotoxic T cells (CTLs) specific for cancer cells and will annihilate those cancer cells.

- Unlike a cancer vaccine designed to treat a particular tumor, a TNFRSF signal enhancement regimen will annihilate any type of solid tumors for treatment.

Currently the development of agonistic antibodies is the mainstream in oncology research.
Limitations of agonistic antibody approaches

- Pharmaceuticalization of OX40/4-1BB ligand proteins is not easy. Although Global Mega Pharmas have targeted T-cell activation with agonistic antibodies, liver toxicity of the 4-1BB agonistic antibody seems a root issue in successful development.

  ➢ Agonistic antibodies should be modified to reduce the toxicity.

  ➢ BioComo proposes an alternative approach to use the natural ligand on the BC-PIV vectors (TAV).

OX40L/4-1BBL
Ligand protein

Anti-OX40 Ab
MEDI10562, MEDI6469
MEDI6383: MedImmune
PF-04518600: Pfizer
INCAGN01949: Incyte
BMS-986178: BMS
RG7888: Roche
GSK317498: GSK

Anti-4-1BB Ab
Urelumab: BMS
Utomilumab: Pfizer
LVGN6051: Lyvgen

For adverse events reported
Alternative options are also needed
Causes of the toxicity issues with agonistic antibodies

**BioComo’s Approach to these Issues**

To enhance TNFRSF signaling, natural TNFSF ligands such as OX40Ls or 4-1BBLs are presented on the surface of TAV and T cells are activated in a natural manner. This technology will lower toxicity while showing high efficacy on tumor suppression.
Our Approaches: Vector-mediated TNFRSF Signal Activation

◆ Activation of TNFRSF by BC-PIV with OX40L/4-1BBL (TAV) without antibodies

World’s first vector system displaying TNFRSF ligands on the envelopes of BC-PIV TAV (T cell-signaling anti-tumor virus)

◆ Mechanism of action of "vector-mediated TNFRSF signal activation"

**Evidence of uptake**

<table>
<thead>
<tr>
<th>Displayed OX40L</th>
<th>1. BC-PIV particles</th>
<th>2. BC-PIV/mOX40L particles</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 kDa</td>
<td>mOX40L</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Displayed 4-1BBL</th>
<th>1. BC-PIV particles</th>
<th>2. BC-PIV/m4-1BBL particles</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 kDa</td>
<td>m4-1BBL</td>
<td></td>
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</tbody>
</table>

① signal activation
② activation
③ attack
Primary criteria for animal studies

Target: Systemic antitumor effects will be triggered through local injection to one site out of multiple solid tumors and will attack non-treated remote cancers.

Pre-treatment

- Injection site
- Non-treated site

After treatment

- Injected site
- Non-treated site

BC-PIV/ OX40L or 4-1BBL (TAV) treatment

Tumor of both injection site and non-treated site are eradicated.
Antitumor Effects of BC-PIV with OX40L

(Methods) CT26 colon cancer cells (5x10^6) were inoculated into two ventral sites of mice. BC-PIV, BC-PIV+anti-OX40 agonistic antibodies (positive controls) or BC-PIV/OX40L (TAV) was administered intratumorally three times every other day after growth to 5-7mm in diameter and then tumor sizes were measured.

(Results) The BC-PIV/OX40L (TAV) induced regression of the treated and distant/untreated tumors similar to those treated with BC-PIV+anti-OX40 antibodies.
Antitumor Effects of OX40L/4-1BBL

Effects were not perfect by the prototype vectors.
Optimized BC-PIV (TAV) eradicated the tumors with no liver damages

Optimized BC-PIV/OX40L and BC-PIV/4-1BBL demonstrated even greater antitumor effects.

Effects of optimized BC-PIV/OX40L and BC-PIV/4-1BBL

No visible liver damages

Optimized BC-PIV/OX40L and BC-PIV/4-1BBL demonstrated even greater antitumor effects.

Appearance 23 days after administration

White arrows: injection sites
Yellow arrows: non-treated sites
BUSINESS PLAN
Optimized BC-PIV/OX40L (TAV), a new anti-tumor TNFRSF Signal Activator, will be developed as BioComo Lead Product (BC-0001).

➢ It is not an antibody. A natural ligand protein present in human is used. This will reduce potential side effects attributable to agonistic antibodies.

➢ The BC-PIV itself induces expression of OX40 receptors on T cells and displays OX40 ligands on BC-PIV surfaces. Their combined effects will activate TNFRSF signals efficiently.

➢ BC-PIV/OX40L (TAV) elicits TNFRSF signals followed by systemic anti-tumor immunity of tumor-specific CTLs, resulting in suppression of non-treated remote tumors.

➢ A novel TNFRSF signal activator, an alternative to agonistic antibodies.
<table>
<thead>
<tr>
<th>Product</th>
<th>Disease Indications</th>
<th>Development Phase</th>
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<tbody>
<tr>
<td>BC-0001 (OX40L)</td>
<td></td>
<td><strong>Research</strong></td>
</tr>
<tr>
<td>BC-0002 (4-1BBL)</td>
<td>Solid tumors</td>
<td><strong>Pre-clinical</strong></td>
</tr>
<tr>
<td>BC-0003 (Back-up)</td>
<td></td>
<td><strong>Phase I/II</strong></td>
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<tr>
<td>BC-0004</td>
<td>RSV Vaccines</td>
<td><strong>Phase III</strong></td>
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<tr>
<td>BC-0005 (Back-up)</td>
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<tr>
<td>BC-0006</td>
<td>Ebola Vaccines</td>
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<tr>
<td>BC-0007 (Back-up)</td>
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