CRB-601: A Highly Potent and Selective Blocking Antibody Targeting the $\alpha_v\beta_8$ Integrin

New York Academy of Sciences
Frontiers in Cancer Immunotherapy
May 11, 2022
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Disclosures

- Authors are employees and shareholders of Corbus Pharmaceuticals
- CRB-601 is an investigational, pre-clinical stage candidate that has not entered clinical testing and is not approved by the FDA for any indication
TGFβ plays a central role in immunoregulation and cancer

- TGFβ has been associated with immune cell exclusion in cancer
- Targeting TGFβ has been challenging
  - Local tumor versus systemic signaling may be key

TGFβ predicts poor clinical outcomes in a subset of cancer patients.

Immunogenomic subtypes in cancer:

- C1: WOUND HEALING
- C2: INF-γ DOMINANT
- C3: INFLAMMATORY
- C4: LYMPHOCYTE DEPLETED
- C5: IMMUNOLOGICALLY QUIET
- C6: TGFβ DOMINANT

Gene expression, immune cell quantification & network mapping:
- 33 different cancer types / 8,000+ tumors

Successfully blocking TGFβ overcomes immune exclusion

- An increase in CD3 immune cell infiltration is associated with the anti-PD/L-1 and anti-TGFβ antibody combination
- Effective therapeutic targeting of TGFβ could be achieved via CRB-601 targeting the αvβ8 integrin

Targeting the integrin αvβ8 represents a novel approach to regulating TGFβ

Recent experience with TGFβ¹

<table>
<thead>
<tr>
<th>TGFβ pathway</th>
<th>Investigational Compound</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti sense TGFβ2</td>
<td>Trabedersen</td>
<td>Anti sense oligo</td>
</tr>
<tr>
<td>αvβ3/5 Integrin inhibitor</td>
<td>Cilengitide</td>
<td>αvβ3/5 mAb</td>
</tr>
<tr>
<td>TGFβRI blockade</td>
<td>LY3022859</td>
<td>mAb</td>
</tr>
<tr>
<td>TGFβ ligand Trap</td>
<td>Fresolimumab</td>
<td>mAb</td>
</tr>
<tr>
<td>TGFβ ligand Trap + PD-1</td>
<td>Bintrafusp alfa</td>
<td>Bifunctional fusion protein</td>
</tr>
<tr>
<td>TGFβRI Kinase inhibitor</td>
<td>Galunisertib</td>
<td>small molecule</td>
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</tbody>
</table>

TGFβ Pathway and Point of Therapeutic Intervention²

Novel point of therapeutic intervention
Blocking the αvβ8 activation of TGFβ in the local tumor micro environment

CRB-601 binds at the Interface between TGFβ and αvβ8
CRB-601 binds to integrin $\alpha_v\beta_8$ with high affinity and selectivity.

Integrin Binding and Selectivity (Surface Plasmon Resonance)

- $K_d$, nM

<table>
<thead>
<tr>
<th>Antibody</th>
<th>$\alpha_v\beta_1$</th>
<th>$\alpha_v\beta_3$</th>
<th>$\alpha_v\beta_5$</th>
<th>$\alpha_v\beta_6$</th>
<th>$\alpha_v\beta_8$</th>
<th>m$\alpha_v\beta_8$</th>
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<tbody>
<tr>
<td>CRB-601</td>
<td>$&gt;200$</td>
<td>$&gt;200$</td>
<td>$&gt;200$</td>
<td>$&gt;200$</td>
<td>1.4</td>
<td>1.4</td>
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</table>

L-TGF$\beta$ Binding Inhibition

- CRB-601 IC50=3.7 nM
- mCRB-601 IC50=1.4 nM
CRB-601 enhances anti-PD-1 therapy in checkpoint inhibition sensitive and resistant murine tumor models

**MC38 (Inflamed Tumor)**

**EMT6 (Excluded Tumor)**

**4T1 (Desert Tumor)**

<table>
<thead>
<tr>
<th>% TGI</th>
<th>MC38</th>
<th>EMT6</th>
<th>4T1</th>
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<tr>
<td>Anti-PD-1</td>
<td>86</td>
<td>38</td>
<td>6</td>
</tr>
<tr>
<td>CRB-601</td>
<td>44</td>
<td>63</td>
<td>10</td>
</tr>
<tr>
<td>Combo</td>
<td>100</td>
<td>96</td>
<td>41</td>
</tr>
</tbody>
</table>

CRB-601: 10 mg/kg BIW
Anti-PD-1: 10 mg/kg BIW
10 animals / group
Animals randomized at 50-80 mm³
Comparisons across arms
*p<0.05, ***p<0.001, ****p<0.0001
CRB-601 enhances anti-PD-1 therapy in early and late intervention

**Early Intervention**
Tumor volume = 50-80 mm$^3$

**Late Intervention**
Tumor volume = 200 mm$^3$

### Table

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MC38 Early</th>
<th>MC38 Late</th>
<th>EMT6 Early</th>
<th>EMT6 Late</th>
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<tr>
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CRB-601: 10 mg/kg BIW
Anti-PD-1: 10 mg/kg BIW
8 (EMT6-late) or 10 animals/group
Comparisons across arms
*p<0.05, ***p<0.001, ****p<0.0001
CRB-601 enhances anti-PD-1 therapy in early and late intervention

Early Intervention
Tumor volume = 50-80 mm$^3$

Late Intervention
Tumor volume = 200 mm$^3$

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<th>Animal Model</th>
<th>Early Intervention</th>
<th>Late Intervention</th>
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<td>MC38 (Inflamed Tumor)</td>
<td>Tumor volume = 50-80 mm$^3$</td>
<td>Tumor volume = 200 mm$^3$</td>
</tr>
<tr>
<td>EMT6 (Excluded Tumor)</td>
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CRB-601: 10 mg/kg BIW
Anti-PD-1: 10 mg/kg BIW
8 (EMT6-late) or 10 animals/group
Comparisons across arms
*$p<0.05$, **$p<0.001$, ***$p<0.0001$
CRB-601 enhances the impact of anti-PD-1 therapy on the number of animals cured of their tumor burden

MC38 implantation
Days -11

Treatment
0 3 7

CRB-601, 10 mg/kg, IP
Anti-PD-1 (RMP1-14), 10 mg/kg, IP

n=10/group

Tumor volume = 200 mm³ (when treatment initiate)
Tumor regression following treatment with CRB-601 and anti-PD-1 in MC38 tumors is associated with T cell infiltration and activation in tumors.

MC38 implantation → Treatment → PD readouts
- Day-14 → Day0 → Day3 → Day 7

- CRB-601, 10 mg/kg, IP
- Anti-PD-1 (RMP1-14), 10 mg/kg, IP

Tumor volume = 250 mm³ (when treatment initiated)

A Tumor weight (g)
B CD8⁺ tumor-infiltrating lymphocytes (TILs)
C Proliferation of CD8⁺ TILs
D PD-1 expression in CD8⁺ TILs

* p < 0.05
CRB-601 + anti-PD1 is associated with tumor-specific immune memory

- Surviving MC38 tumor bearing mice treated with CRB-601 + anti-PD1 were re-challenged with MC38 tumors at day 52 post treatment initiation
- Survival and regrowth compared to treatment naïve mice was monitored for 70 days

Source: Company data on file.
Blockade of αvβ8 in combination with anti-PD-1 increased TIL populations in immune excluded EMT6 tumors

Tumor volume = 200 mm³ (when treatment initiated)

**p<0.05; ***p<0.01; ****p<0.001; *****p<0.0001
Blockade of αvβ8 in combination with anti-PD-1 also increased NK and M1 macrophages in immune excluded EMT6 tumors

EMT6 orthotopic implantation

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<th>Days</th>
<th>Treatment</th>
<th>PD readouts</th>
</tr>
</thead>
<tbody>
<tr>
<td>-14</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>10</td>
</tr>
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CRB-601, 30 mg/kg, IP
Anti-PD-1 (RMP1-14), 10 mg/kg, IP

Tumor volume = 200 mm$^3$
(when treatment initiated)

Blockade of αvβ8 in combination with anti-PD-1 also increased NK and M1 macrophages in immune excluded EMT6 tumors

*<p<0.05; **<p<0.01; ***<p<0.001; ****<p<0.0001
Summary and Conclusions

- CRB-601 exhibits high affinity (low nM Kd) to human and murine $\alpha_v\beta_8$ and high selectivity with no appreciable binding to other RGD-binding integrins.

- CRB-601 significantly inhibits tumor growth as a single agent and enhances the efficacy of anti-PD-1 immunotherapy in checkpoint inhibitor-sensitive & resistant tumor models.

- CRB-601 alone or in combination with anti-PD-1 mAb led to a significant increase in tumor-infiltrating T cells, NK cells and M1 polarized macrophages within EMT6 tumors.

- CRB-601 holds promise as a potential combination partner for cancer immunotherapies.

- We are on track for an IND in H1 2023.
Collaborators

**Corbus Pharmaceuticals:**
- Daqing Wang
- Maneesh Singh
- Eric Haines
- Suzie Ferreira
- Rachael Brake

**ZM Scientific**
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- Eugene Zhukovsky

**University of California, San Francisco**
- Dr. Steven Nishimura