TGFβ is a secreted protein produced by multiple lines of leukocytes and tumors that promotes cancer progression primarily via the suppression of both the innate and adaptive immune systems. This makes TGFβ a promising immunotherapeutic target in cancer. It is ubiquitously expressed in a latent (LTGFβ) form and LTGFβ is known to promote or maintain an immunosuppressive phenotype within the tumor microenvironment (2). Integrin αvβ8 specifically binds to LTGFβ. This interaction is essential for the activation of LTGFβ-mediated signals in a variety of cancer cell types. Interestingly, it has been recently shown that integrin αvβ8-liganded LTGFβ activation can act directly through the TLR7 and does not require the release of active TGFβ (2). Intact and intact-αvβ8-liganded TGFβ activation has been shown to block immunosuppressive T reg differentiation and enhance the recruitment of cytotoxic T cells into the tumor microenvironment (3, 4).

Here, we demonstrate the use of Surface Plasmon Resonance Imaging (SPI) as a novel clinical approach to document the integrin αvβ8 binding to modulate the immune landscape within the tumor and to enhance resistance to immune checkpoint therapy. CRB-601 is a selective and potent integrin αvβ8-blocking antibody that enhances the activity of immune checkpoint inhibitors in vivo and holds promise as a potential combination partner with TGFβ1 immunotherapies. Investigational New Drug (IND) enabling studies are currently underway.

Figure 1: TGFβ is held in an inactive state in association with latency-associated peptide (LAP) and is presented on cell surfaces. Figure 2: The ability of CRB-601 to block binding of TGFβ to αvβ8 was measured by a Surface Plasmon Resonance Assay. CRB-601 was immobilized on a polystyrene plate and incubated with LN229 cells expressing αvβ8. Bound LN229 cells were quantified by Crystal Violet. Data were fit to a 4-parameter displacement curve to determine IC50.

Table 1. Surface Plasmon Resonance Binding Affinities (Kd, nM) to Human αvβ8, and Marine Integrin αvβ8

<table>
<thead>
<tr>
<th>Antibody</th>
<th>αvβ8 (nM)</th>
<th>αvβ8 (nM)</th>
<th>αvβ8 (nM)</th>
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<tr>
<td>CRB-601</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
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<tr>
<td>mCRB601</td>
<td>ND</td>
<td>ND</td>
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</table>

Conclusions

- CRB-601 exhibits low rm affinity to human mαvβ8 and high selectivity with no appreciable binding to other proteins.
- mCRB-601 significantly inhibits MC38 tumor growth as a single agent and enhances the efficacy of anti-TGFβ1 immunotherapy.
- mCRB-601 treatment effects on tumor growth, alone and in combination with anti-PD-1, correlates with reduced αvβ8 integrin expression and infiltration into the tumor microenvironment of CD8+ T cells with anti-PD-1 treatment and augmented immune cell contribution to tumor clearance.
- The combination of CRB-601 and anti-PD-1 therapy protected mice from tumor rechallenge.

References

2. Campbell MS, et al. (2020) Cemio伐 voters integrin

Disclosures and Acknowledgements

- This study was sponsored by Corbus Pharmaceuticals, Inc. Subject to any regulatory approval, CRB-601 is an investigatory product and this presentation does not imply initiation or marketing of the product.