Characterization of CRB-601

**Binding specificity**

- **Raj B**
- **OVCA3**
- **Raj OVCA3-t1**

**Relationship between αvβ6 expression on tumor cells and antioxidant activity of blocking antibody CRB-601**

**CRB-601 alone and in combination with anti-PD-1 mAb reverses immune-mediated killing**

**Conclusions**

- CRB-601 is a potent and selective integrin αvβ6 blocking monoclonal antibody.
- CRB-601 significantly inhibits tumor growth as a single agent and enhances the efficacy of anti-PD-1 mAb-mediated immunotherapy in CPI-sensitive and CPI-resistant tumor models.
- CRB-601 activity was significantly increased in tumors expressing EMT activity and levels of αvβ6 compared to tumors expressing low levels.
- CRB-601 alone and in combination with anti-PD-1 led to a significant increase in tumor-infiltrating T cells, NK cells and M1 ratio in CRB-601 treated tumors, suggesting that CRB-601 treatment overcomes immune exclusion in EMT-expressing tumors.
- CRB-601 holds promise as a potential combination partner for cancer immunotherapy.
- CRB-601 is planned for in H1 2023.

**References**


**Abstract**

Increased transforming growth factor β (TGFβ) signaling within the tumor microenvironment (TME) is associated with immune exclusion, resistance to checkpoint inhibitor (CPI) therapy, and poor patient outcomes, making TGFβ a promising immunotherapeutic target in cancer (1). TGFβ is ubiquitously expressed as a latent form (LTGBF) and presented on cell surfaces by LTGBF binding proteins (e.g. GARP and LTPR1) as part of the large latent complex (LLC) wherein it is activated by binding to integrins. Integrin αvβ6 specifically binds to LTGBF, and this interaction is essential for the activation of the TGFβ-receptor complex. Therefore, Therapeutic Pharmaceuticals is developing a humanized monoclonal antibody, CRB-601, that binds specifically with high affinity to αvβ6 and blocks its critical interaction with LTGBF.

CRB-601 was selected as a development candidate due to its high binding affinity and specificity to αvβ6, and high potency for blocking the αvβ6-LTGBF interaction. CRB-601 binding affinity was evaluated in syngeneic murine tumor models. Mice bearing subcutaneously implanted murine colon carcinoma MC38 and pancreatic ductal adenocarcinoma Panc-2, or orthotopically implanted murine cancer models EMT6 and 4T1 cells were treated with isotype control, anti-mouse PDL-1, CRB-601 alone and combinations of CRB-601 with PDL-1. As a single agent, CRB-601 significantly inhibited CPI-sensitive MC38 and resistant EMT6 tumors. In combination with anti-PDL-1, CRB-601 not only enhanced efficacy of anti-PD-1 therapy in immune-infiltrated MC38 tumors, but also reversed the PD-1 resistance in tumor immunity excluded EMT6 tumors. Notably, in the Panc-2 and 4T1 models, both were regarded as “desert tumors” that are non-responsive to current CPI combination treatment with CRB-601 and anti-PD-1 mAb significantly enhanced the antitumor efficacy of anti-PD-1 therapy. Flow cytometry analysis of EMT6 tumors showed a resided TAM, correlating increased EMT6 tumors into immune cell-infused tumors. Changes included marked increases in infiltration of T cells, NK cells and CD163+ polarized macrophages in tumors exposed to CRB-601 or the combination.

Flow cytometry analysis of Raj B, OVCA3 and Raj-OVCA3 tumor cells expressing αvβ6, blocking αvβ6, and stimulating αvβ6 showed enhanced binding of CPI’s to tumor cells expressing αvβ6 and increased αvβ6 expression on tumor cells in those models. p-values were calculated by one-way ANOVA followed by Tukey’s multiple comparisons test. p<0.05, *p<0.01, **p<0.001.

**Results**

- CRB-601 inhibits tumor growth as a single agent and enhances anti-PD-1 CPI therapy in CPI-sensitive and CPI-resistant murine tumor models.
- CRB-601 enhances anti-PD-1 therapy in CPI sensitive and resistant murine tumor models. Mice (n=10/group) bearing CPI sensitive-immunofluorescent MC38 CPI resistant-immunofluorescent MC38 and CPI resistant-immunofluorescent MC38 pancreatic ductal adenocarcinoma Panc-2 were treated with 10mg/kg ip once control (0), anti-mouse PDL1 mAb (RMP14-1), 10mg CRB-601 mAb or CRB-601 mAb and RMP14-1 in combination twice weekly for 3 weeks. p-values were calculated by one-way ANOVA or t-test. p<0.05, *p<0.01, **p<0.001.
- Treatment with CRB-601 in combination with anti-PD-1 mAb induces long-lasting CD8+ T cell-dependent immunity against cancer.

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- We thank Dr. Steven Nohria and UCSF colleagues for scientific advice and development of the anti-PD-1 mAb antibody.
- CRB-601 is an investigational, preclinical-stage candidate that has not entered clinical testing and is not approved by the FDA for any indication.