CRB-601, an integrin αvβ8 blocking antibody entering Phase I: pre-clinical and translational biomarkers for indication selection

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Background

TGFβ is a cytokine associated with immunosuppression in metastatic solid tumors. Efforts to target this pathway have been unsuccessful to date. TGFβ is produced as a dimeric membrane bound latent protein (L- TGFβ) in which TGFβ is held in an inactive complex with its pro-peptide, latency associated protein (LAP) and a latent binding protein. Integrin a_vB_8 is a key activator of L-TGFβ acting at the synapse between tumor and immune cells. CRB-601 is a high affinity IgG4 monoclonal antibody with selectivity for integrin a_vB_8.

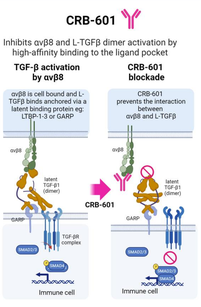
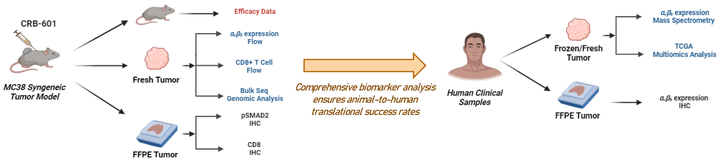


Figure 1. Model of a_vB_8-mediated activation of latent TGFβ and inhibition by CRB-601.

Methods

- Syngeneic mouse tumor model MC38 (immune-inflamed model) was assessed for CRB-601 induced anti-tumor activity, immunological changes and biomarkers of response.
- CRB-601 treated tumors were assessed for modulation of immune cell populations using flow cytometry, genomic and IHC.
- Modulation of TGFβ was assessed by pSMAD2 IHC.
- Assessment of protein expression of a_vB_8 was done using proprietary IHC assay, mass spectrometry a_vB_8 data and TGFβ pathway related genes were correlated in primary human tumors.



Results

Levels of $\alpha_v\beta_8$ expression predict the antitumor activity of $\alpha_v\beta_8$–blockade by the CRB-601 mAb

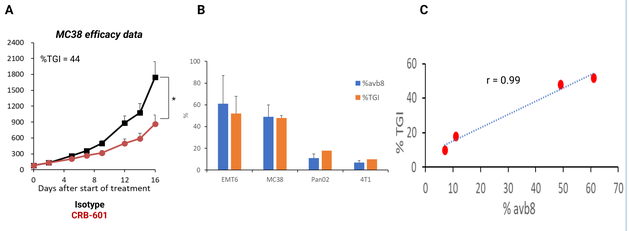


Figure 2. (A) CRB-601 anti-tumor activity in MC38 mouse model (n=10/gp). Mice were treated with 10 mg/kg of CRB-601 or isotype control twice weekly for 3 weeks. *p* values represent one-way ANOVA or t-test. **p* <0.05. (B & C) Relationship between tumor a_vB_8 expression & anti-tumor activities of CRB-601.

Downregulation of pSMAD2 expression levels in CRB-601 treated MC38 tumors is indicative of TGF*β* pathway modulation

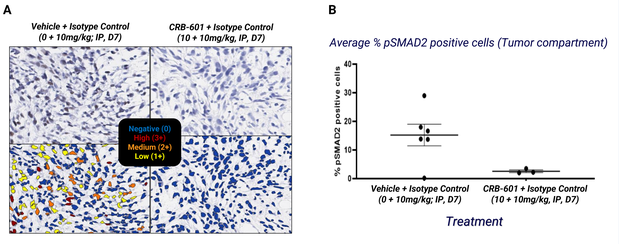


Figure 3. (A) Protein expression of pSMAD2 by IHC in MC38 bearing mice treated with CRB-601 (IP dosing on D0 and D3, harvested on D7) (B) Quantitative IA methodology used for assessment of % pSMAD2 positive cells.

CRB-601 induces immunomodulatory effects in MC38 TME, represented by an increase in cytotoxic CD8+ T cells

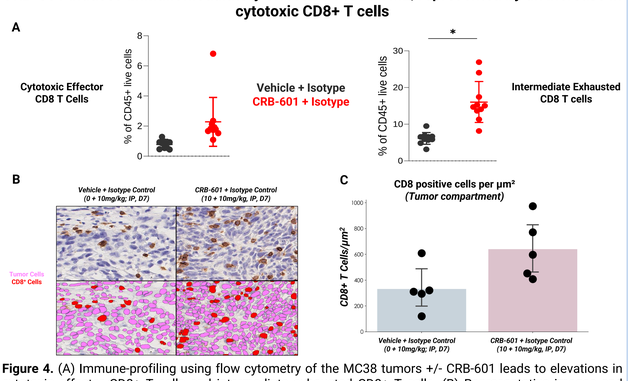


Figure 4. (A) Immune-profiling using flow cytometry of the MC38 tumors +/- CRB-601 leads to elevations in cytotoxic effector CD8+ T cells and intermediate exhausted CD8+ T cells. (B) Representative images and quantitation of CD8 IHC staining (C) which reveals an increase in DAB/CD8-positive cells per µm² tumor tissue upon treatment with CRB-601.

CRB-601 treatment leads to modulation of TGF*β* pathway and immune system related genes in MC38 tumors

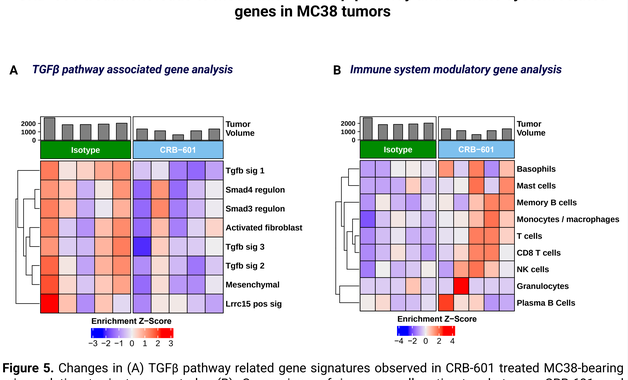


Figure 5. Changes in (A) TGFβ pathway related gene signatures observed in CRB-601 treated MC38-bearing mice relative to isotype controls. (B) Comparison of immune cell estimates between CRB-601 and isotype treated MC38 tumors derived from deconvolution of bulk RNASeq data. Upregulation of gene expression in various immune compartments reflecting an increase in these populations.

$\alpha_v\beta_8$ protein expression in human tissue micro-arrays (TMAs) using proprietary IHC assay developed by Corbus

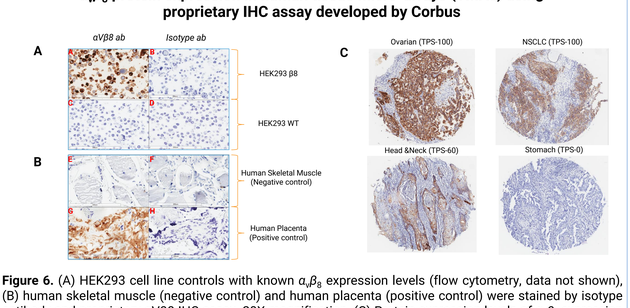


Figure 6. (A) HEK293 cell line controls with known a_vB_8 expression levels (flow cytometry, data not shown), (B) human skeletal muscle (negative control) and human placenta (positive control) were stained by isotype antibody and proprietary αVβ8 IHC assay. 20X magnification. (C) Protein expression levels of a_vB_8 expression were evaluated on various human cancer TMA (tissue microarray) cores using clinically validated proprietary Corbus IHC assay, TPS scores were generated by a pathologist.

ITGB8 Gene (TCGA) and protein expression (Mass spectrometry) analysis identified disconnect between gene and protein expression for $\alpha_v\beta_8$

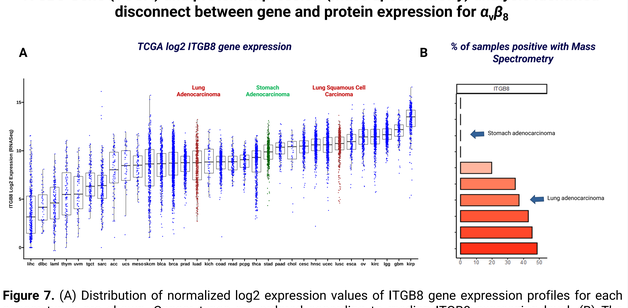


Figure 7. (A) Distribution of normalized log2 expression values of ITGB8 gene expression profiles for each cancer types are shown. Cancer types are ordered according to median ITGB8 expression level. (B) The percentage of samples where ITGB8 protein was detected in Mass Spectrometry data for each cancer type. A protein was considered to be detected in a sample if the relative protein abundance was greater than 0.

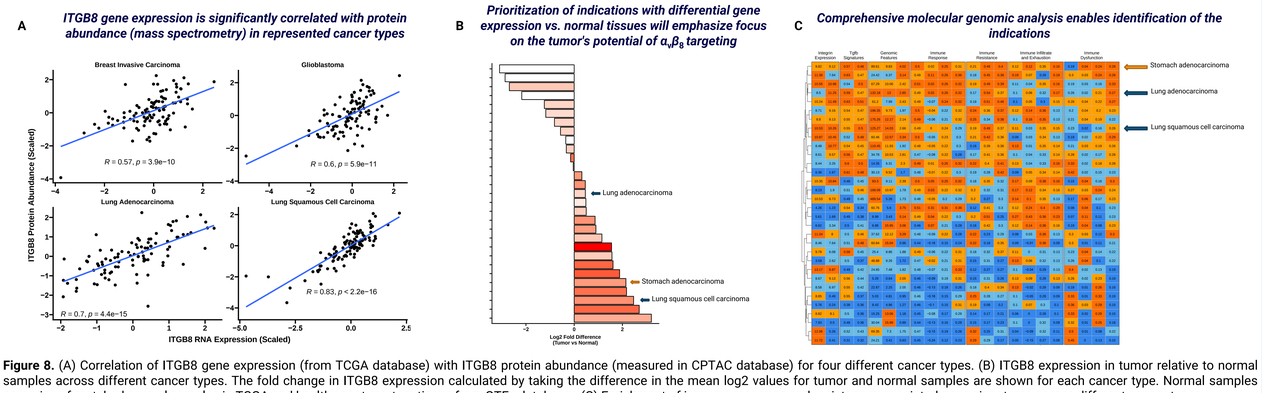


Figure 8. (A) Correlation of ITGB8 gene expression (from TCGA database) with ITGB8 protein abundance (measured in CPTAC database) for four different cancer types. (B) ITGB8 expression in tumor relative to normal samples across different cancer types. The fold change in ITGB8 expression calculated by taking the difference in the mean log2 values for tumor and normal samples are shown for each cancer type. Normal samples comprise of matched normal samples in TCGA and healthy post-mortem tissue from GTEx database. (C) Enrichment of immune response and resistance associated gene signatures across different cancer types.

Conclusions

- CRB-601 is a potent and selective integrin a_vB_8 blocking mAb that demonstrates anti-tumor effect which was significantly increased in tumors expressing high levels of a_vB_8.
- CRB-601 demonstrated immunomodulatory effects as reflected in changes in cytotoxic CD8+ T cell population and gene expression in the TME.
- Integrin a_vB_8 blockade led to modulation in TGFβ pathway related genes and downregulation of pathway biomarker pSMAD2.
- Corbus developed a proprietary a_vB_8 IHC assay which has enabled us to understand the prevalence and expression pattern of the a_vB_8 in human tumors.
- Understanding gene and protein expression levels for various solid tumors may enable rational indication and patient selection.
- CRB-601 is planned for IND in H2 2023.

Disclosures and Acknowledgements

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2. We thank Dr. Steven Nishimura and UCSF colleagues for scientific advice and development of the CRB-601 antibody.
3. 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.

References

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