CRB-601: Unlocking the Potential of αvβ8 Blockade - Antitumor Activity and Immune Remodeling

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Frontiers in Cancer Immunotherapy, May 2023

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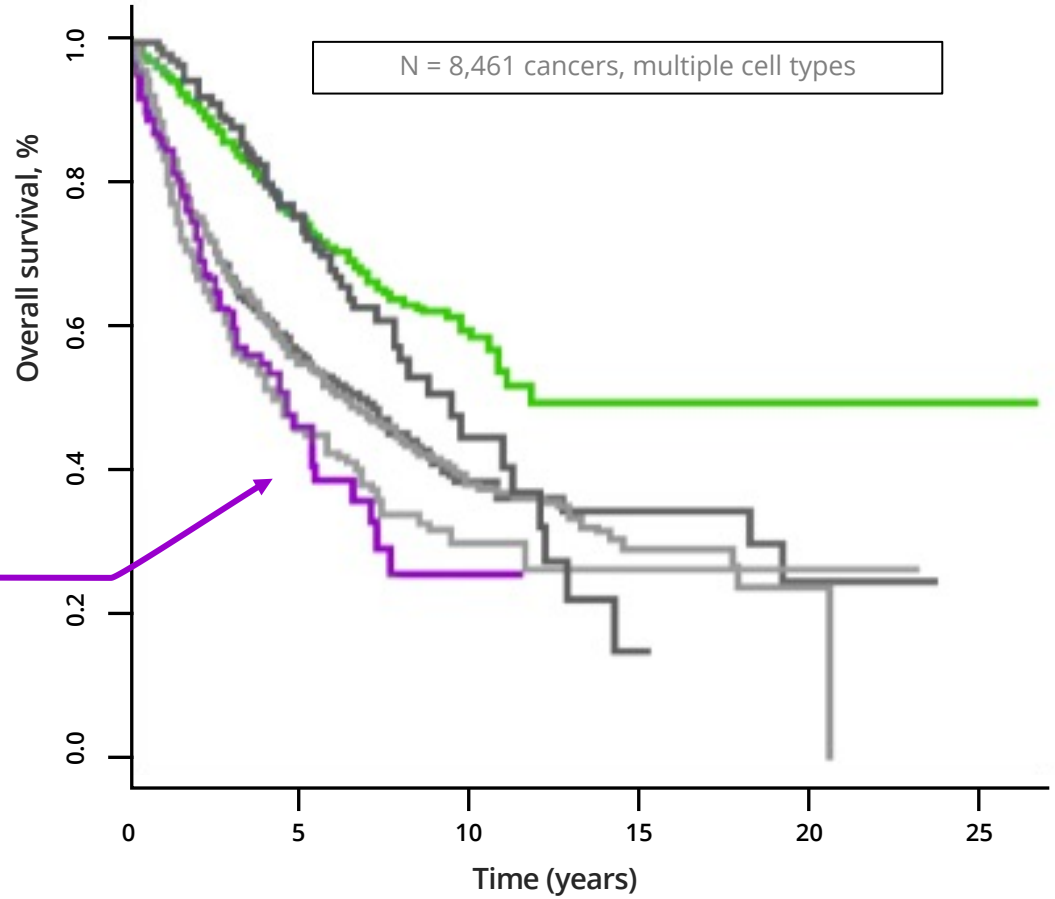
TGFβ predicts poor clinical outcomes in a subset of cancers

Immunogenomic subtypes in cancer

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

TGFβ predominance gene signature

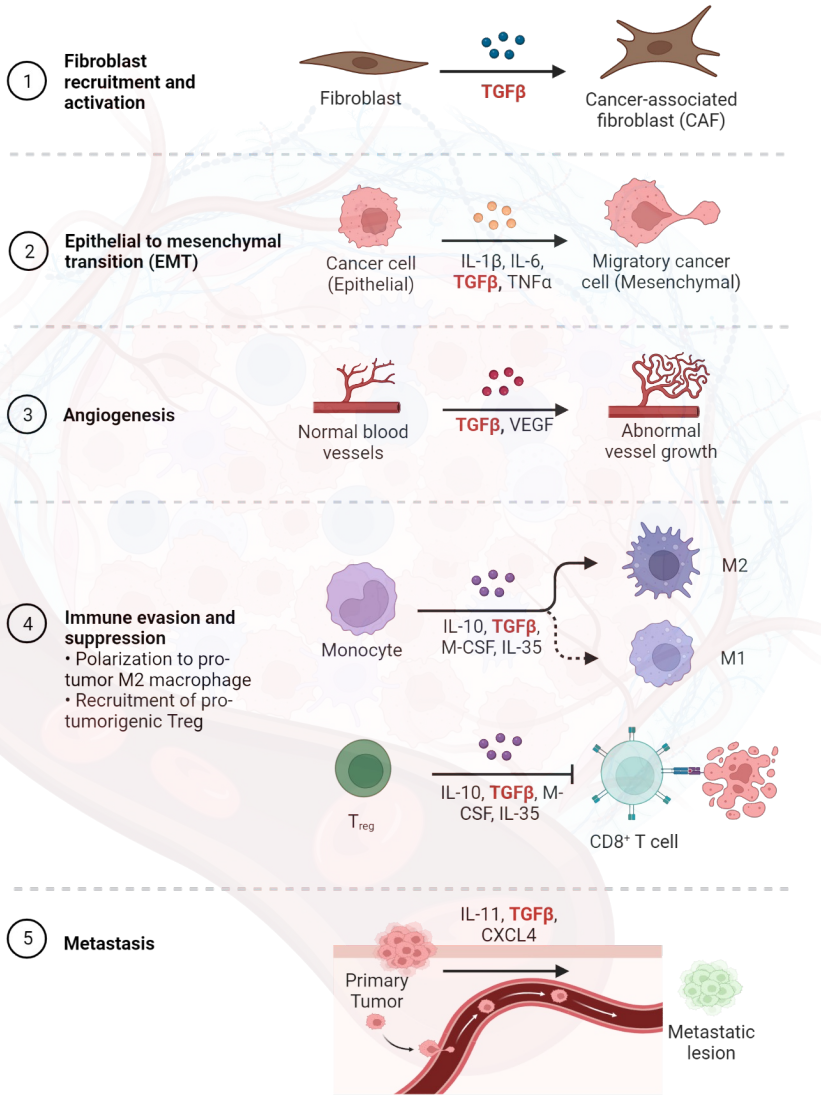


Gene expression, immune cell quantification & network mapping

- 33 different cancer types / 8,000+ tumors

Source: Thorsson, et al. The Immune Landscape of Cancer, Immunity. 2018; 48:817

Dysregulation of the TGFβ pathway in cancer: complex implications on tumor microenvironment and immune escape mechanism



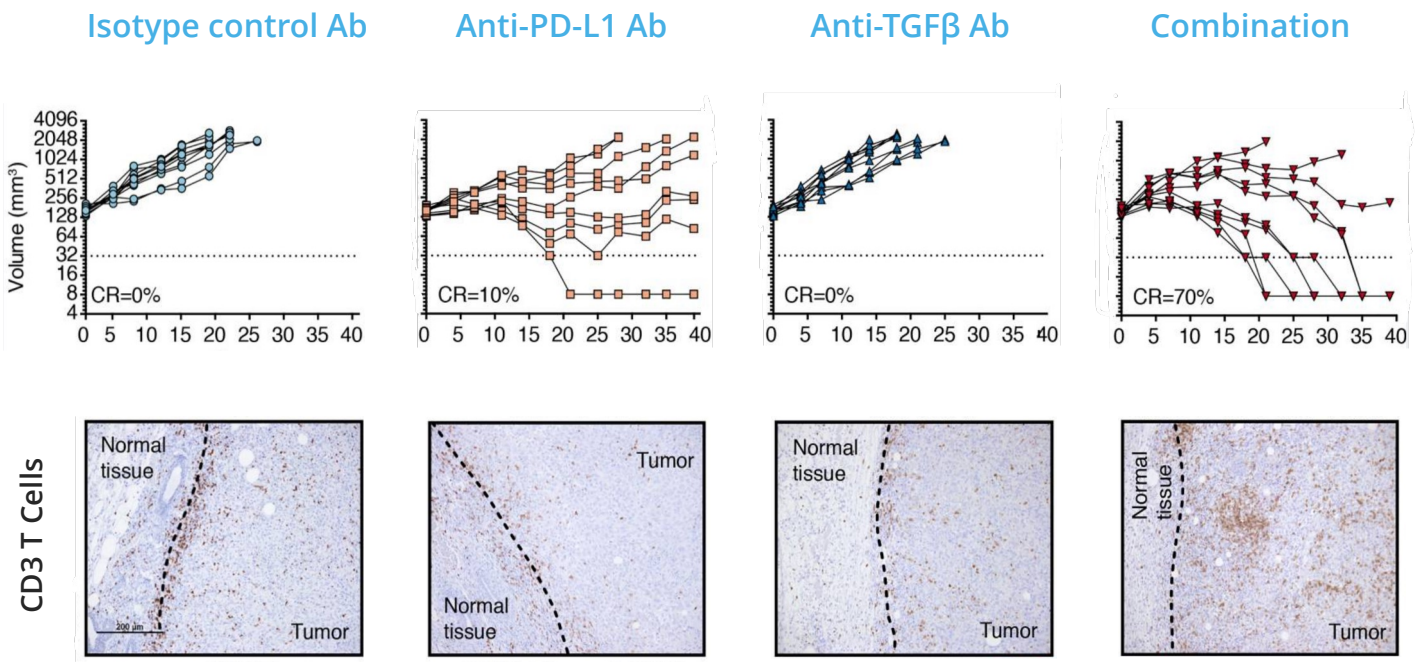
Dysregulation of the TGFβ pathway can promote tumor growth, metastasis, and immune evasion by altering the tumor microenvironment.

How do we determine which of these mechanisms are dominant in a tumor microenvironment?

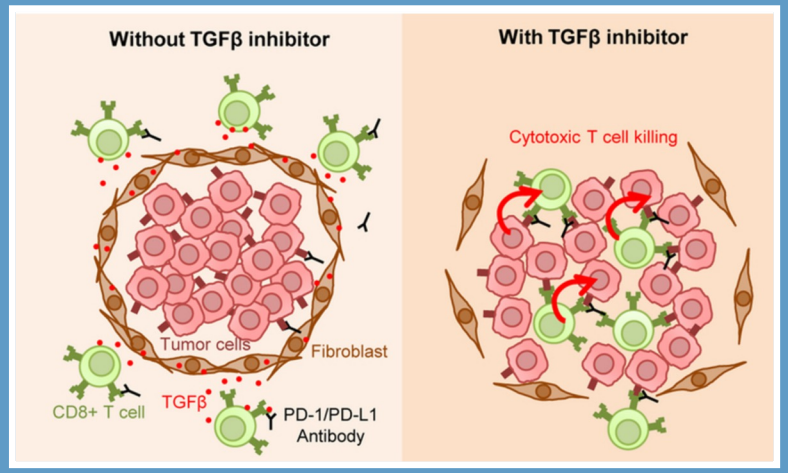
Source: S. Mariathasan; Nature 2018, D Tauriello; Nature 2018, D Thomas; Cancer Cell 2005, E Batlle; Immunity, 2019
Prepared in Bio Render

TGFβ inhibition overcomes an environment of immune exclusion

Immune tolerance / Immune evasion is a major effect of TGFβ in cancer



Stromal TGFβ signaling is a determinant of immuno-exclusion

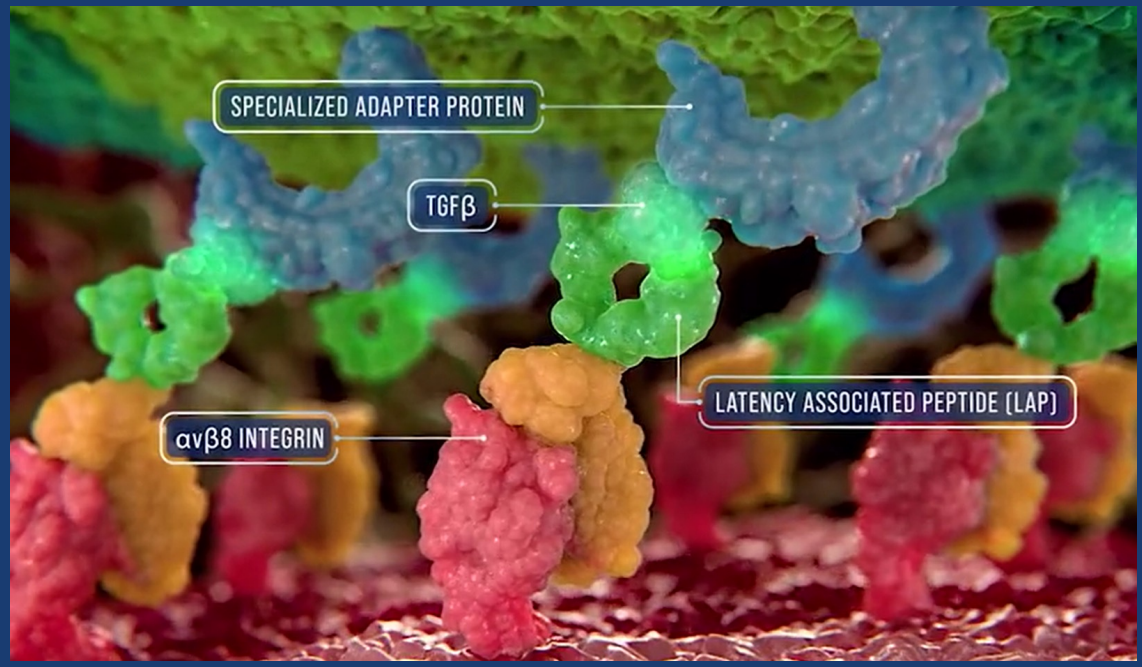


- An increase in CD3 immune cell infiltration is associated with the anti-PD/L-1 and a pan anti-TGFβ antibody combination

Sources: 1. Mariathsasan, et al., Nature. 2018; 554:547. 2. Ganesh & Massagué., Immunity 2018: 626-628.

CRB-601

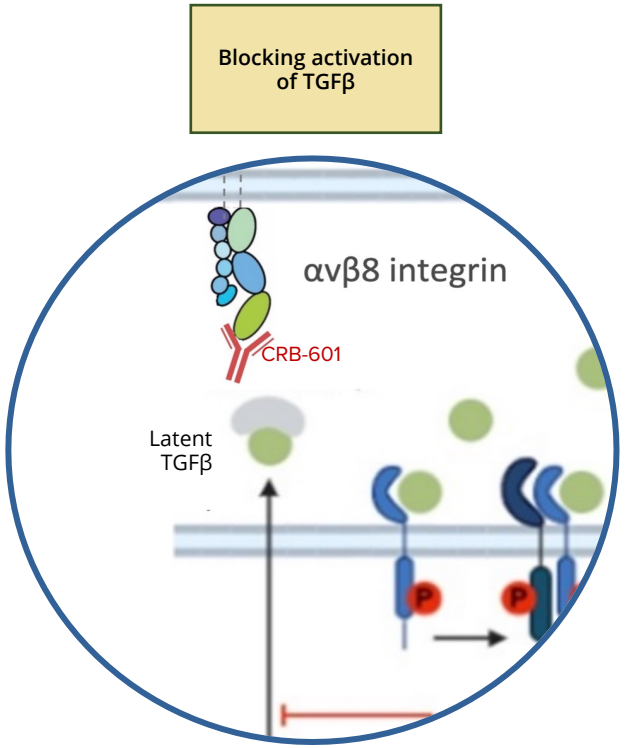
An avb8 integrin blocking antibody



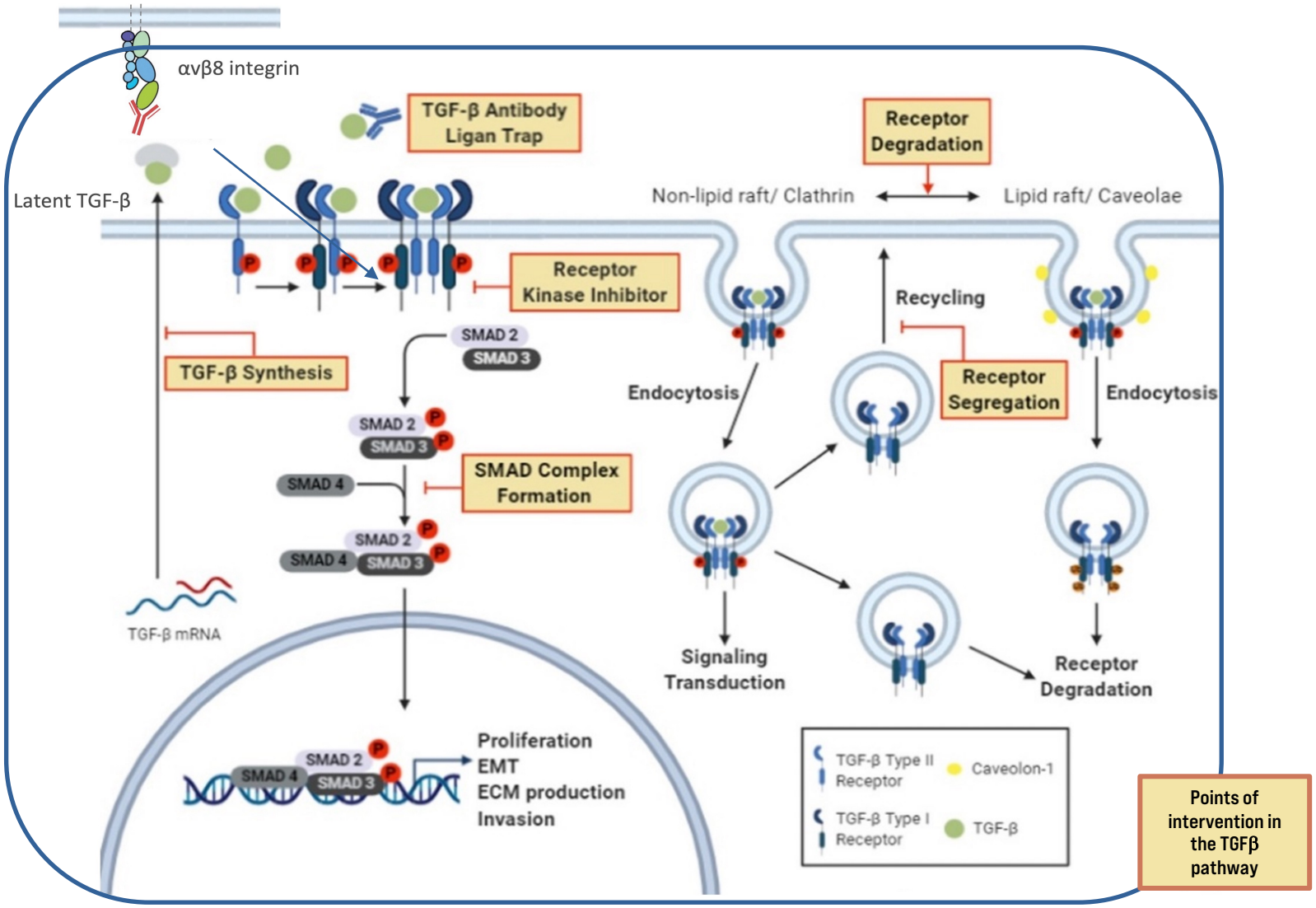
Blockade of the integrin avb8 prevents an early step in TGFβ activation

Novel point of therapeutic intervention

Blocking the αvβ8 activation of TGFβ in the local tumor microenvironment



CRB-601 binds at the interface between latent TGFβ and αvβ8



Sources: 1. Reviewed in Teixeria., 2020. 2. Huang et al., 2021. Recent progress in TGFβ inhibitors for cancer therapy.

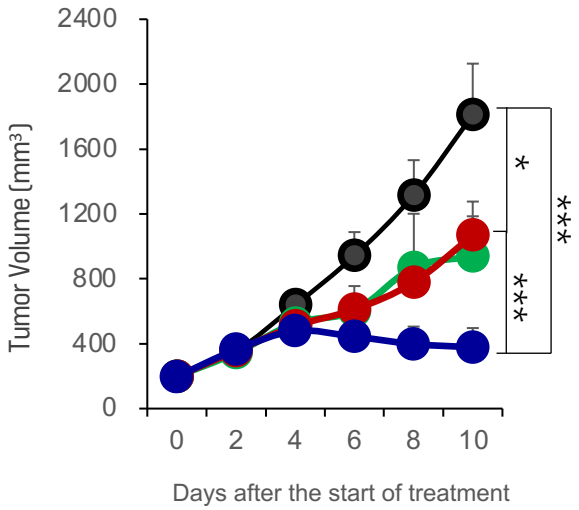
Emerging competition demonstrates the interest in this node of TGFβ regulation

	CRB-601	PF-06940434	SRK-181	ABBV-151	TBD	TBD
MOA	αvβ8	αvβ8	L-TGFβ	GARP (TGFβ1)	αvβ8/β1	αvβ8
Clinical Stage	IND in H1 2023	Phase 1	Phase 1	Phase 1	IND	Preclinical
Indications	Solid Tumors	Solid Tumors	Solid Tumors	Solid Tumors	Solid Tumors	TBD
Type	Monoclonal Antibody	Monoclonal Antibody	Monoclonal Antibody	Monoclonal Antibody	Small Molecule	Small Molecule
ROA	IV	IV	IV	IV	Oral	Oral

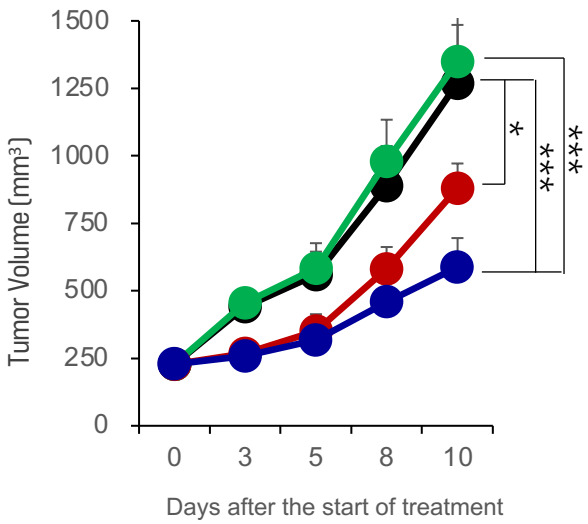
Source(s): Company websites, internal analysis

CRB-601 enhances anti-PD-1 therapy in checkpoint inhibition sensitive and resistant murine tumor models

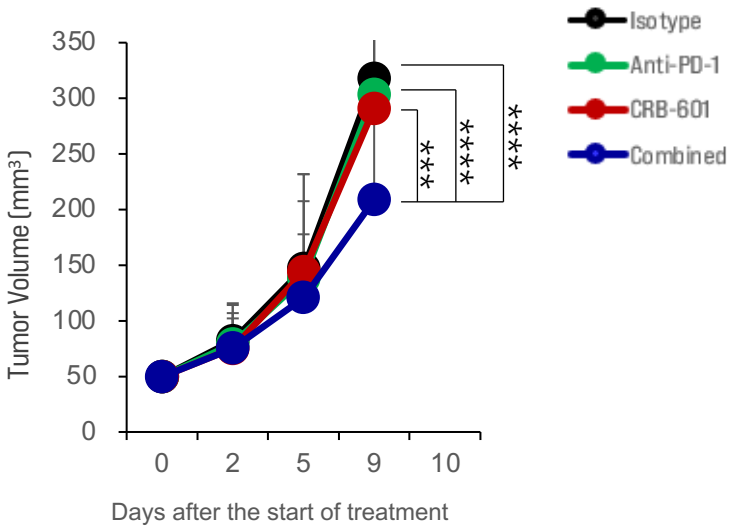
MC38 (Inflamed Tumor)



EMT6 (Excluded Tumor)



4T1 (Desert Tumor)



Checkpoint blockade sensitivity

Sensitive → Resistant

% TGI	MC38	EMT6	4T1
Anti-PD-1	54	-8	6
CRB-601	46	37	10
Combo	89	65	41

CRB-601: 10 mg/kg BIW

Anti-PD-1: 10 mg/kg BIW

10 animals / group

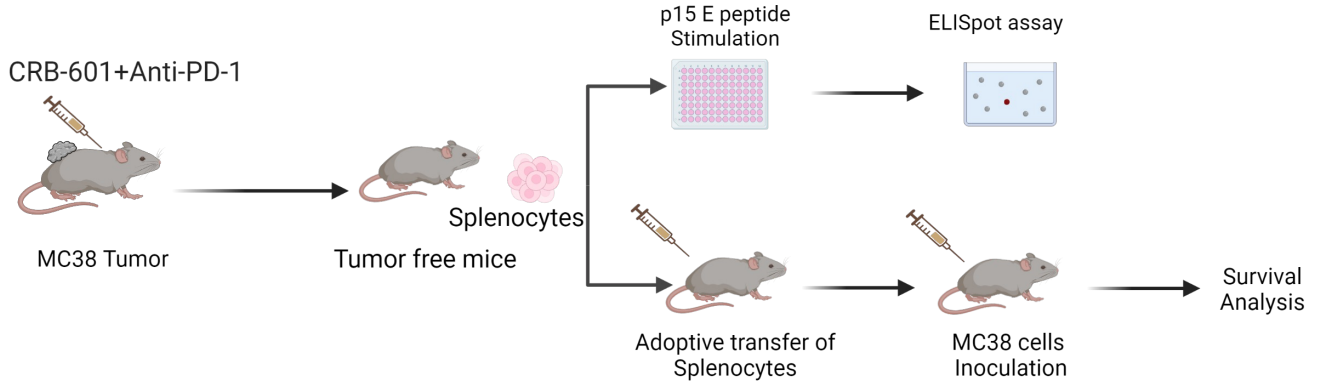
Animals randomized at 50-80 mm³

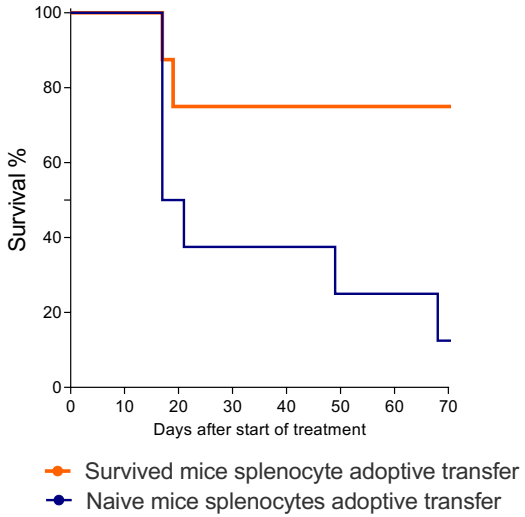
Comparisons across arms

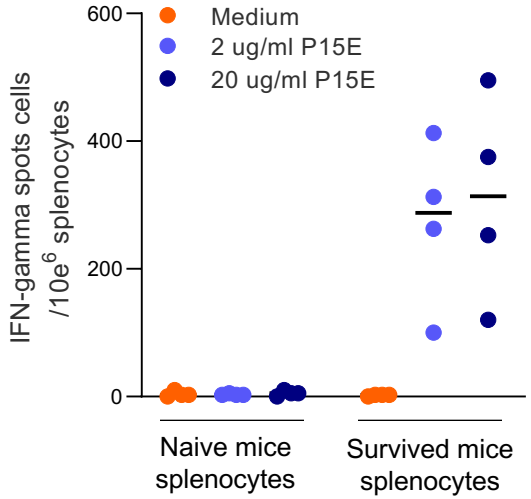
*p<0.05, ***p<0.001, ****p<0.0001

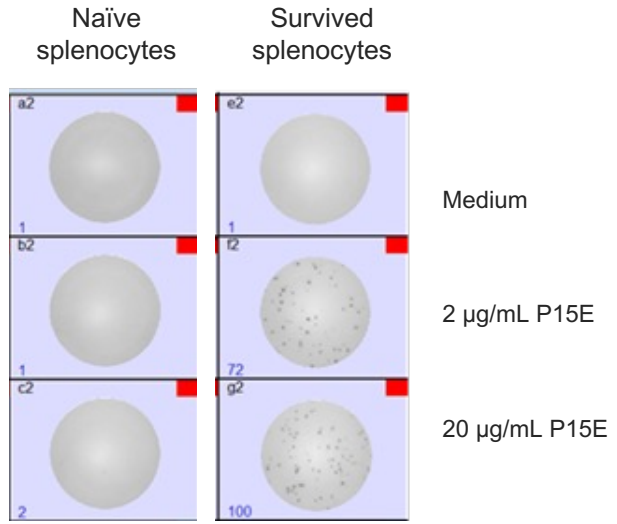
Source(s): Corbus data on file

CRB-601 in combination with anti-PD-1 induced long-lasting tumor-specific cytotoxic T cells response







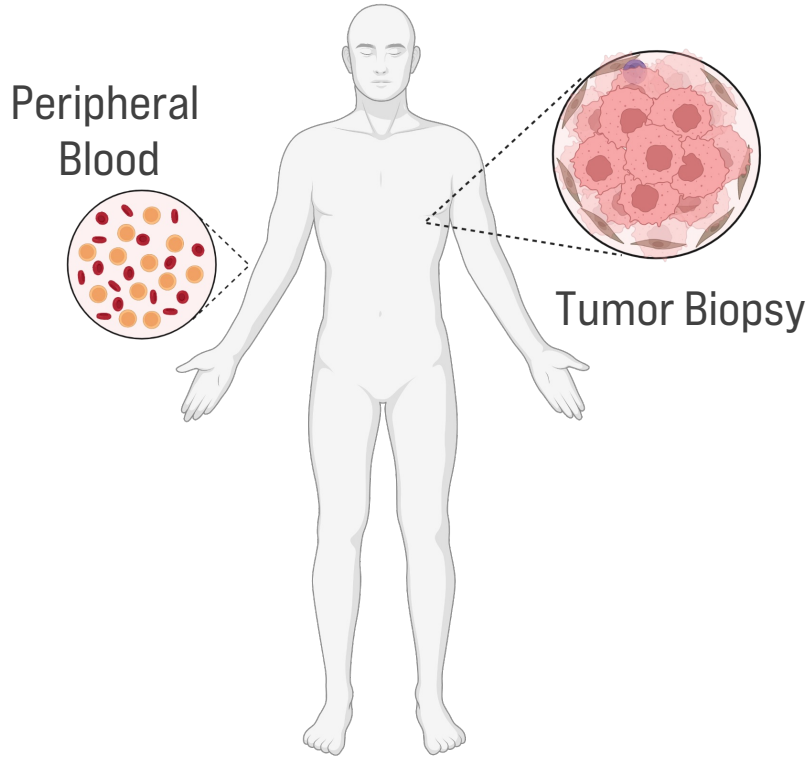


- Robust tumor antigen-specific T cells response in ELISpot assay.
- Rechallenge Tumor failed to grow in adaptive immune cells transferred mice.

Source(s): Corbus data on file

Exploring correlations between the TME and the systemic immune profile

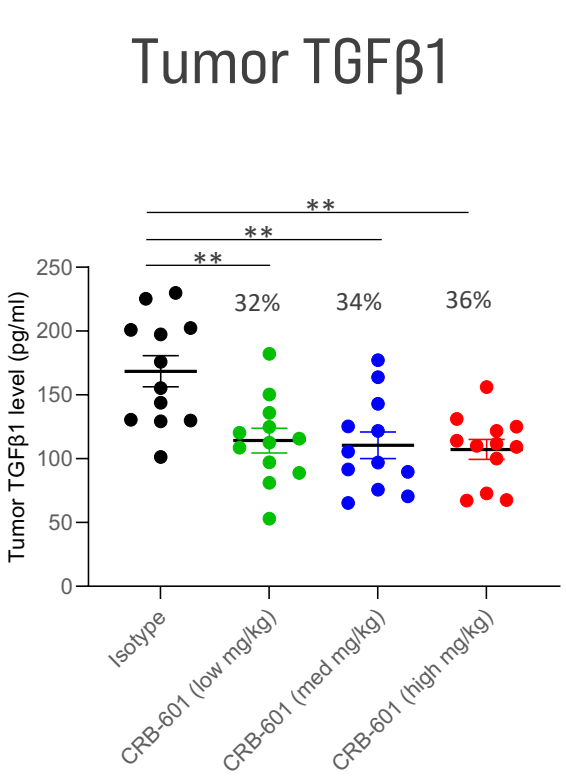
Pharmacodynamic markers

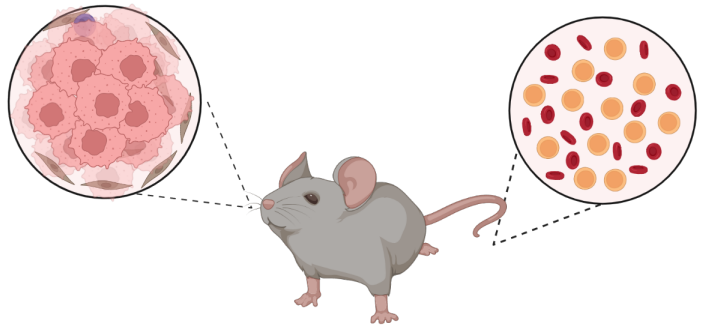


- How do you measure effects in the TME in an accessible and reproducible way
- Peripheral blood is easy to access but may not be reflective
- Tumor tissue is ideal but hard to access consistently due to cost, access and safety
- Question: Can we observe changes in the peripheral immune cells that reflect immune changes in the TME

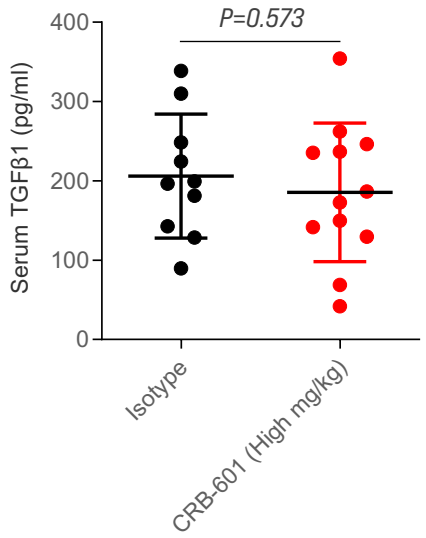
Dose-dependent antitumor activity of CRB-601 correlates with lower levels of TGFβ1 in the tumor microenvironment but not soluble TGFβ in circulation

Tumor TGFβ1





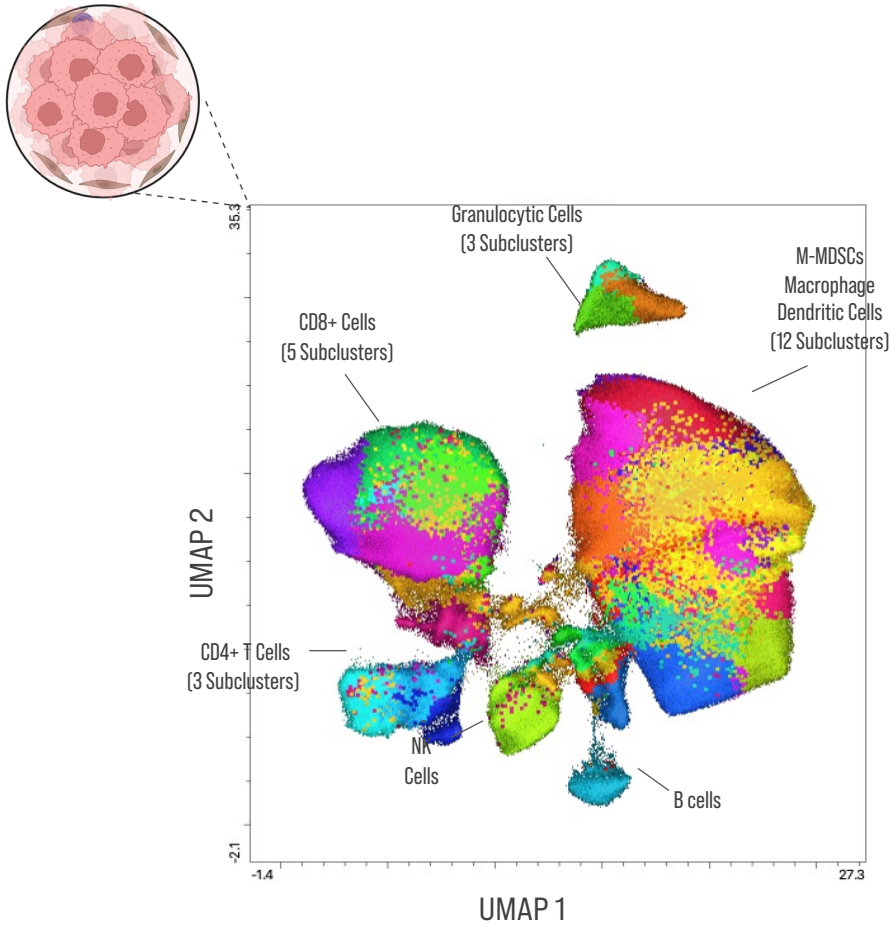
Plasma TGFβ1

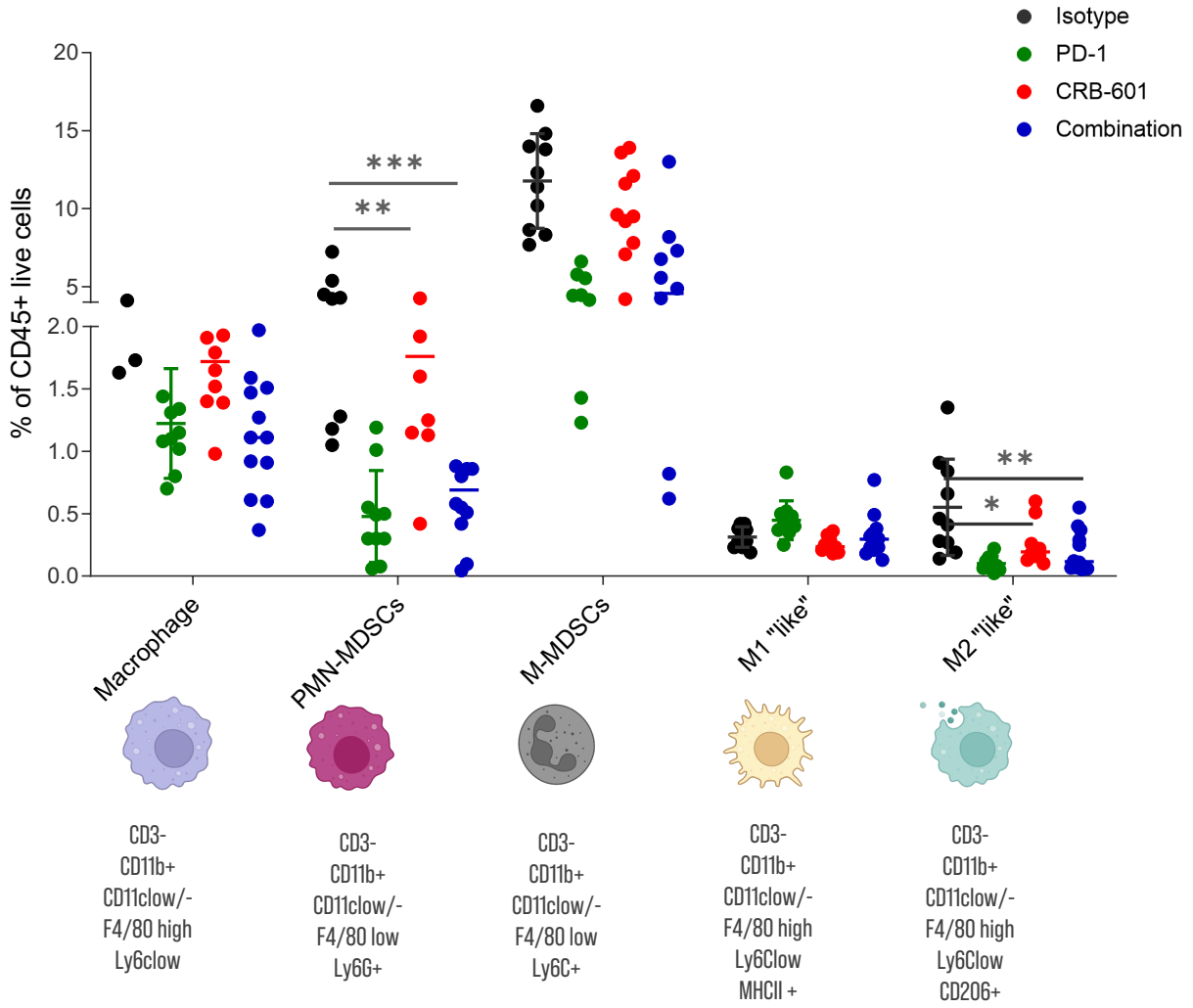


Soluble TGFβ levels in the periphery may not accurately reflect cytokine activity in the TME of EMT6 model

Source(s): Corbus data on file

CRB-601: Reshaping the landscape of myeloid cells in MC38 mice tumors

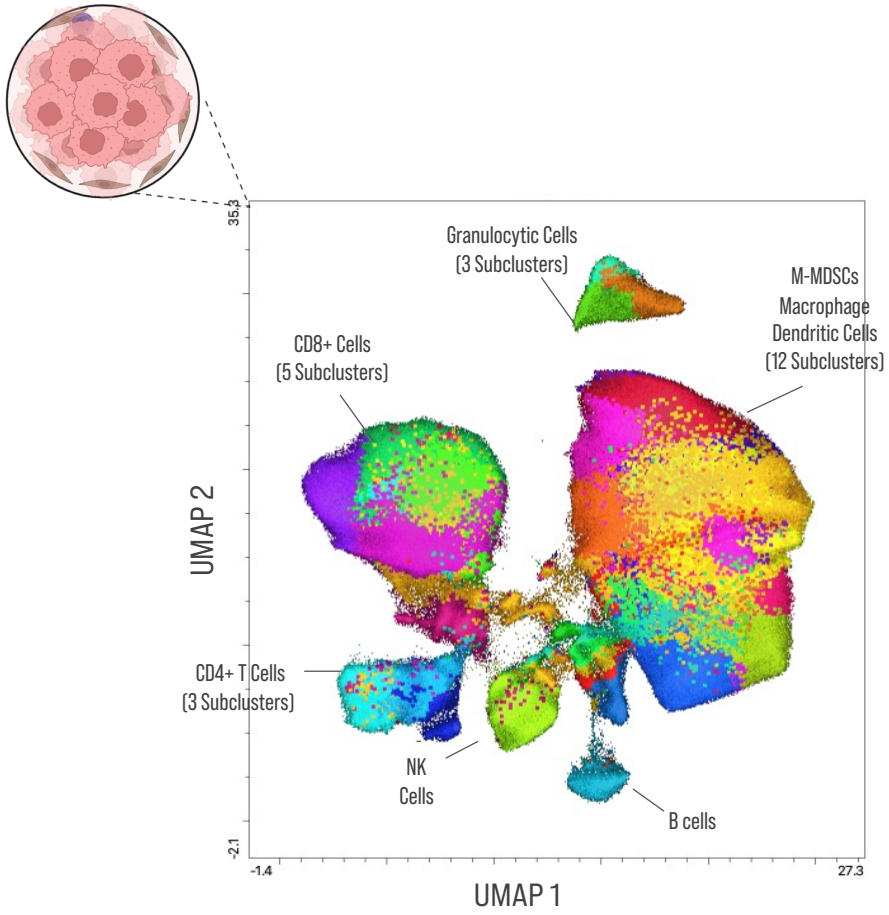




- 22 antibody flow cytometry panel
- 1.25 million live CD45+ cells analyzed
- 31 immune clusters from high dimensional flow analysis
- Sample processing (1) Downsample (2) UMAP (3) X-Sift (4) Euclid (5) Cluster Explorer
- Animals have undergone 10 days of treatment.

Source(s): Corbus data on file

CRB-601: Reshapes the landscape of effector T and NK cells in MC38 tumors



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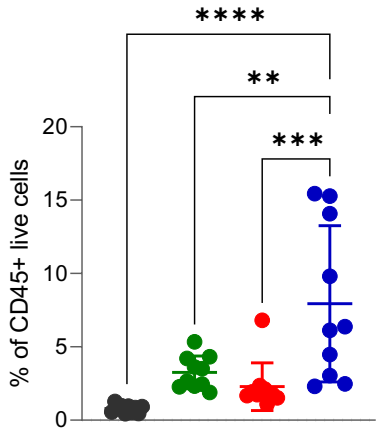
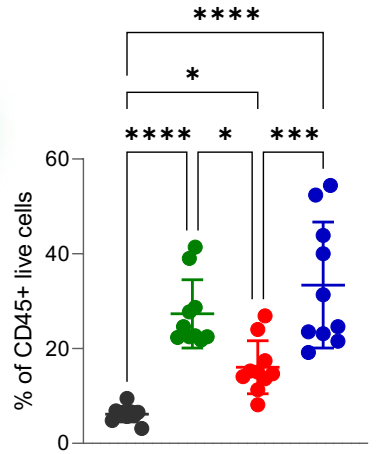
Cytotoxic Effector CD8 T Cells

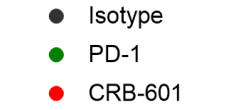
CD3+CD8+
Ki67+
Granzyme B+
TIM3med
PD-1med



Intermediate Exhausted CD8 T cells

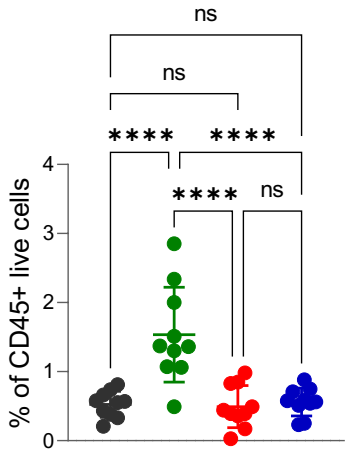
CD3+CD8+
TIM3low
PD1low
Ki67+
Granzyme B+





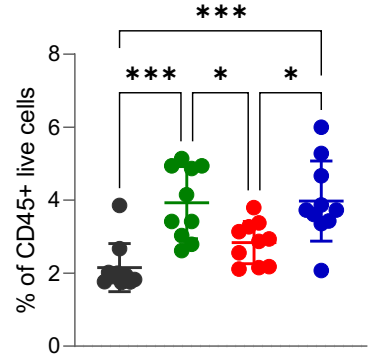
Terminally Exhausted CD8 T cells

CD3+ CD8+
TIM3high
PD-1high
Ki67-
Granzyme B-



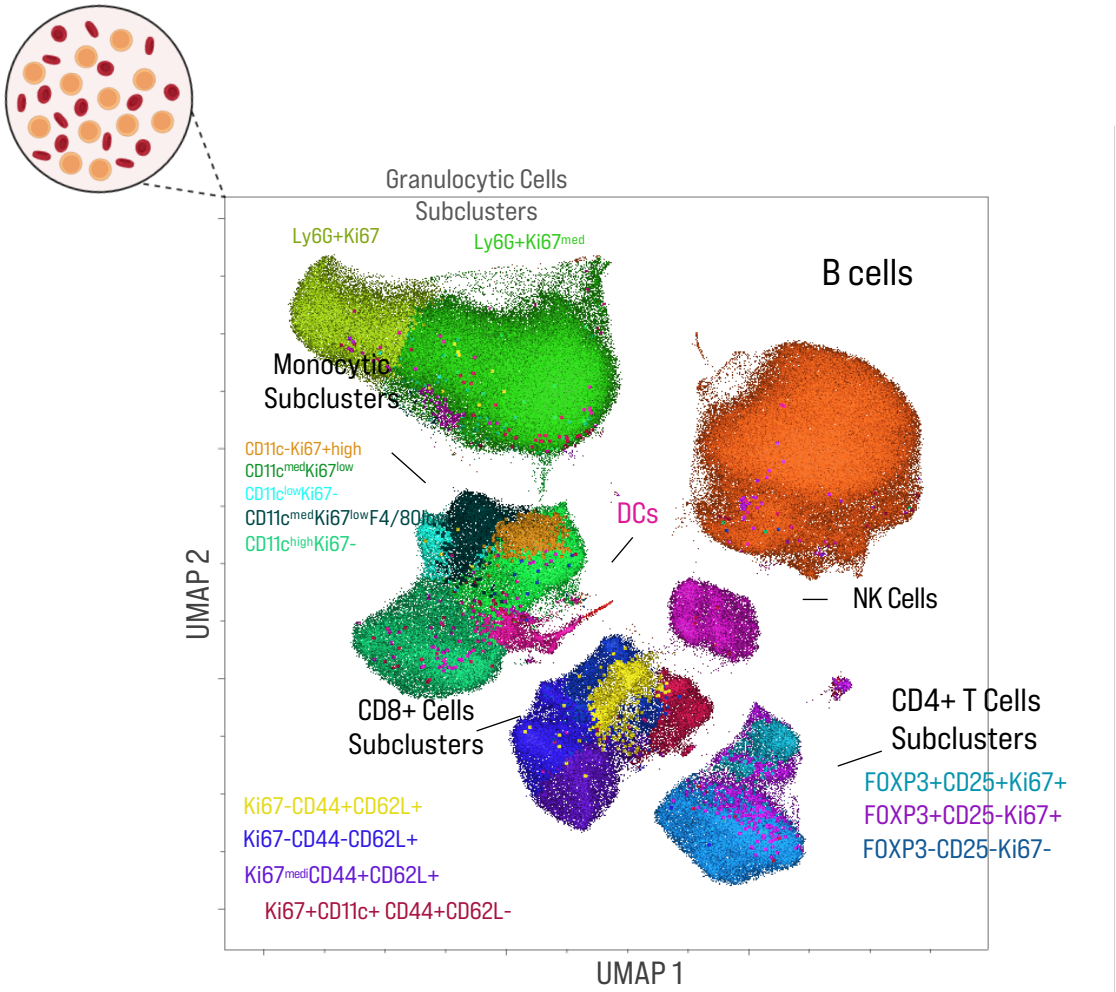
Natural Killer Cells

CD3-
Nkp46+

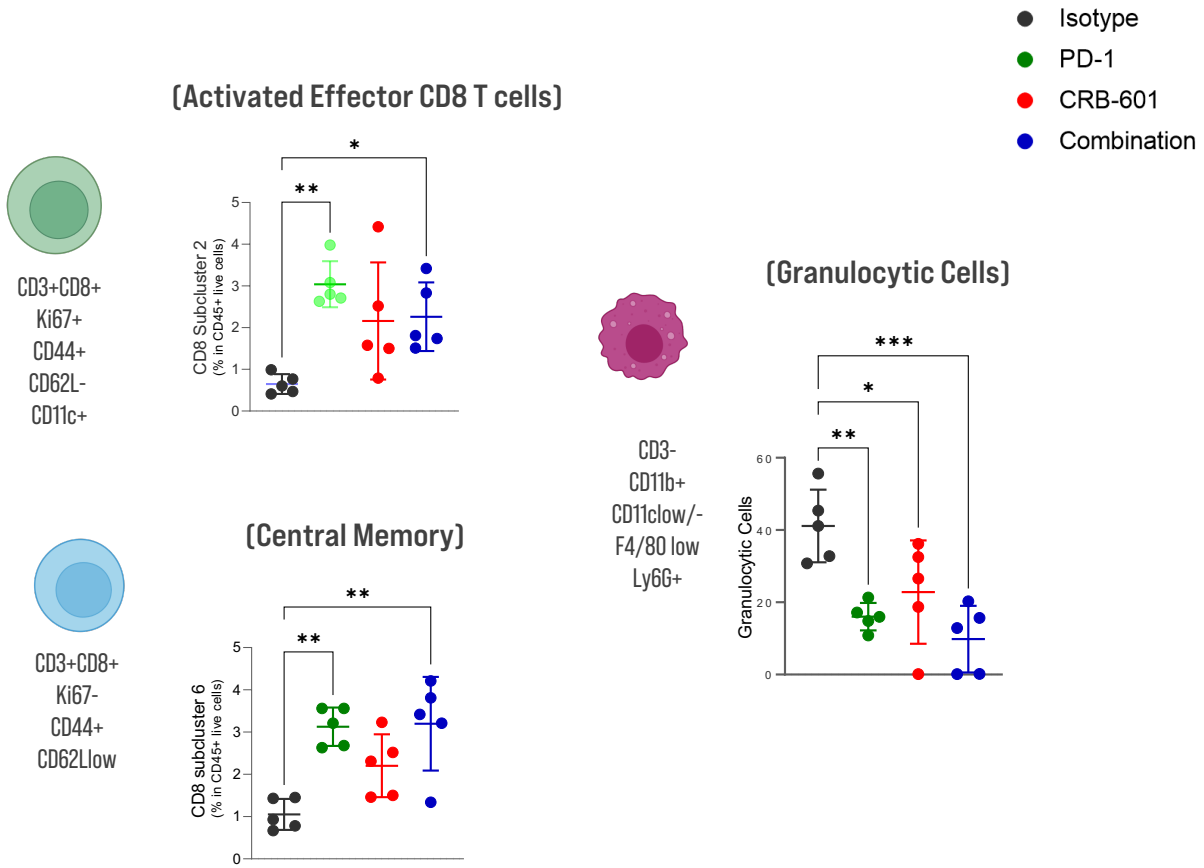


Source(s): Corbus data on file

A parallel comparison of immune changes in peripheral blood of CRB-601 treated mice and tumor microenvironment



21 Color flow cytometry panel, n=5 mice/group 1.25 million Live CD45+ Cells
Sample processing: (1) Downsampling (2) UMAP (3), X-Sift (4) Euclid, (5) Cluster Explorer
Animals have undergone 10 days of treatment.



Source(s): Corbus data on file

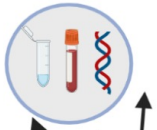
Decoding the dominant immune escape mechanisms of a patient's tumor is key to finding the rational combination partner for CRB-601

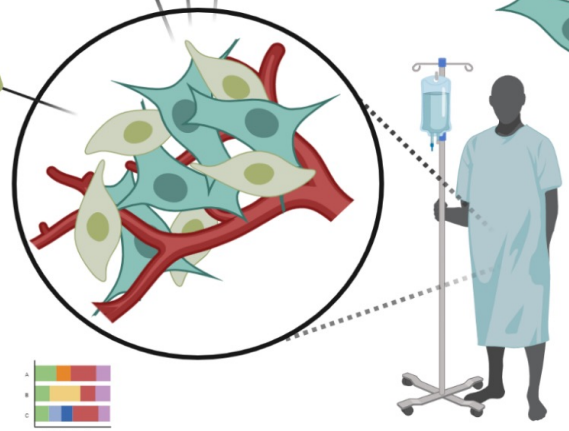
1 Tumor heterogeneity

Building better model systems to reflect immune escape profiles

3 Patient selection markers

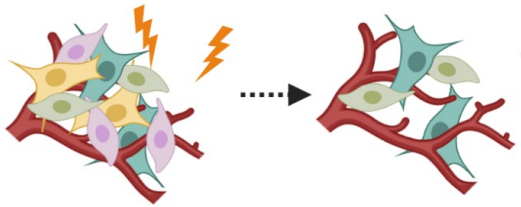
Identification of patient selection markers for stratification and response to therapy





2 Diagnose immune phenotypes along a patient journey

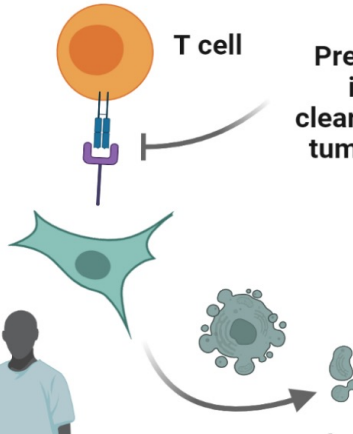
Selective therapeutic pressure can change 'immune exclusion' phenotypes



Re testing at relapse

4 Dominant immune escape mechanism

Several mechanisms can drive immune resistance in a single tumor



Stimulating paracrine growth factors to signal cancer cell growth

✔ Achieving deeper responses

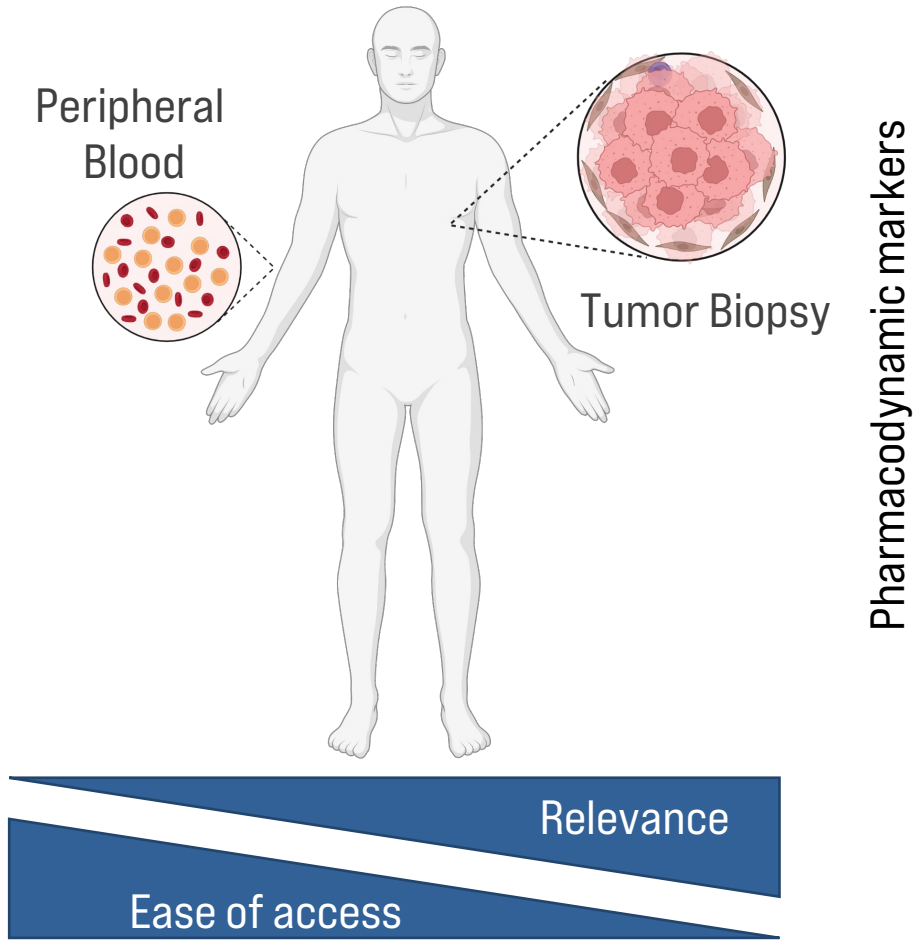
Optimizing immune pharmacology of combination therapy

Combination therapy with non-overlapping mechanism of action

Checkpoint + ITGB8

Conclusions

- CRB-601 inhibits tumor growth as a single agent and enhances the efficacy of anti-PD-1 immunotherapy in checkpoint inhibitor-sensitive and immune-excluded tumor models.
- Blockade of αvβ8 instigates the expansion of effector cytotoxic T and NK cells, eliciting a robust anti-tumor response in syngeneic mouse models.
- In peripheral blood, we can identify the relevant responding CD8 T cell type, a discovery that may pave the way for understanding and predicting clinical responses.
- We are on track for an IND in H2 2023.



Thankyou

Collaborators

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University of California
San Francisco

UCSF immunoprofiler
CONSORTIUM

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Corbus team