

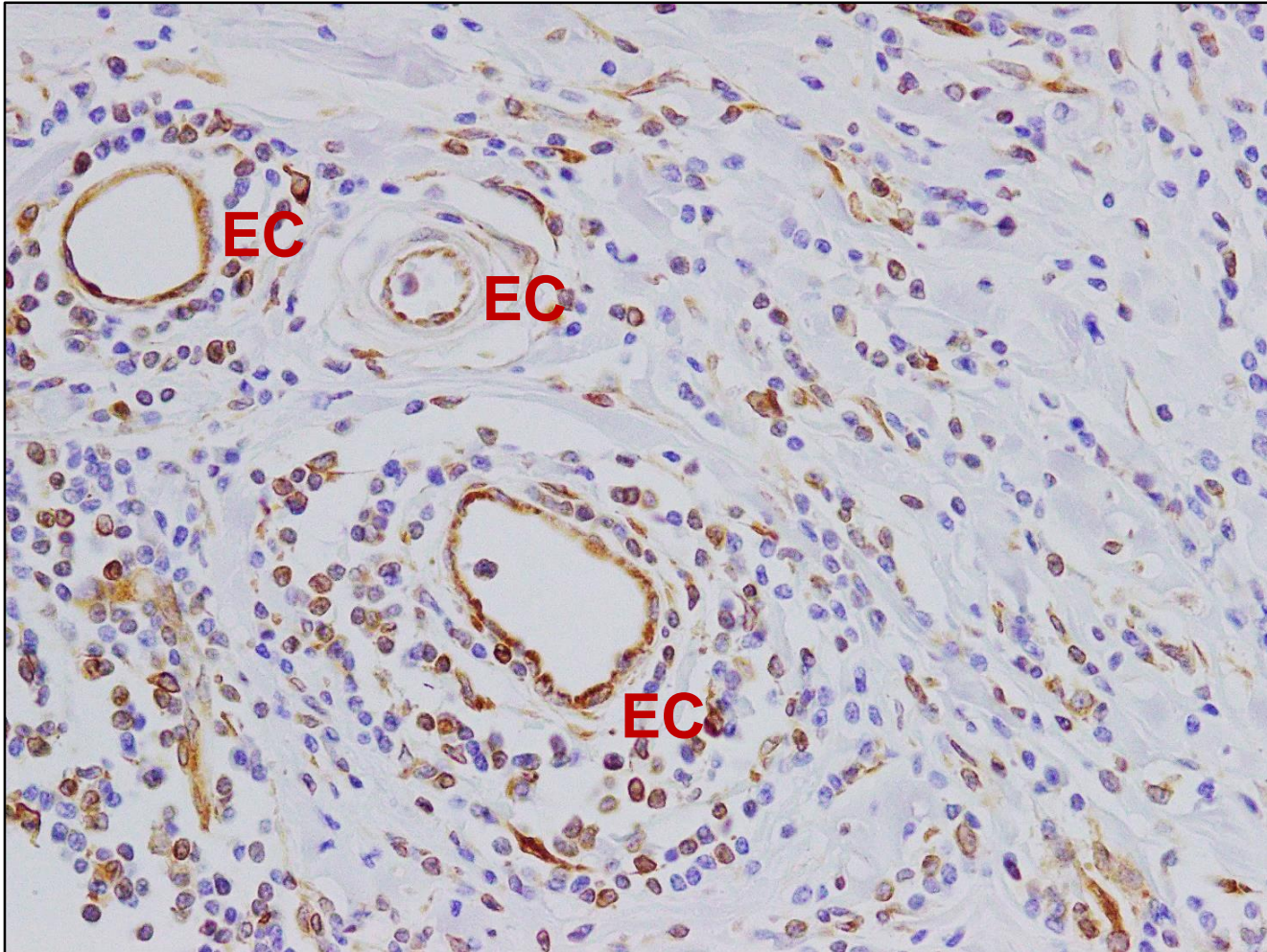
연구중심병원 정기 세미나

**STING normalizes tumor vasculatures
and synergizes with anti-angiogenic therapy
to enhance cancer immunity**

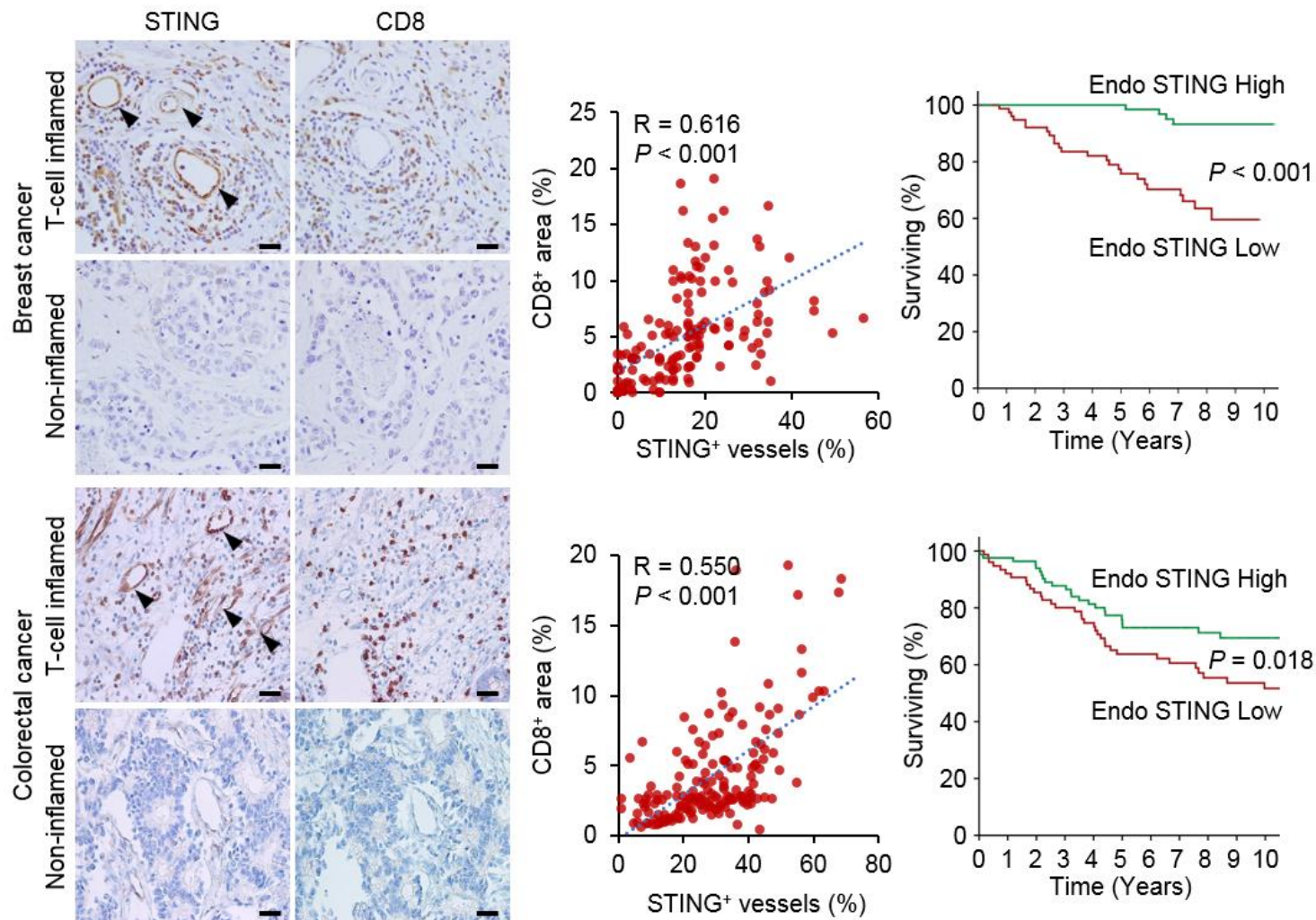
김 찬

분당차병원 혈액종양내과

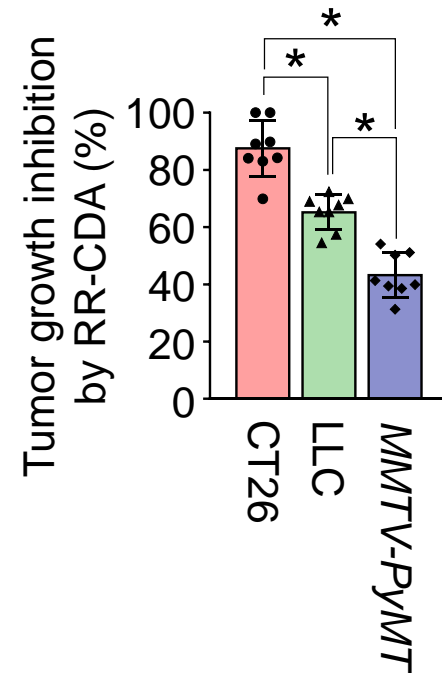
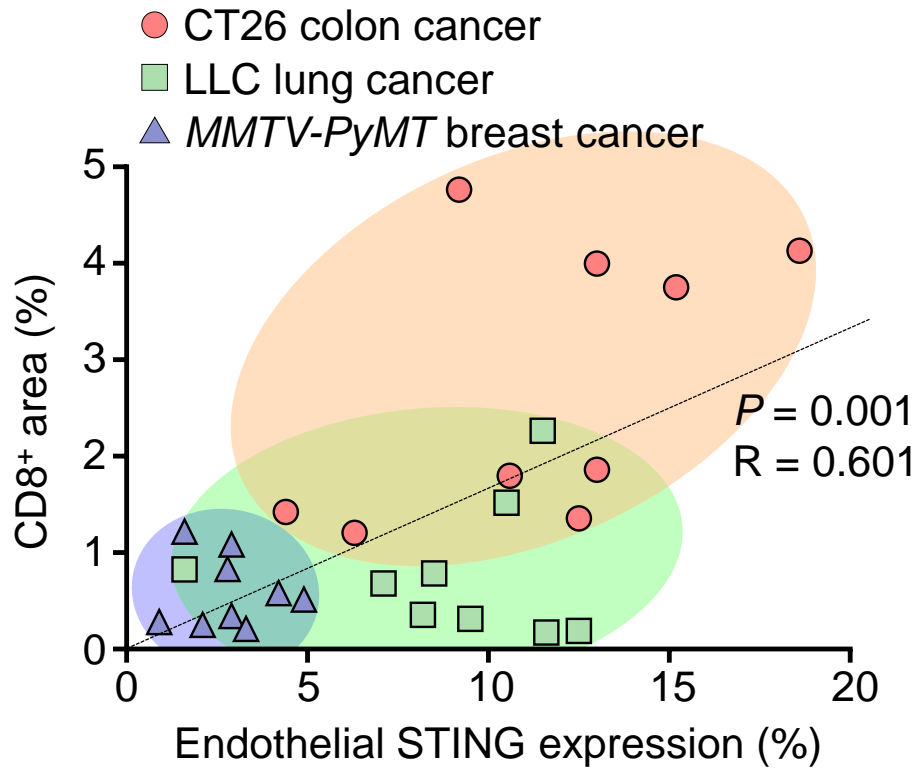
STING is highly expressed in **tumor endothelial cells** of human cancers



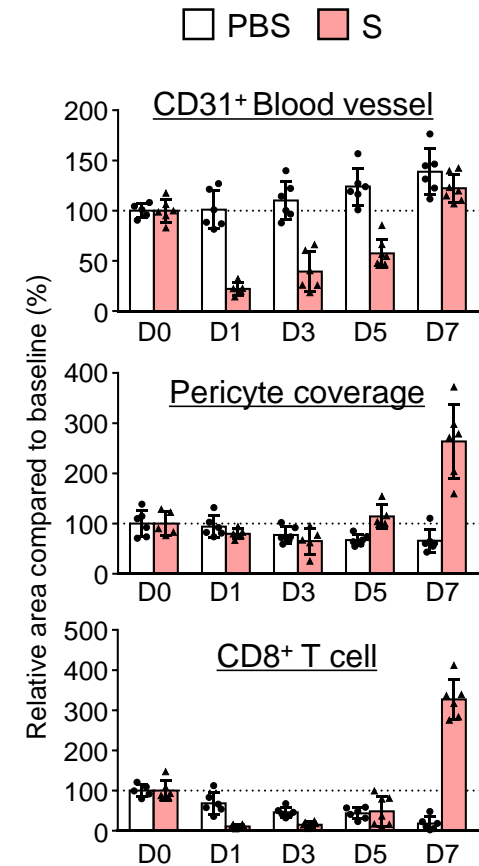
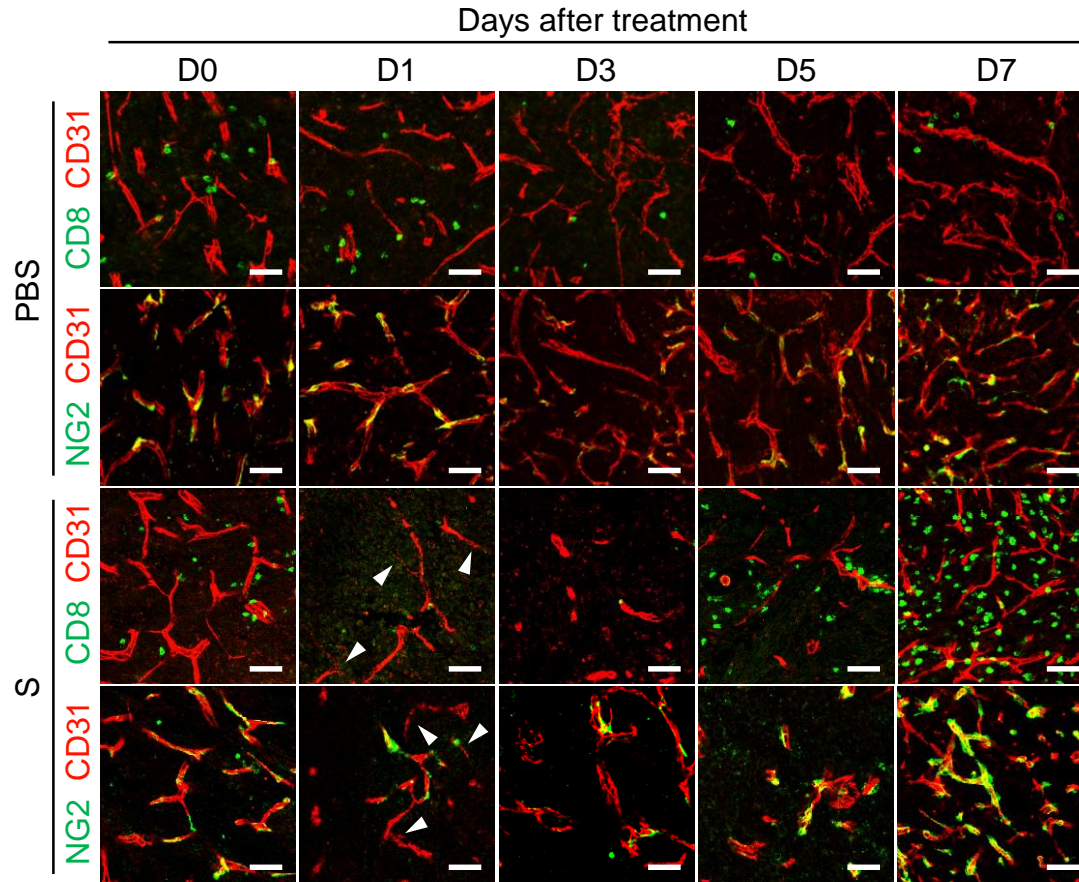
Endothelial STING expression correlates with CD8⁺ TILs and overall survival in human cancers



Endothelial STING expression in syngeneic mouse tumor models



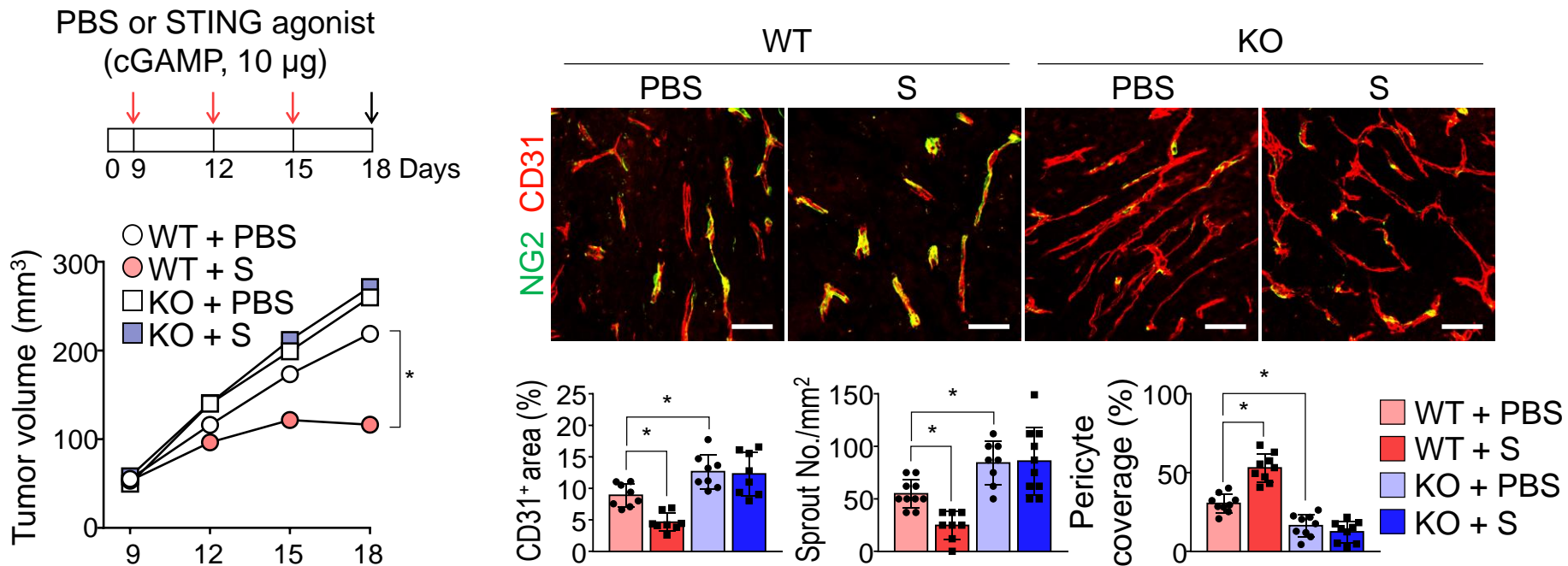
STING agonist remodels tumor microenvironment



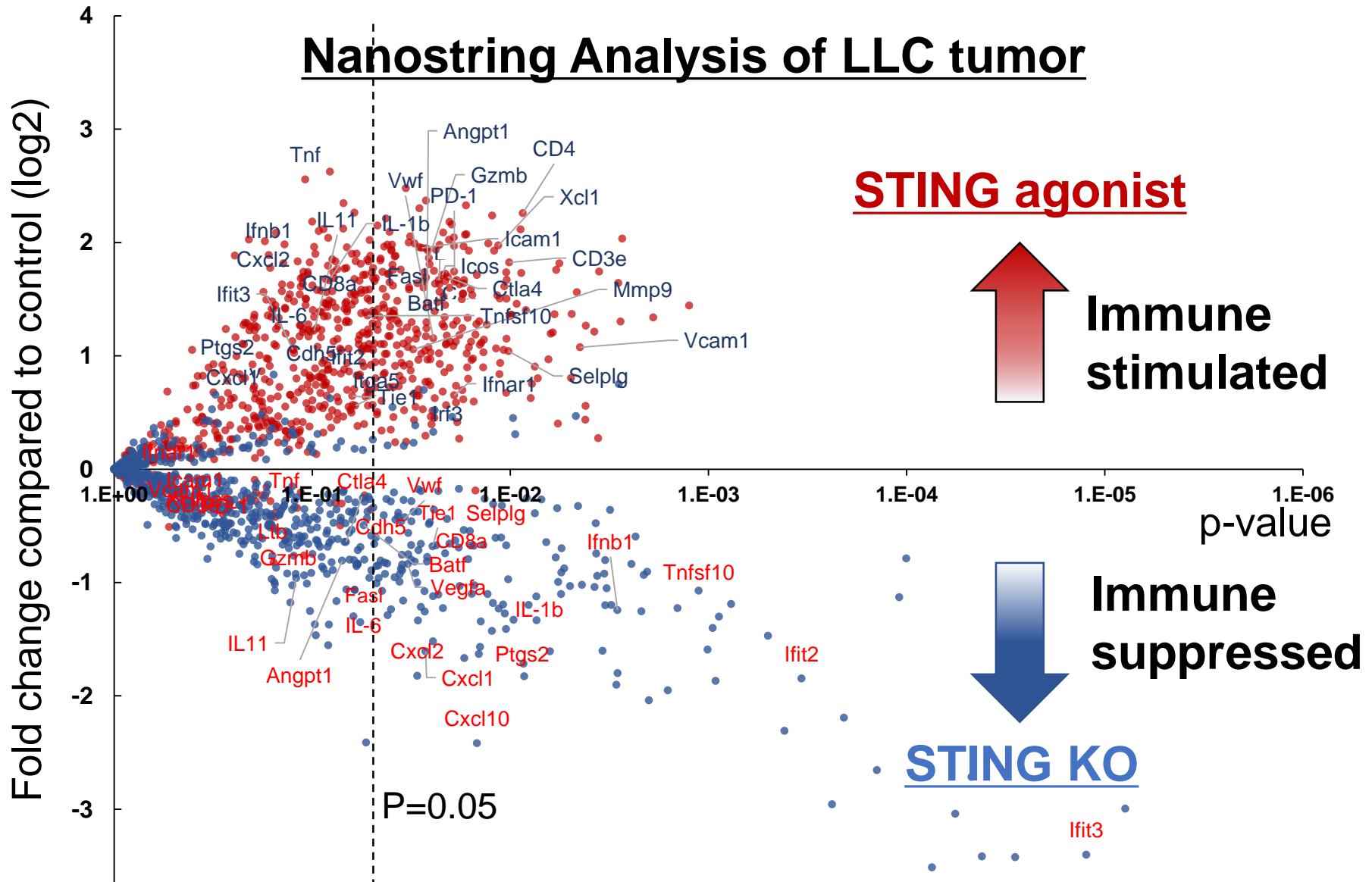
Angiogenesis ↓, Vascular maturation ↑, CD8+ T cell immunity ↑

STING is a negative regulator of sprouting tumor angiogenesis

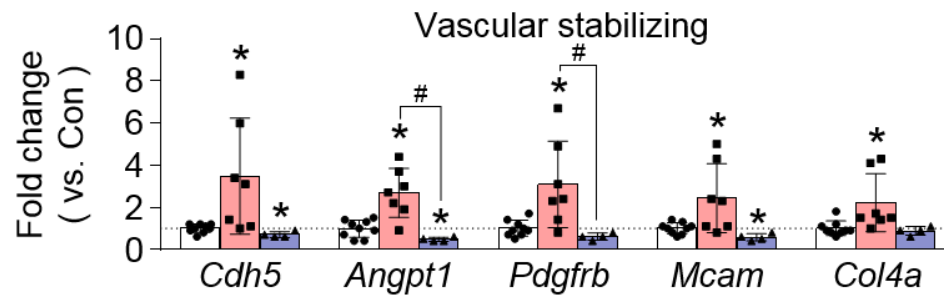
Nanostring Analysis of LLC tumor



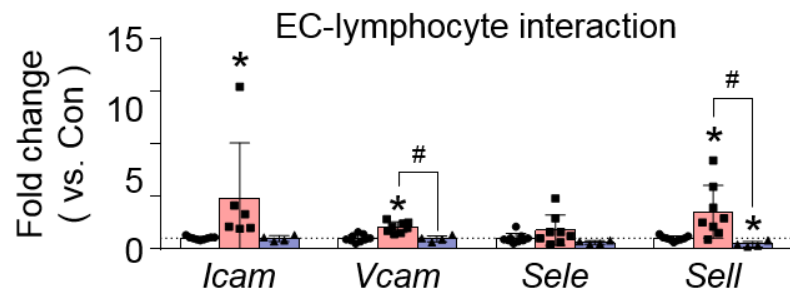
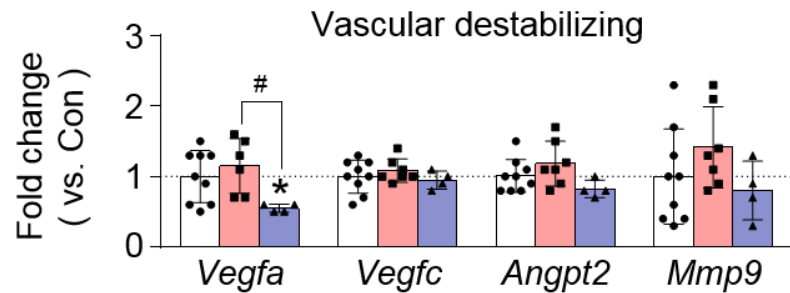
STING pathway regulates tumor immune phenotype



STING signaling regulates Vascular-immune network



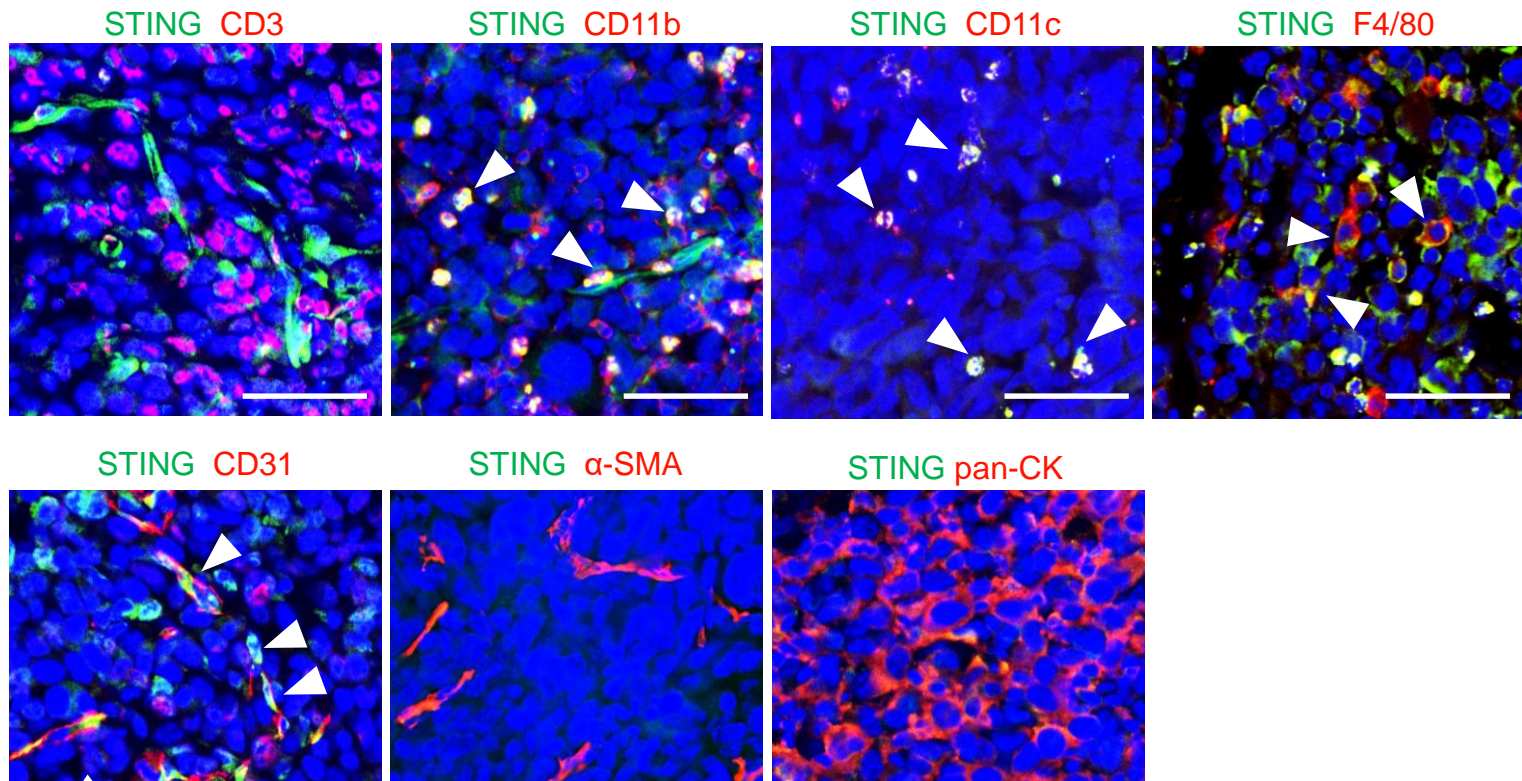
**Vascular
normalization** ↑



**Endothelial-lymphocyte
interaction** ↑

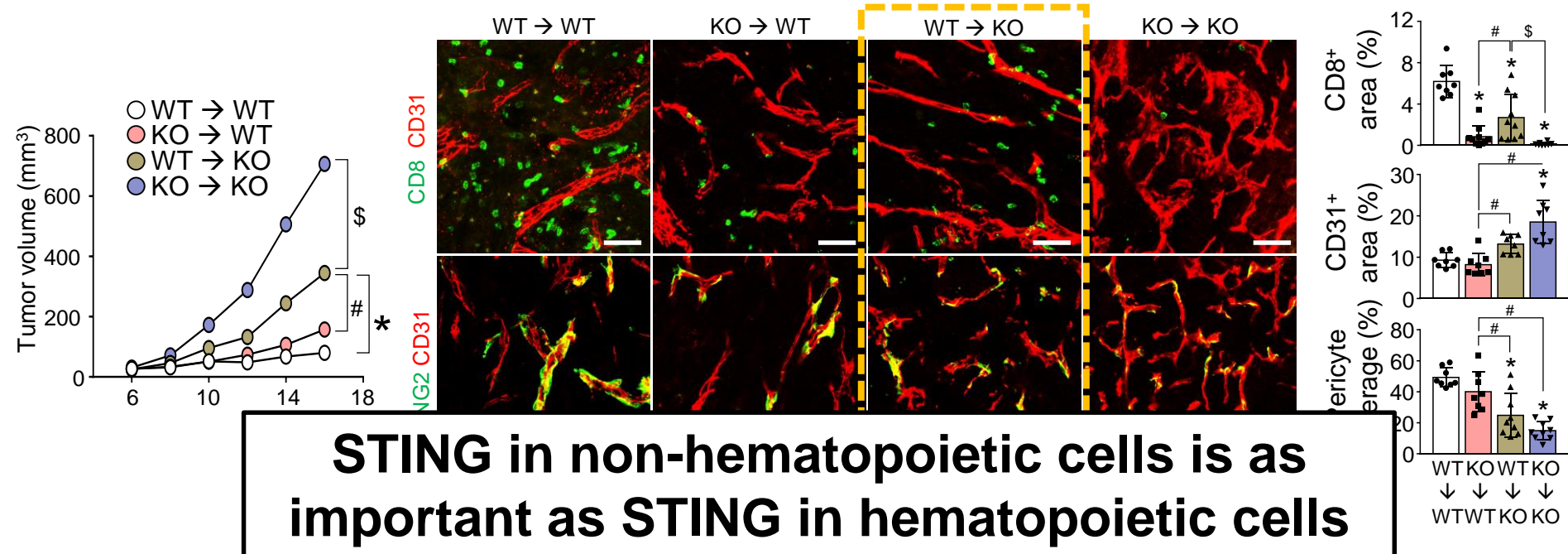
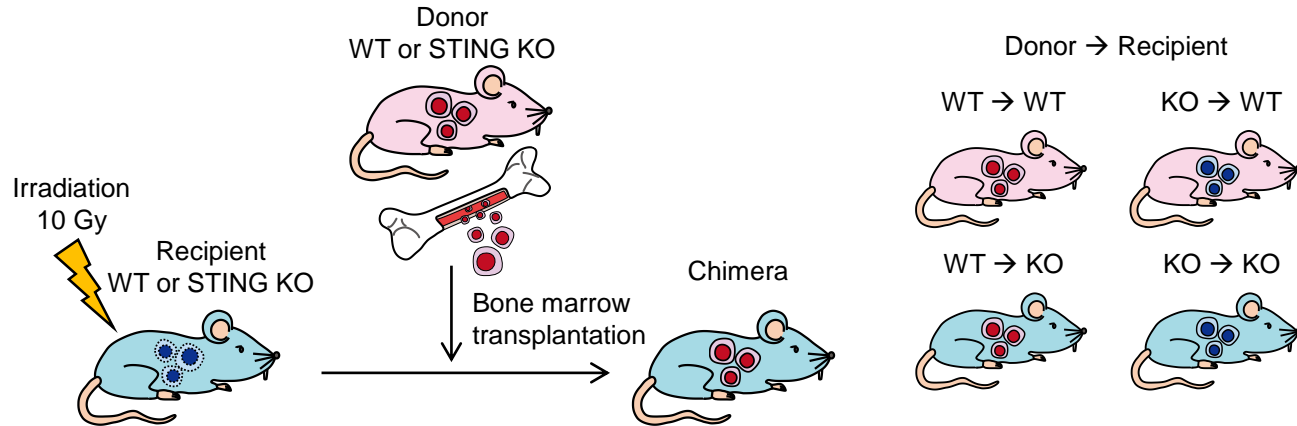
STING expressing cells In tumor microenvironment

LLC tumor



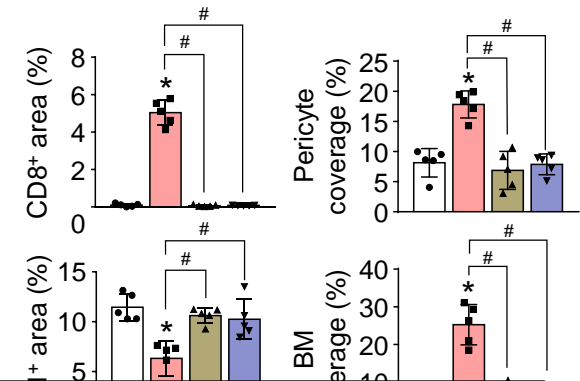
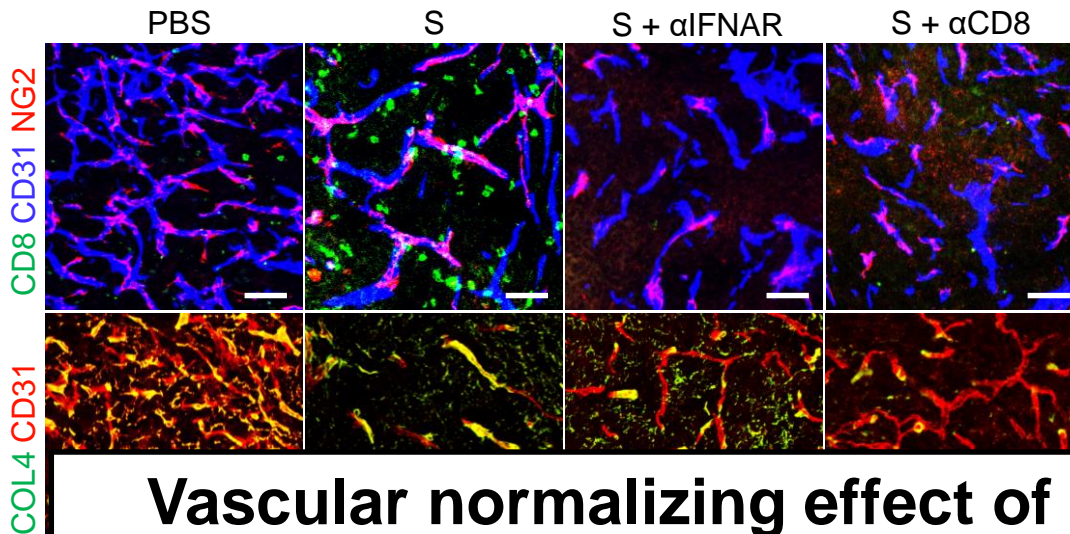
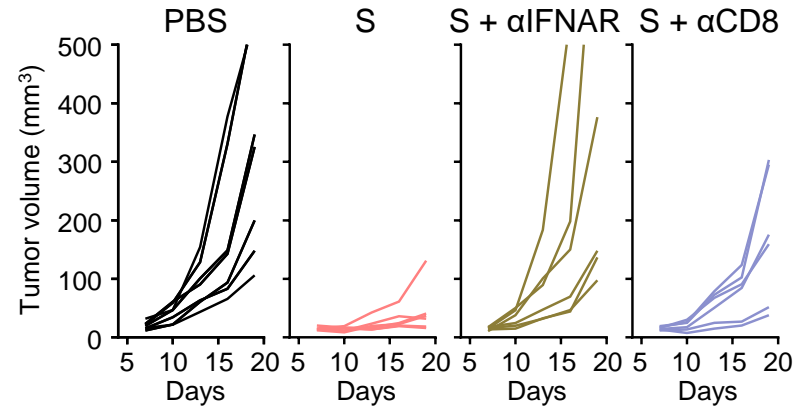
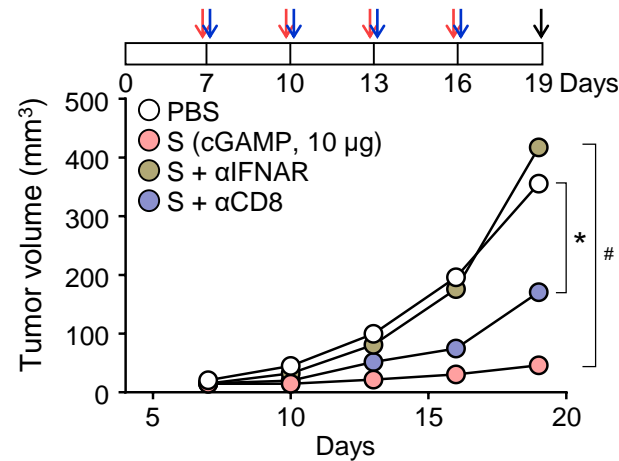
Immune (myeloid) AND non-immune (esp. endothelial)
Which is important?

STING in immune cell vs. non-immune cells ?



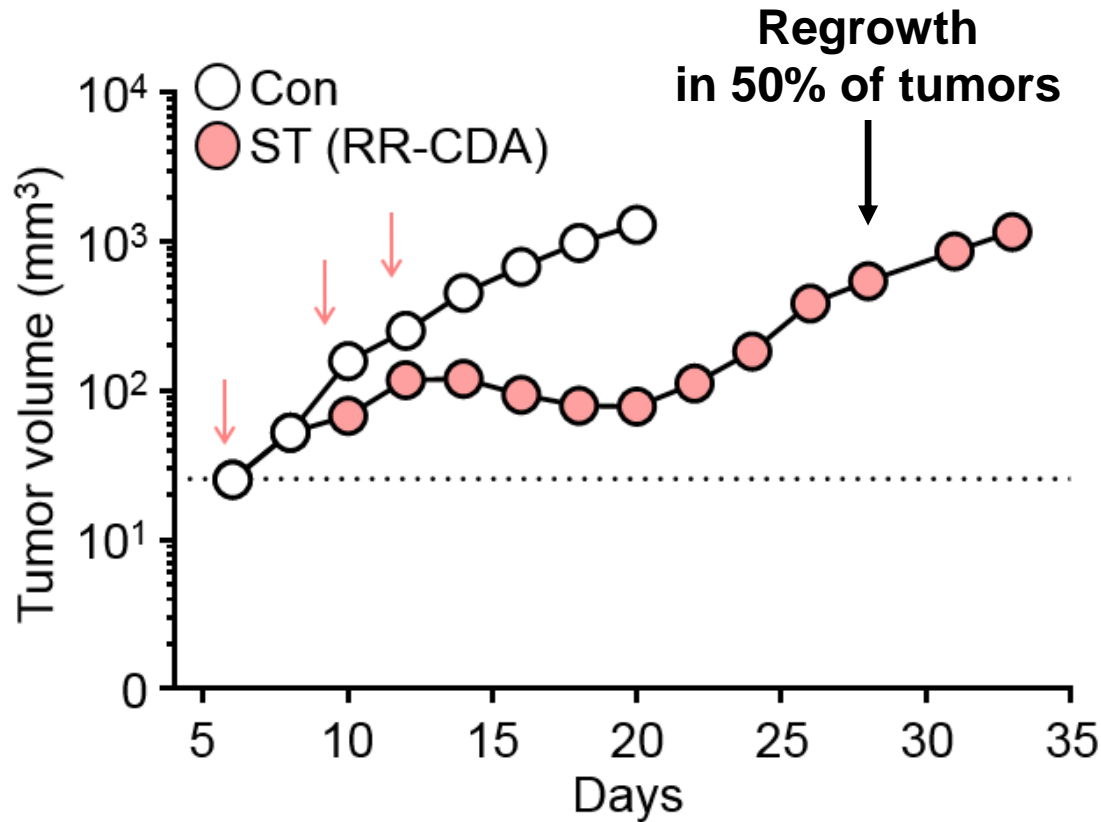
STING in non-hematopoietic cells is as important as STING in hematopoietic cells

The efficacy of STING agonist depends on Type I IFN signaling and CD8⁺ T cells



Vascular normalizing effect of STING agonist is dependent on Type I IFNs and CD8⁺ T cells.

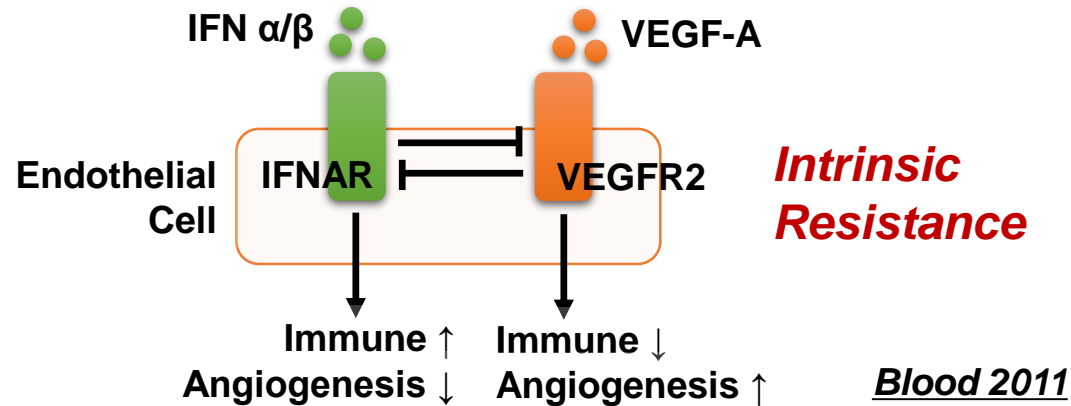
Limitations of STING monotherapy



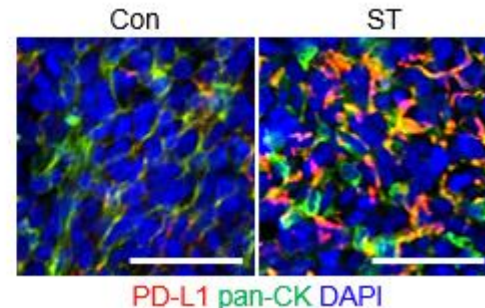
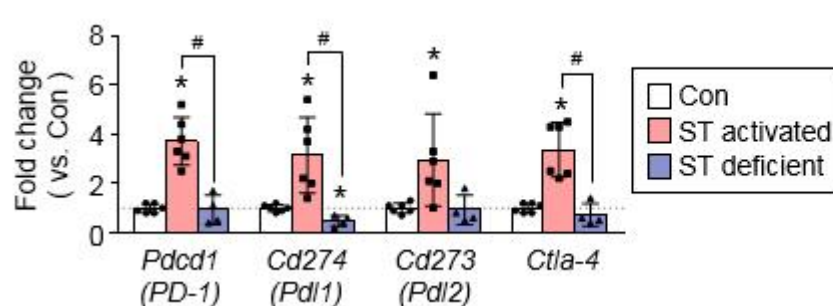
1. Regrowth of tumors
2. Insufficient abscopal effect

Potential resistance mechanism for STING monotherapy

1. Mutual antagonism of Type I IFN and VEGFR2 signaling



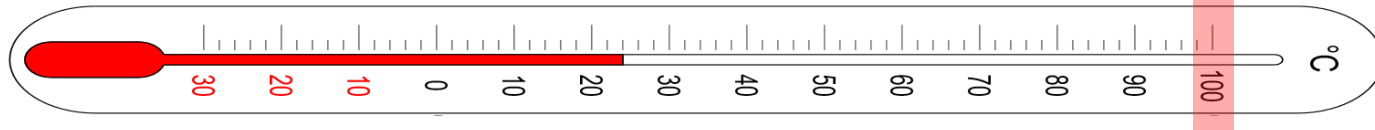
2. Upregulation of immune checkpoints after STING Tx.



Adaptive Resistance

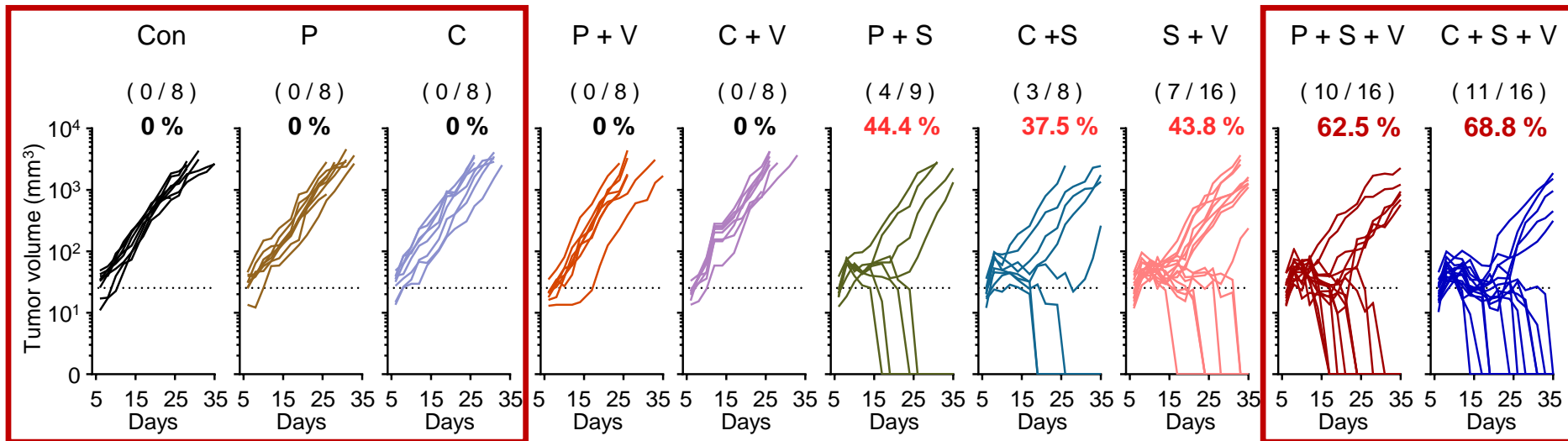
Optimal Combination Immunotherapy: Beyond Immunologic Boiling Point

All or None Responses after immunotherapy



P: anti-PD1, **C:** anti-CTLA4, **V:** anti-VEGFR2, **S:** STING agonist

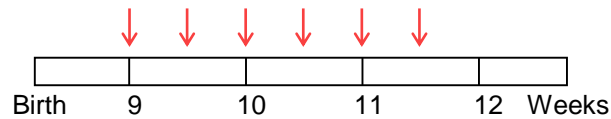
LLC tumors



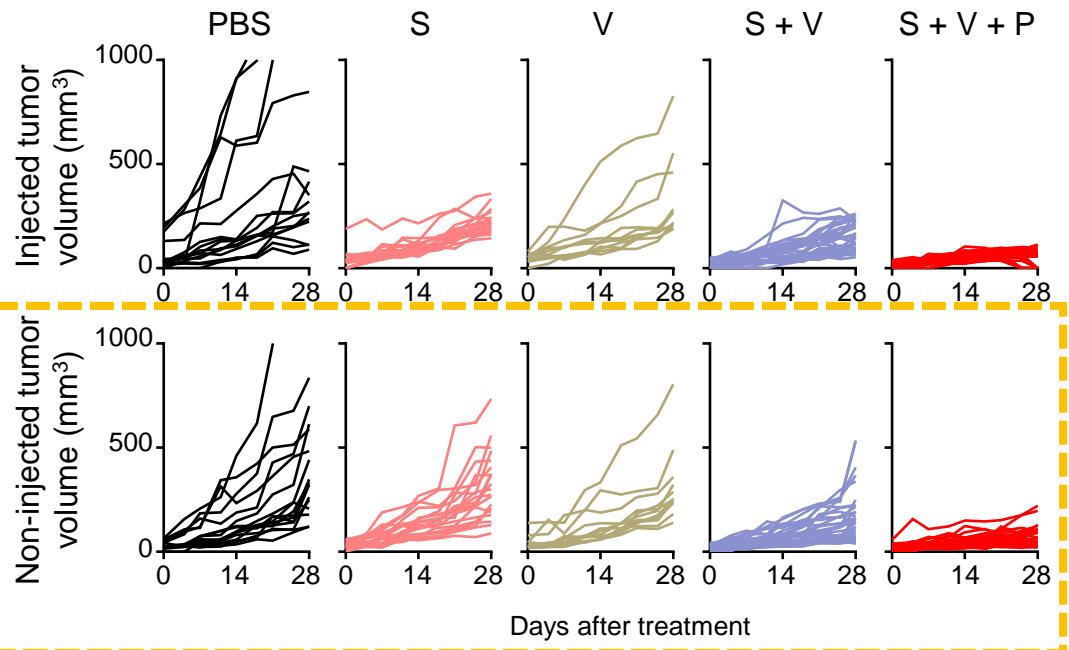
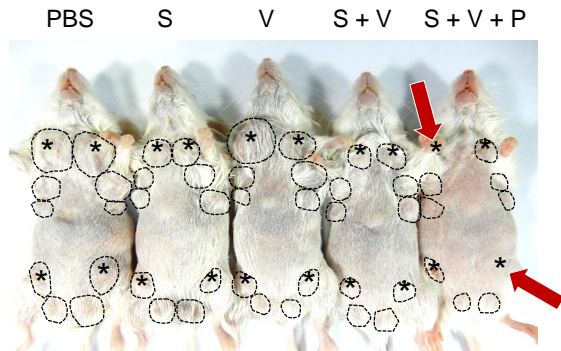
**We can overcome intrinsic resistance to ICIs
through optimal combination.**

Triple Combination immunotherapy (STING+ α VEGFR2+ICI) induced abscopal effects

MMTV-PyMT transgenic breast cancers

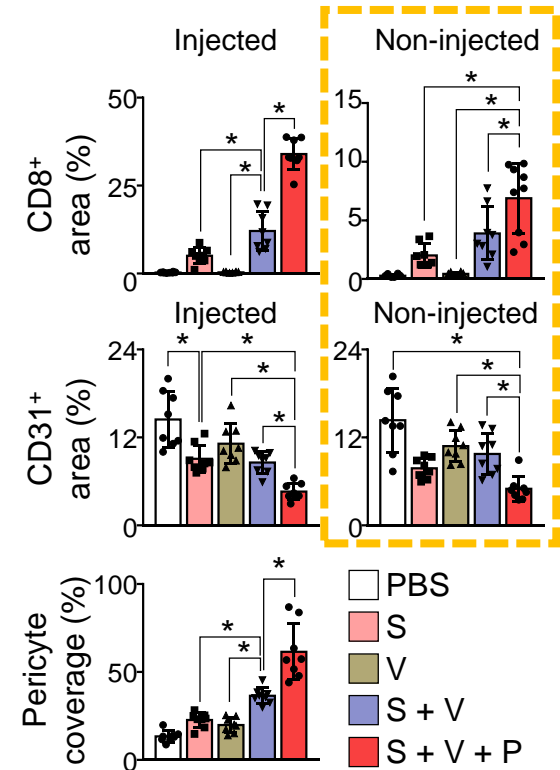
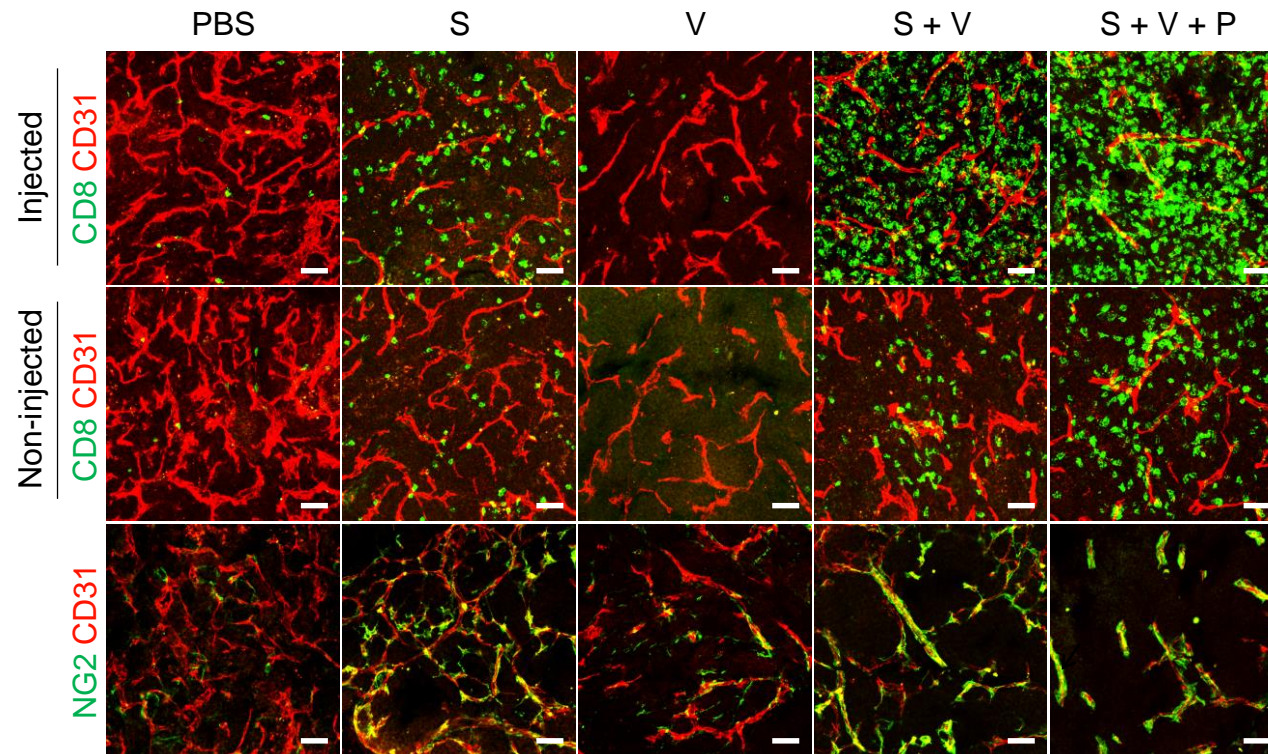


↓ STING agonist (RR-CDA, 25 μ g)
↓ DC101 and/or α PD-1



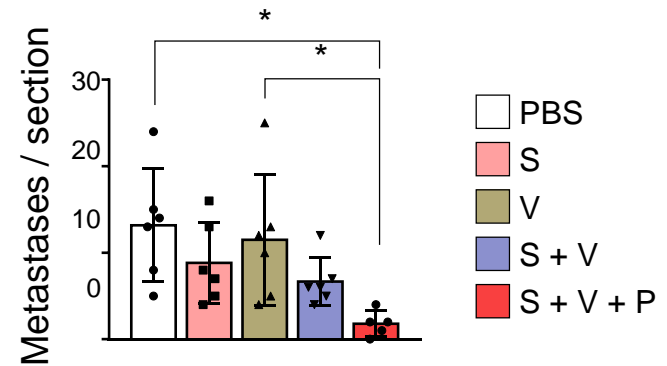
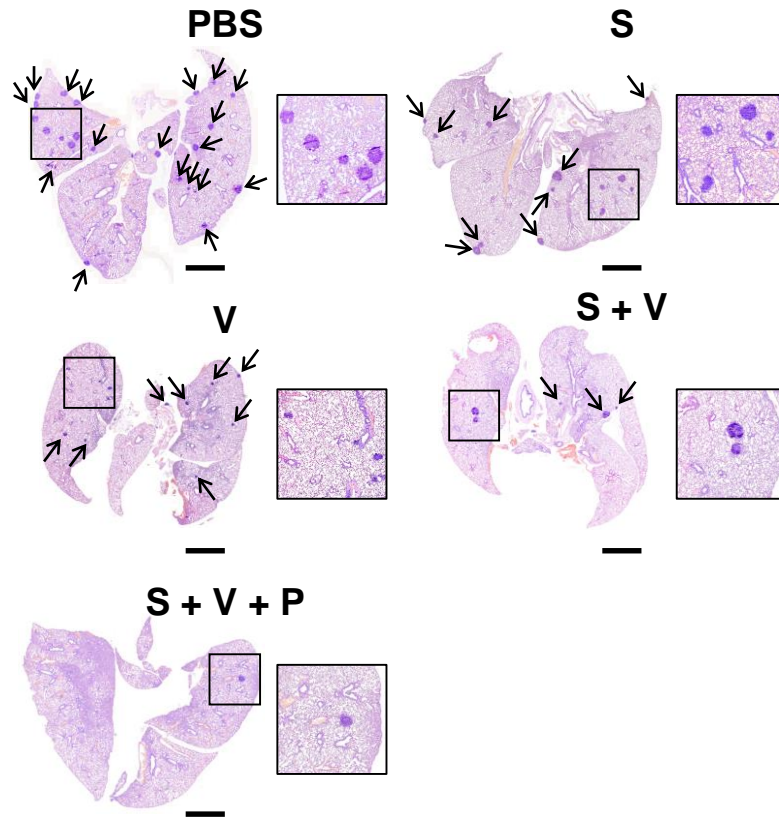
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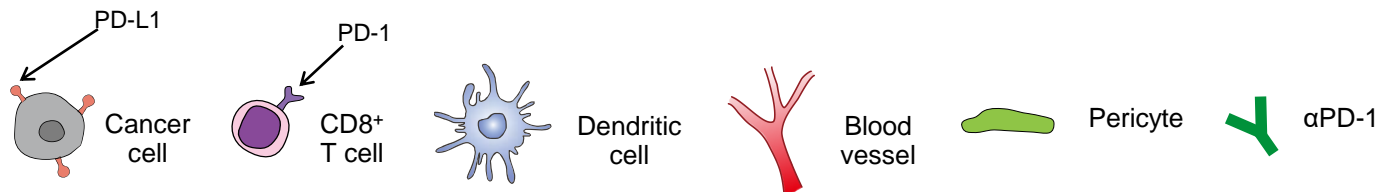
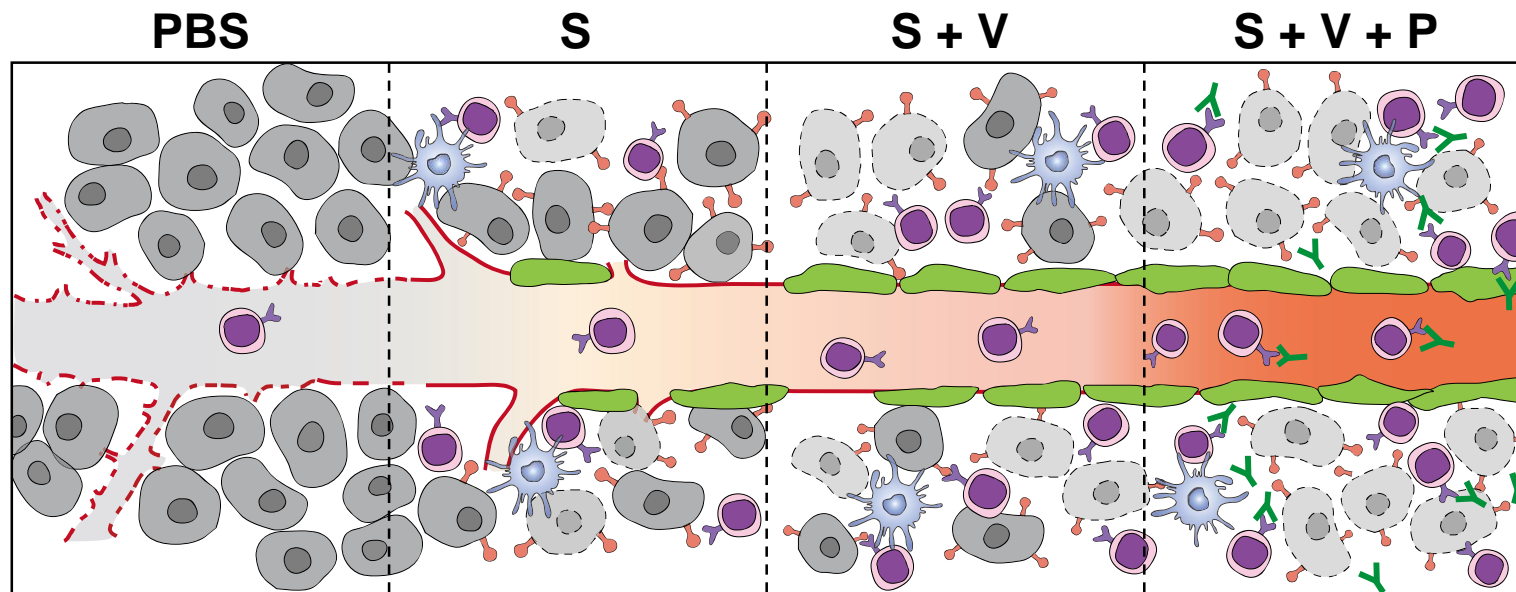


Triple Combination immunotherapy (STING+ α VEGFR2+ICI) suppresses metastases

MMTV-PyMT transgenic breast cancers



Optimal regulation of TME (esp. tumor vessels) is critical for STING-based immunotherapy



Thank You for listening !

JCI The Journal of Clinical Investigation

STING activation reprograms tumor vasculatures and synergizes with VEGFR2 blockade

Hannah Yang, ... , Hong Jae Chon, Chan Kim

J Clin Invest. 2019. <https://doi.org/10.1172/JCI125413>.

Research In-Press Preview Angiogenesis Immunology

Graphical abstract

The graphical abstract is a schematic diagram divided into four vertical panels representing different treatment groups: PBS, S, S+V, and S+V+P. Each panel shows a cross-section of a tumor with a central blood vessel. The components shown are Cancer cells (grey), CD8+ T cells (purple), Dendritic cells (blue), Blood vessels (red), Pericytes (green), and αPD-1 (green arrow). In the PBS group, cancer cells are densely packed, and the blood vessel is narrow. In the S group, there is some immune cell infiltration. In the S+V group, the blood vessel is wider and more organized. In the S+V+P group, the immune response is most pronounced, with many CD8+ T cells and dendritic cells present, and the blood vessel is significantly reprogrammed.

Legend:

- PD-L1 (on Cancer cell)
- PD-1 (on CD8+ T cell)
- Dendritic cell
- Blood vessel
- Pericyte
- αPD-1

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AAGR American Association for Cancer Research

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