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Vasoactive intestinal peptide signaling: a novel checkpoint pathway in pancreatic ductal adenocarcinoma

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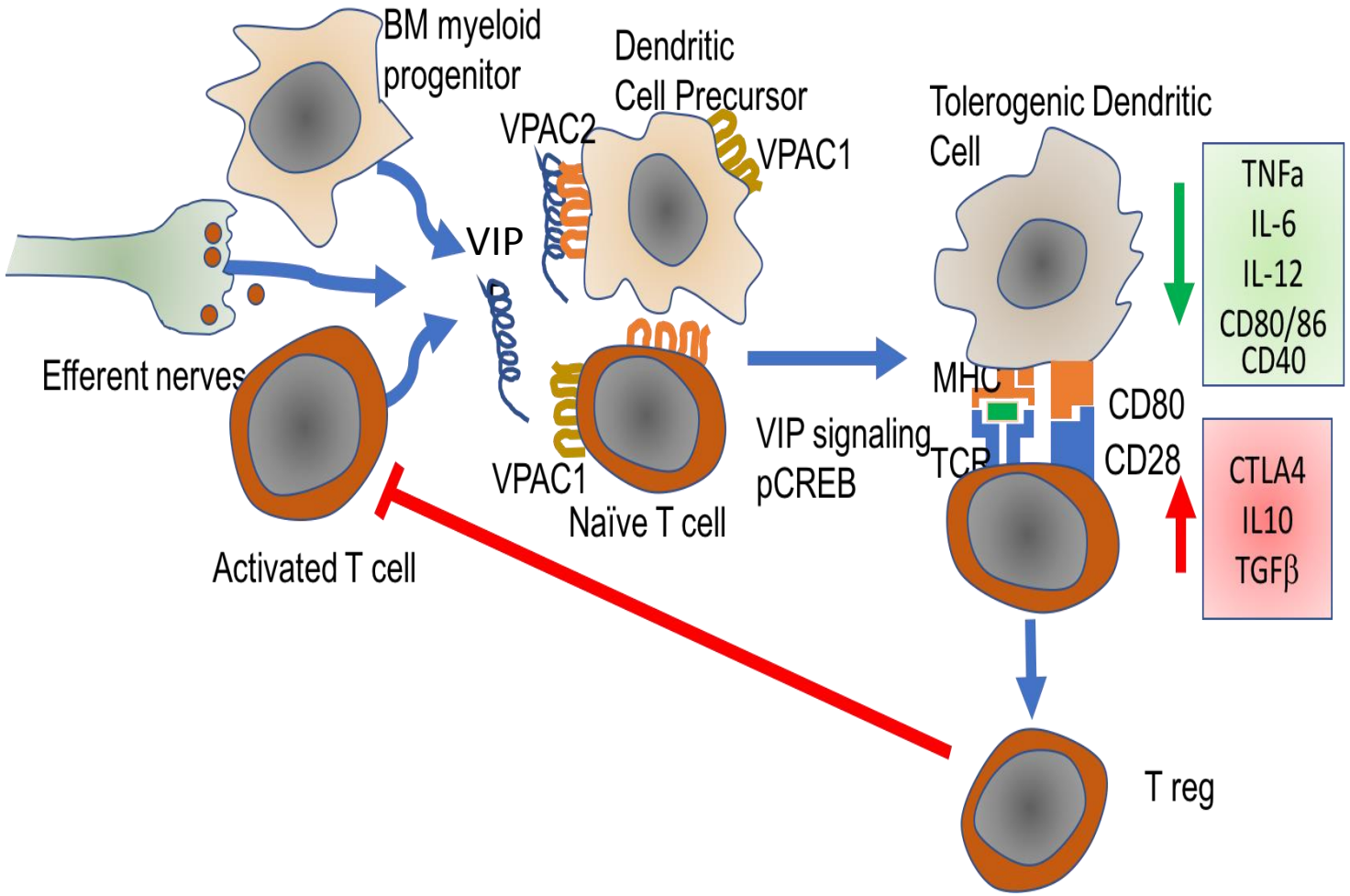
Disclosure

I have no financial disclosure or conflicts of interest with the material in this presentation.

Vasoactive intestinal peptide: an immunosuppressive neuropeptide

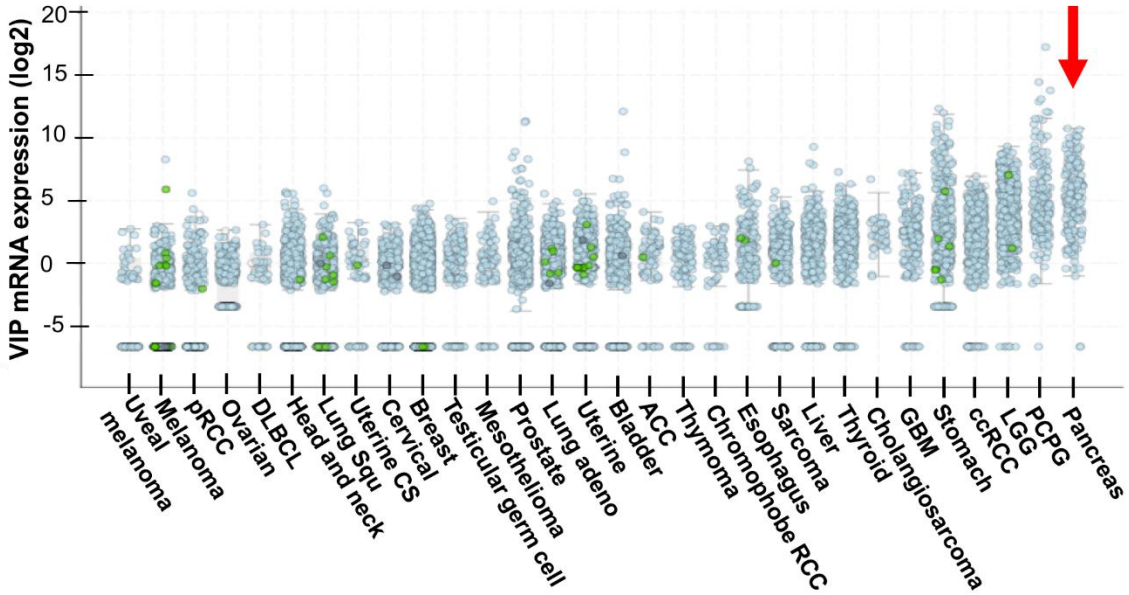
- 28 amino acid neuropeptide
- Secreted by nerve terminals, GI track and immune cells
- Commonly associated with regulating gut motility and blood pressure
- Immunosuppressive properties:
  - Decreases T cell proliferation
  - Decreases secretion of proinflammatory cytokines
  - Polarizes CD4+ T cells towards Th2 response



Delgado M et al. *Amino Acids*. 2013;45(1):25–39.

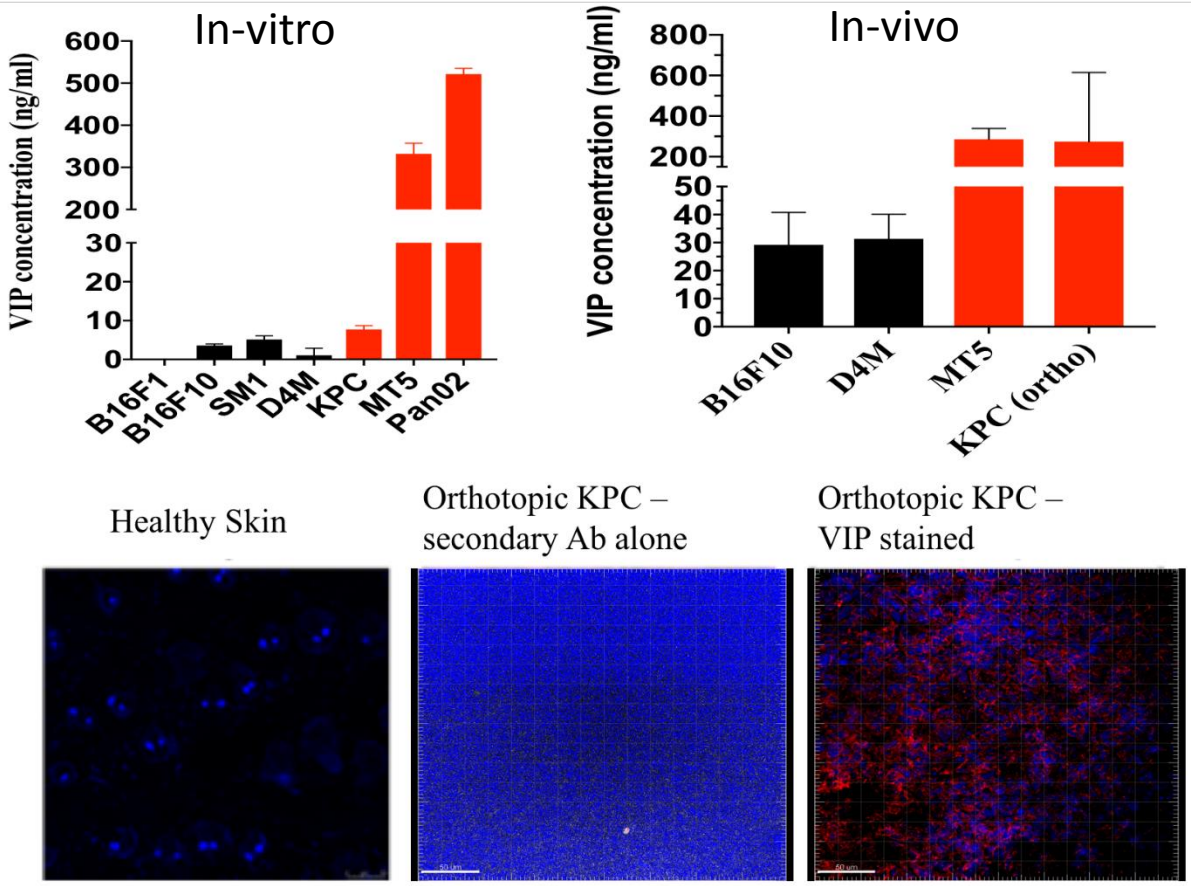
PDAC overexpresses vasoactive intestinal peptide

A. Elevated VIP mRNA expression in human PDAC



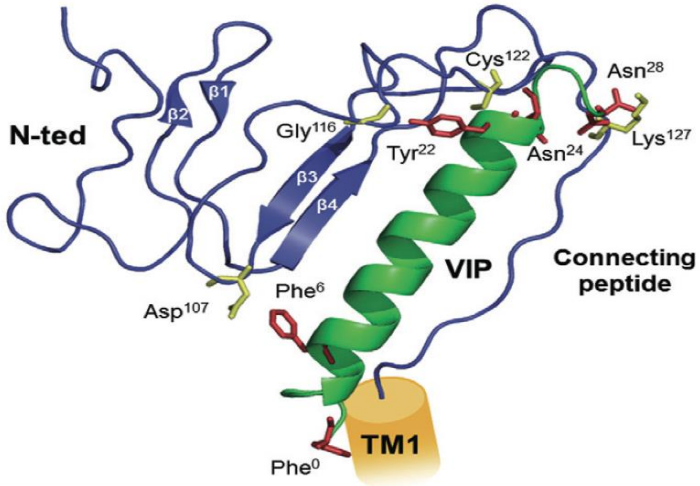
Data obtained from The Cancer Genome Atlas (TCGA)

B. Elevated VIP in mouse PDAC tumors



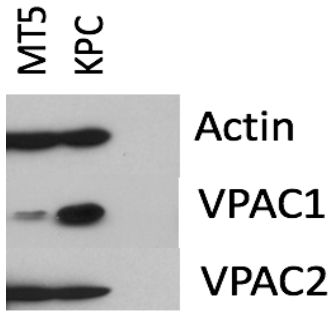
VIP receptor antagonist does not directly kill PDAC cells

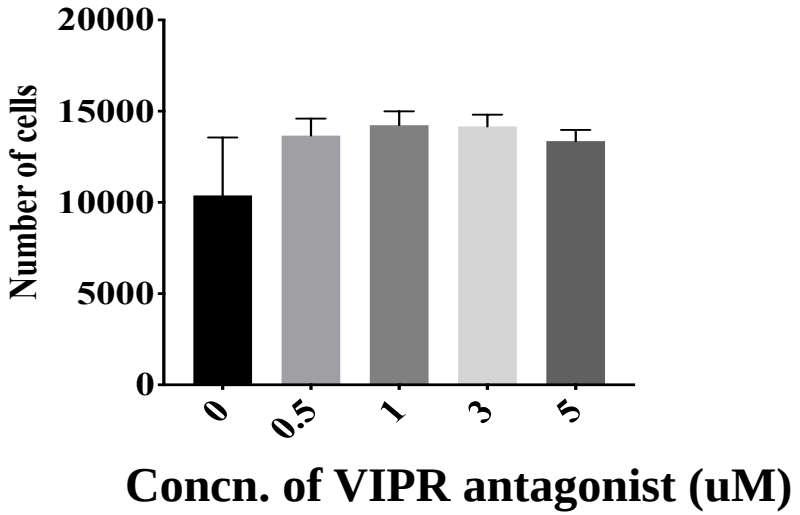
A. Structural model of VPAC1 receptor N-ted and docking of VIP



Couvineau and Laburthe 2002 Br. J. Pharm

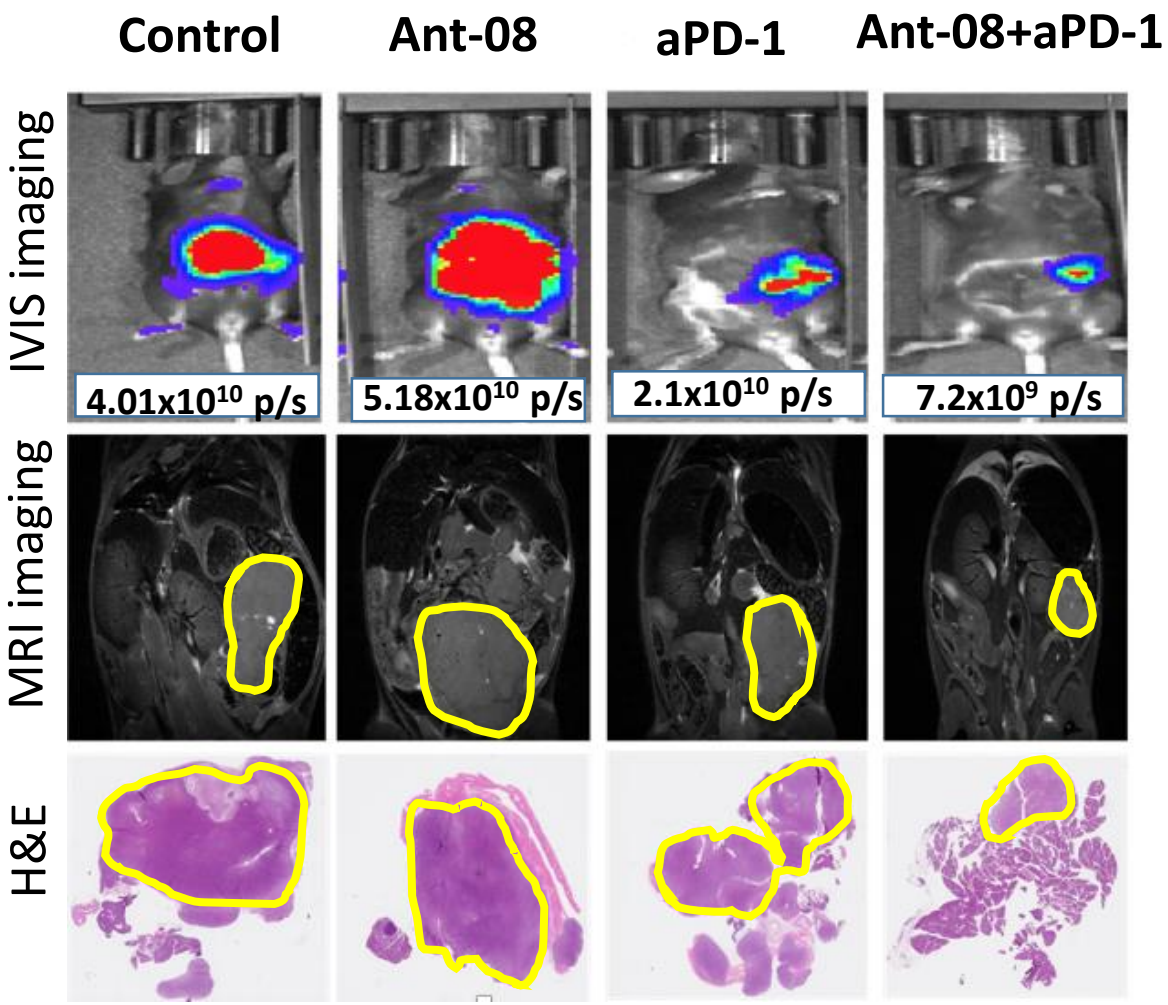
B. PDAC cells express VIP receptors but their growth/viability is not directly affected by VIPR antagonist

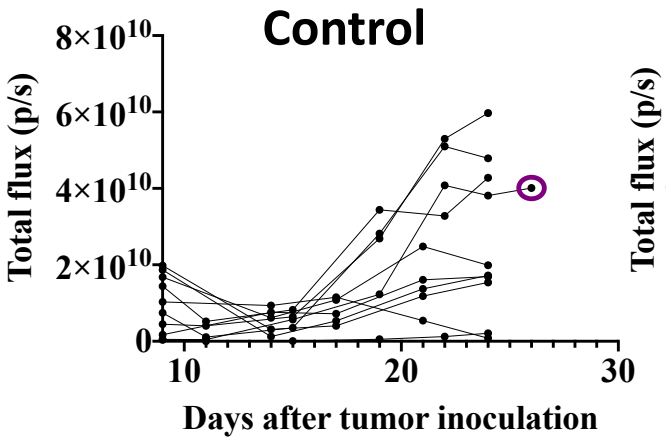


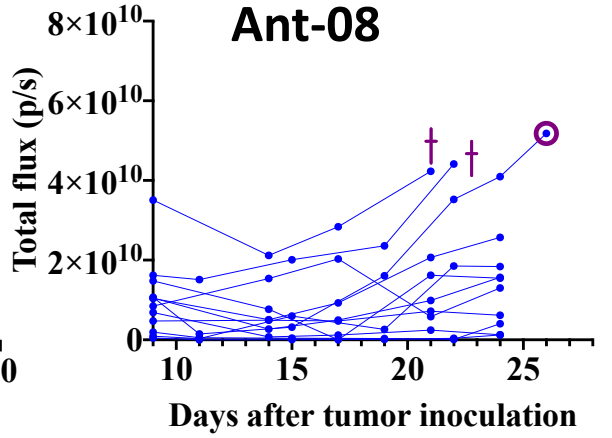


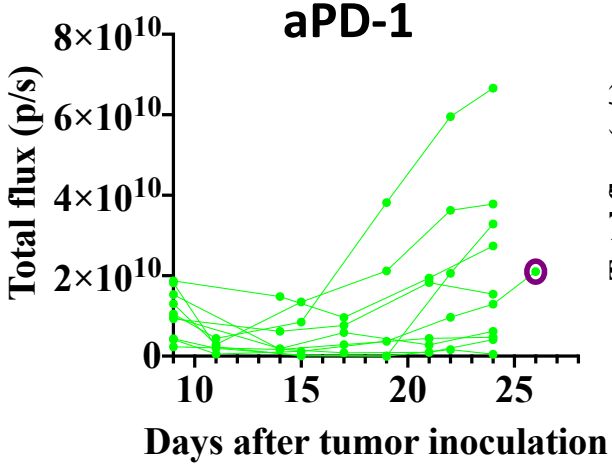
Peptide	Sequence	Kd/Ki (nM)
VIP	HSDAVFTDNYTRLRKQMAVKYLNSILN- amide	2+0.3nM
VIPR antagonist	KPRRPYTDNYTRLRKQMAVKKYLNSILN - amide	50-100nM

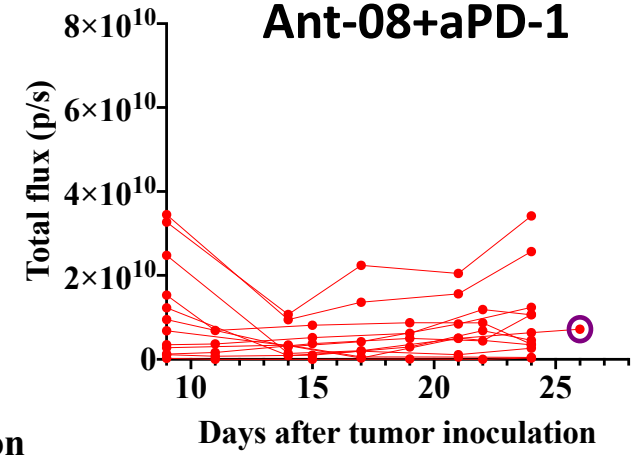
Synergy between VIPR antagonist (Ant-08) and anti-PD1 enhances anti-tumor response to KPC in orthotopic PDAC model.







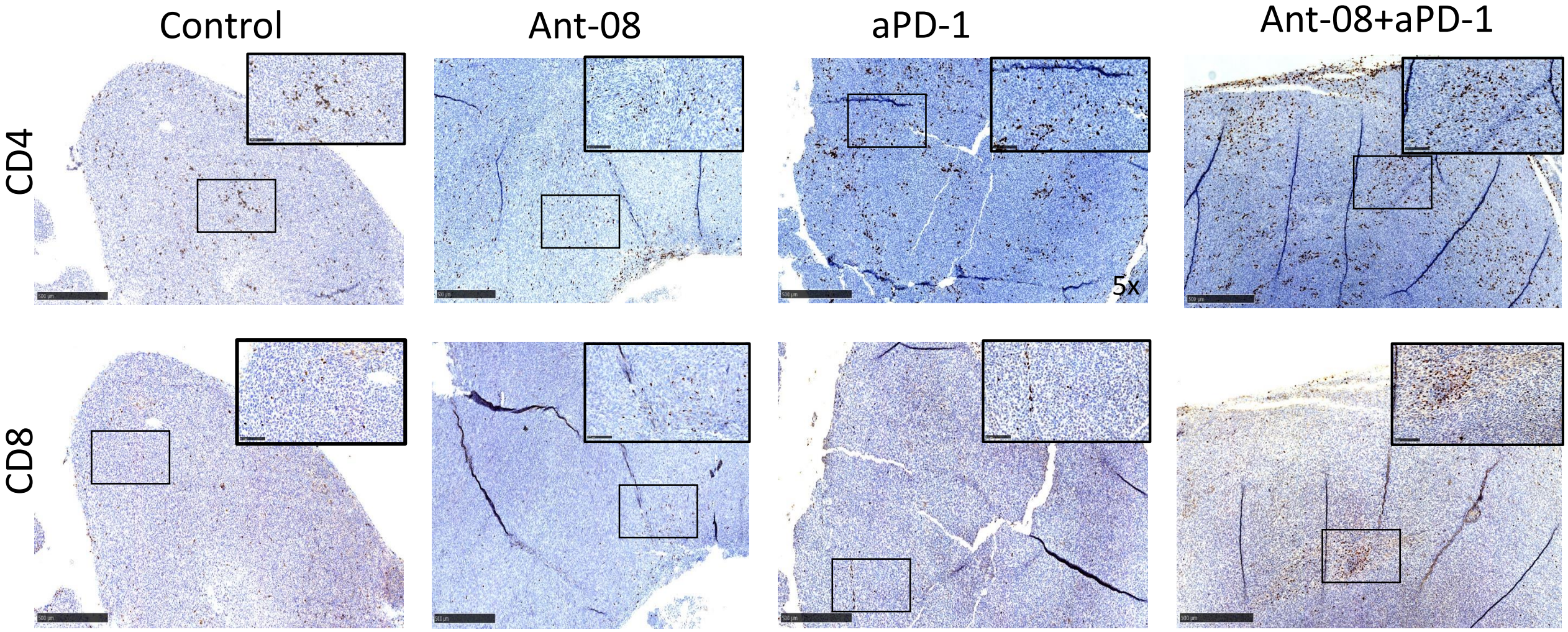




† Mice sacrificed before Day 25 due to excessive tumor burden

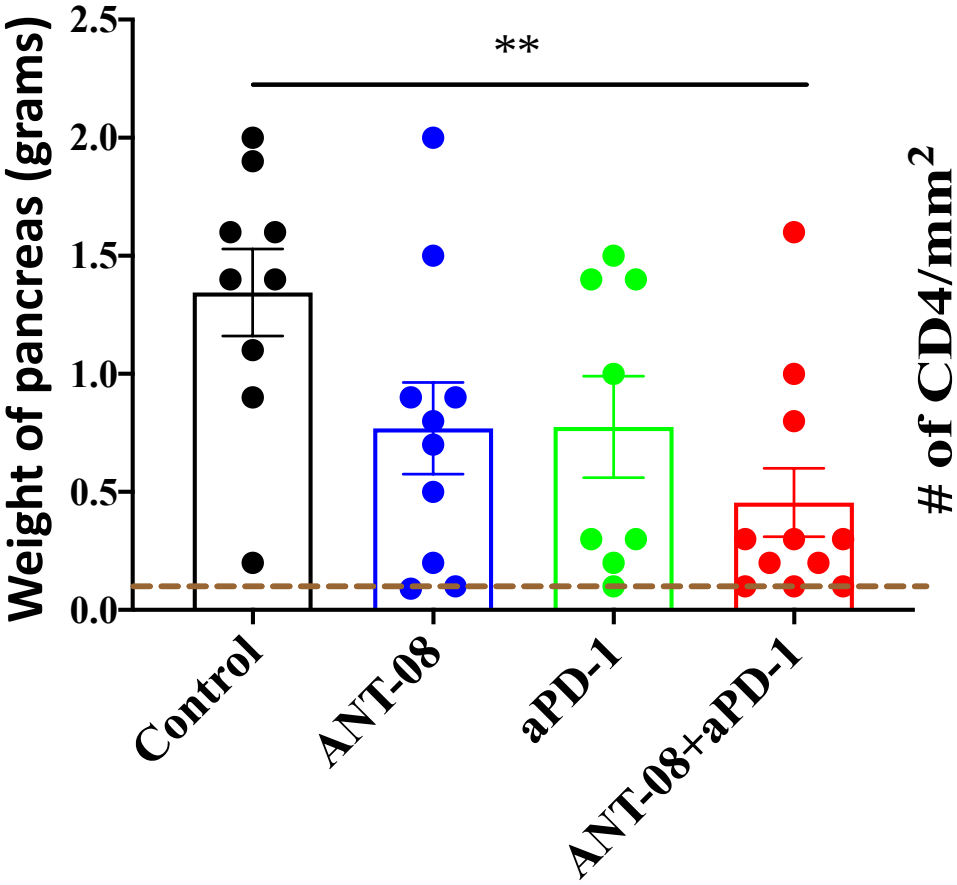
○ MRI imaged mice on day 27

Increased T cell infiltration upon Ant-08+aPD-1 treatment

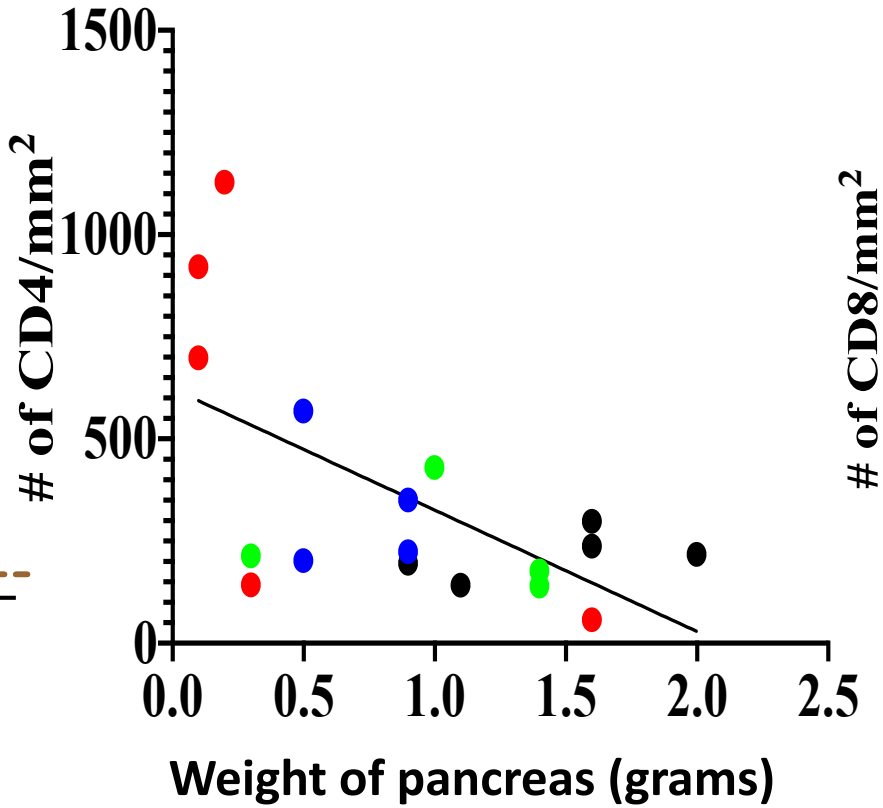


Enhanced anti-tumor response and increased T cell infiltration after treatment with Ant-08+aPD-1

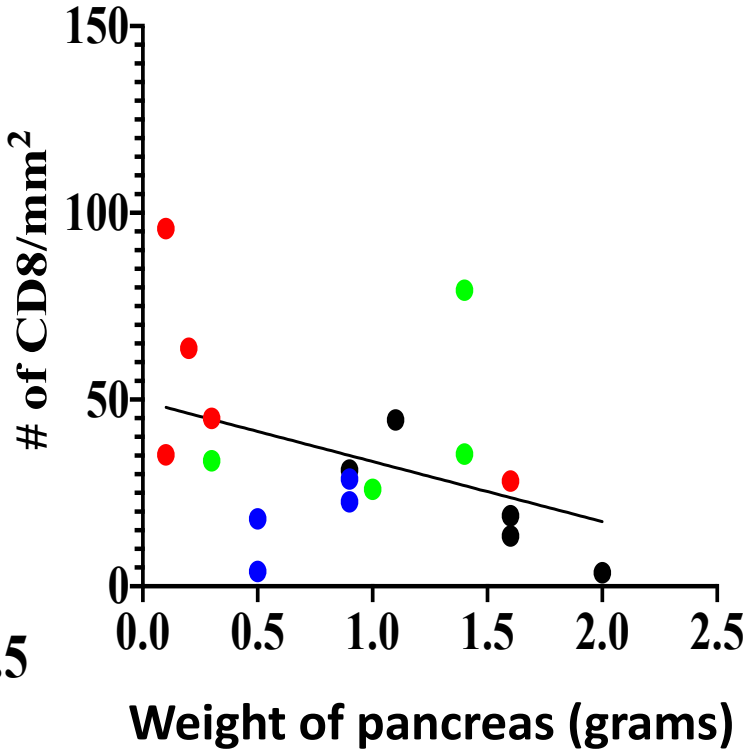
A. Tumor burden



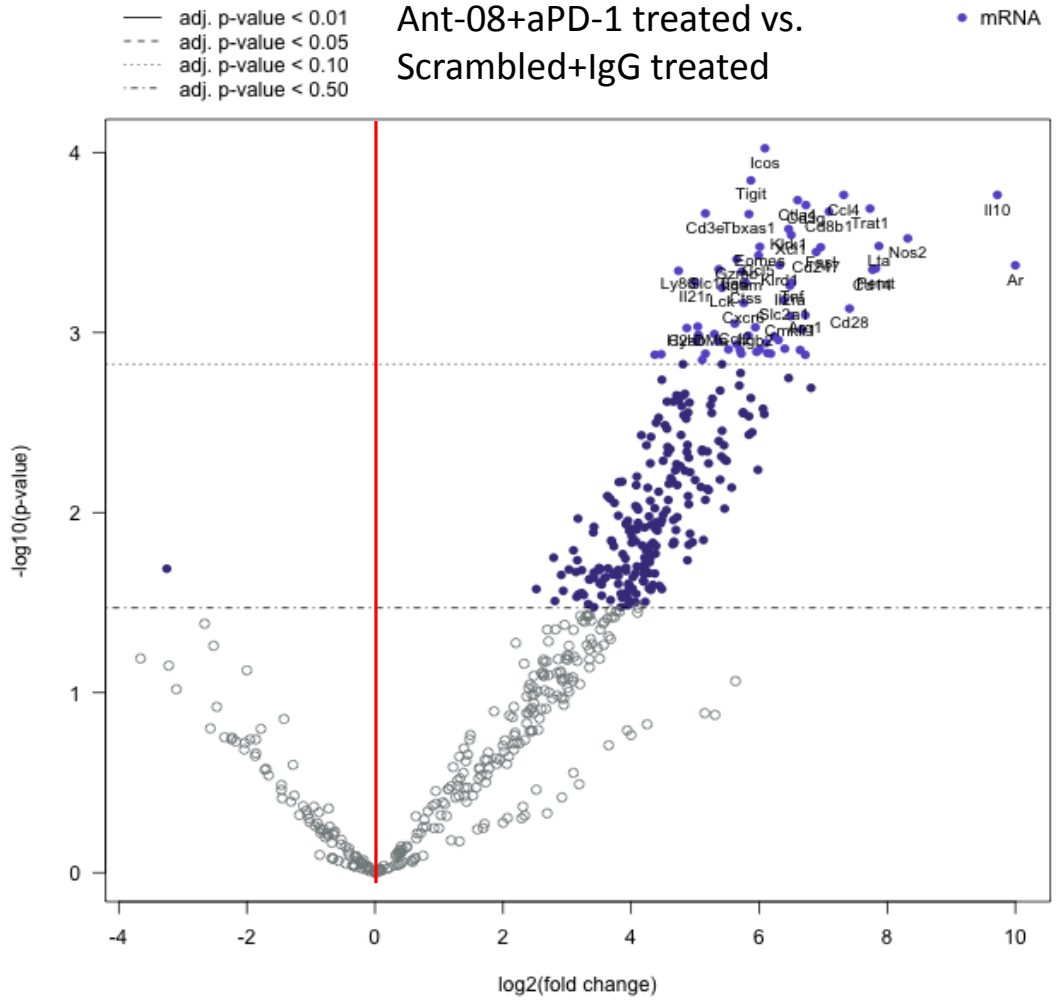
B. CD4 infiltration



C. CD8 infiltration



Nanostring analysis of tumor infiltrating T cells confirms T cell driven anti-tumor response in Ant-08+aPD1 treated mice



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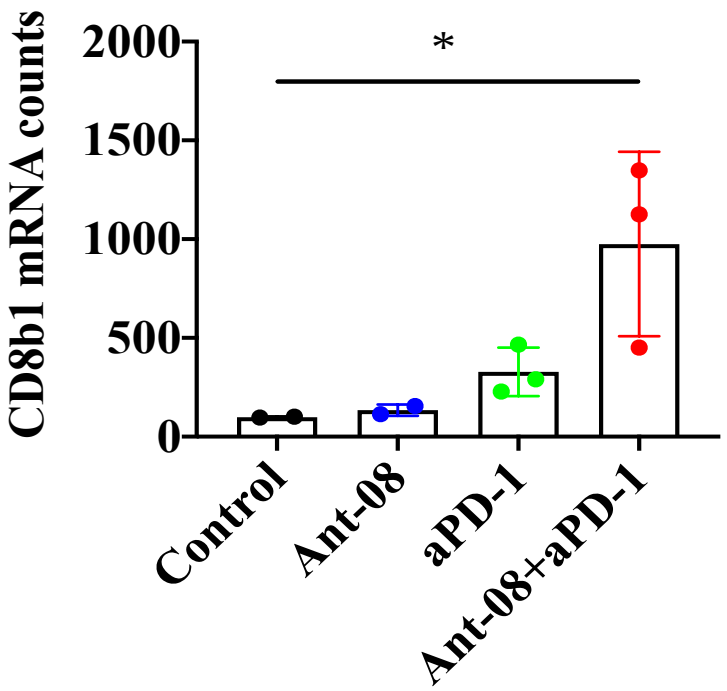

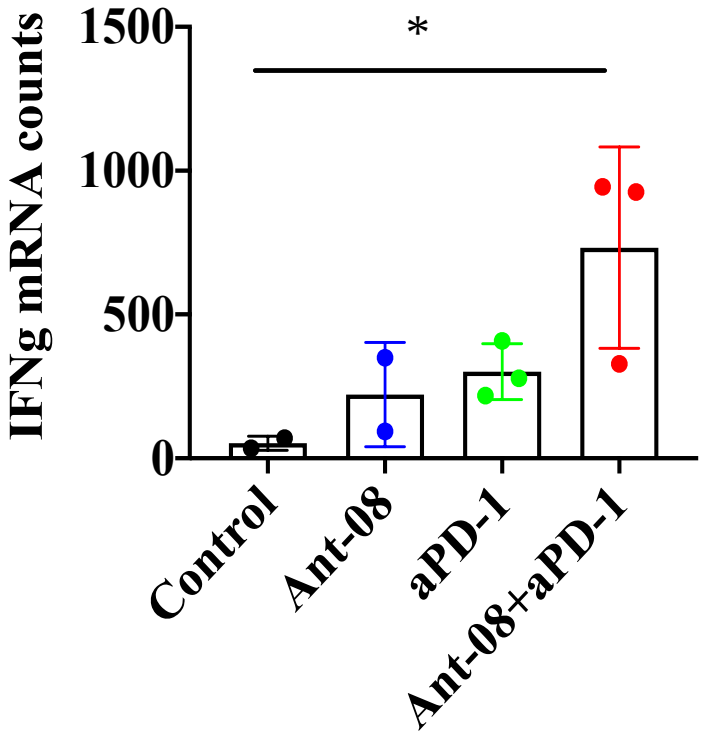

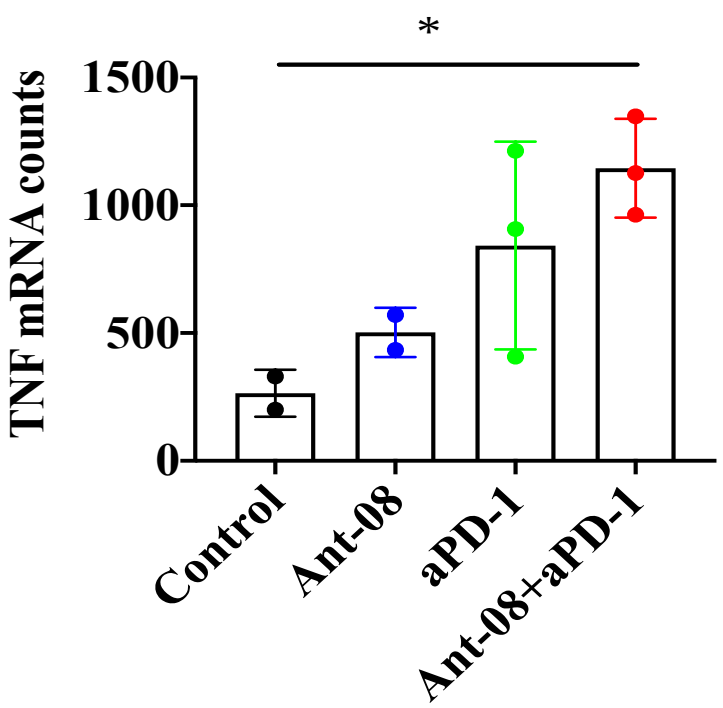

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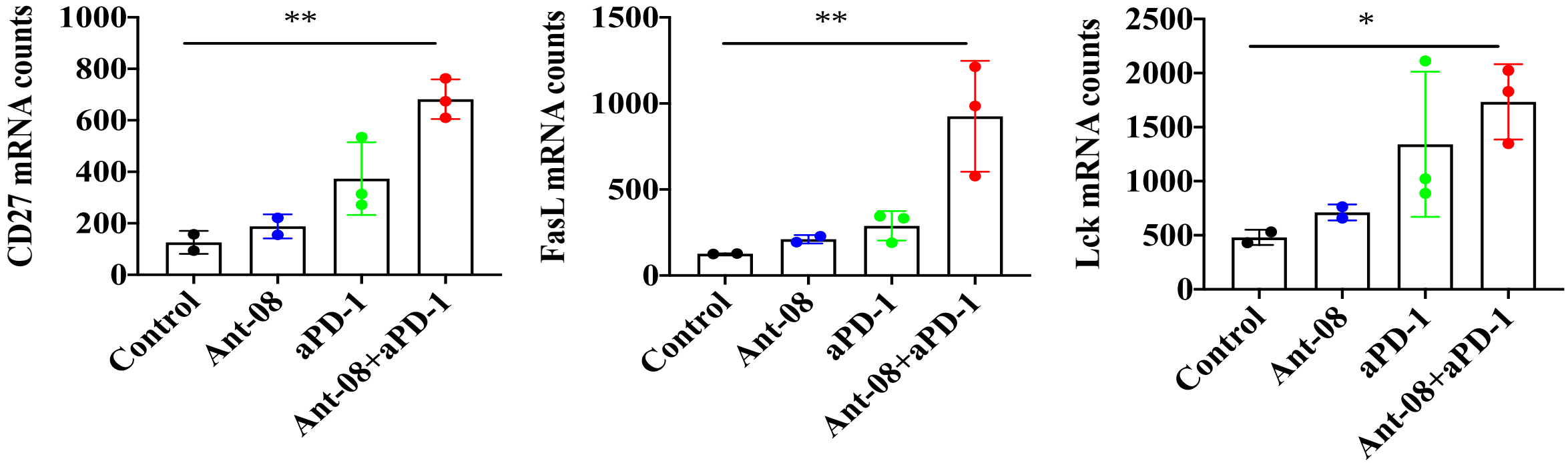

Conclusion

- Overexpression of VIP in PDAC tumors is a potential mechanism of immune escape via a novel immune checkpoint pathway.
- Inhibiting VIP signaling in combination with anti-PD1 blockade increases T cell infiltration and decreases tumor burden in mouse PDAC models.
- Conservation of VIP sequence across species and similar effect of VIP antagonists on mouse and human T cells suggests potential for clinical translation.

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Collaborators

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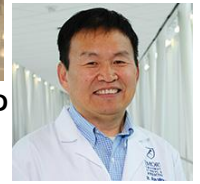

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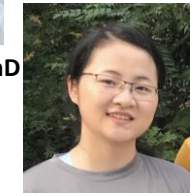
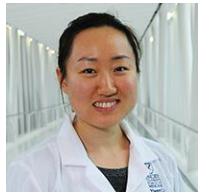


Jingru Zhu



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Adoptive Cell therapy

Core Labs at Emory

Integrated genomics core

Cancer Tissue Pathology

Cancer Animal Models

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EMORY UNIVERSITY SCHOOL OF MEDICINE

Adaptive biotechnologies

Experiments in pipeline

- Mice bearing PDAC wildtype and VIP knocked out cells will be tested for differences in
  - Levels of intracellular cyclic AMP
  - Chemokine expression
  - Genes involved in T cell receptor based antigen recognition
  - Cytotoxicity of T cells

- Efficacy of VIP antagonists will be tested in GEMM models of PDAC