PD1 Blockade Augments Adoptive T Cell Therapy via Endogenous T Cells Rather than Direct Enhancement of Transferred T Cells

John Davies

Postdoctoral Fellow
Hinrichs Lab
NIH/NCI/ETIB

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Disclosures

- No personal disclosures

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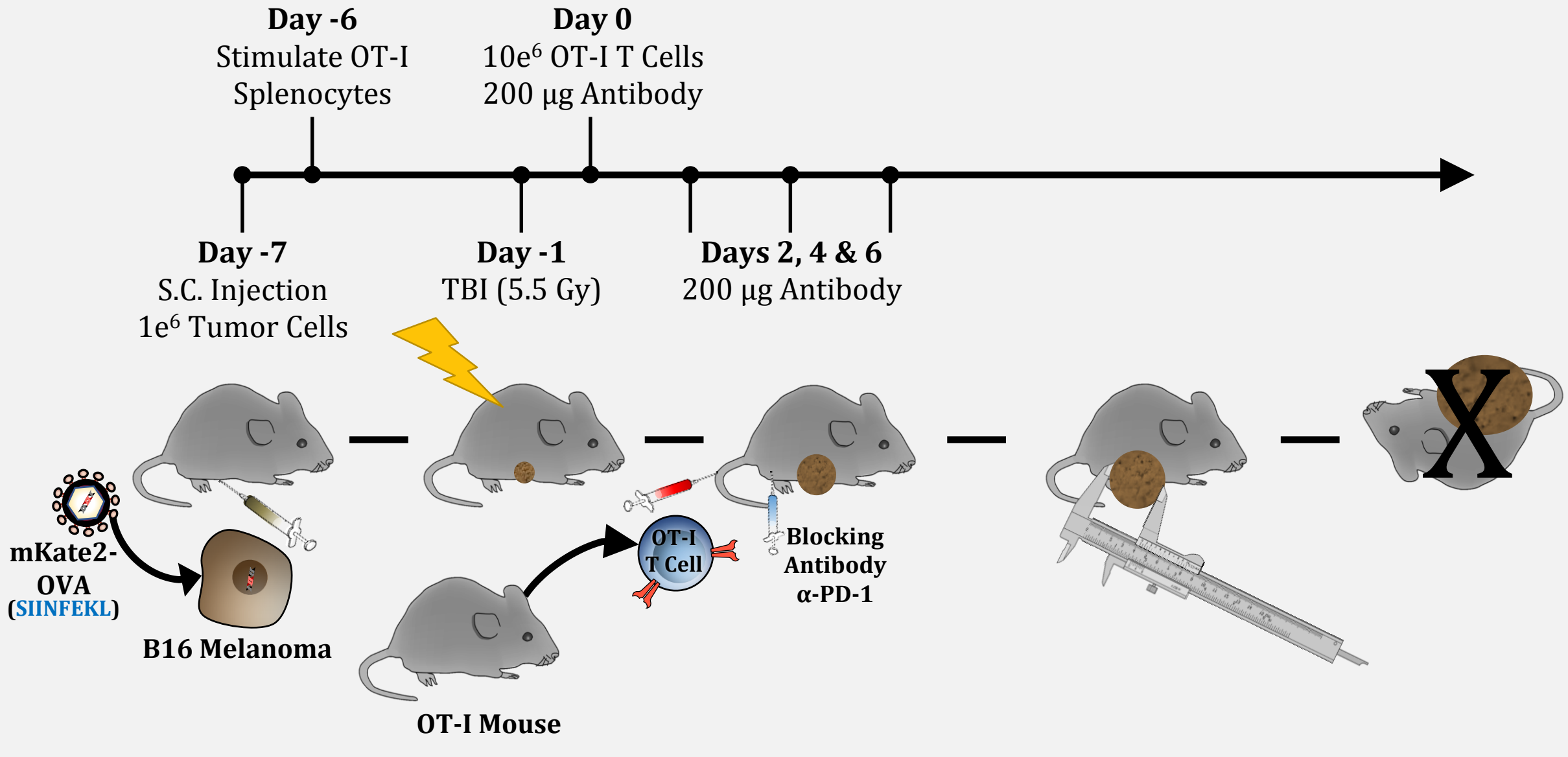
Rationale

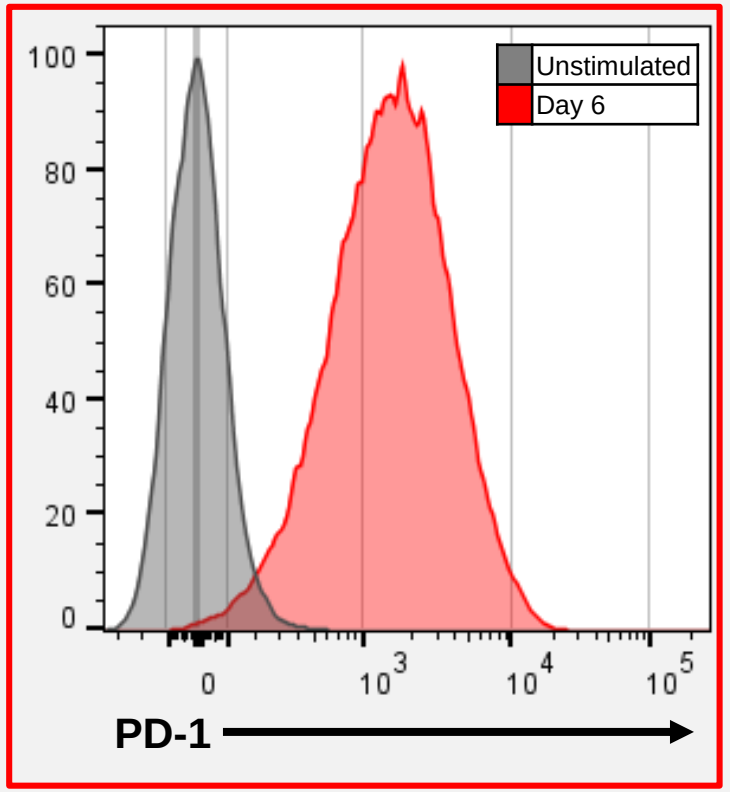
- Adoptive T cell therapy (ACT) has clinical activity in human cancers
- T cells express the inhibitory receptor PD-1
- Tumors, and many other cell types, express PD-L1 (a ligand for PD-1)
- PD-1 axis blockade has clinical activity in some cancers

❖ Adoptively transferred T cells may experience PD-1 mediated inhibition. Therefore, ACT may be improved when used in combination with PD-1 axis blockade

Experimental Syngeneic Model

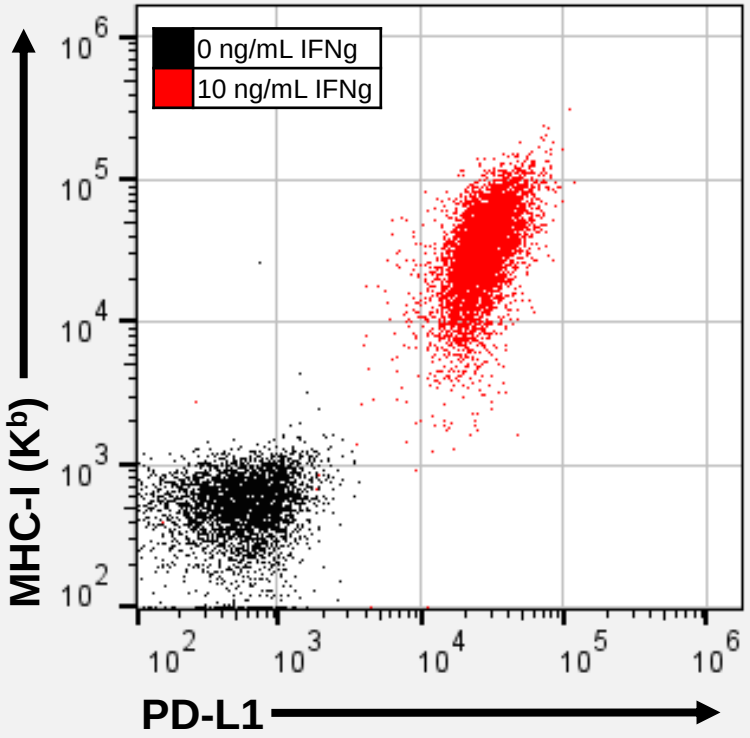


Expression of PD-1 on Infused T Cells and PD-L1 on Tumors

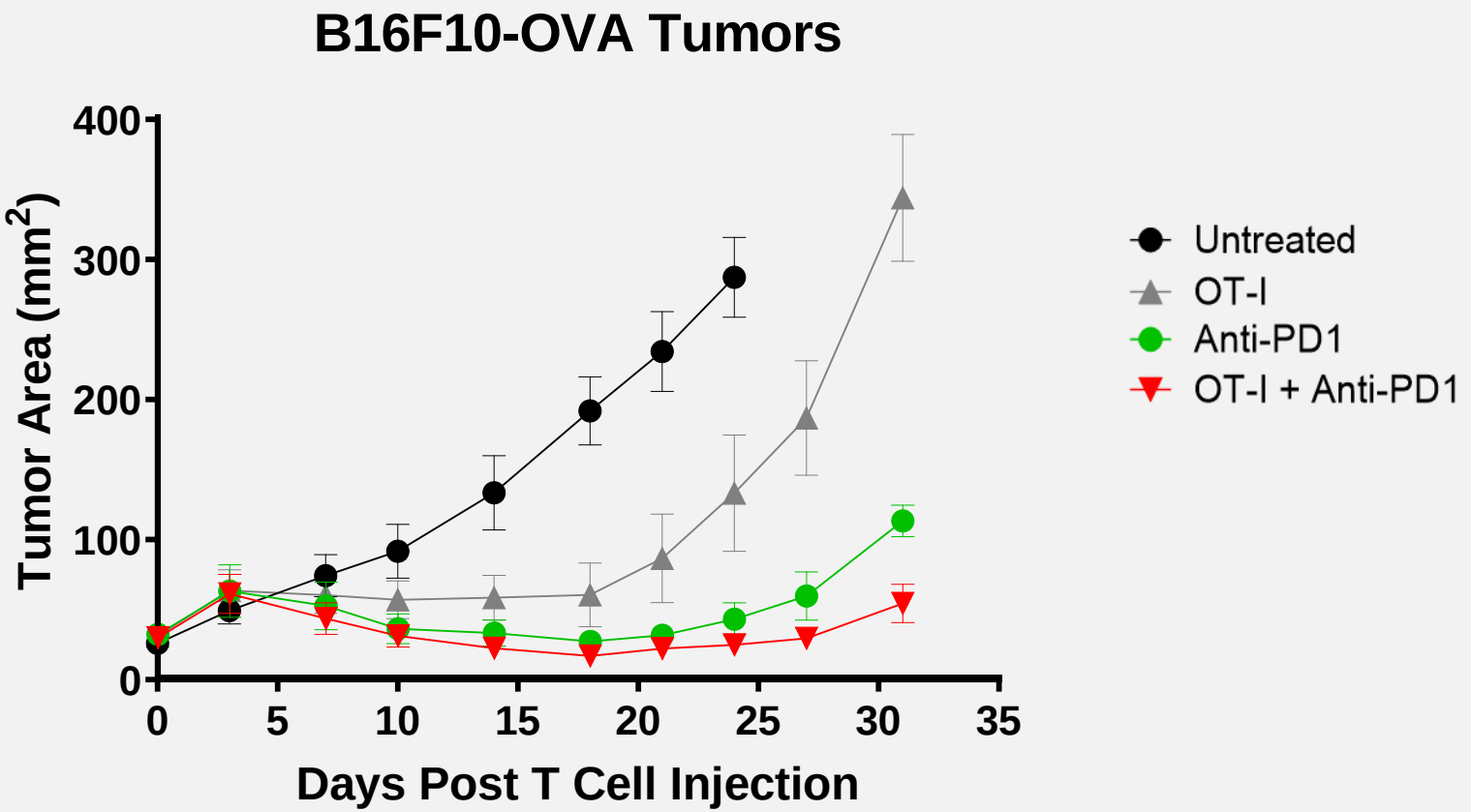


T Cells
Day of Transfer

B16F10 Upregulation of PD-L1 & MHC-I



PD-1 Blockade Provided an Additive Benefit to ACT



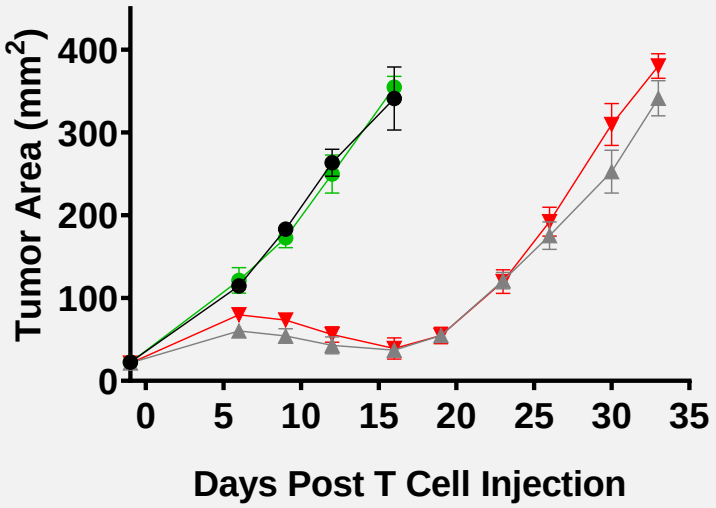
Summary of Tumor Treatment

- OT-I T cells mediated regression of OVA antigen bearing tumors
  - This treatment was improved with PD-1 blockade

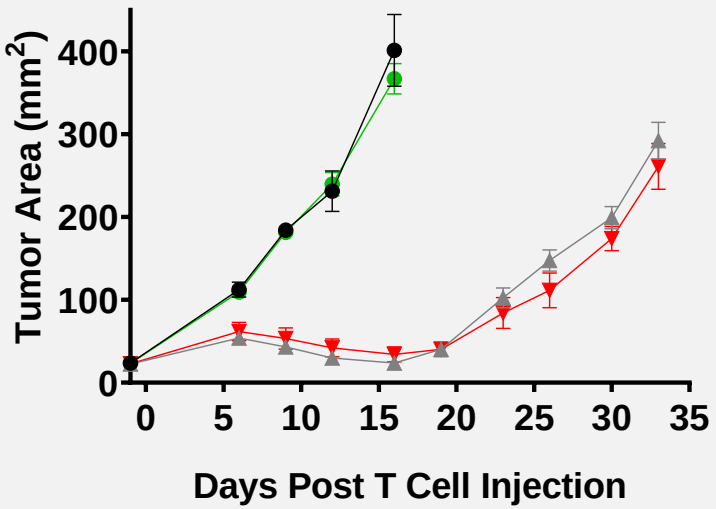
What is the contribution of endogenous T cells to the efficacy of anti-PD1 during ACT?

The Efficacy of PD-1 Blockade During ACT Required Endogenous Anti-Tumor T Cells

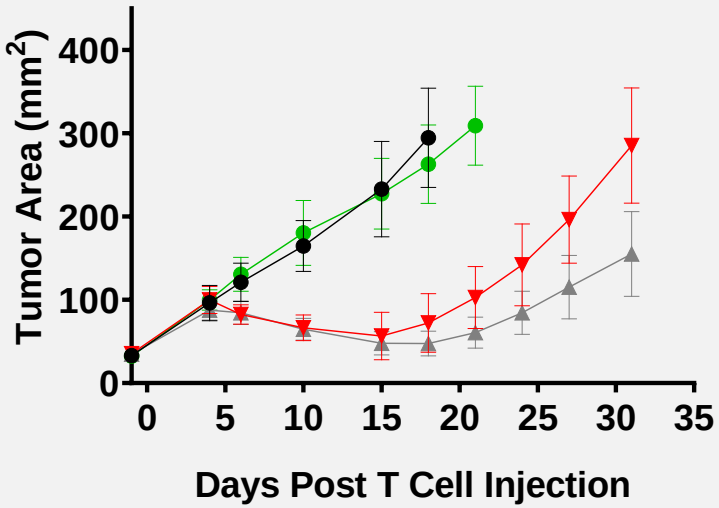
Rag1$^{-/-}$ Hosts
Deficient in Adaptive Immunity

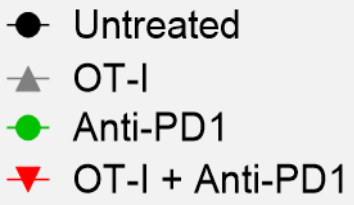


Trac$^{-/-}$ Hosts
Deficient in alpha-beta T cells



P14 TCRtg Hosts
Restricted T cell Repertoire

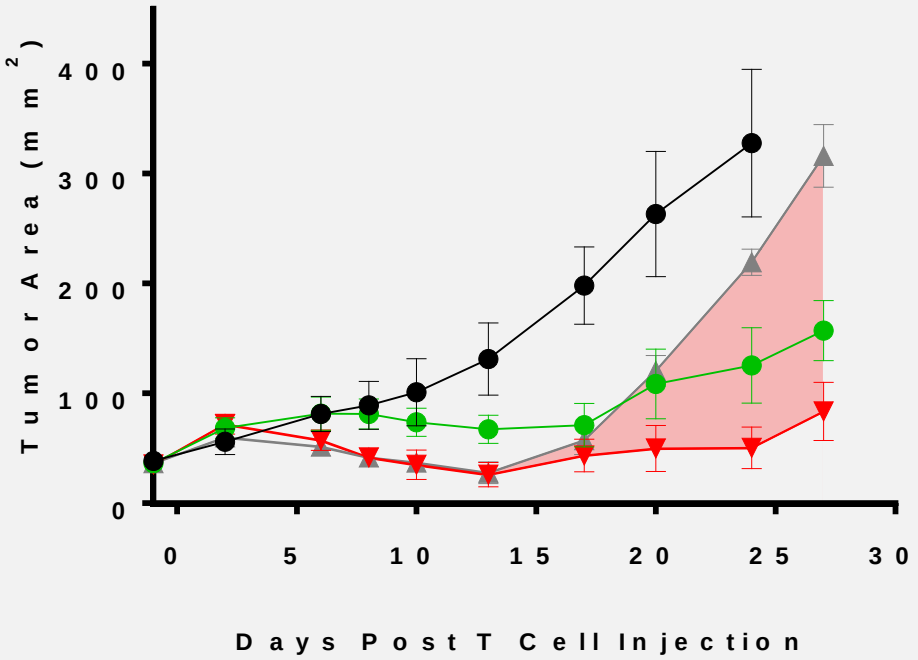




The Requirement of Endogenous T Cells for anti-PD-1 Efficacy was also Observed in the P14:gp33 ACT Model

Wild-Type Hosts

Complete Immune System



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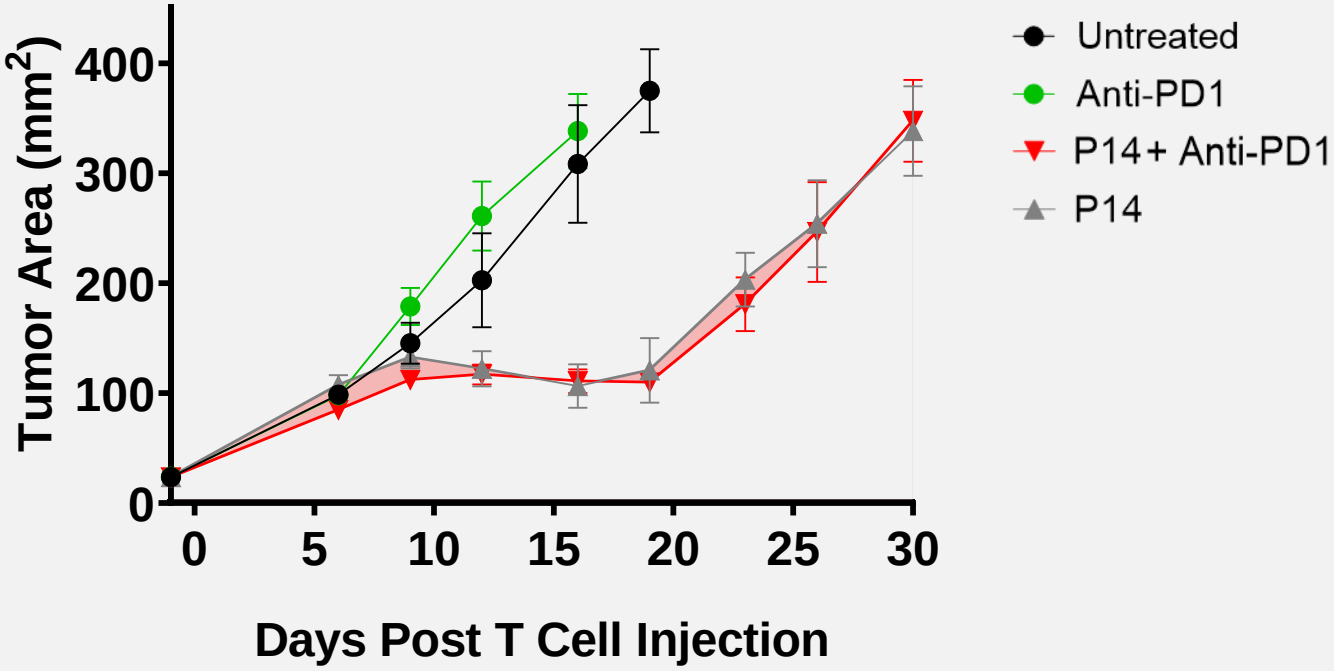
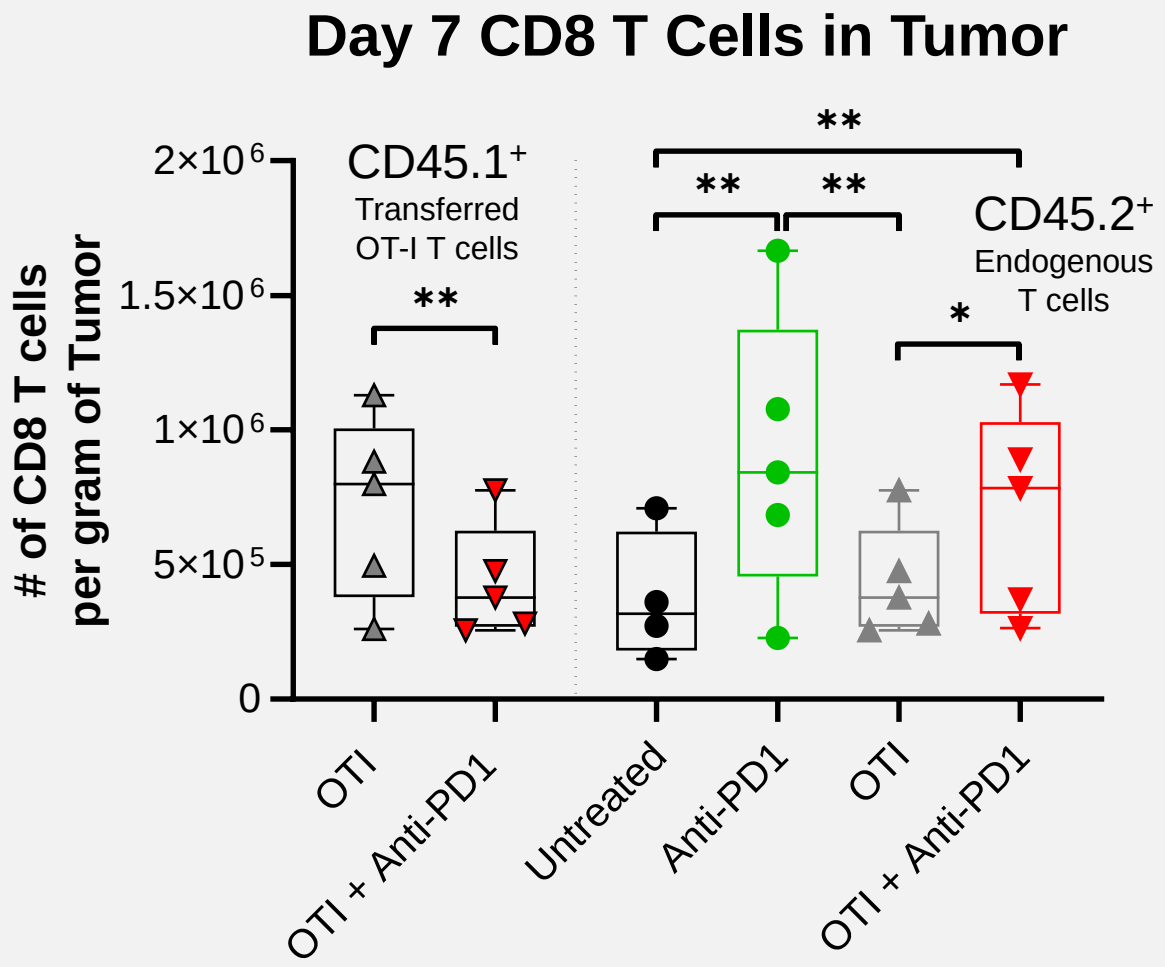


Tumor Infiltrating Endogenous T Cells Increased After PD-1 Blockade

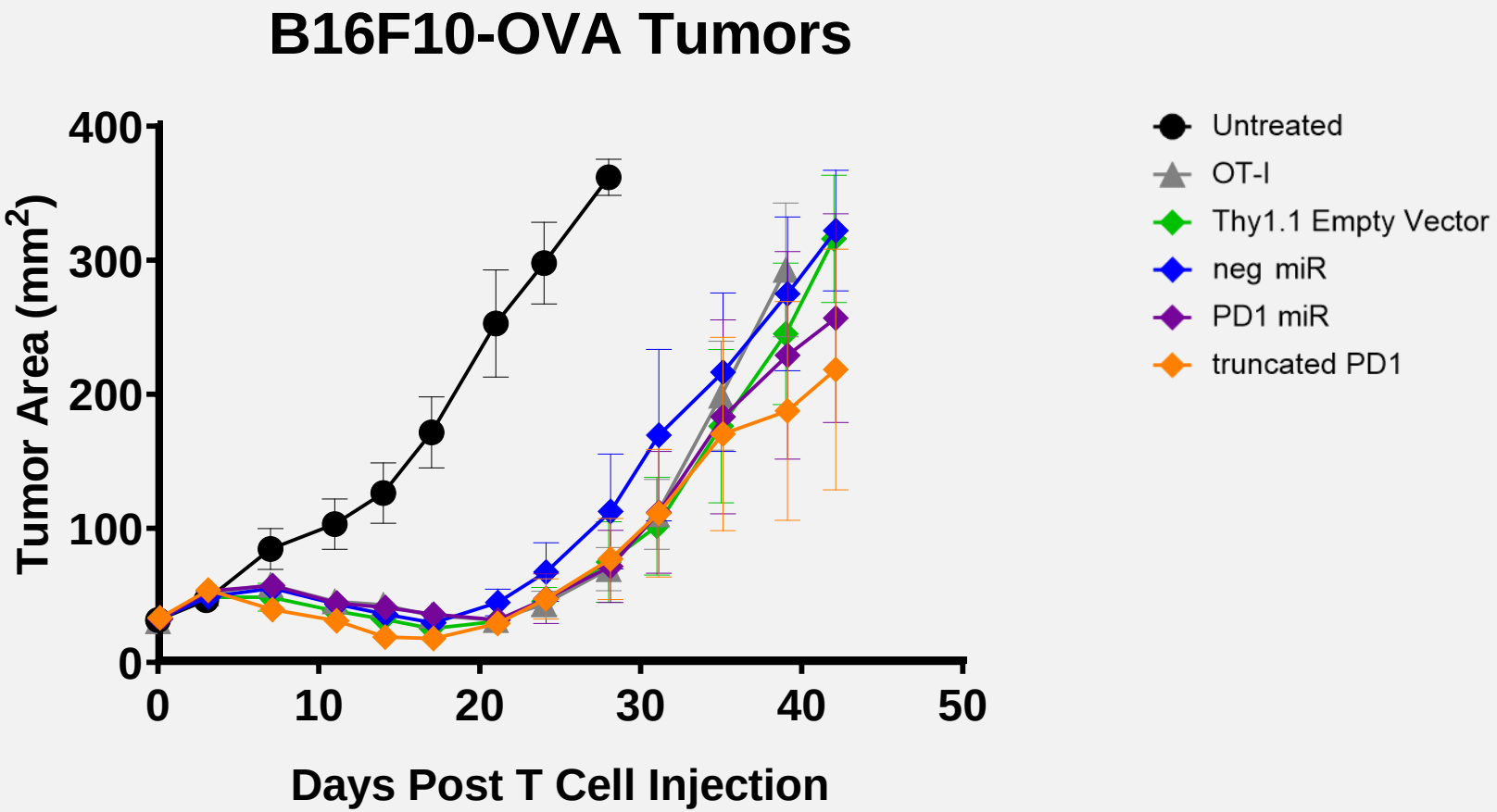


Summary of Tumor Treatment

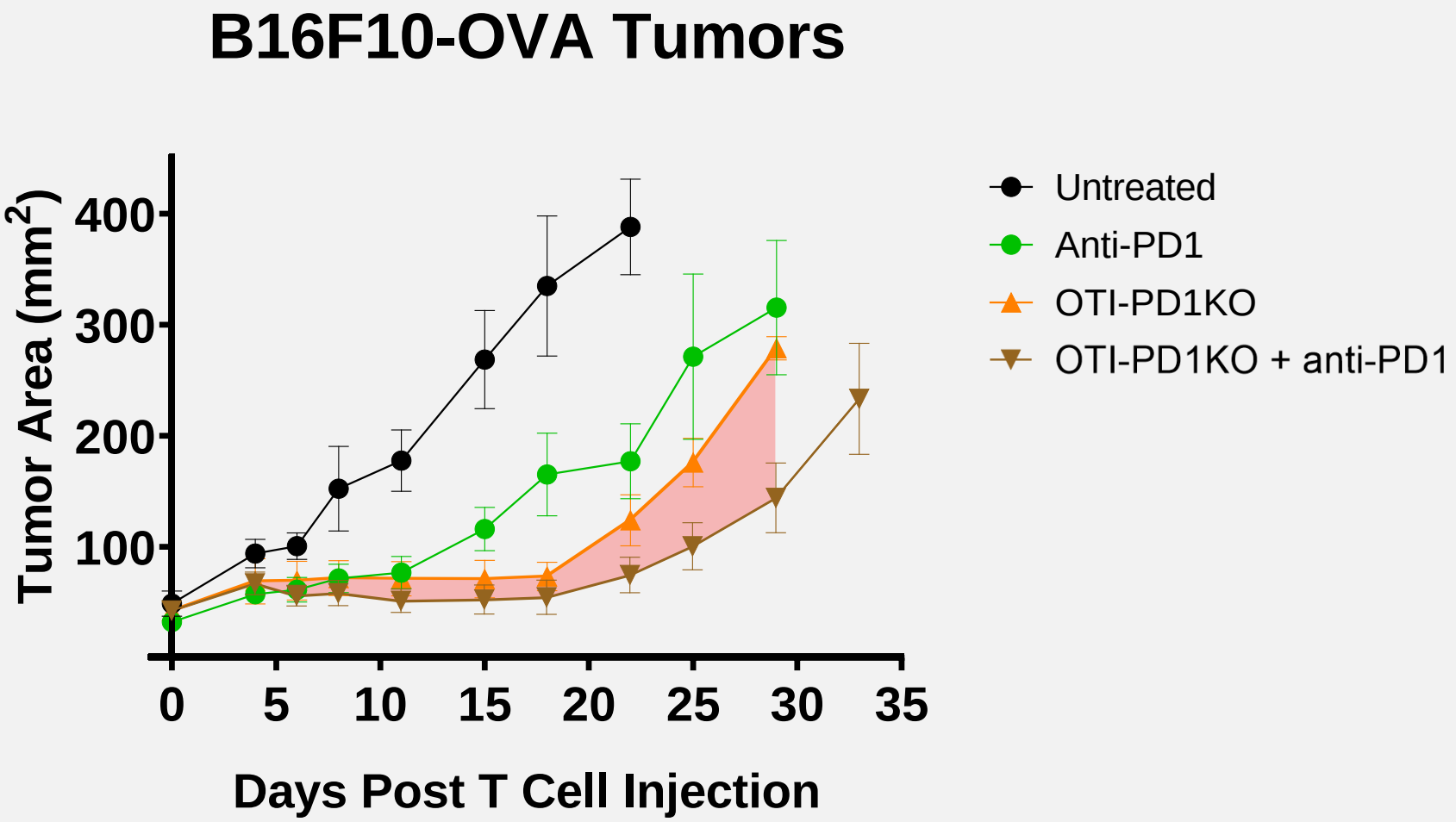
- OT-I T cells mediated regression of OVA antigen bearing tumors
  - This treatment was improved with PD-1 blockade
- PD-1 blockade was dependent on endogenous anti-tumor T cells
- These observations were consistent in two independent T cell models
- Adoptively transferred T cells did not appear to directly benefit from PD-1 axis blockade
  - They decreased in number and frequency

Would reduction of PD-1 signaling directly on transferred T cells increase efficacy of ACT?

PD-1 miR & Truncated PD-1 Engineered T Cells Failed to Enhance ACT



PD-1 Blockade Improvement was Independent of Adoptively Transferred T Cells



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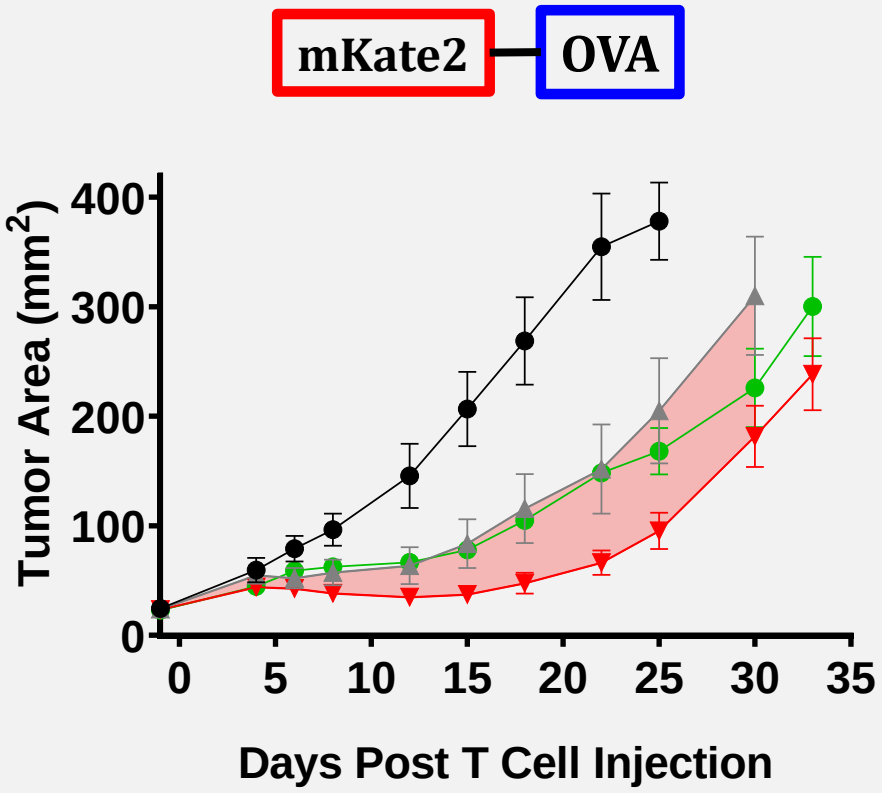
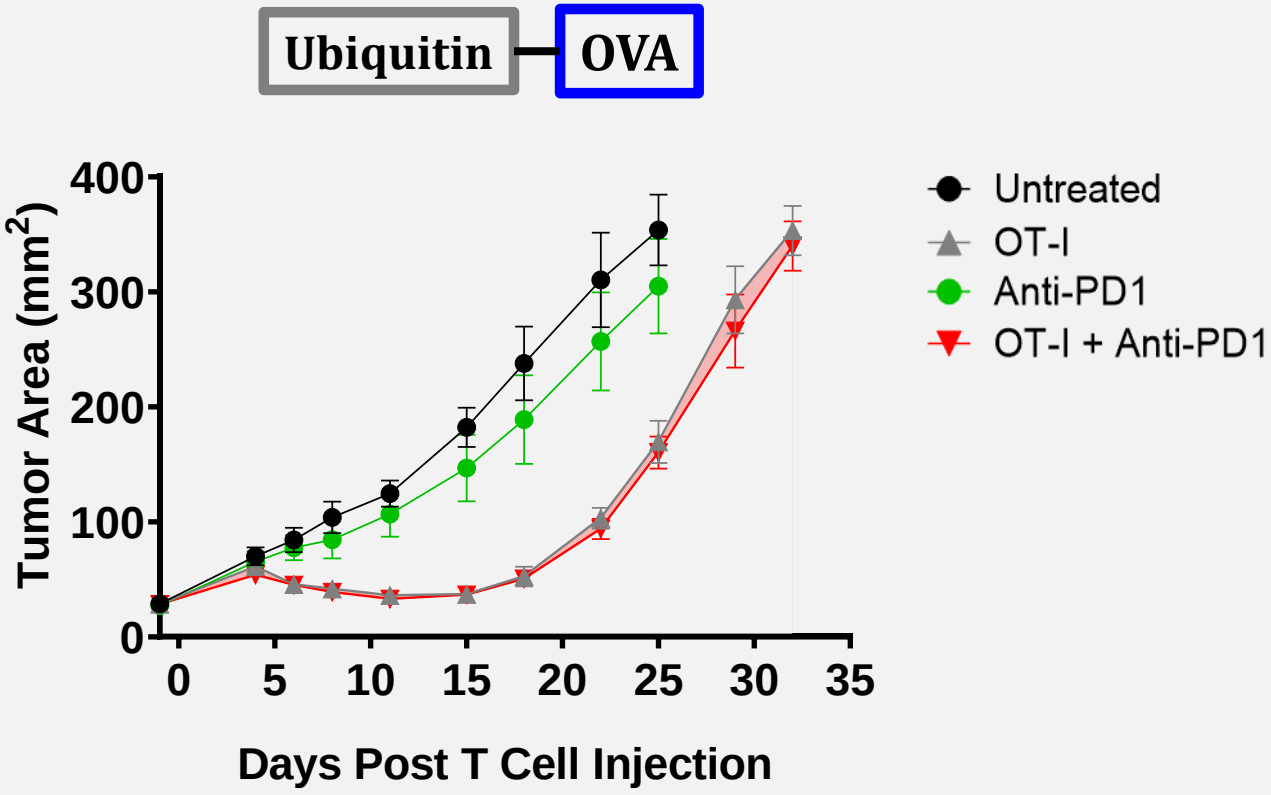
- These observations were consistent in two independent T cell models of ACT
- Adoptively transferred T cells did not appear to directly benefit from PD-1 axis blockade
  - They decreased in number and frequency
- Reduction of PD-1 signaling on adoptively transferred T cells did not improve therapy
- PD1-KO OT-I T cell therapy was improved with the addition of anti-PD1

How does tumor immunogenicity interact with anti-PD1 efficacy during ACT?

PD-1 Blockade Provided Added Benefit to ACT for Tumors Expressing mKate2



Multiple Antigens
OT-I Target



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  - They decreased in number and frequency
- Reduction of PD-1 signaling on adoptively transferred T cells did not improve therapy
- PD1-KO OT-I T cell therapy was improved with the addition of anti-PD1
- PD-1-responsive endogenous T cells were directed towards mKate2

Conclusions

- Disruption of PD-1 signaling does not appear to directly benefit adoptively transferred T cells
- The benefit of anti-PD-1 is dependent on the presence of endogenous anti-tumor T cells

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