Inhibition of the T cell oxygen sensing machinery promotes anti-tumor immunity

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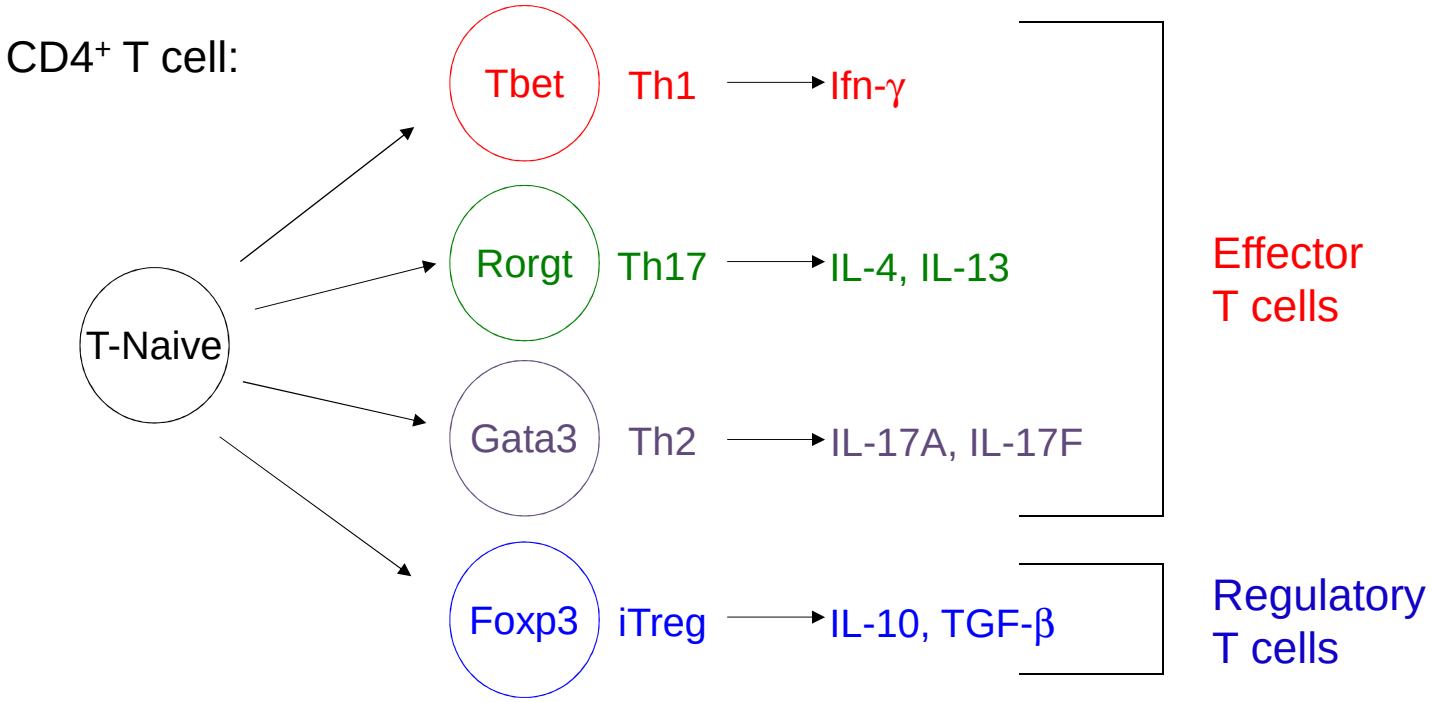
Site specific immunity and the metastatic niche

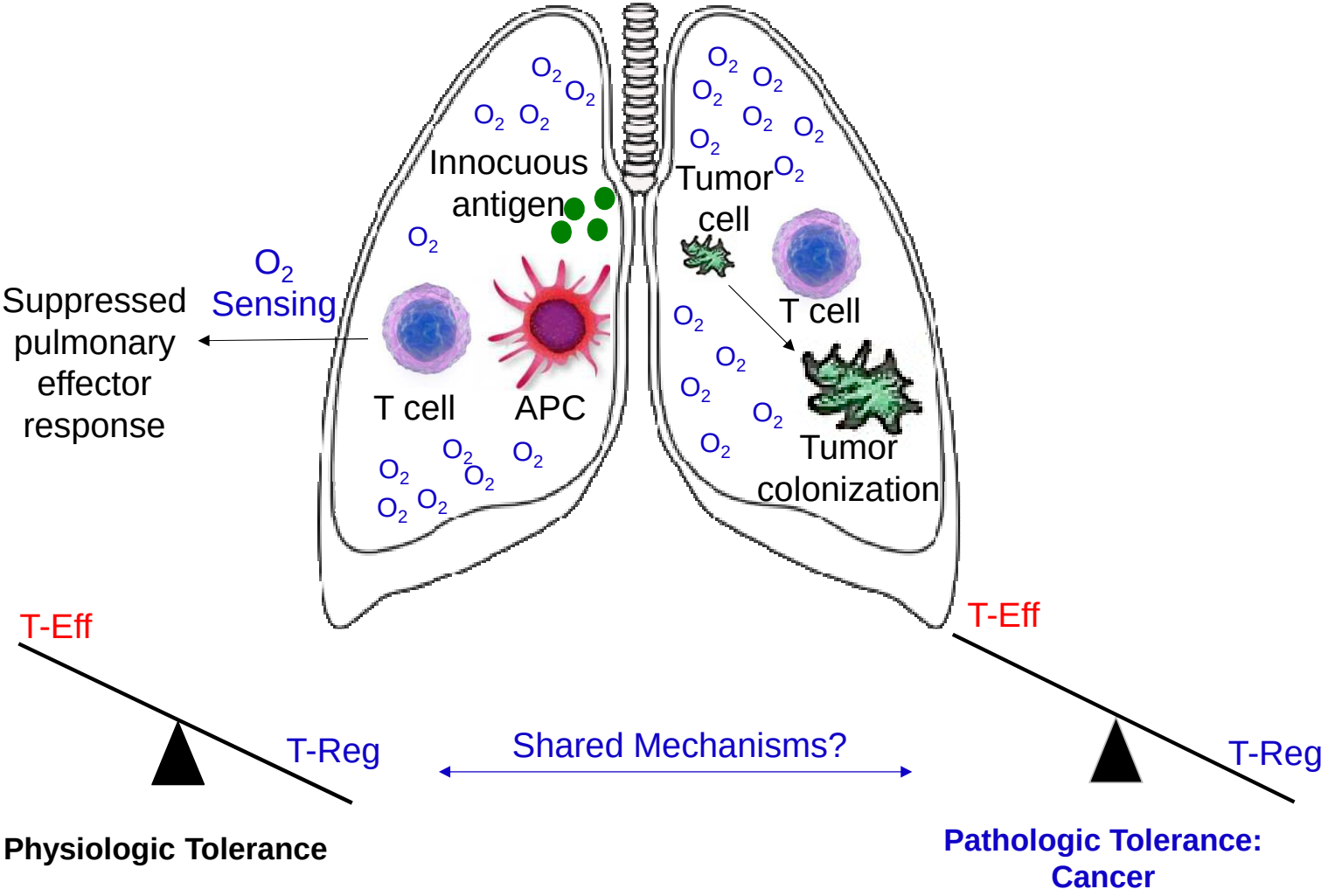
- The lung is one of the most common sites of metastasis for many cancers
- The propensity for tumor cells to colonize the lung has been attributed to the extensive capillary network within this organ.
- Upon extravasation into the target organ parenchyma invading tumor cells encounter a local immune response.

Could unique factors that influence immune responses in the lung establish this site as an “immunologically favorable metastatic niche?”

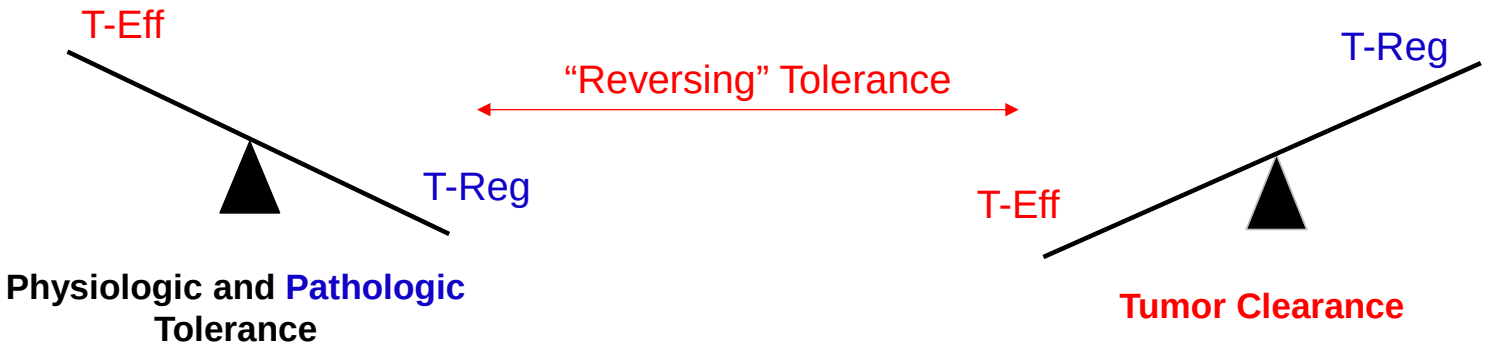
Immunologic diversity is maintained by CD4$^+$ T cell functional specification



The lung is an immunologically tolerant site



Investigating T cell oxygen sensing in pulmonary immunity and metastasis

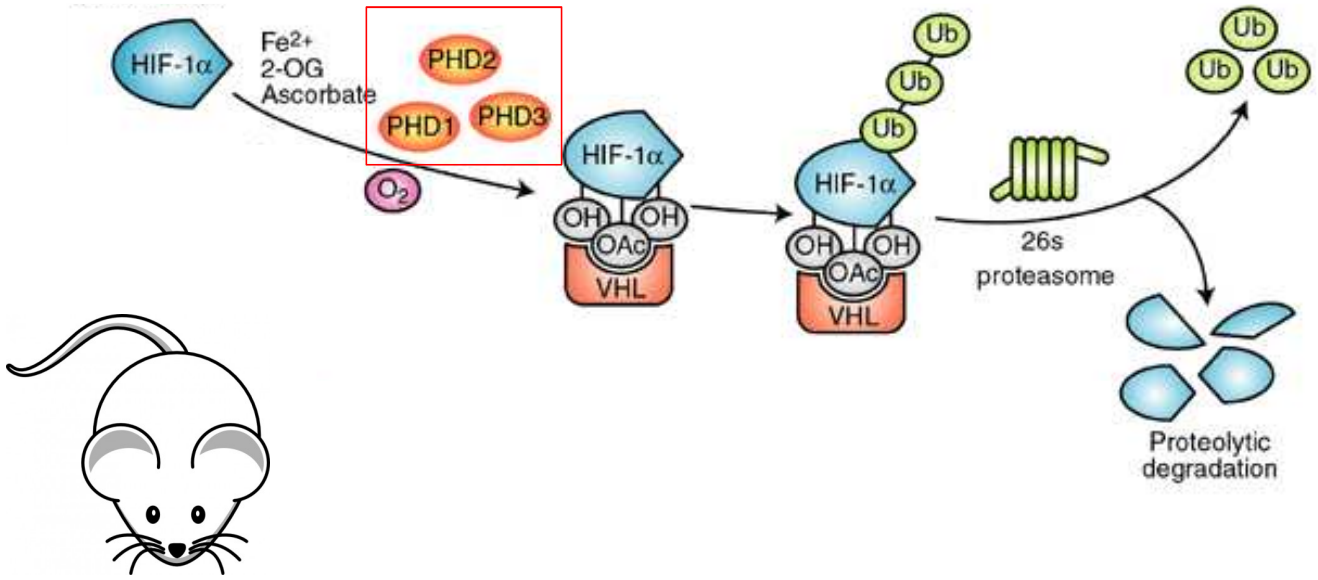


1. Immune Homeostasis: Is T cell oxygen sensing involved in directing physiologic tolerance in the lung?

2. Tumor Colonization: Is this program co-opted by tumors to promote lung metastasis?

3. Tumor Clearance: Can T cell oxygen sensing be inhibited to promote immune mediated tumor clearance?

T cell oxygen sensing is mediated through the prolyl hydroxylase domain containing (Phd) proteins

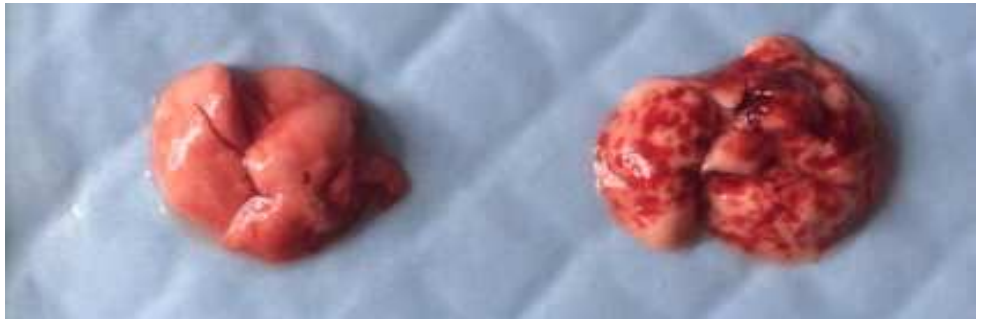


WT: PhdALL$^{fl/fl}$ CD4-Cre$^{-/-}$

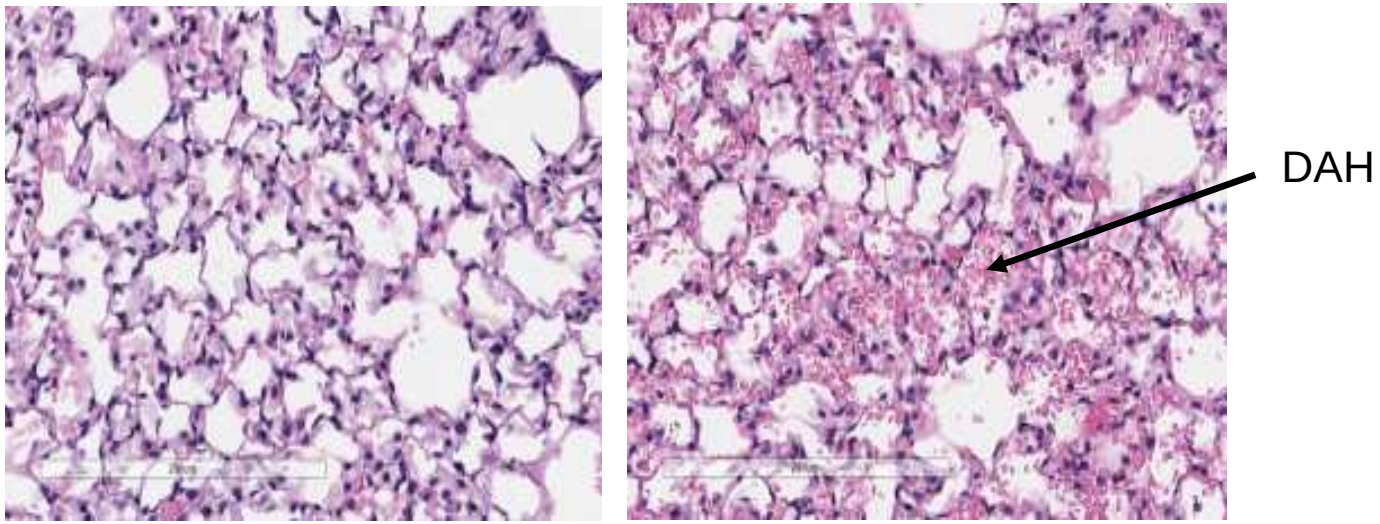
Phd-tKO: Phd1,2,3$^{fl/fl}$ CD4Cre$^{+/-}$

T cell oxygen sensing prevents spontaneous pulmonary inflammation

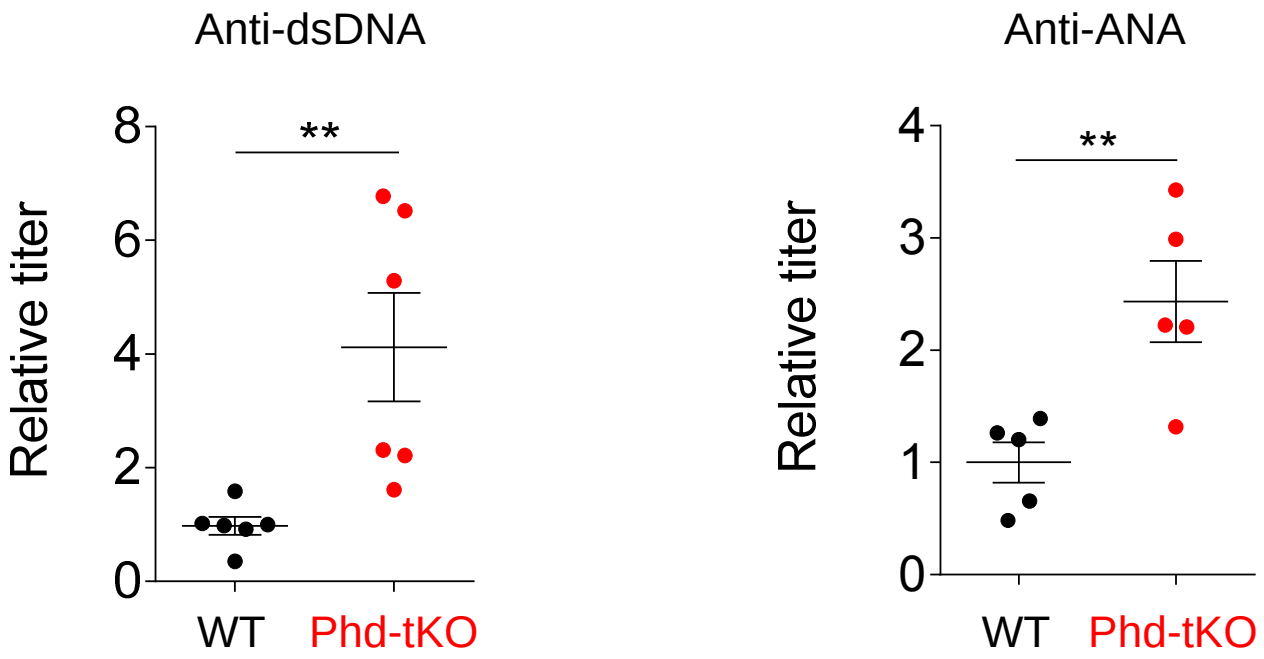
WT Phd-tKO



WT Phd-tKO

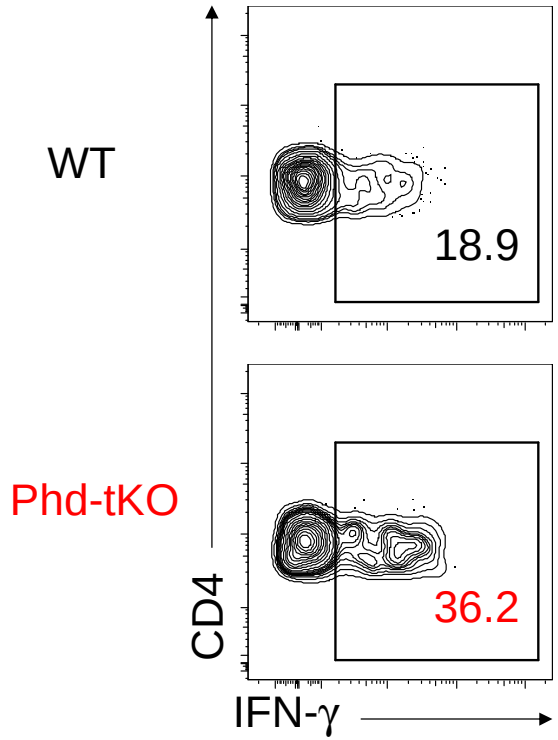


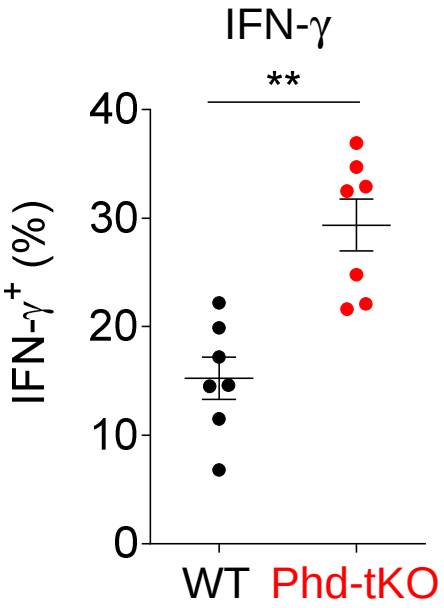
Phd-tKO mice have elevated serum auto-antibodies



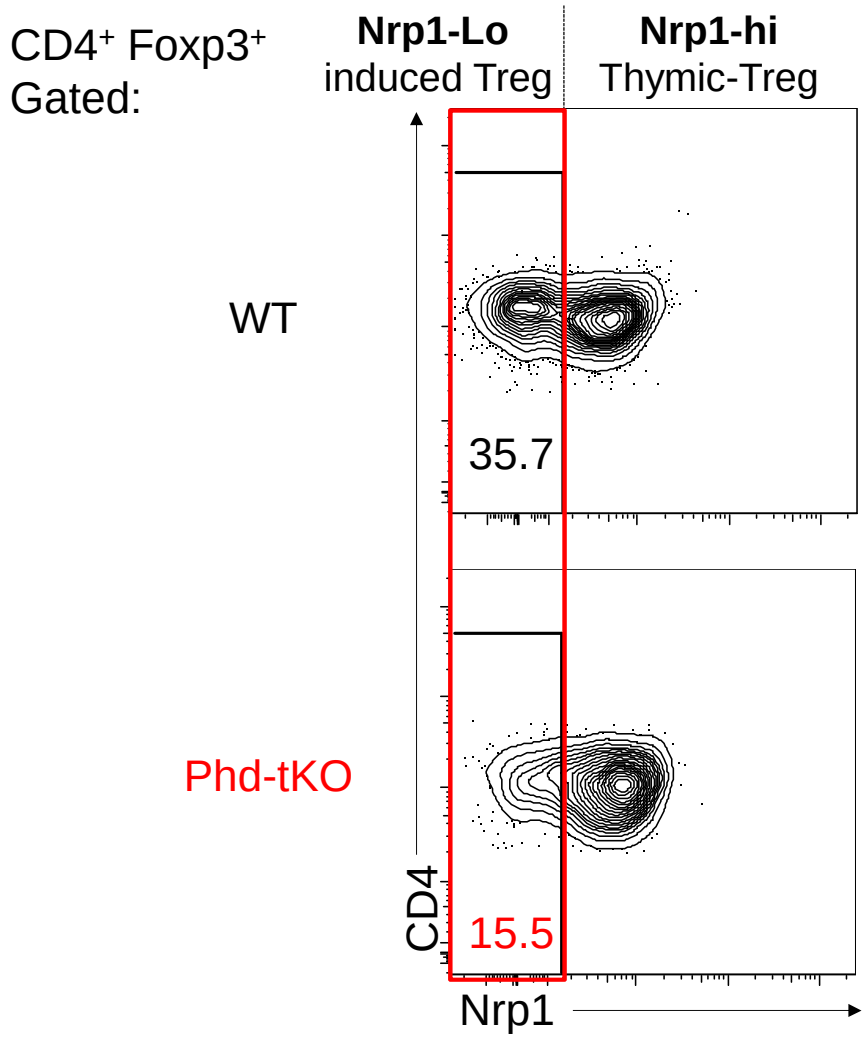
Lung resident Phd-tKO CD4$^+$ T cells have increased capacity to produce IFN-γ

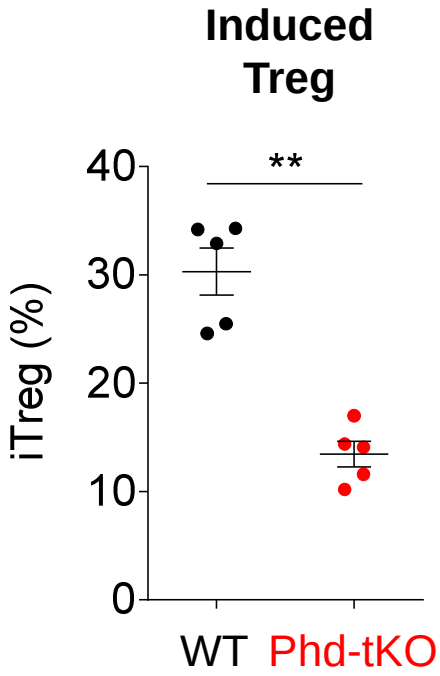
CD4$^+$ T cells:





CD4+ T cell oxygen sensing is required for accumulation of Nrp^{Lo} iTreg within the lung



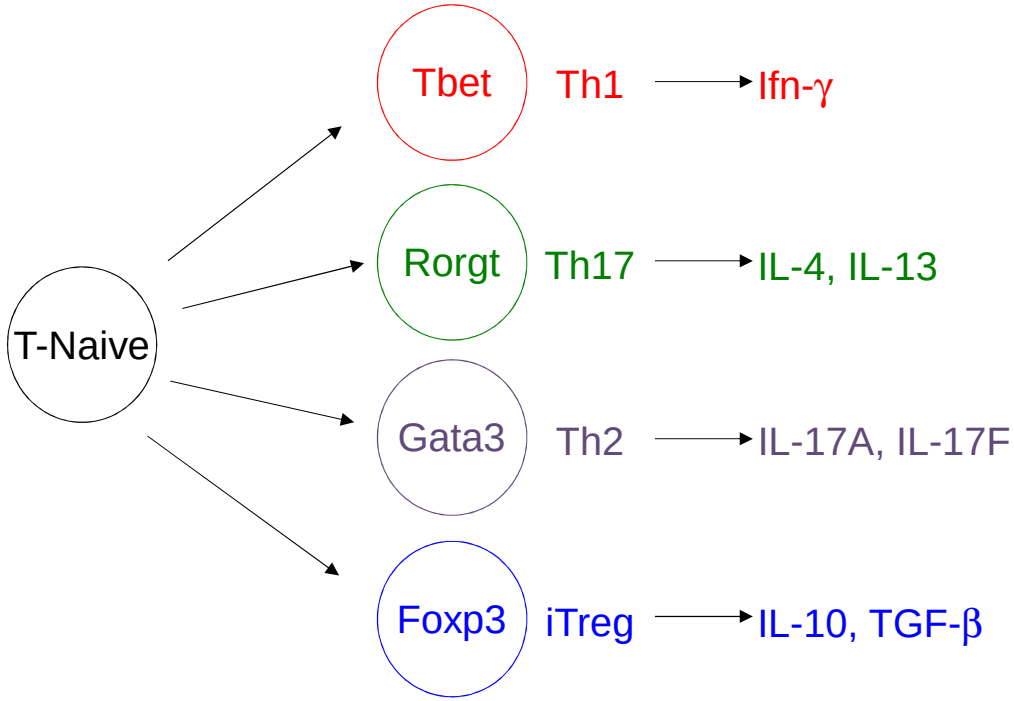


Summary of Phd-tKO mice

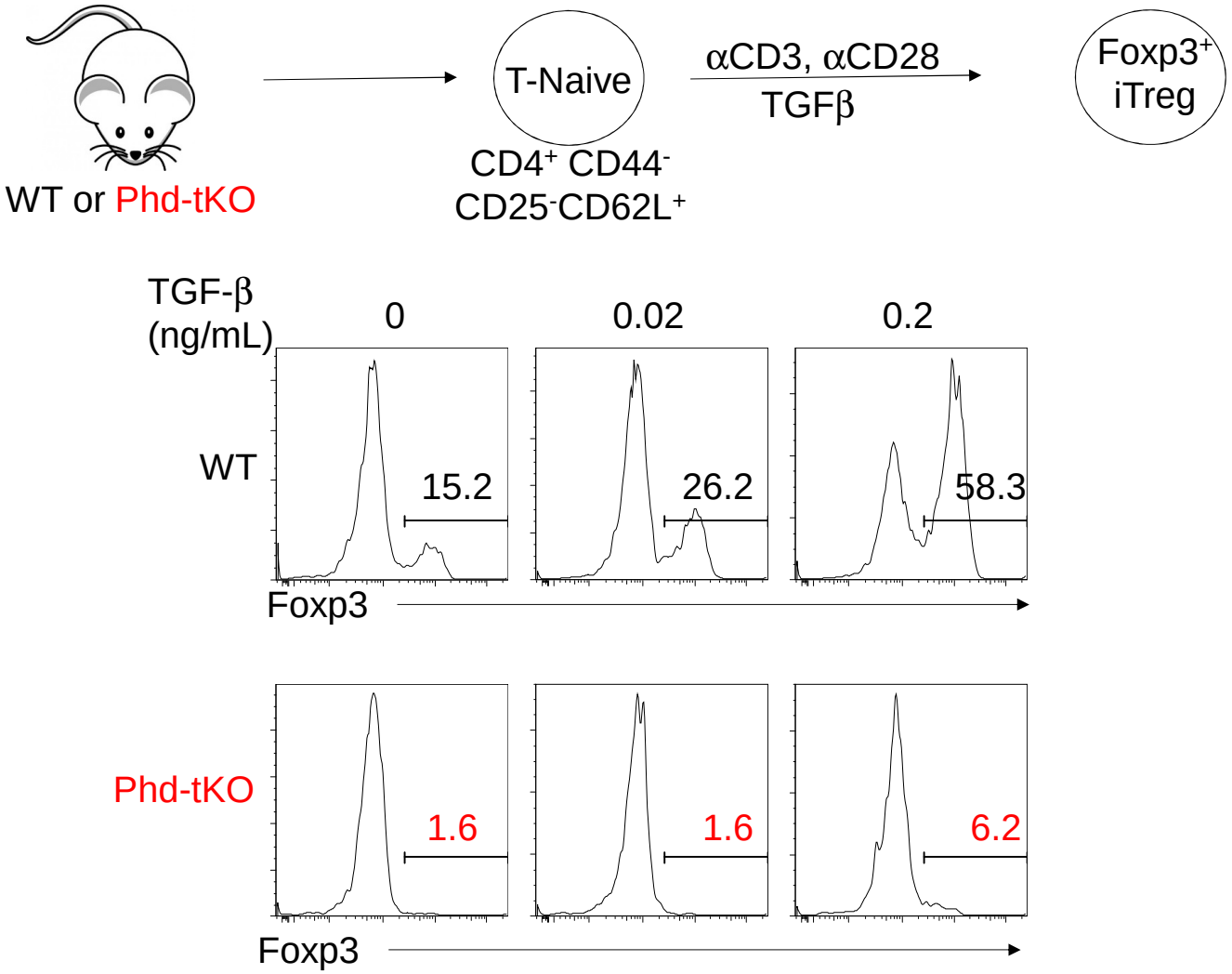
Lung resident $CD4^+$ T cells from Phd-tKO mice demonstrate:

- Increased capacity to produce effector cytokine Ifn-γ
- Reduced percentage of $Foxp3^+$ induced Tregs

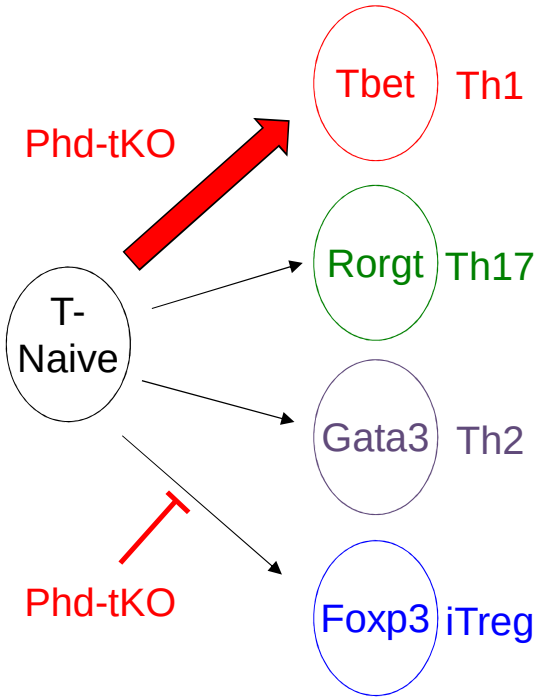
Is T cell oxygen sensing required for appropriate specification of $CD4^+$ T cells?

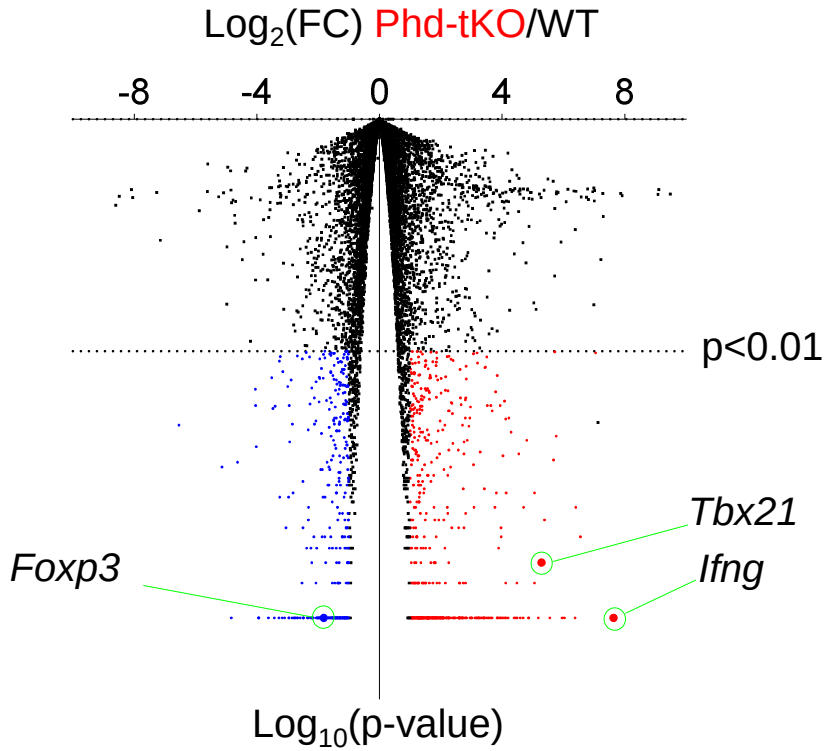


T cell oxygen sensing is required for iTreg specification

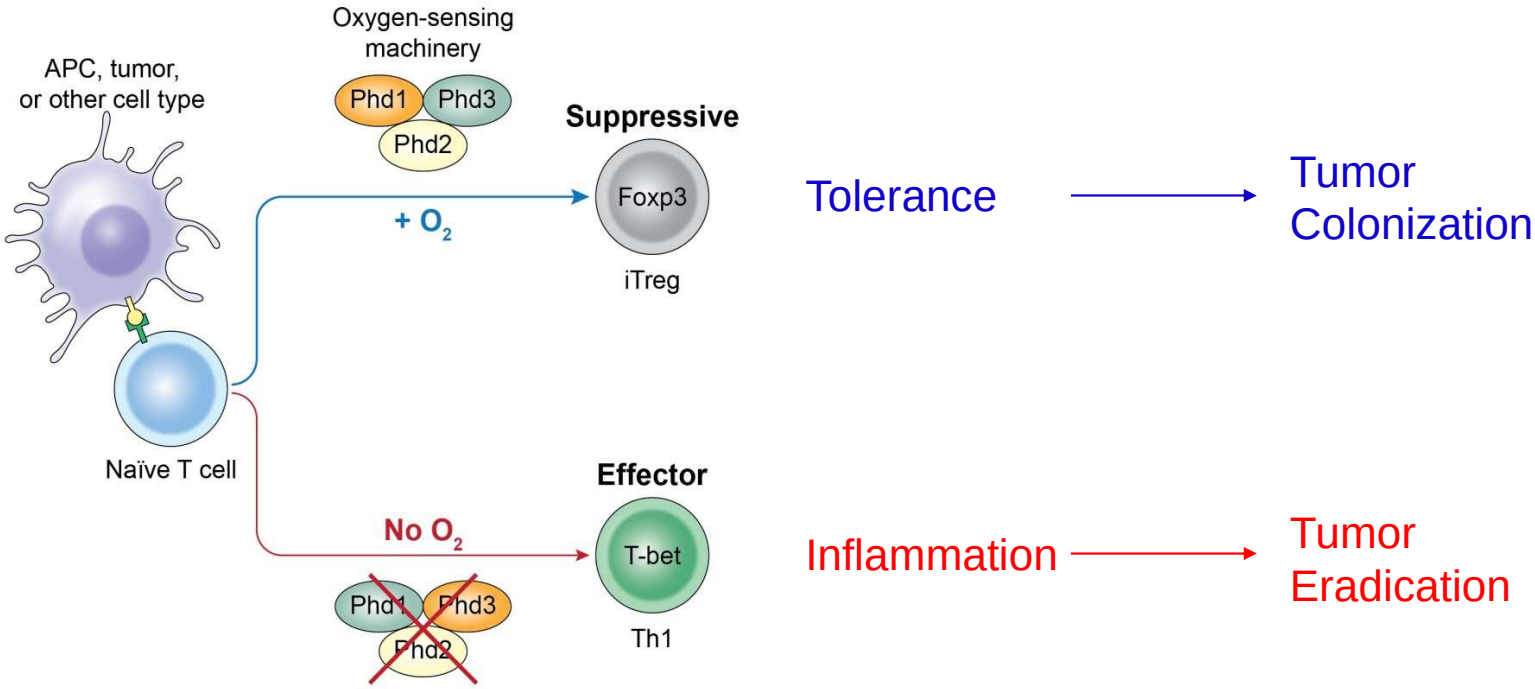


T cell oxygen sensing represses Th1 differentiation





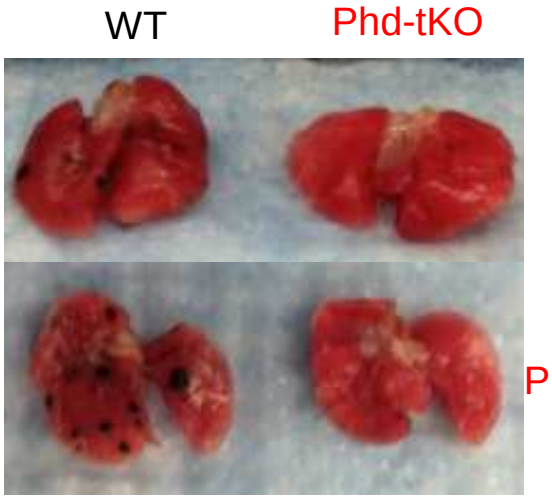
T cell oxygen sensing maintains physiologic tolerance in the lung by promoting iTreg development and inhibiting Th1 effector responses

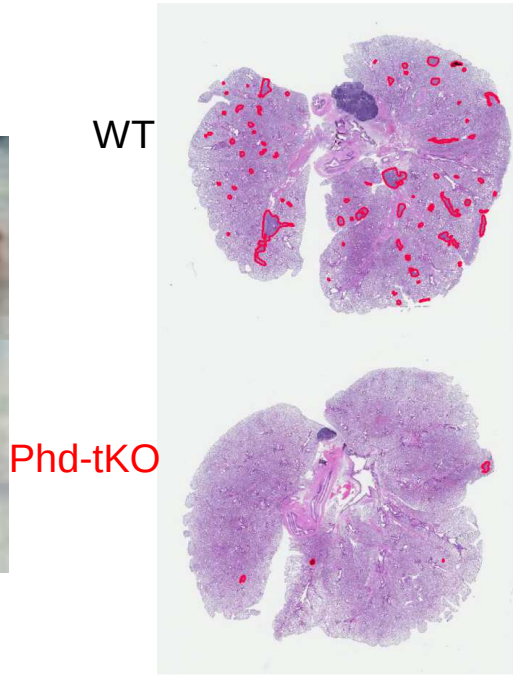


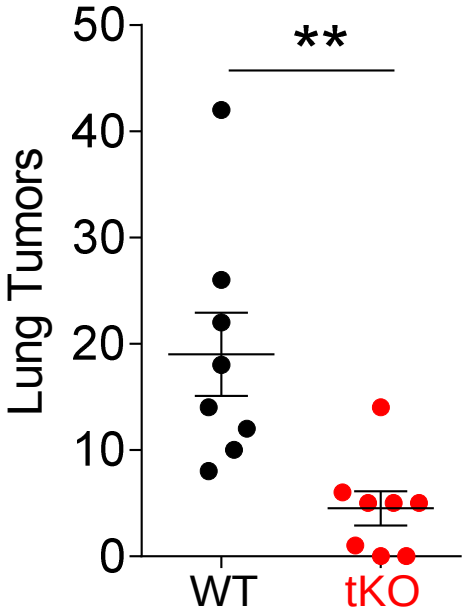
2. Tumor Colonization: Is T cell oxygen sensing involved in promoting tumor colonization of the lung?

3. Tumor Clearance: Can T cell oxygen sensing be inhibited to promote immune mediated tumor clearance?

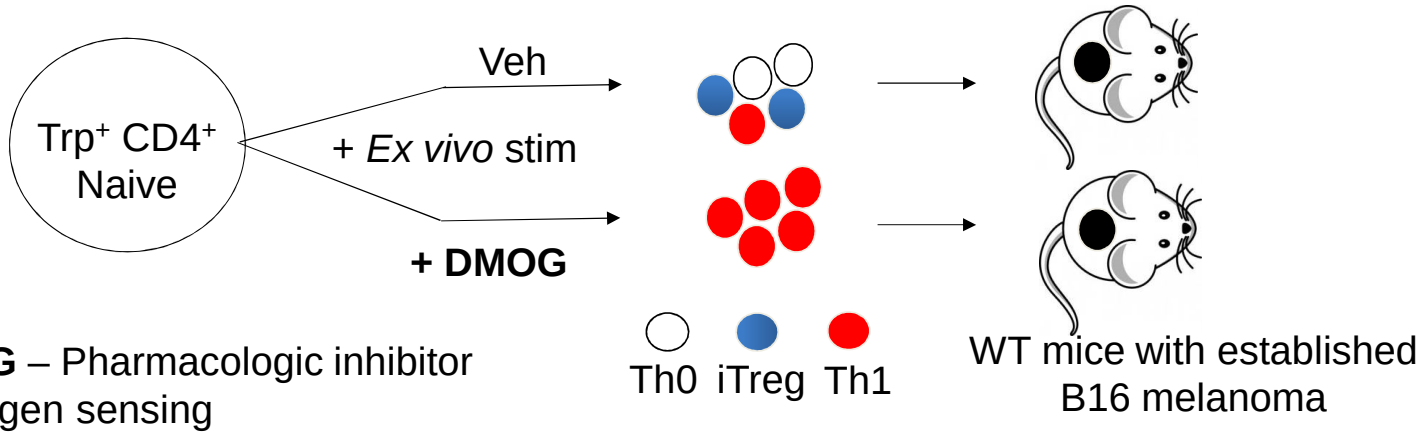
T cell oxygen sensing licenses tumor colonization in the lung





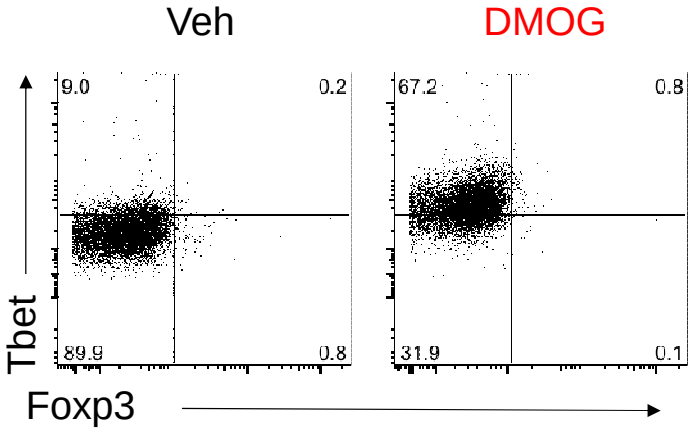


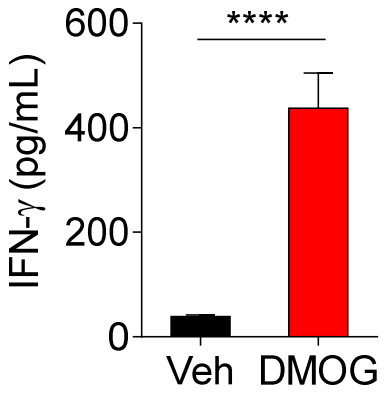
Pharmacologic inhibition of oxygen sensing in Adoptive Cell Transfer Therapy



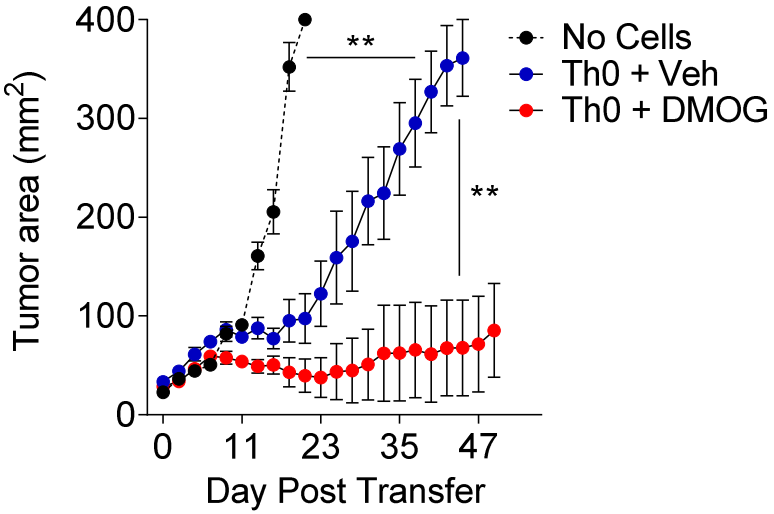
DMOG – Pharmacologic inhibitor of oxygen sensing

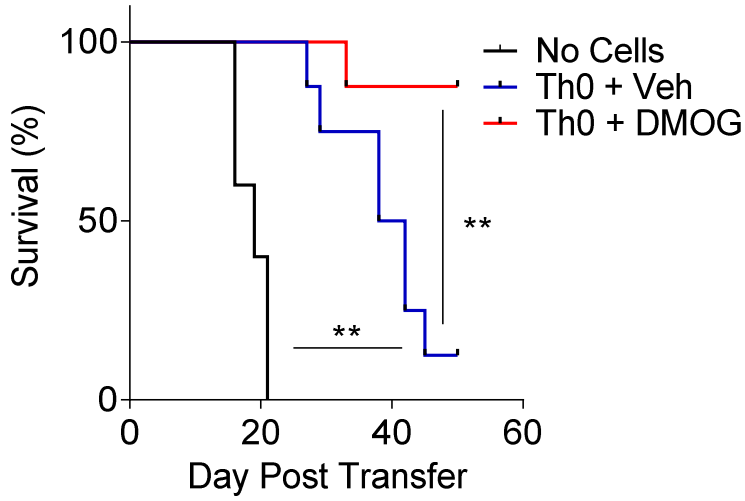
Trp+ CD4+ :



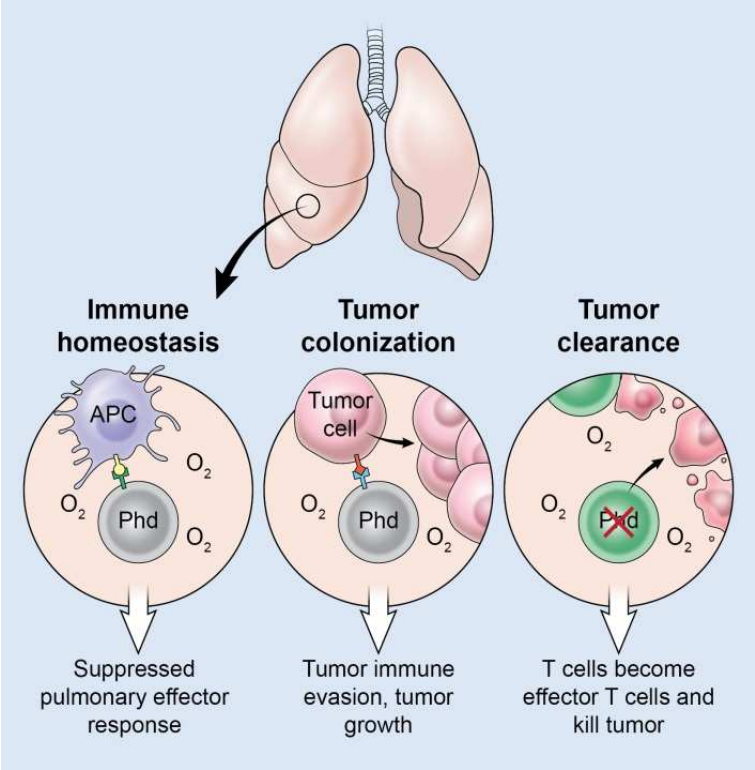


Pharmacologic inhibition of T cell oxygen sensing improves anti-tumor efficacy of tumor specific CD4$^+$ T cells





Summary and Conclusions



- T cell oxygen sensing is required for pulmonary immune homeostasis
- Through T cell oxygen sensing, environmental oxygen establishes an immunologically favorable metastatic niche in the lung
- Inhibition of T cell oxygen sensing can promote effector responses against tumors

Acknowledgements

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