Tim-3 as a target for tumor immunotherapy

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Disclosures

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Outline

- **Immune checkpoint molecules:**
  - **Tim-3 vs PD-1**

- **Role of Tim-3 and PD-1 in anti-tumor immunity:**
  - **-T cell exhaustion**
  - **-Regulatory T cells**

Immune checkpoint molecules

- Definition- negative regulatory molecules upregulated on activated T cells that serve to contract ongoing T cell responses thereby preventing uncontrolled immune responses and ensuing immunopathology

- CTLA-4, PD-1, Tim-3, Lag-3

- Cancer - Dysregulated expression of immune checkpoint molecules on T cells

- Clinical relevance: immunotherapies that target immune checkpoint molecules have been shown to improve immunity in cancer (mice and human)

T cell exhaustion

- Exhaustion- state of T cell dysfunction- failure to proliferate and exert effector function in response to TCR stimulation

- Hierarchy of exhaustion- loss of proliferation/CTL function and IL-2, then loss of TNFα, then loss of IFNγ

- Express PD-1 and blockade of PD-1/PD-L1 interactions partially restores T cell function

- Exhausted T cells also express Tim-3 (HIV, HCV)
and blockade of Tim-3 signaling restores T cell function

Tim-3 vs PD-1

Expression:

- PD-1 is upregulated on all T cells 24-72 hrs after activation
- Tim-3 is selectively expressed on IFN-γ-secreting $CD4^+$ and $CD8^+$ T cells

Signaling:

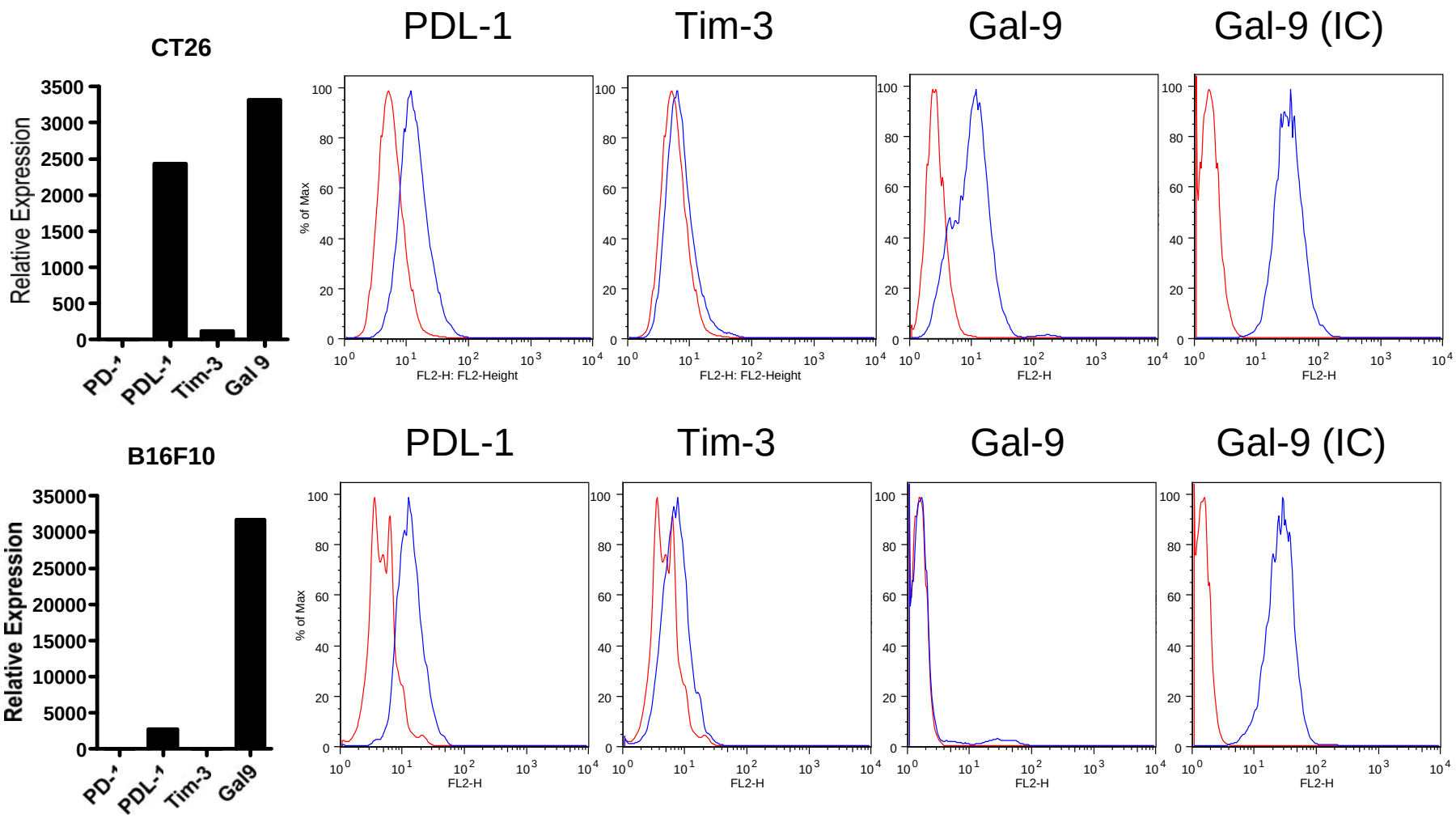
- PD-1 has ITIM and ITSM motifs in cytoplasmic tail
- Tim-3- 6 tyrosine residues in cytoplasmic tail- no ITIM or ITSM

Ligands:

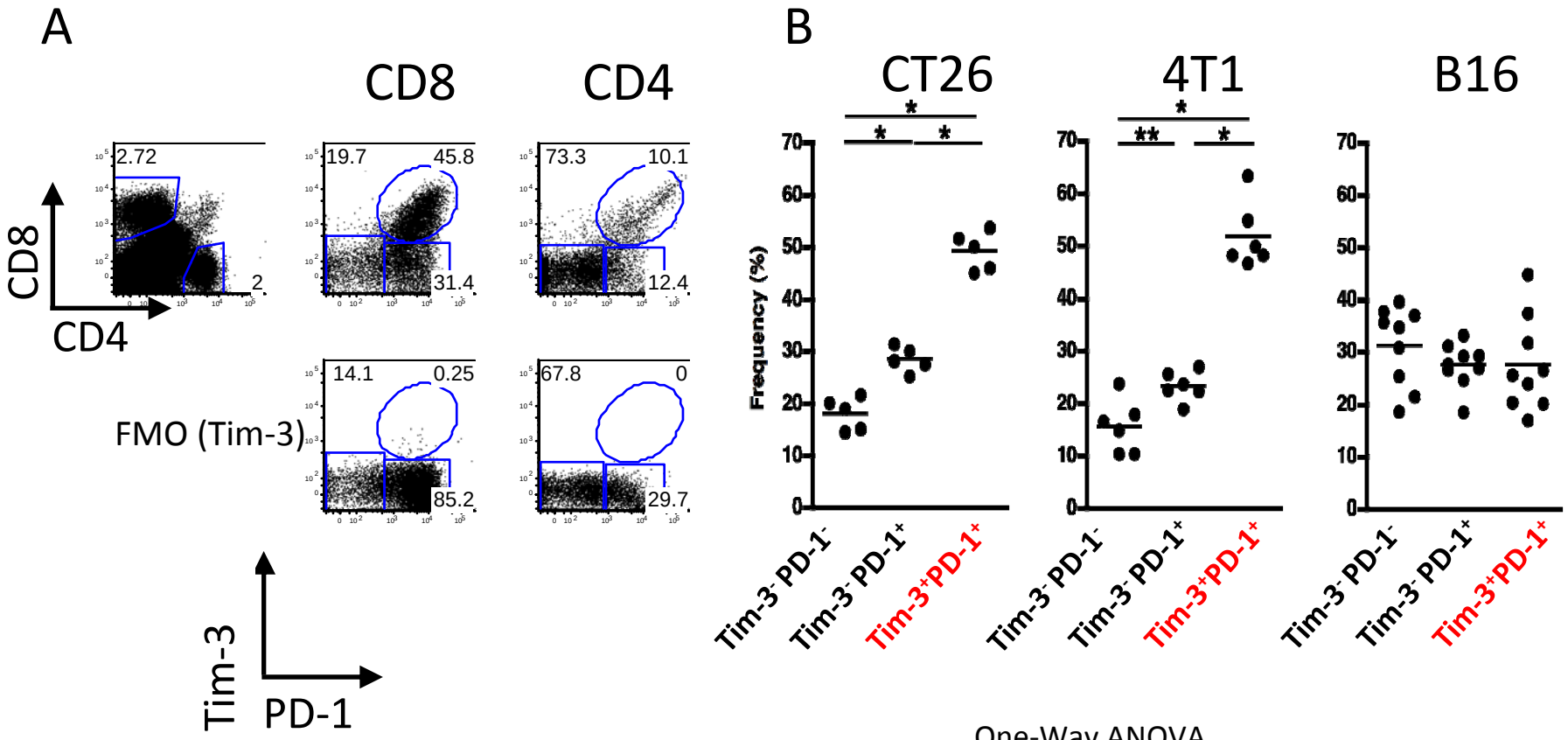
- For PD-1: PD-L1 (widely expressed) and PD-L2
- For Tim-3: galectin-9- widely expressed

- Both Tim-3 and PD-1 ligands are upregulated by IFNs and expressed on tumors

Expression of Tim-3/PD-1 and their ligands on tumor cell lines

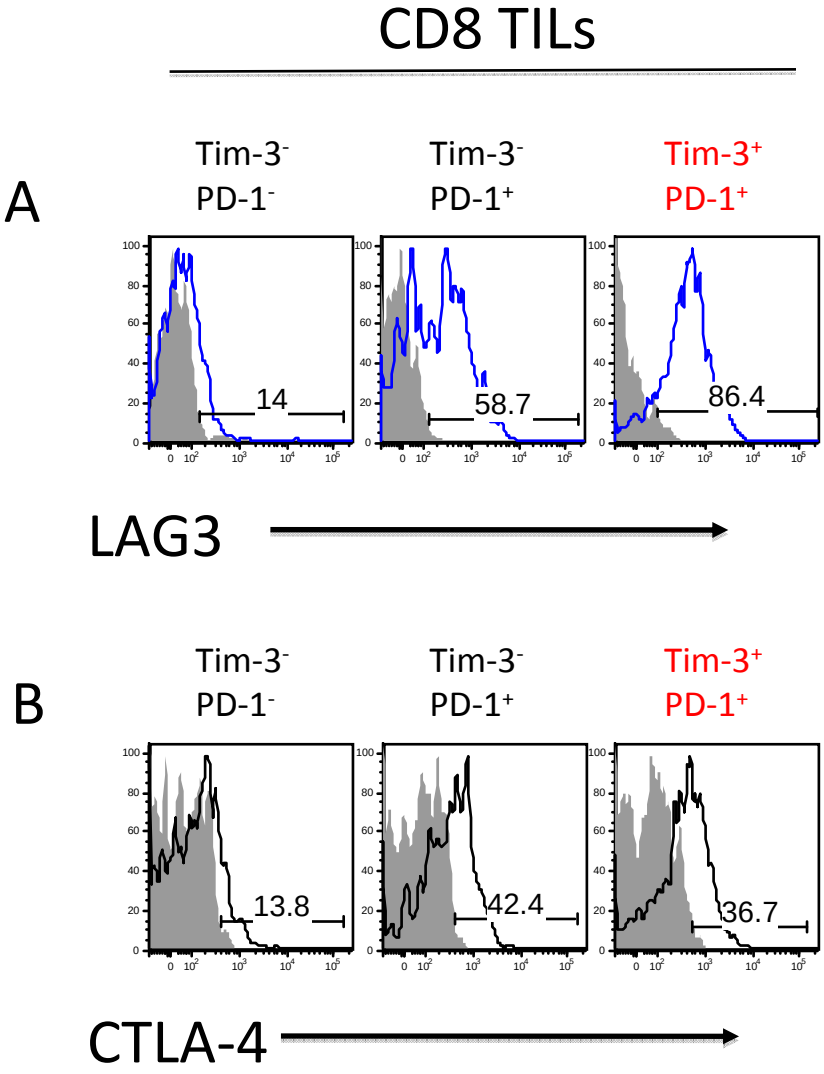


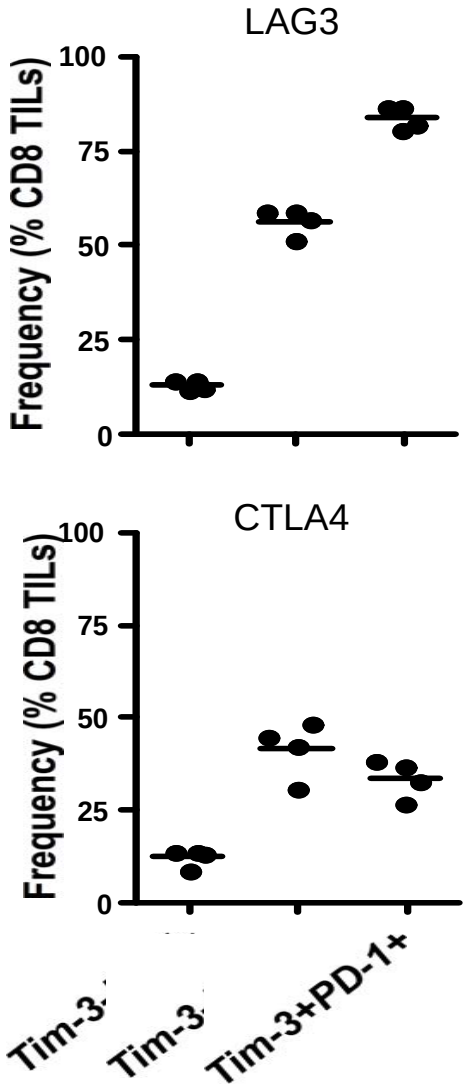
High frequency of Tim-3^{+} PD-1^{+} cells in CD8 positive Tumor Infiltrating Lymphocytes (TILs)



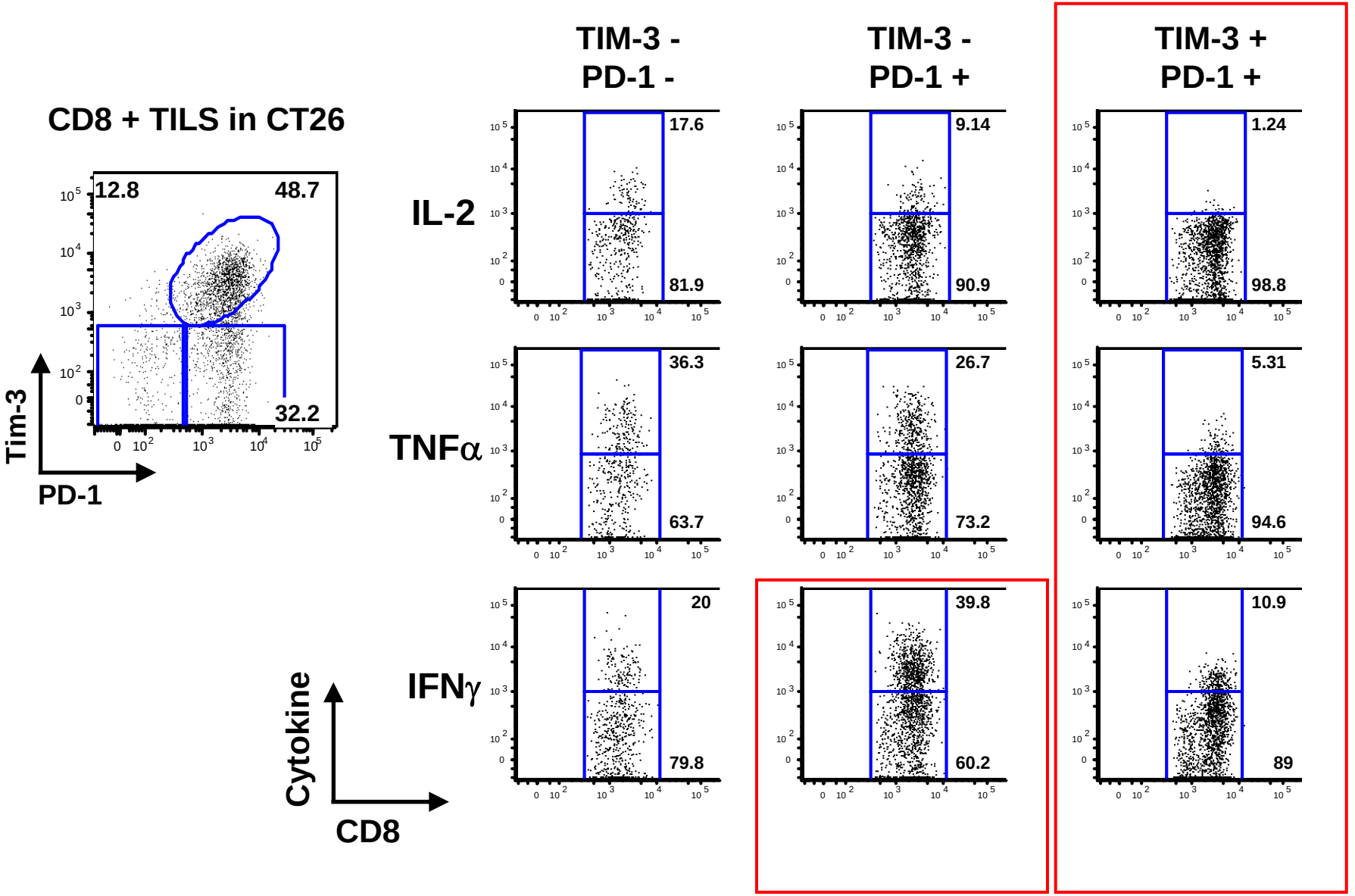
One-Way ANOVA,
Tukey's multiple comparison test
*p<0.001, **p<0.05

LAG3 and CTLA-4 expression on Tim-3 and PD-1 expressing TILs

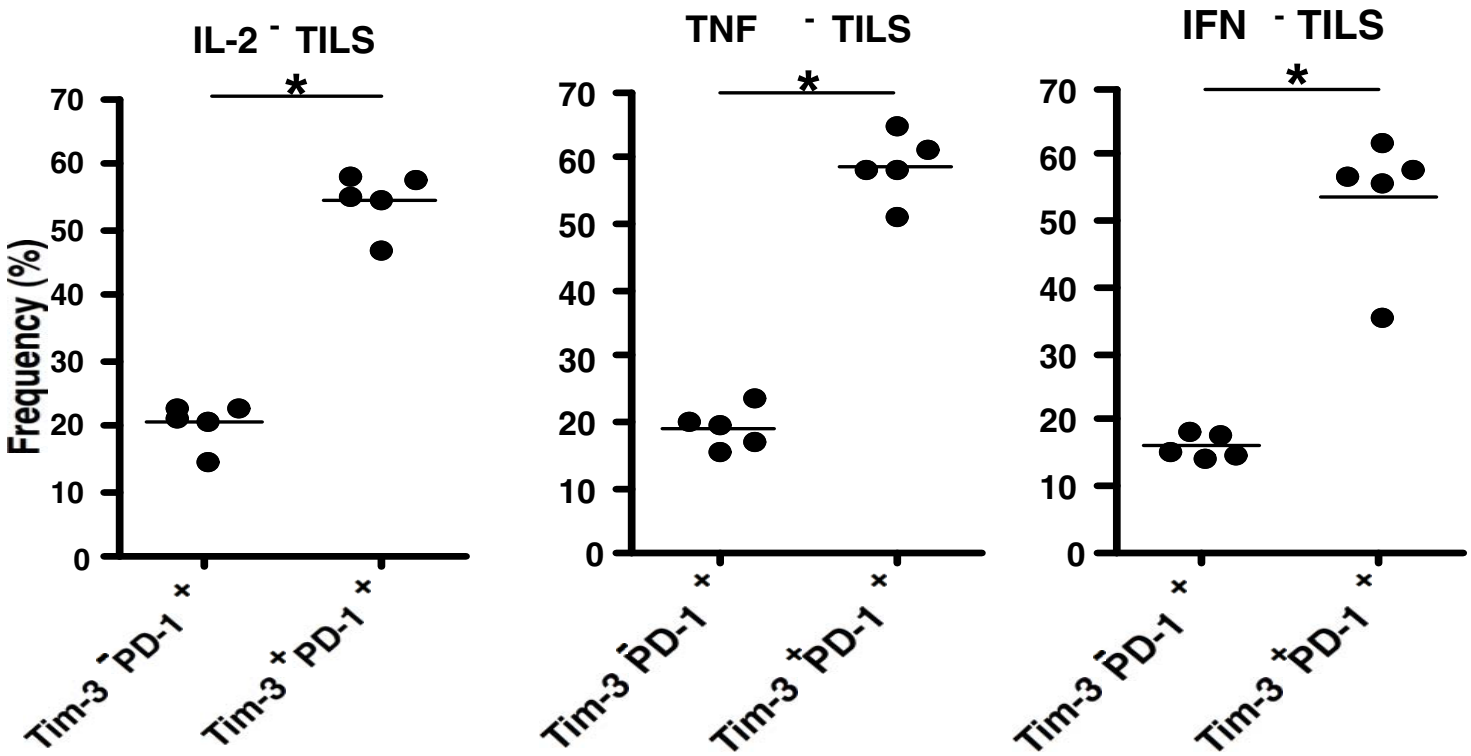




Tim-3^{+}PD-1^{+} CD8 TILS are more impaired in cytokine production relative to Tim-3^{-}PD-1^{-}TILS

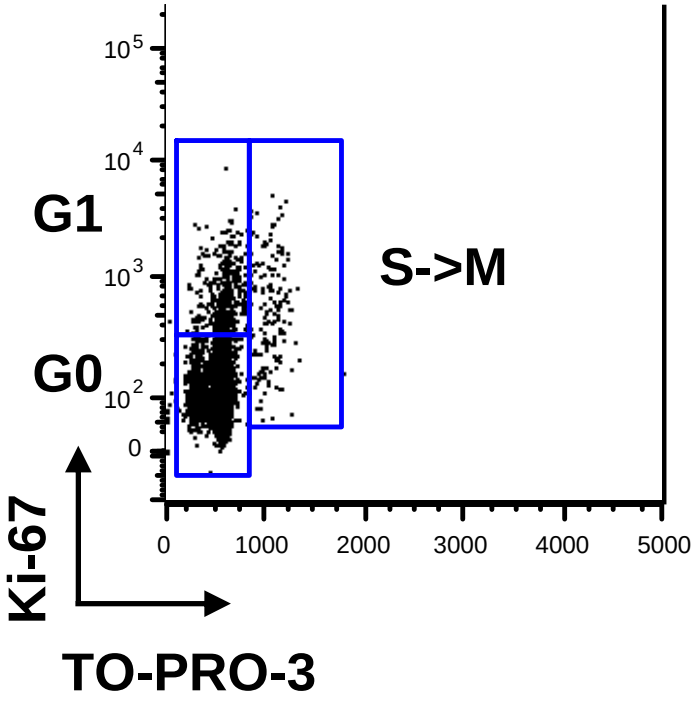


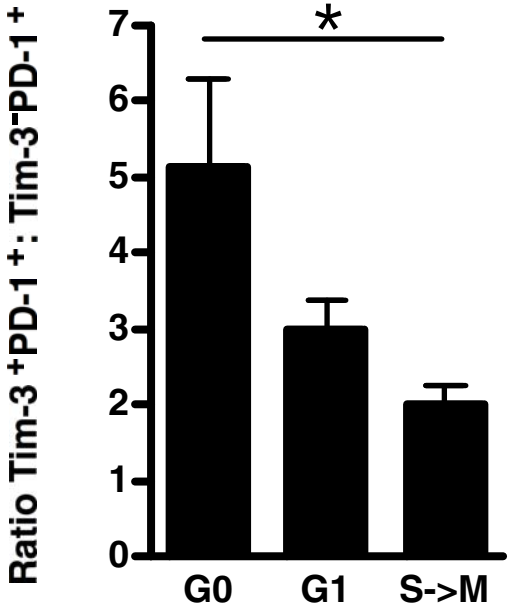
Tim-3 and PD-1 expression in cytokine non-producing TILS



*p<0.0001

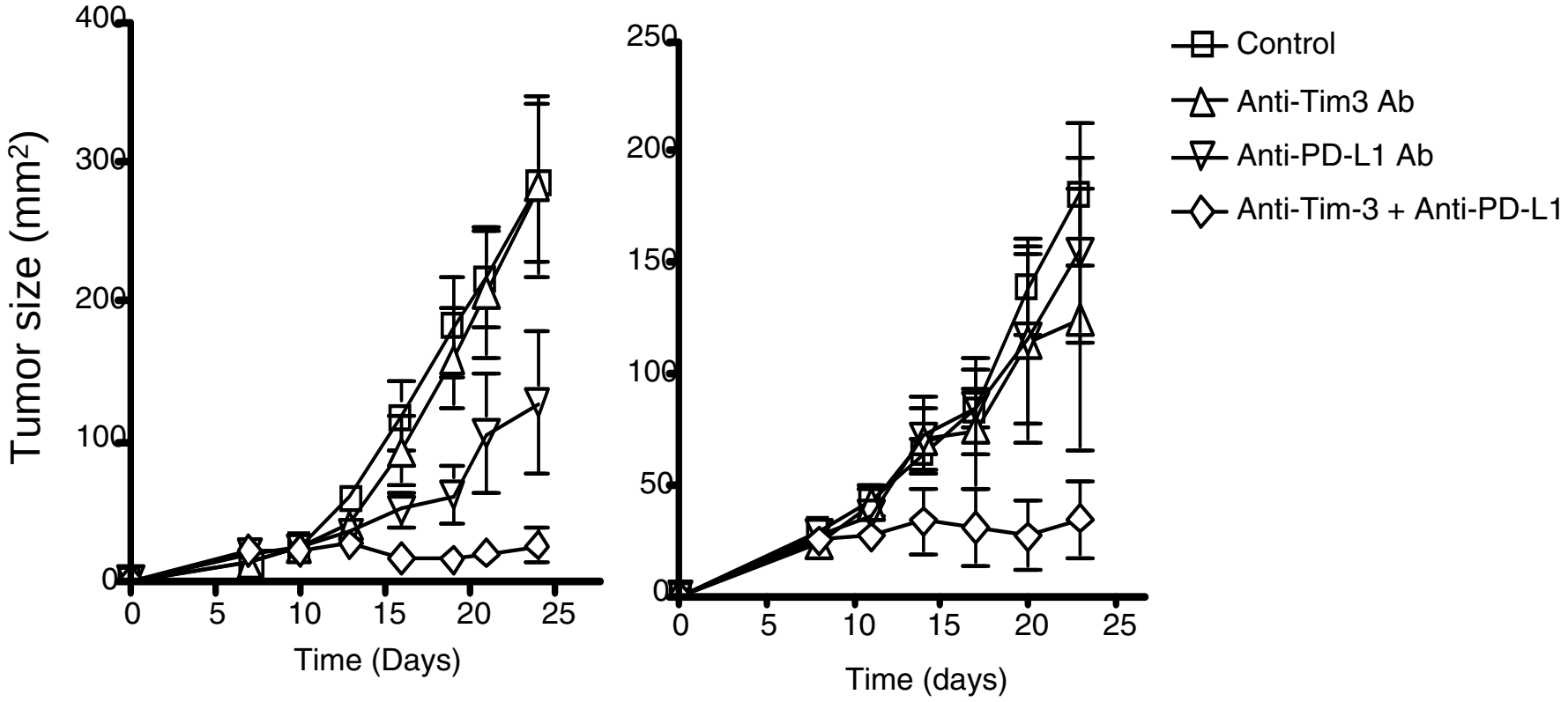
Tim-3 and PD-1 expression in CD8^{+}TILS entering cell cycle



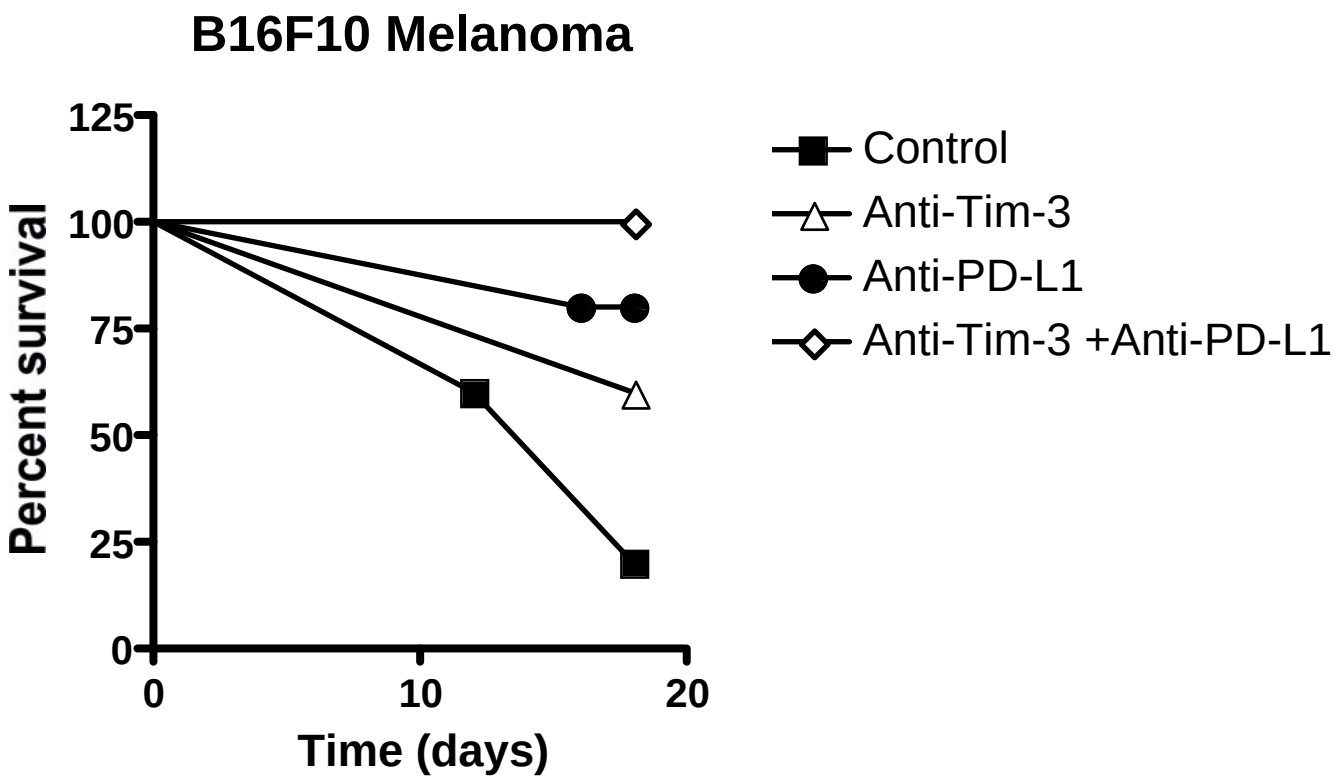


P<0.05, One-Way ANOVA, Tukey's Multiple Comparison Test

Effect of targeting the Tim-3 and PD-1 signaling pathways on CT-26 tumor growth

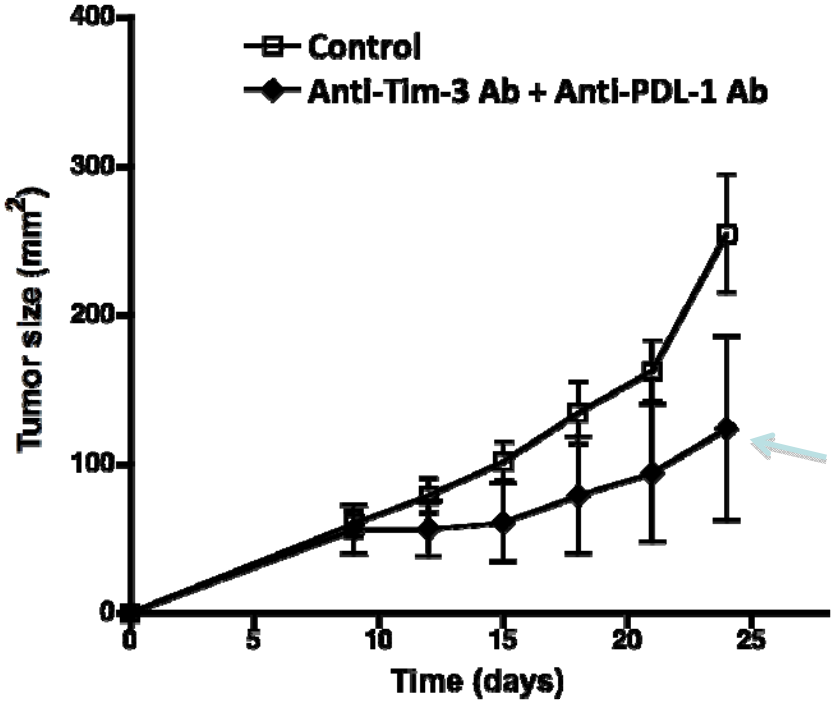


Combined targeting of Tim-3 and PDL-1 in melanoma



Anti-Tim-3 and Anti-P-L1 Antibody Treatment of established Tumors

CT26

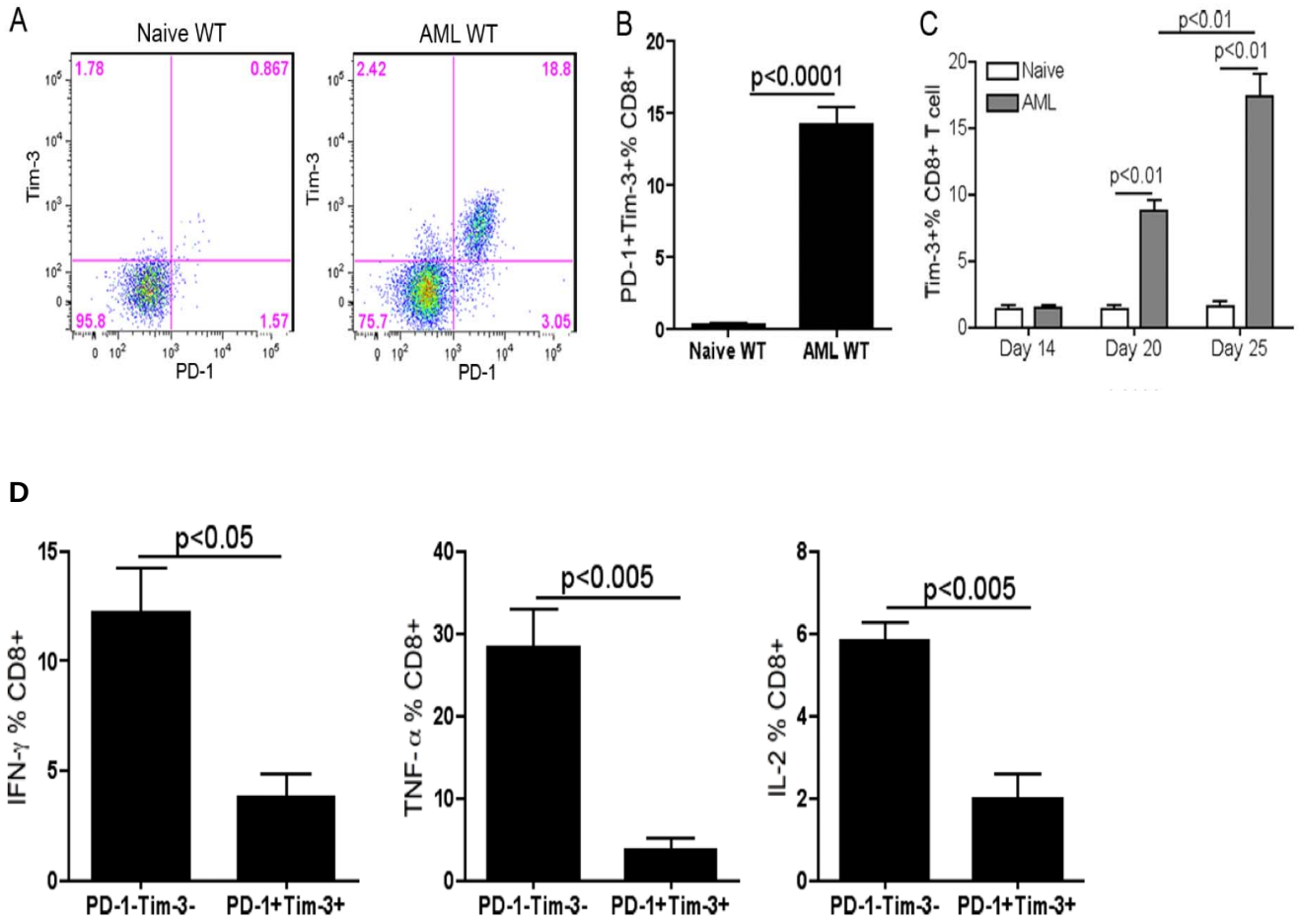


2/5 complete regression

Anti-Tim3 Ab

Anti-PD-L1 Ab

Tim-3 and PD-1 marks exhausted cells in AML



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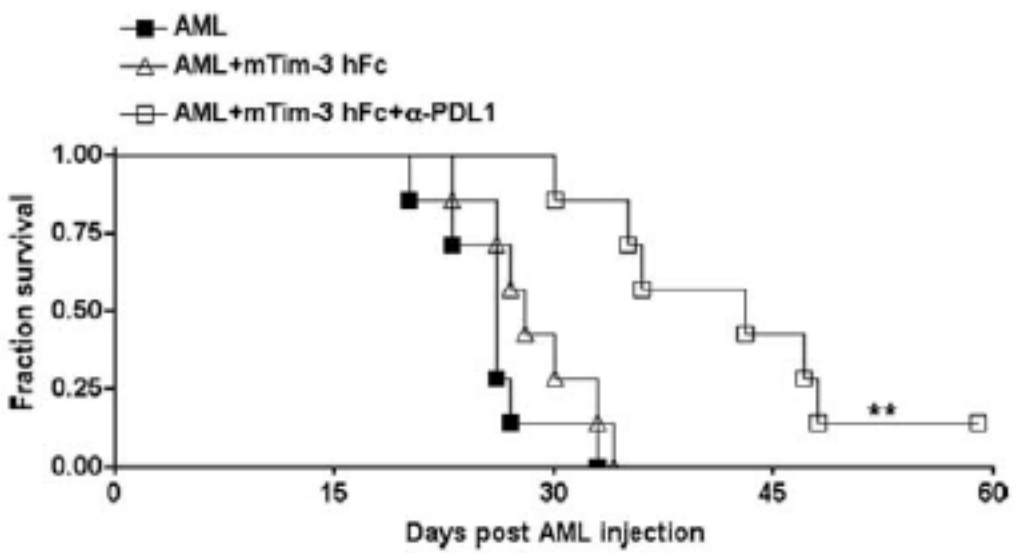
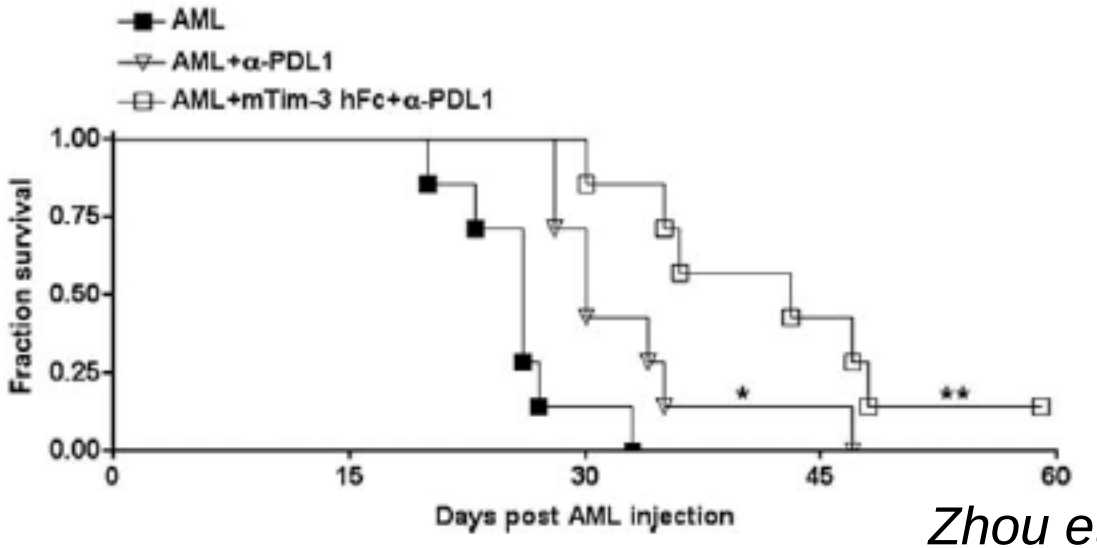
Combined therapy increases survival in AML





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Why target both Tim-3 and PD-1?

Pre-clinical models of cancer

- Tim-3 and PD-1 are uniquely co-expressed in TILs
  - CD4 FoxP3+ Tregs
  - CD8 exhausted phenotype
- In both solid and non-solid cancers combined targeting of the Tim-3 and PD-1 pathways is a highly effective therapy
- *Human cancer (melanoma mets)*
  - $CD8^+$ TILN vs PBL: exhausted phenotype only in TILN,

    Expression of inhibitory receptors (Tim-3,PD-1) enriched in TILN (*Baitsch et al JCI 2011*)
  - Blockade of Tim-3 and PD-1 (*in vitro*) synergizes to

    increase cytokine production in melanoma specific

    T cells (*Fourcade et al JEM 2010*)

Additional reasons to target Tim-3 in cancer

- Tim-3 has a role in promotion of myeloid-derived suppressor cells (MDSC) (*Dardalhon et al, JI 2010*)

- Tim-3 is expressed on cancer stem cells- AML (human)

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