Stem-like $CD8^+$ T cells in the response to checkpoint blockade immunotherapy

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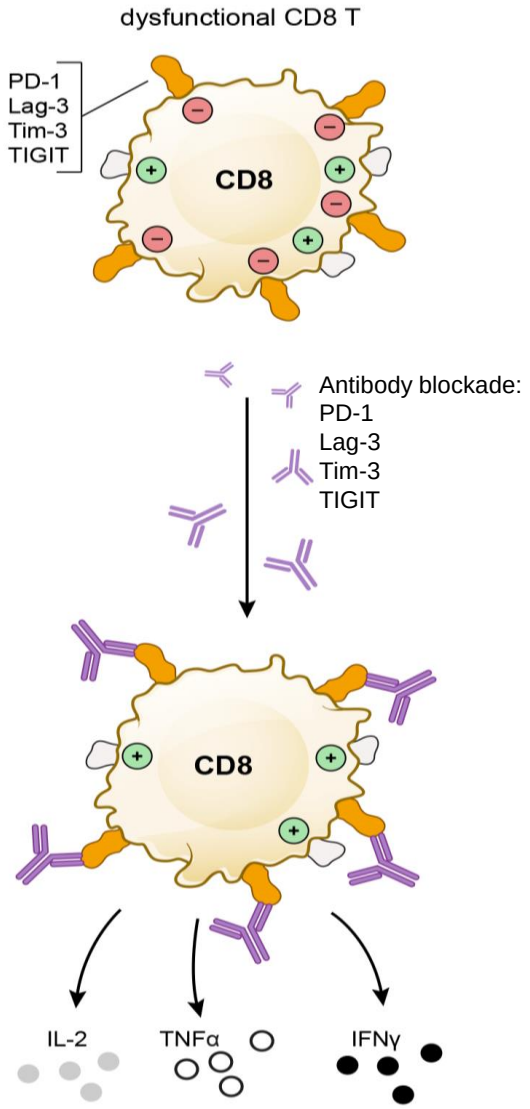
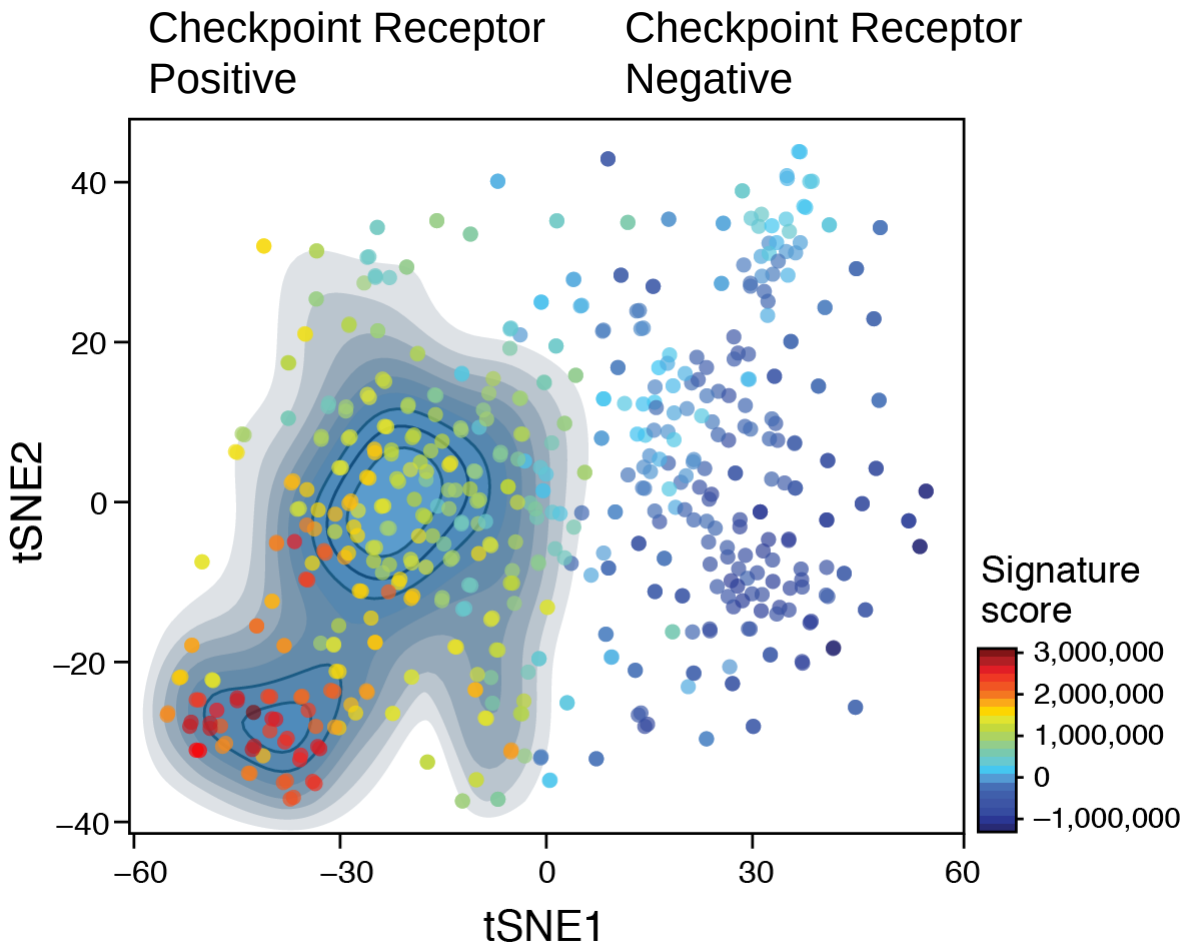
T Cell Dysfunction, Co-inhibitory Receptors, and Immunotherapy

- *Dysfunctional T cell express co-inhibitory or immune checkpoint receptors, eg. CTLA-4, PD-1, Tim-3*
- *Debate about whether checkpoint blockade therapies can modulate dysfunctional T cells*
- *Many patients still fail to respond to checkpoint blockade*
- *Important to achieve a better understanding of how checkpoint blockade alters CD8$^+$ TILs response and what constitutes response to therapy*



Expression of T cell dysfunction signature in CD8^{+} TILs



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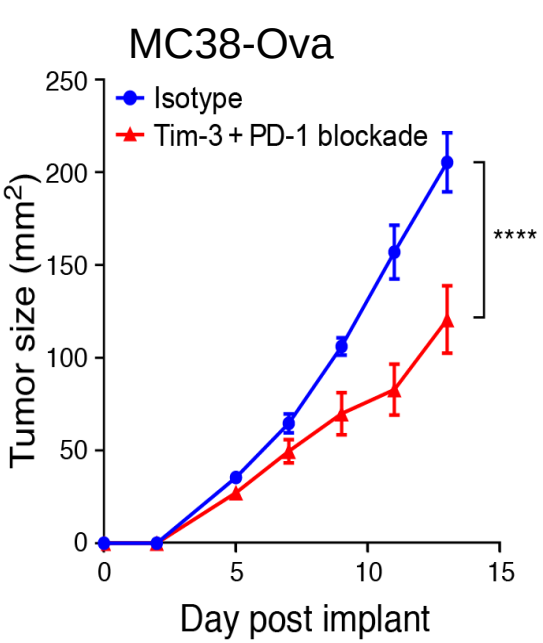
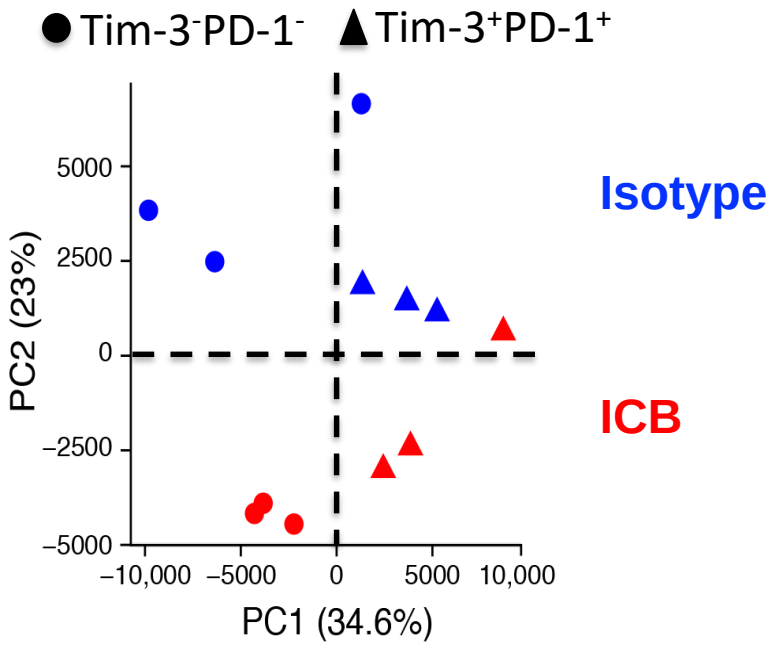
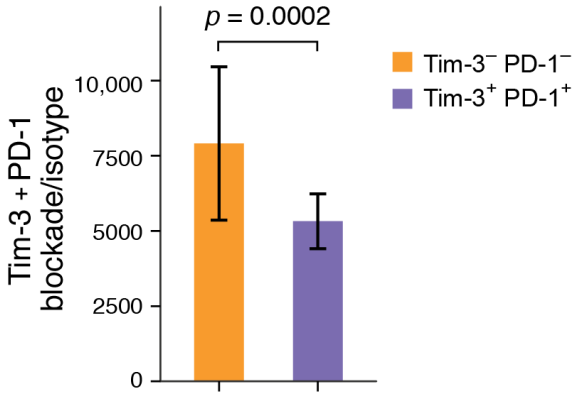
ICB induces greater transcriptional change in checkpoint receptor negative CD8$^+$ TILs







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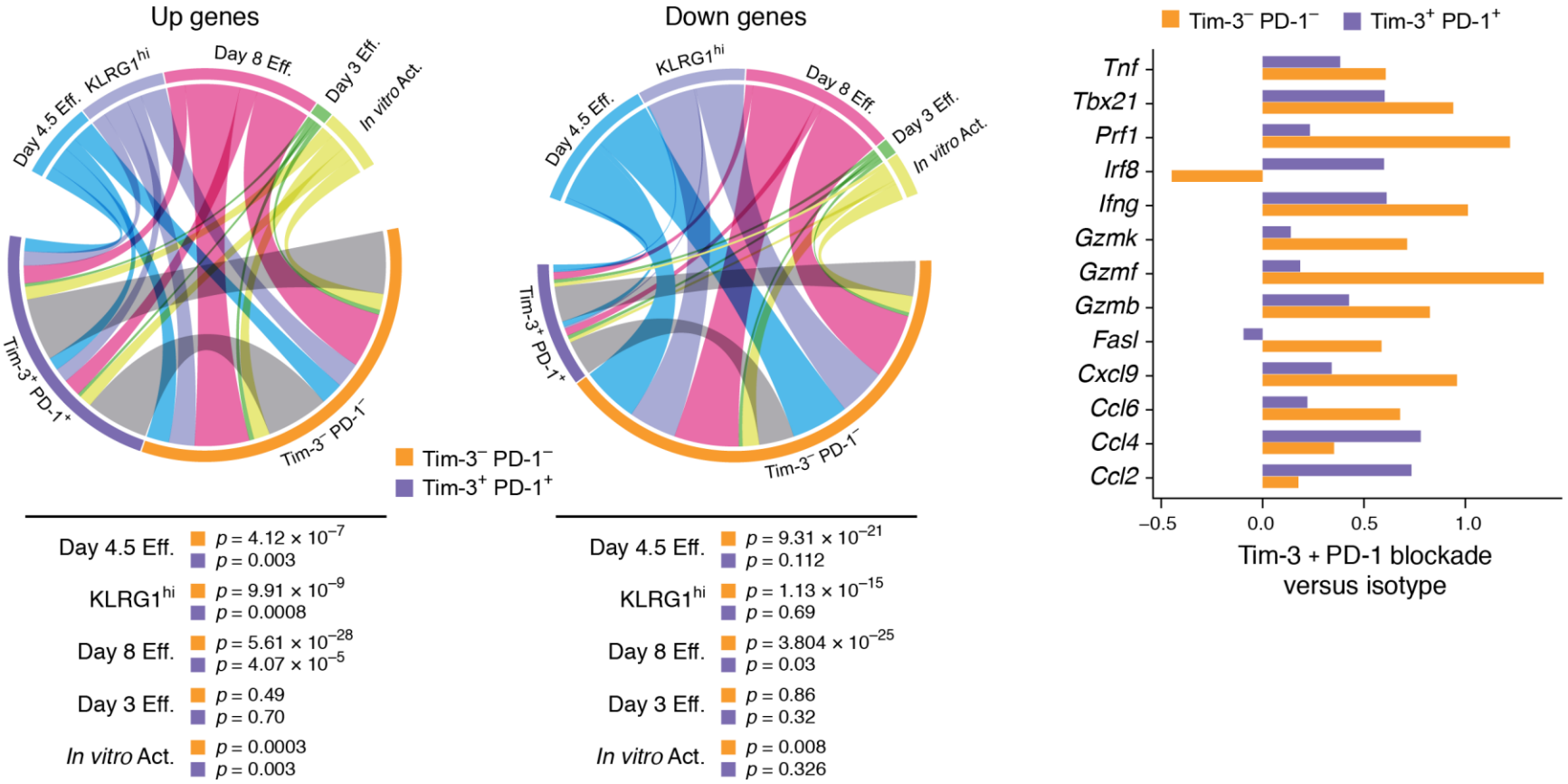
Transcriptional changes upon ICB correspond to acquisition of effector T cell function



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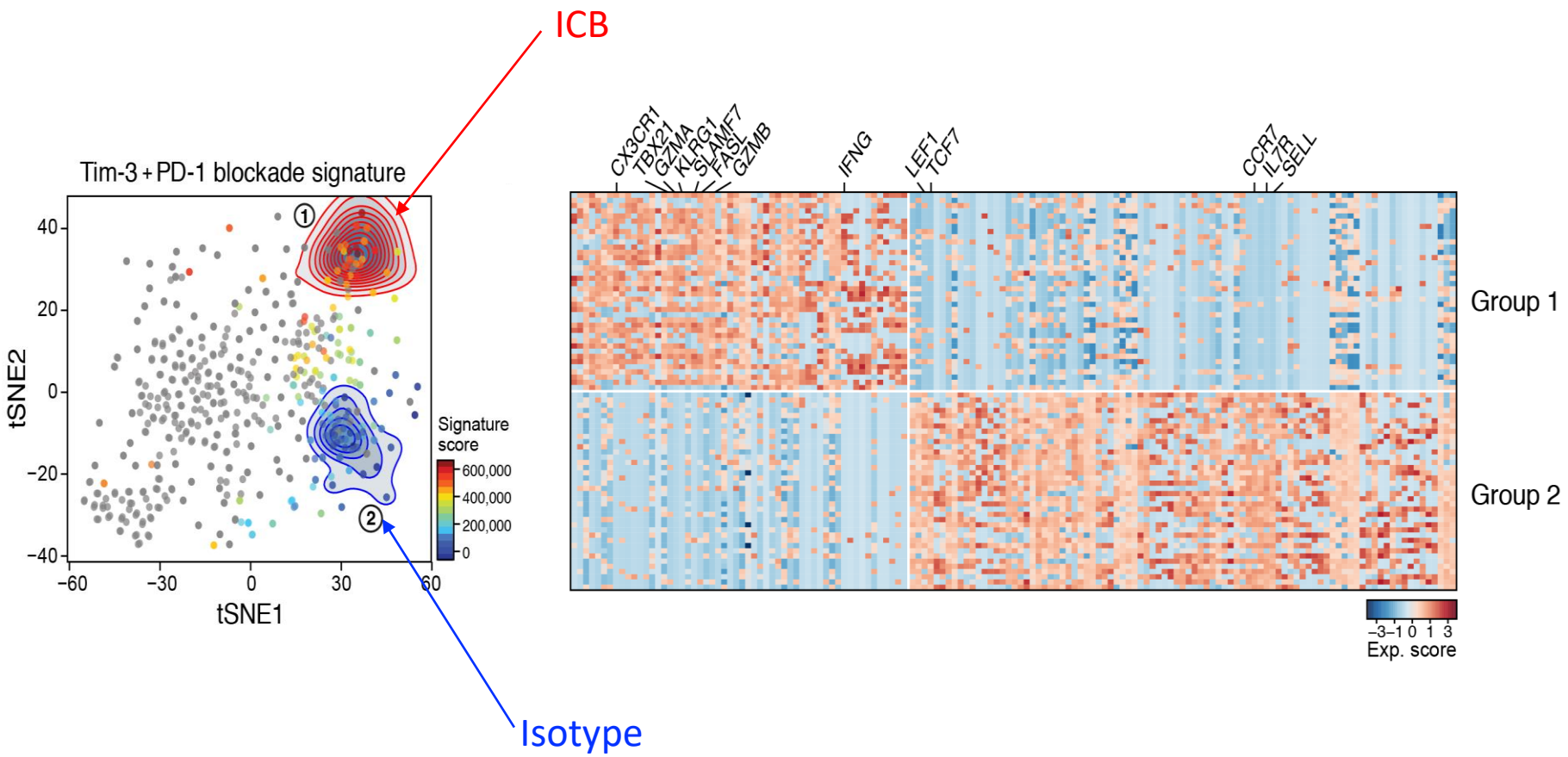
Checkpoint blockade gene signature highlights two groups of cells within PD-1^{-} CD8^{+} TILs



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Novel subpopulations within PD-1^{-} CD8^{+} TILs

GSEA	Naive	Memory-Precursor	Effector
Proliferation	—	Ki-67+	Ki-67+
Cytotoxicity	—	GZMB, CD107a	GZMB, CD107a
Cytokine	—	IL-2, IFNg, TNFa	IFNg
Ag specificity	—	Ova+	Ova+

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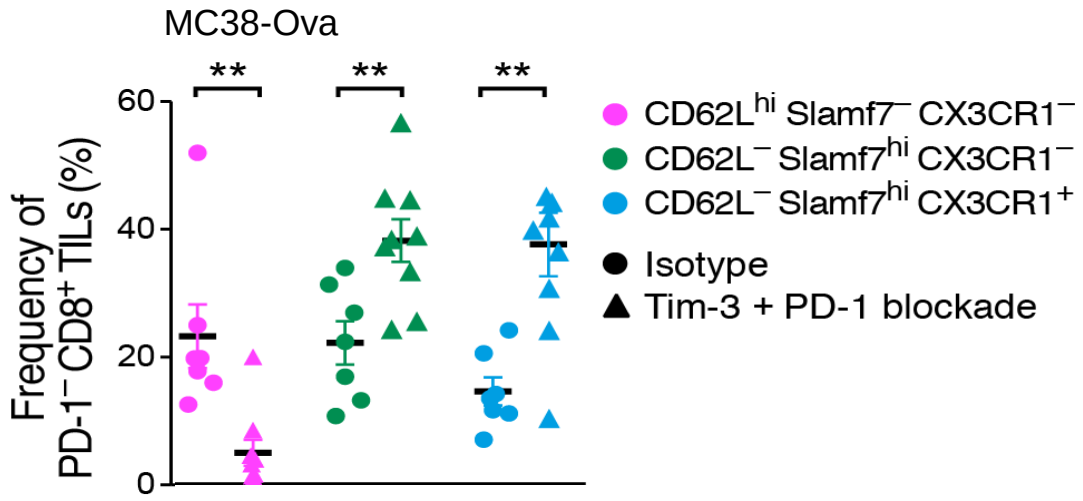
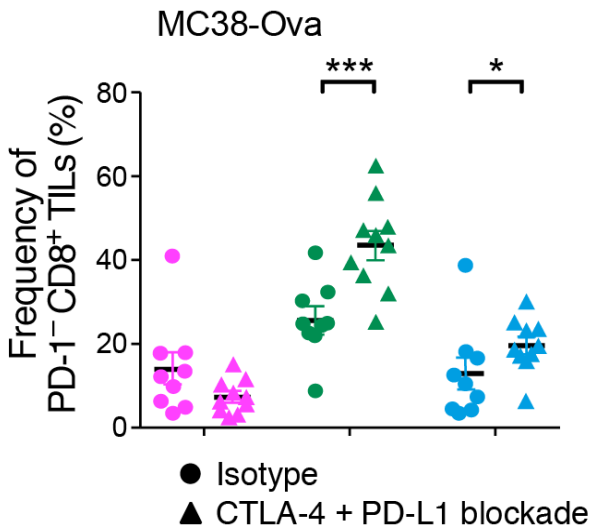
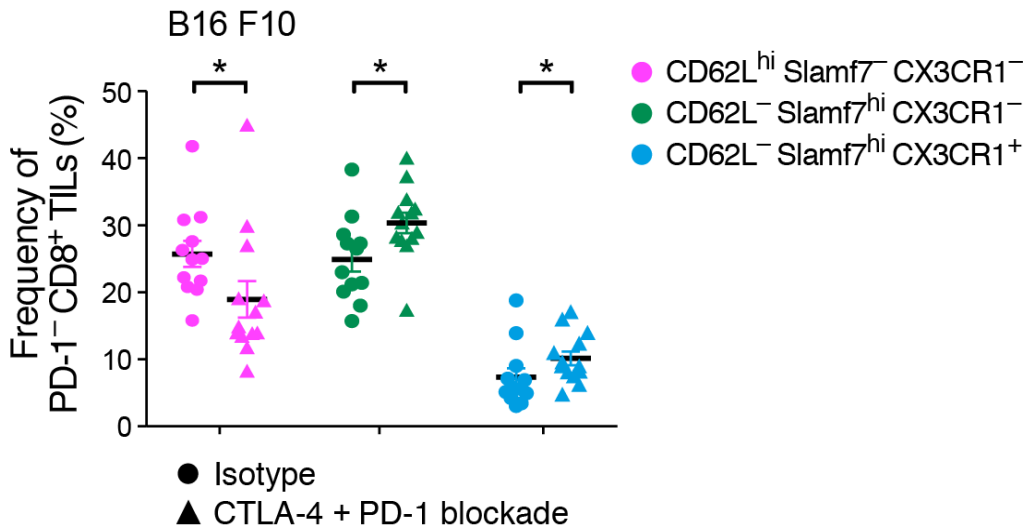
Shifts in PD-1^{-} CD8^{+} TILs subsets across tumor types and upon different checkpoint blockade therapies







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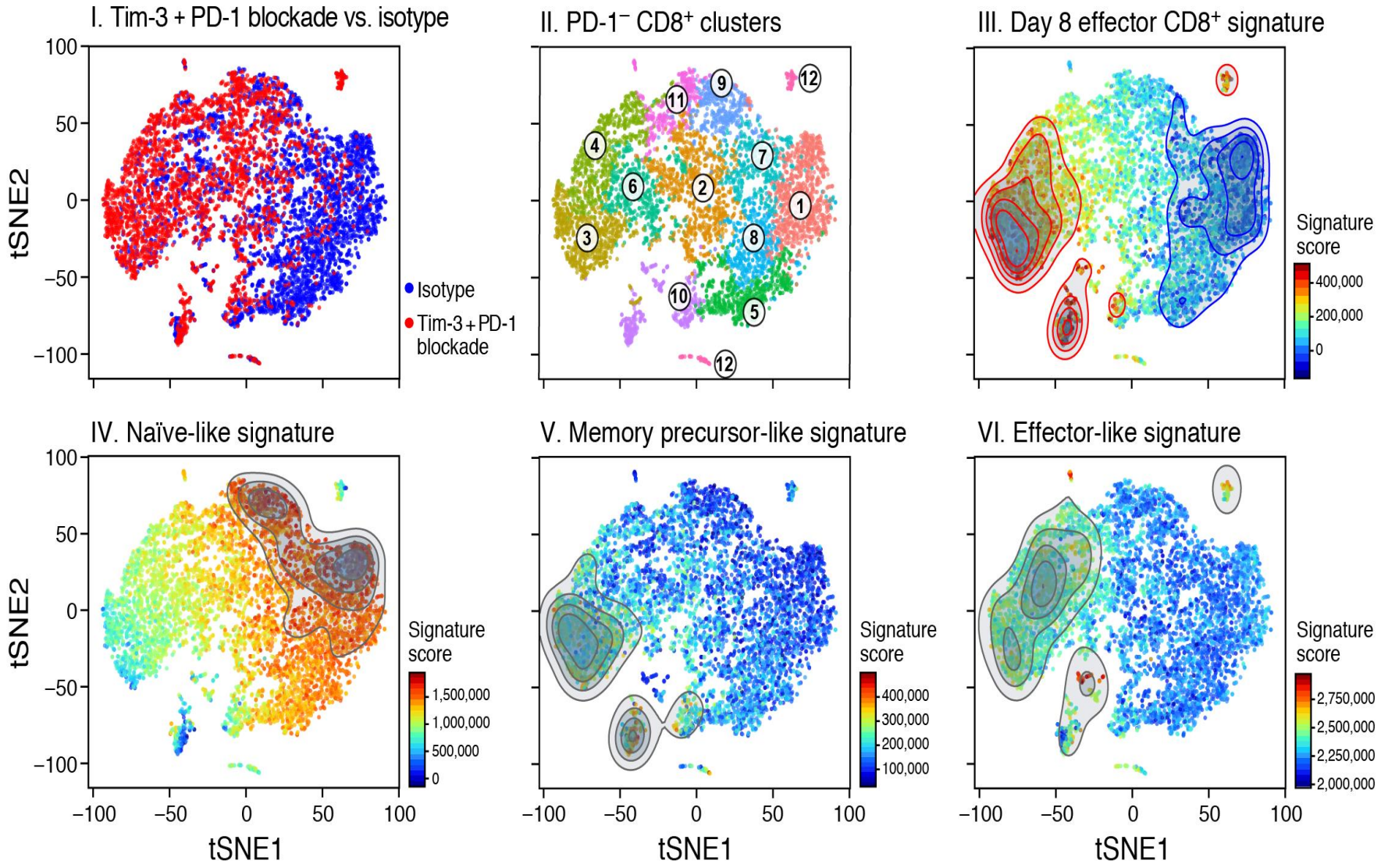

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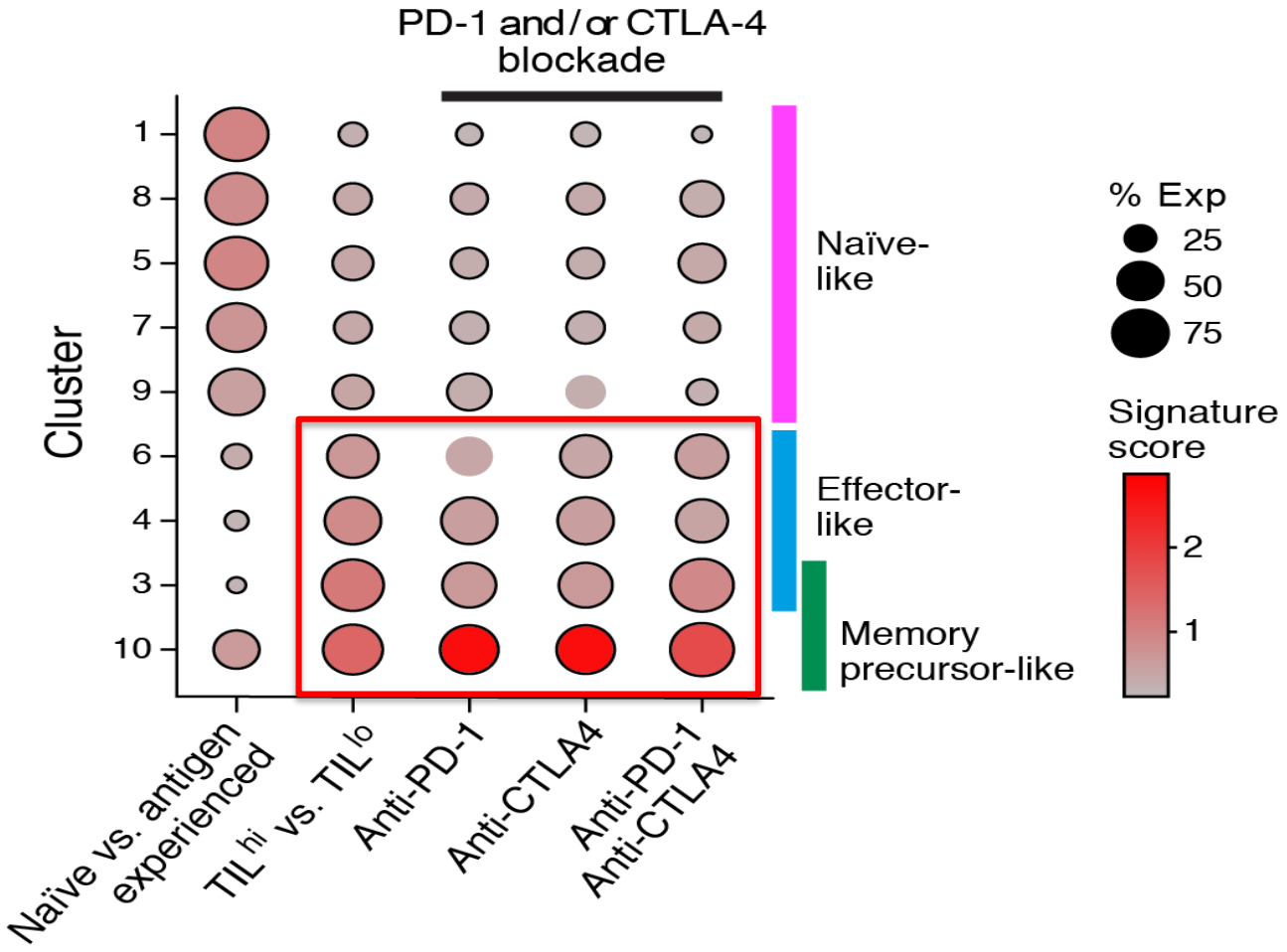
Effector-like and memory-precursor like PD-1^{-} CD8^{+} TILs share features with T cells from patients treated with ICB



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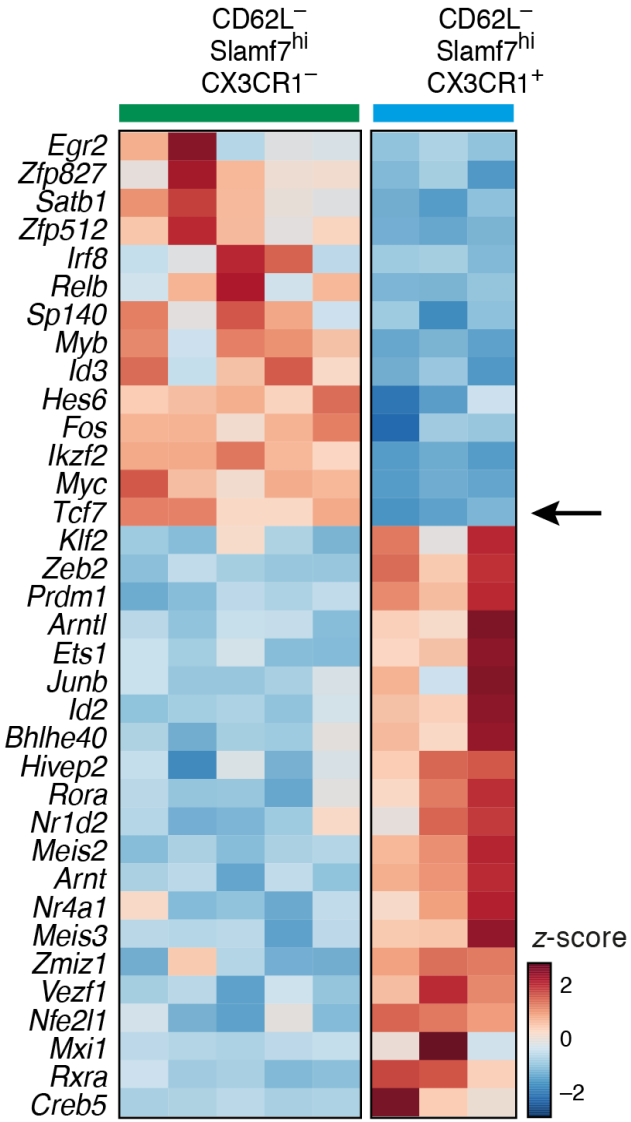
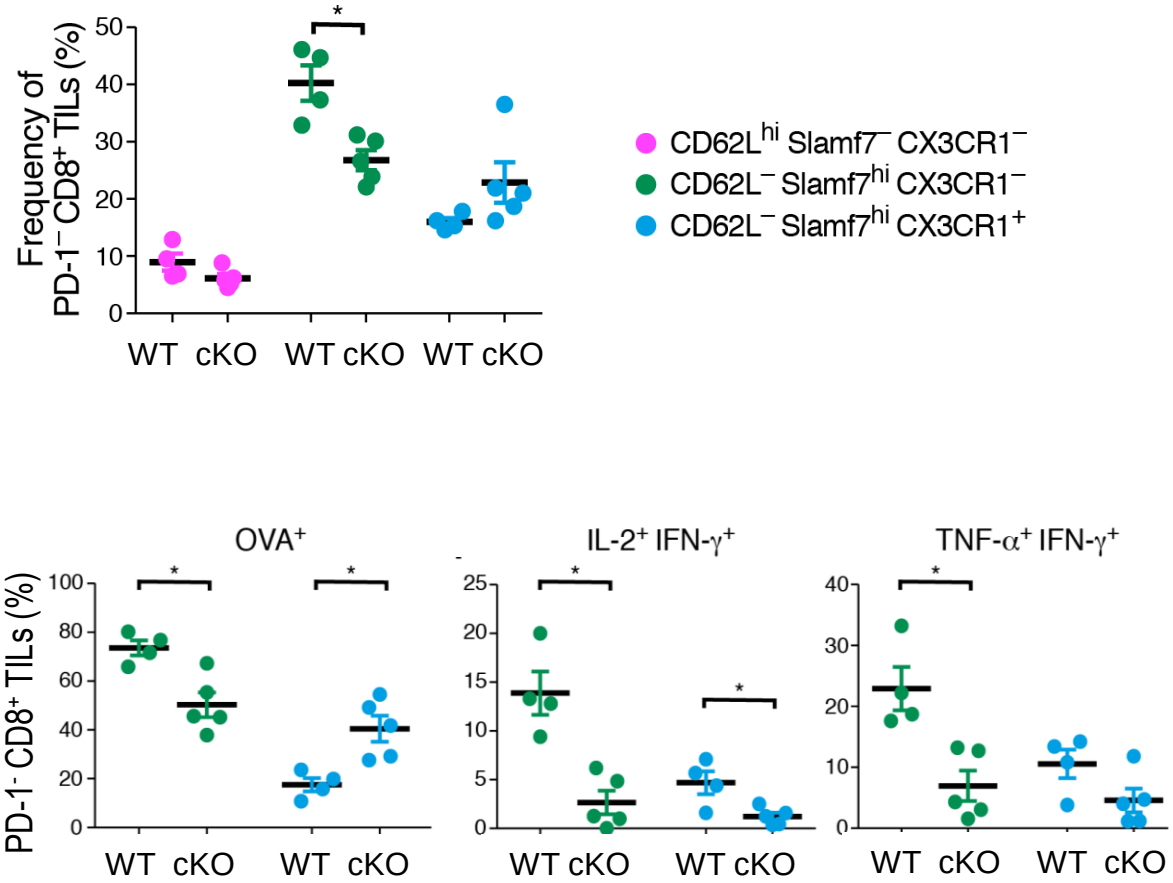
Tcf7 (TCF1) is a regulator of memory-precursor CD8^{+} PD-1^{-} TILs





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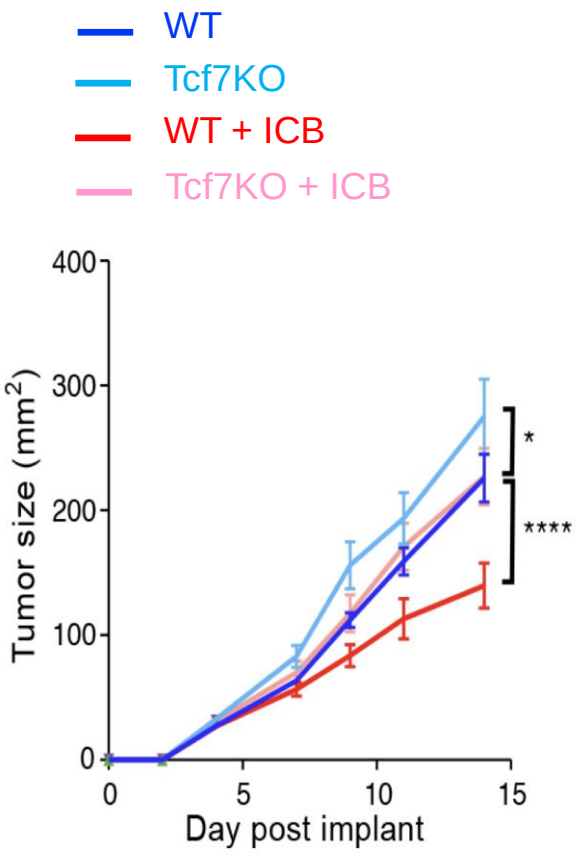
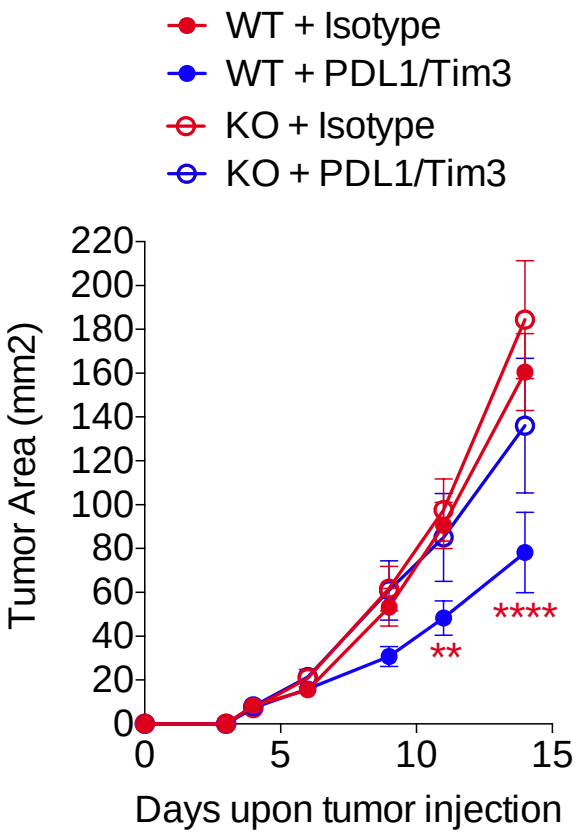
Loss of *Tcf7* in CD8$^+$ T Cells limits response to ICB and other immunotherapies

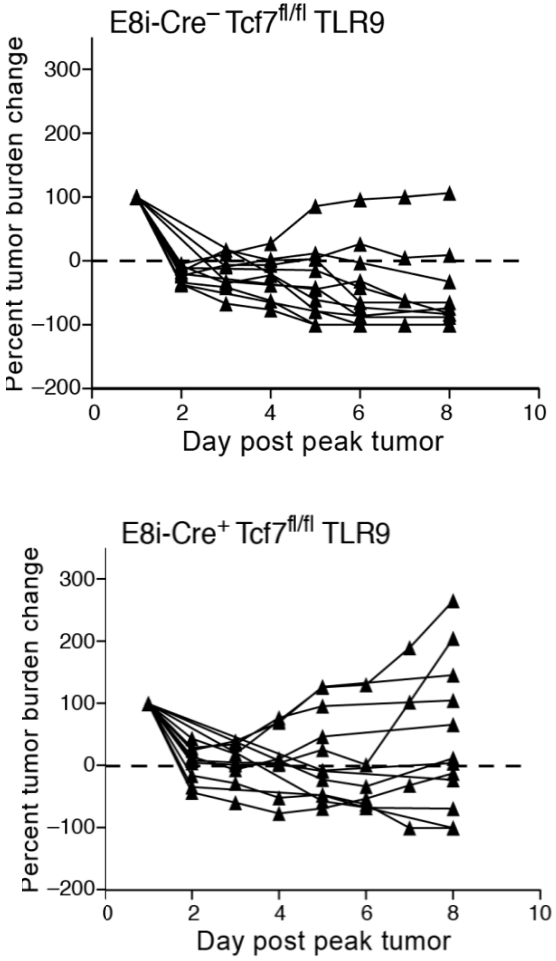
MC38-OVA Tumor



B16-OVA Tumor



TLR9 Agonist



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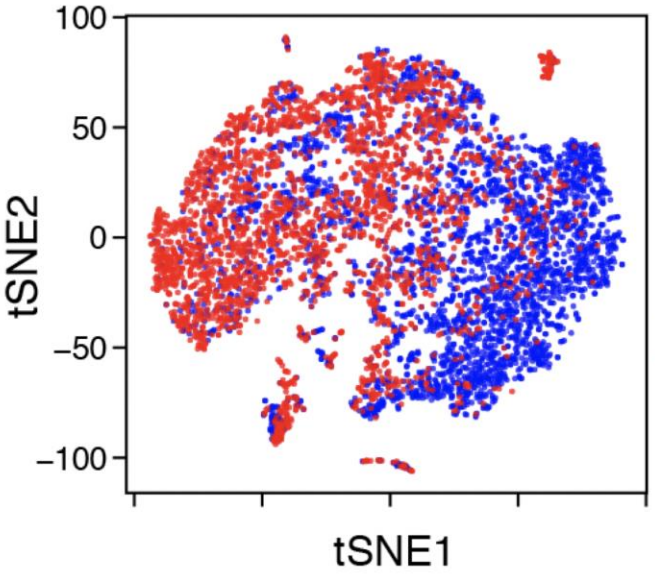
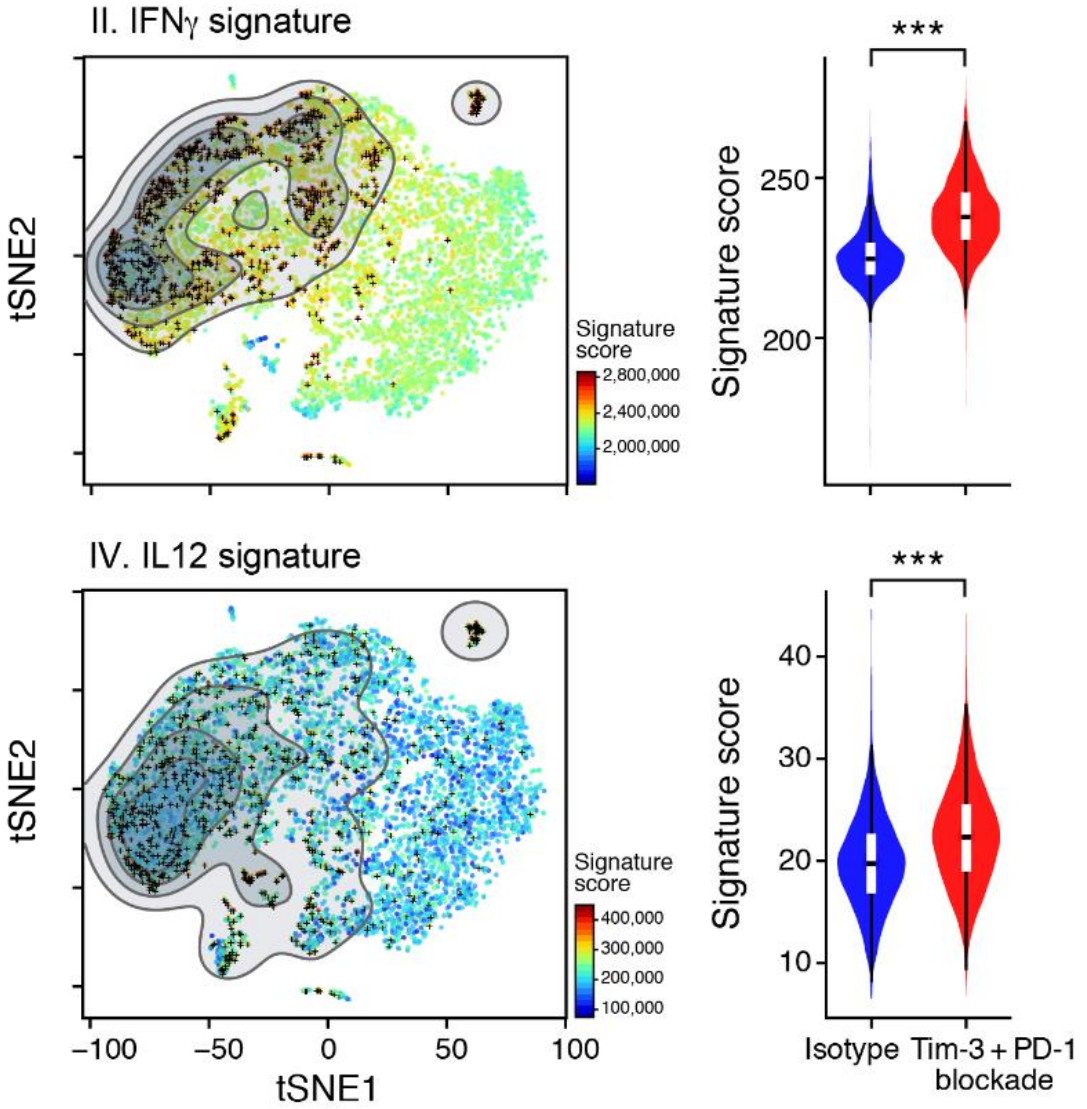
PD-1^{-} CD8^{+} TILs respond to ICB-induced inflammation

Isotype / PD1-Tim3-blockade



Similar results for IL-6 and IL1b



Summary

- *Discovered previously unappreciated changes in PD-1$^-$ CD8$^+$ TILs upon ICB*
- *Discovered a stem-like memory-precursor subset regulated by Tcf7 (TCF-1) that shares features with a stem-like PD-1$^+$T cells as well as T cells associated with response to ICB in patients*
- *Loss of Tcf7 (TCF-1) limits the response to ICB and other immunotherapies*
- *ICB may work through both direct and indirect mechanisms to harness the CD8$^+$ T cell response*

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