OX40 agonist immunotherapy expands tumor reactive CD8 T cells and synergizes with PDL1 blockade to promote tumor regression

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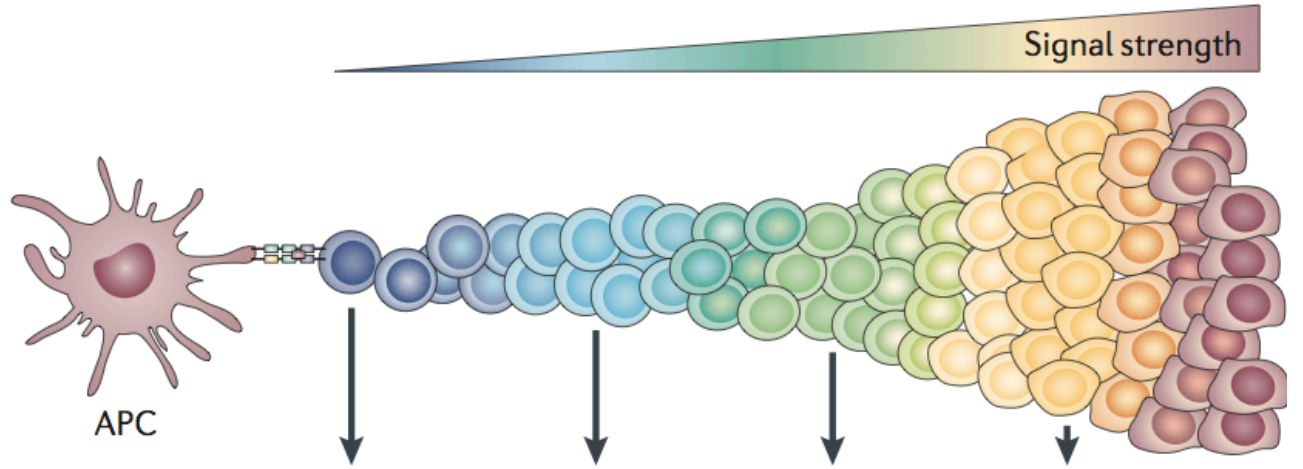
Disclosures

I have no financial interests to disclose.

T cell receptor signal strength influences anti–tumor T cell function



unction					
	IFNγ	–	+	++	+++
	IL-2	–	++	+++	+/–
	Cytoxicity	–	+/–	+	+++

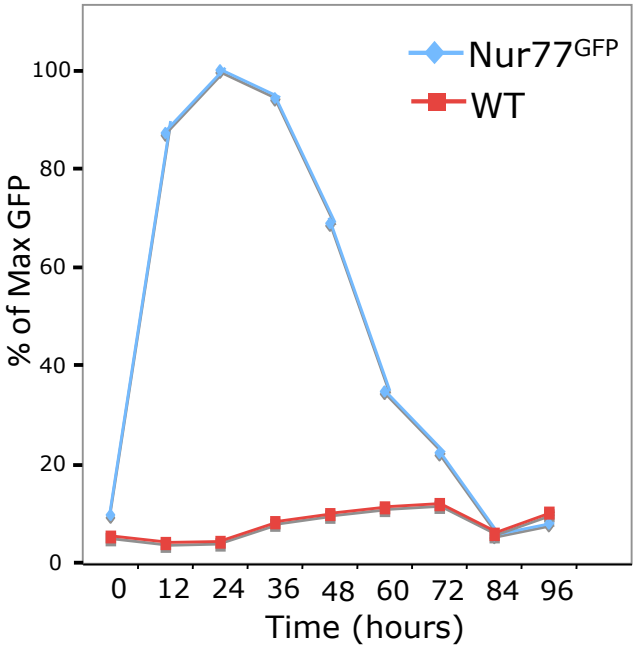
How do you assess TCR signal strength in the polyclonal environment?

Assessing TCR affinity using a novel BAC transgenic mouse

RP24-366J14 (134,703 bp chr15)

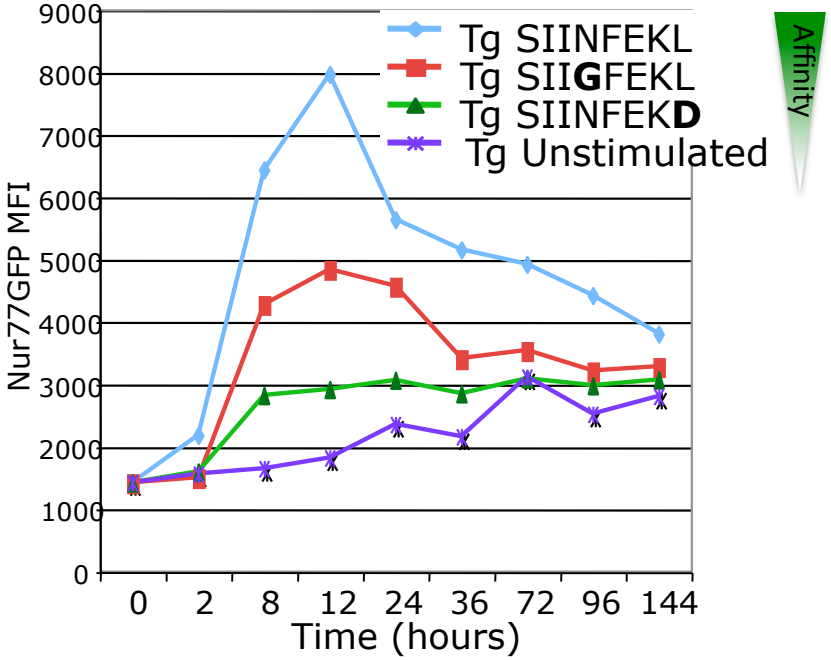
In vivo

A.T. of **OT-I**/Nur77^{GFP} T cells, infect with *LM-**SIINFEKL***, harvest spleen & analyze



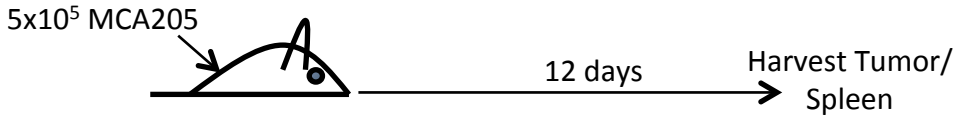
In vitro

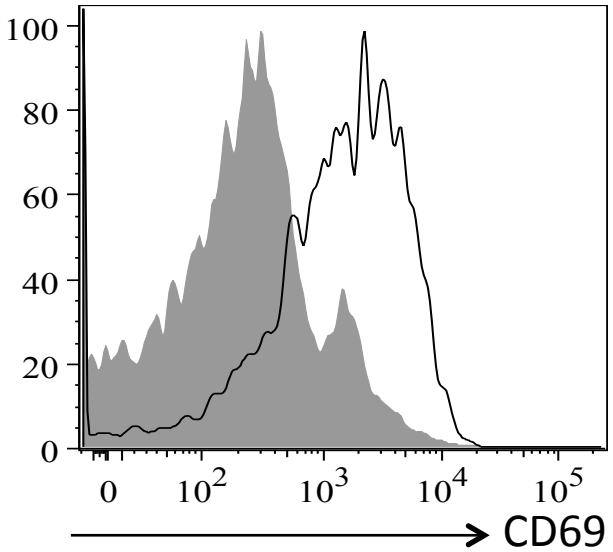
Purified **OT-I**/Nur77^{GFP} lymphocytes, stimulated with splenocytes pulsed with **SIINFEKL** APLs

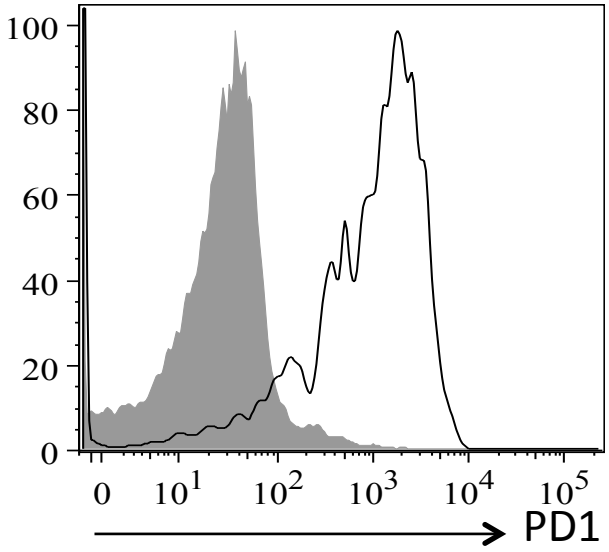


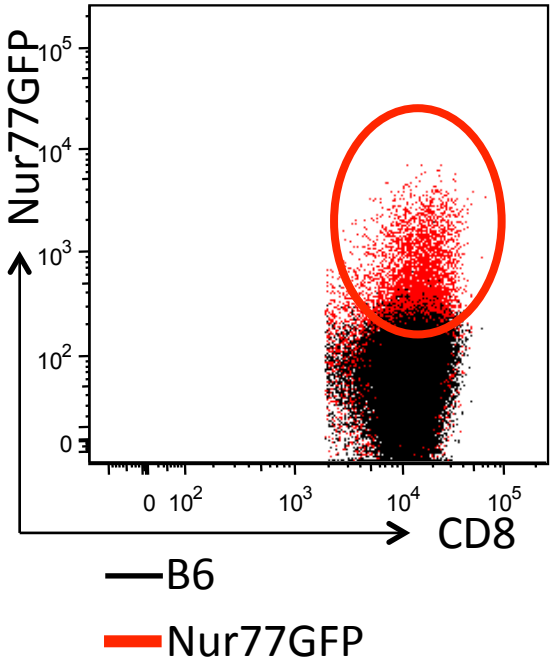
Moran AE et al. JEM 2011

Visualizing polyclonal tumor antigen specific T cell activation



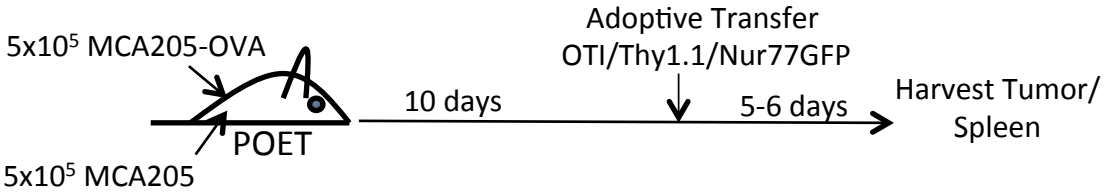


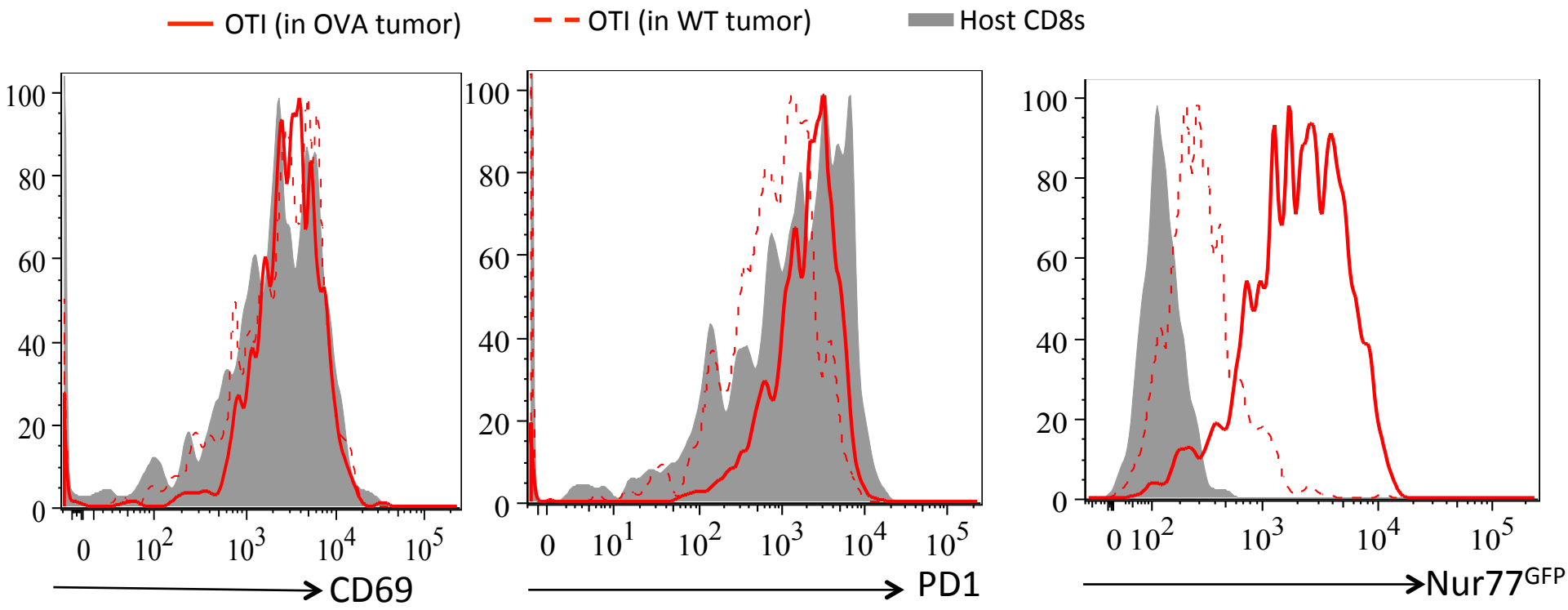




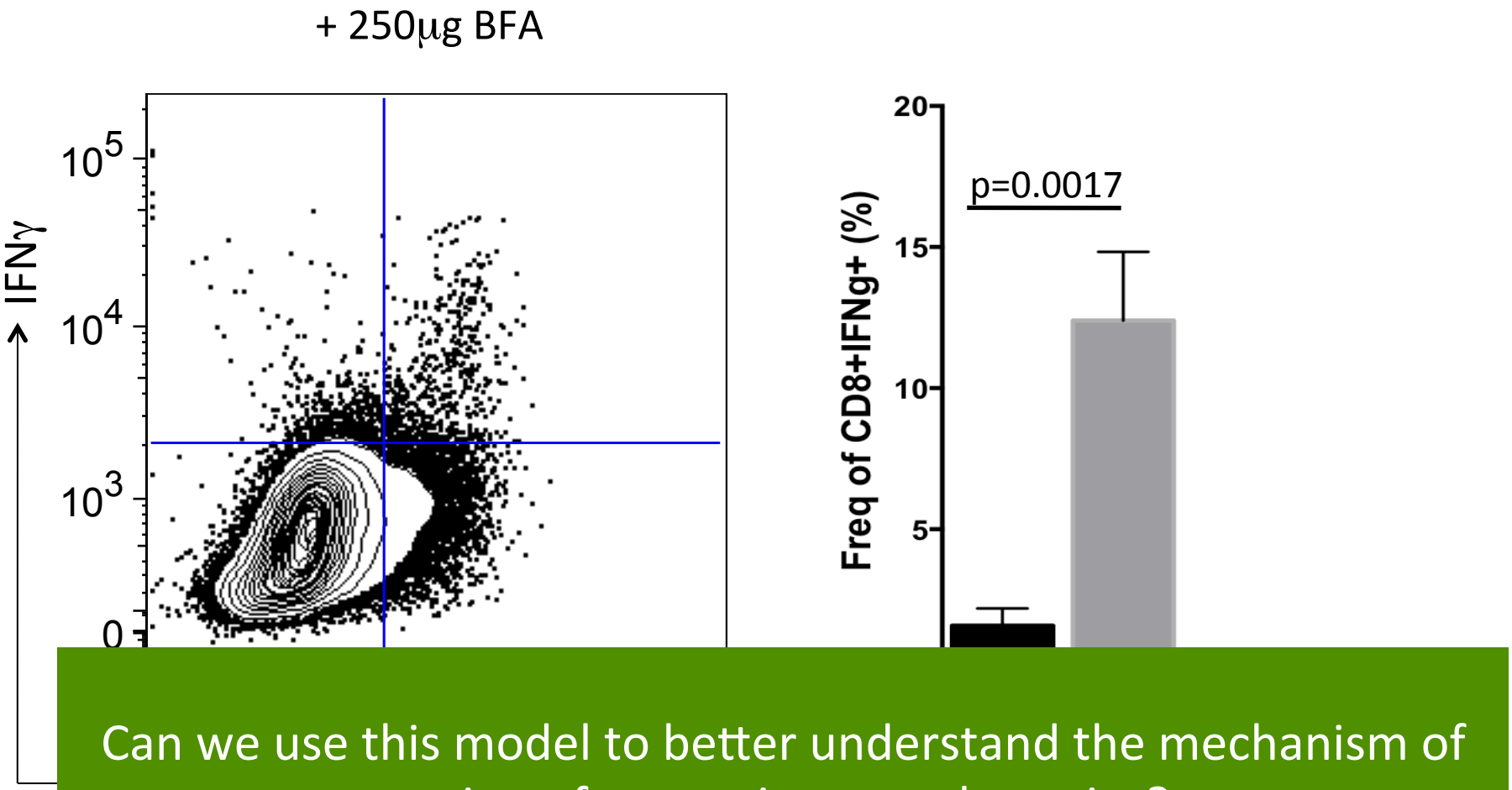
Gated on live/TCRβ+/CD8+

Visualizing tumor antigen specific T cell activation





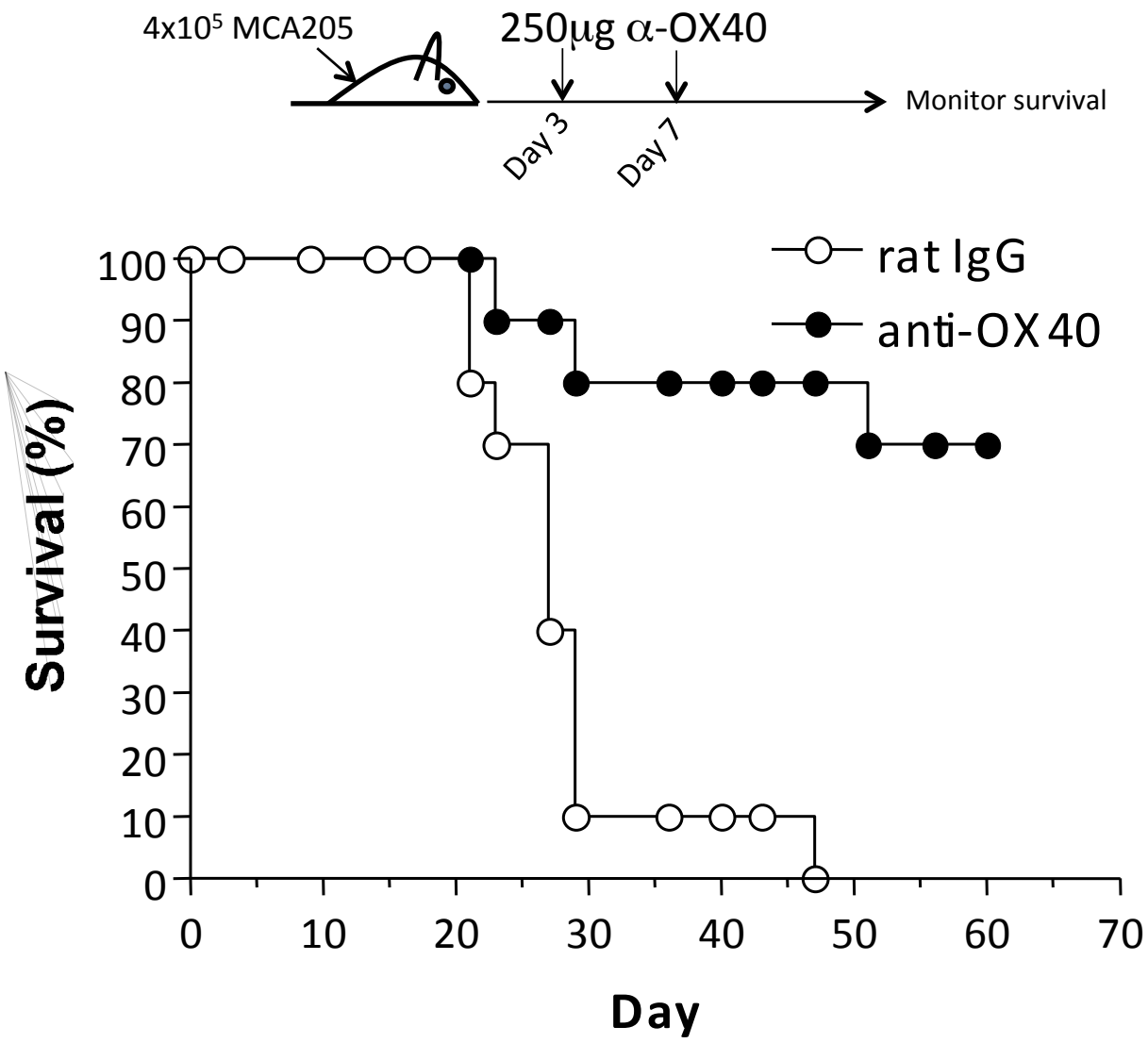
$CD8^{+}Nur77GFP^{hi}$ TIL are enriched for effector cytokine secreting cells



Can we use this model to better understand the mechanism of action of cancer immunotherapies?

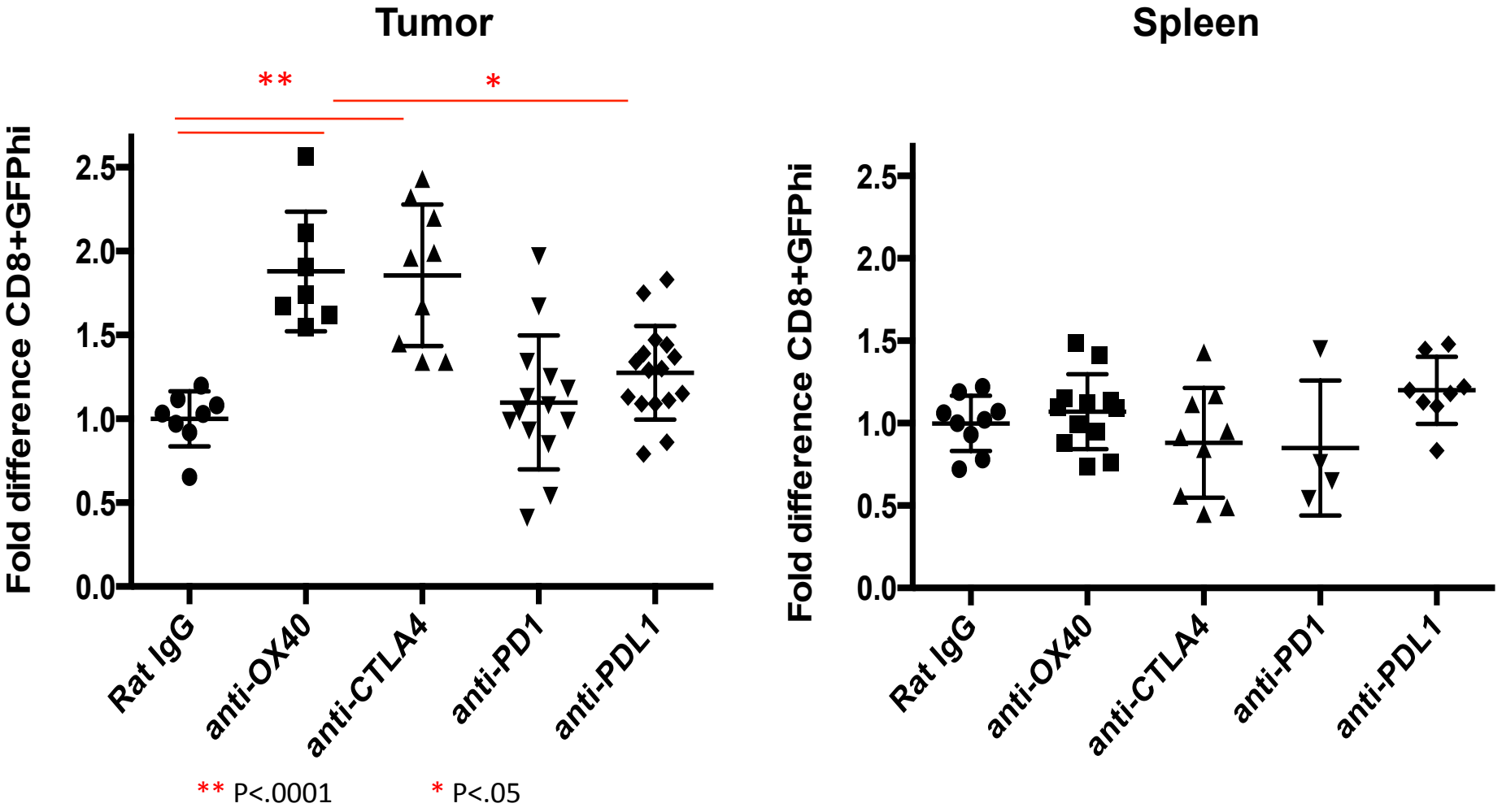
N=6 mice, 2 independent experiments

Anti-OX40 promotes the survival of MCA205 tumor bearing mice

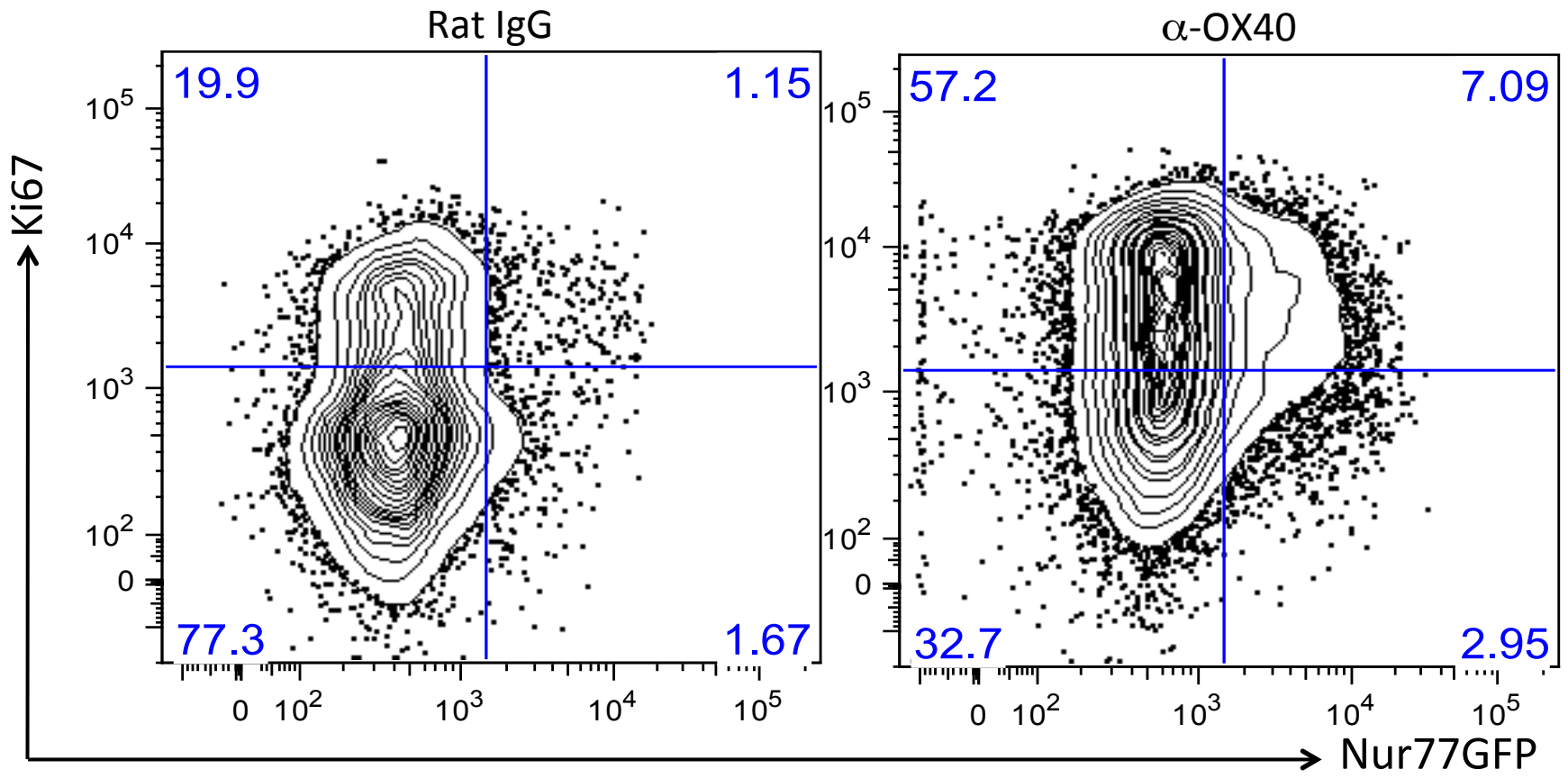


Immunotherapy increases the frequency of CD8+ Nur77GFP^{hi} polyclonal tumor infiltrating lymphocytes

Tumors were ~50mm2 prior to starting immunotherapy. Treatments as follows:
1) Rat IgG/α-OX40 (OX86)/CTLA4 (9H10): 2 x 250μg i.p. 4 days apart
2) α-PD1(G4)/α-PDL1(10F.9G2): 4 x 200μg i.p. 3 days apart

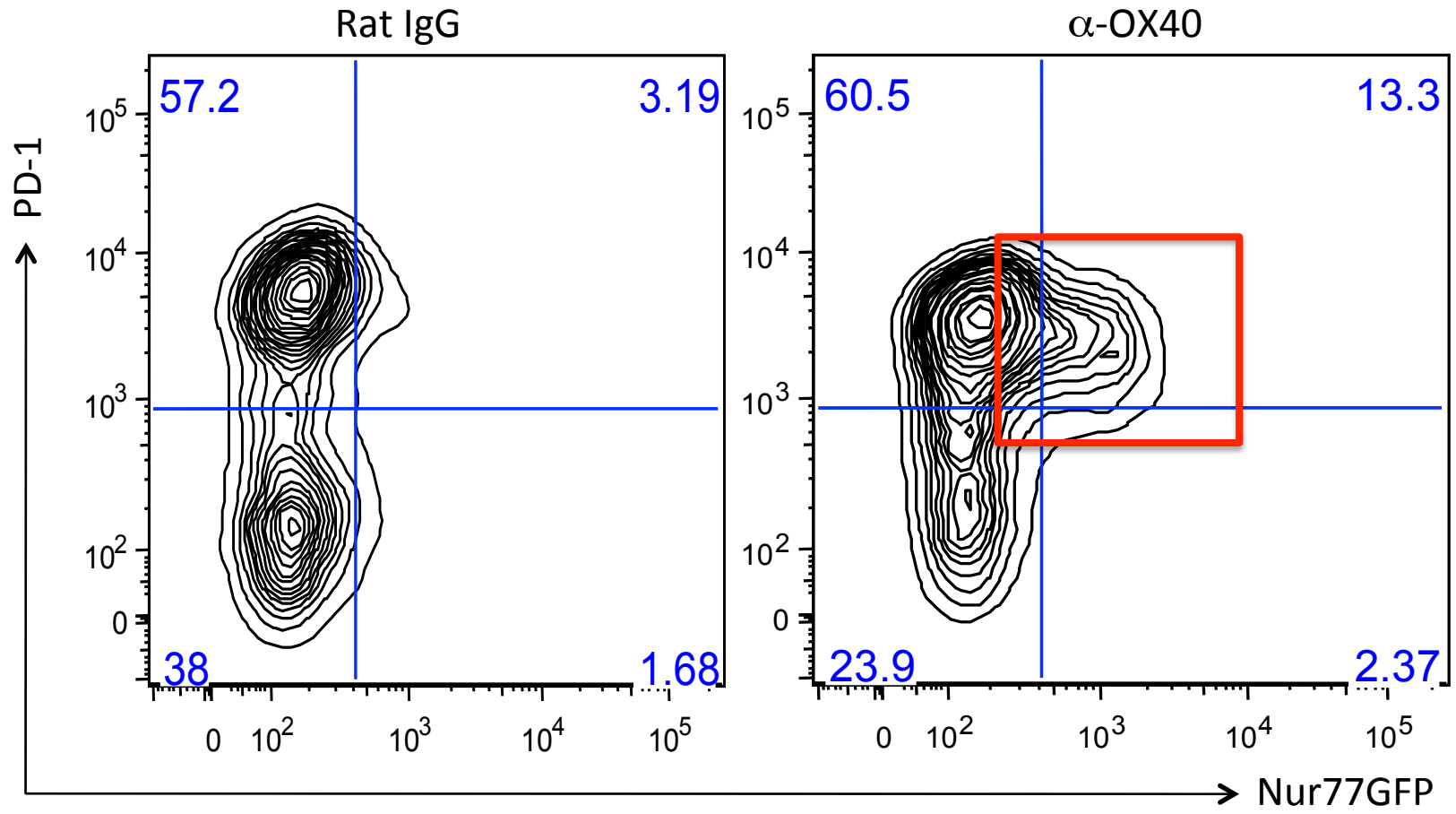


OX40 agonists promote the proliferation of both CD8+ Nur77GFP^{hi} and GFP^{low} TIL



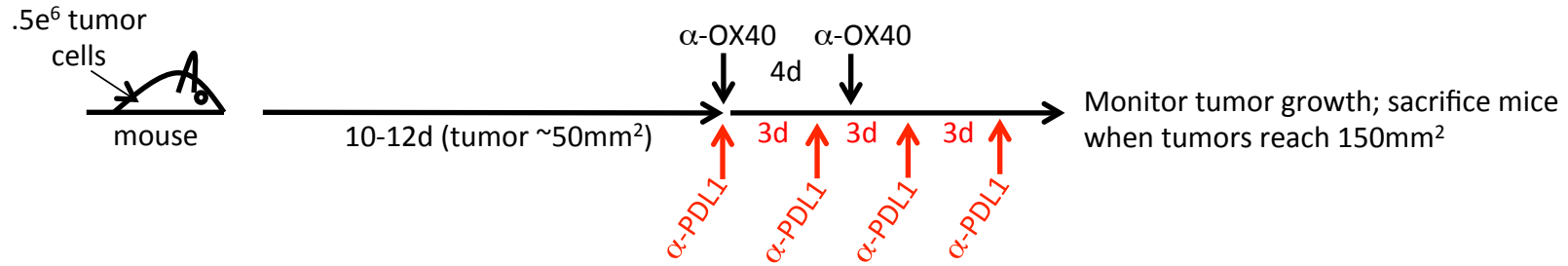
N=20 mice, 6 independent experiments

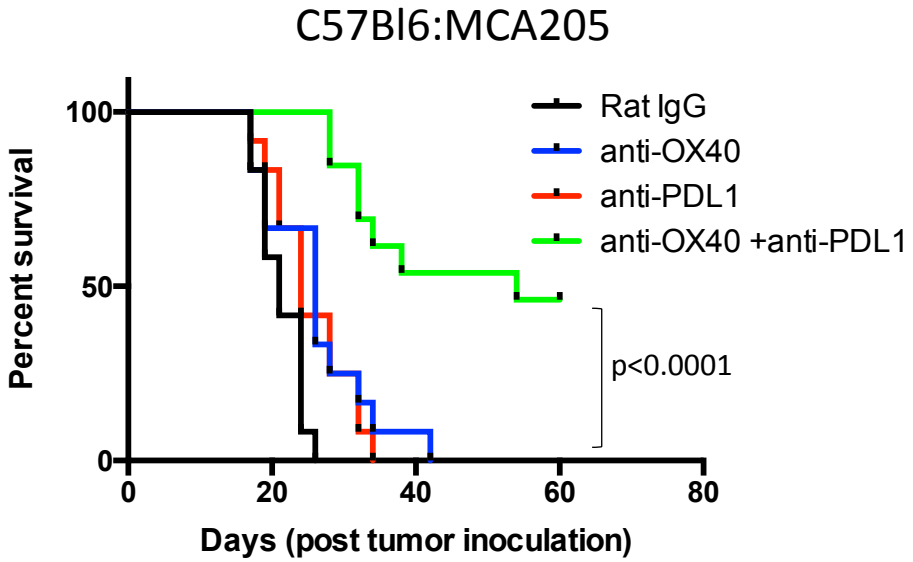
Agonist OX40 immunotherapy changes the phenotype of TILS

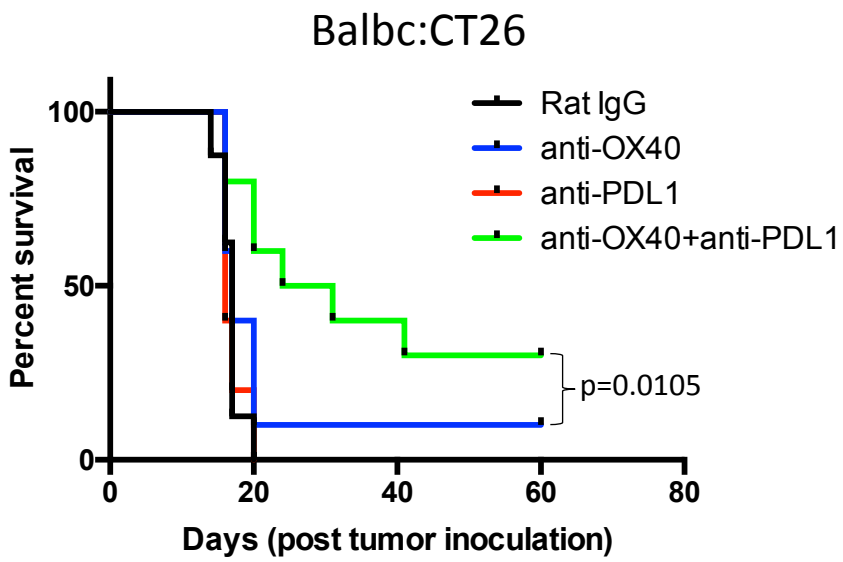


N=16 mice, 4 independent experiments

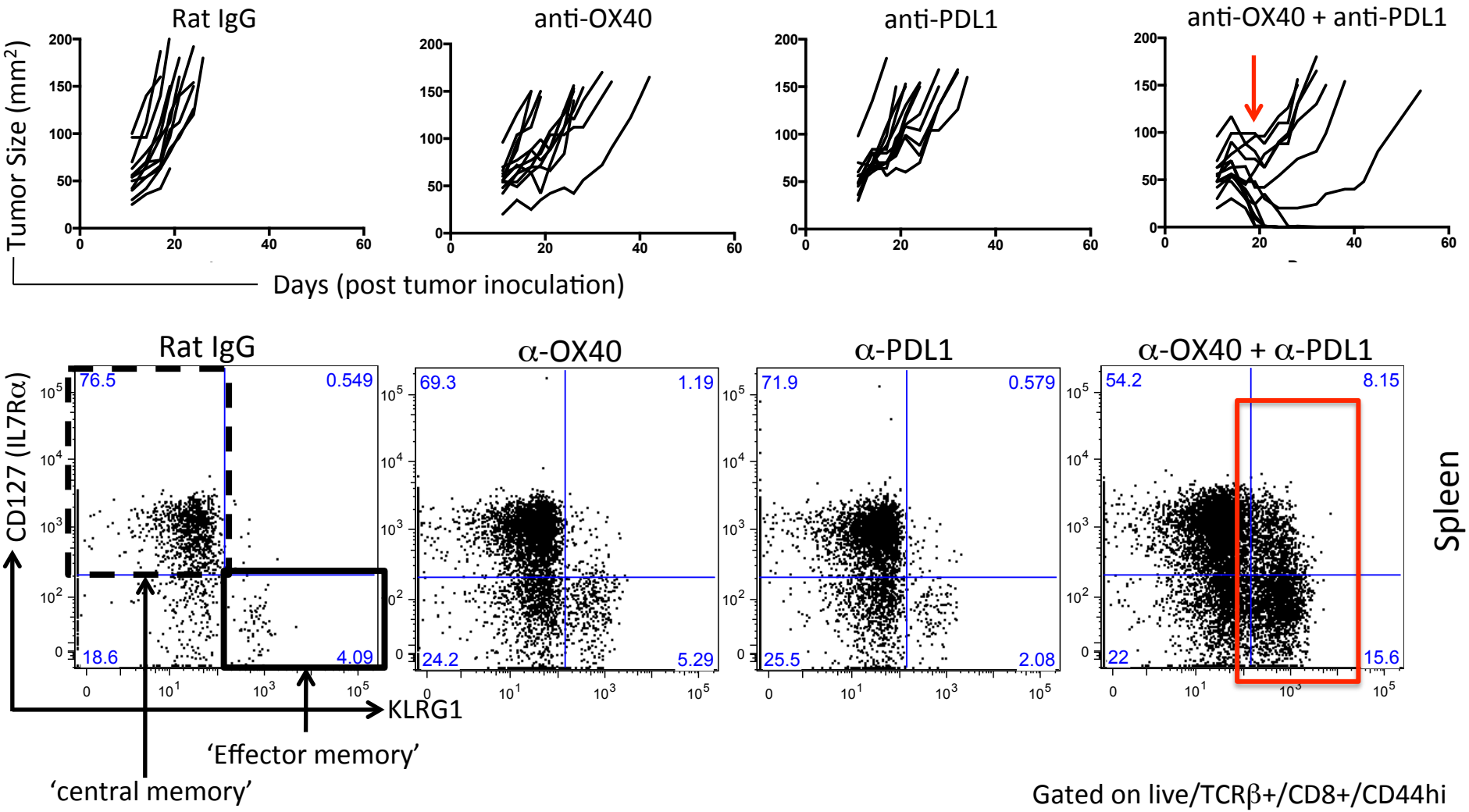
Combination immunotherapy with α-PDL1 and α-OX40 is more potent than either agent alone



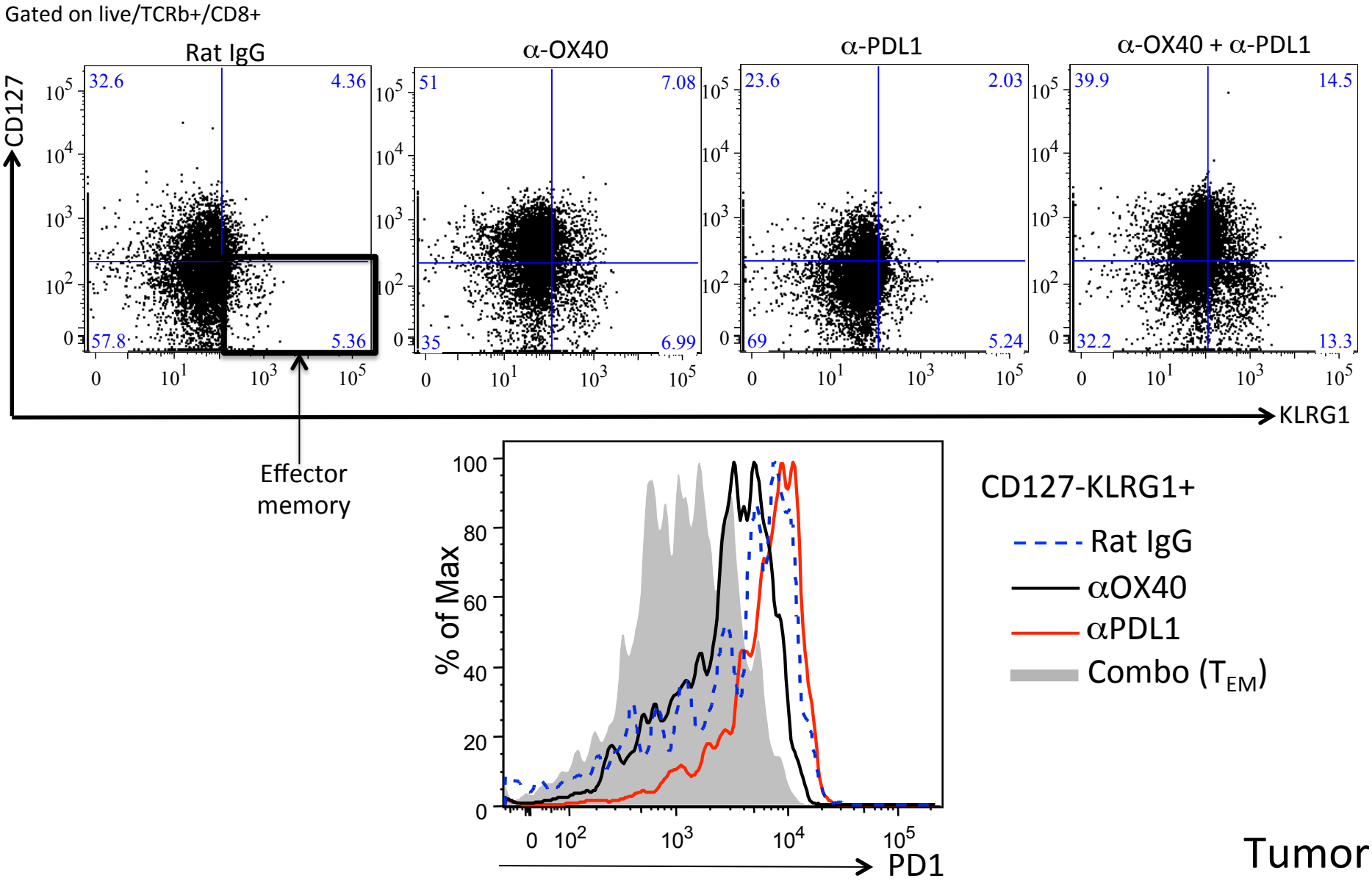




Combination α-OX40 + α-PDL1 immunotherapy increases the frequency of CD8+ effector memory T cells



α-OX40 + α-PDL1 immunotherapy increases tumor resident CD8+ effector memory T cells



Conclusions

- Traditional markers of T cell activation can be misleading and Nur77GFP expression appears to have greater 'antigen specific' fidelity.

- The tumor is enriched for a population of polyclonal tumor antigen specific CD8 T cells receiving strong TCR signals (as measured by Nur77GFP) and immunotherapy expands this population of T cells.

- Combination of a PDL1 blocking antibody with an agonist OX40 antibody synergize to delay tumor growth and promote tumor regression in tumor bearing mice.

- Targeting both PDL1 and OX40 promotes the expansion of effector memory T cells in the tumor, draining LN, and spleen of tumor bearing mice; and these CD8+ T_{EM} have increased Nur77GFP and decreased PD1 expression.

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