



cima

CENTRO DE INVESTIGACIÓN MÉDICA APLICADA
UNIVERSIDAD DE NAVARRA

Therapeutic activity of the combination of anti-CD137, OX40 and B7-H1 on a spontaneous mouse model of hepatocarcinoma

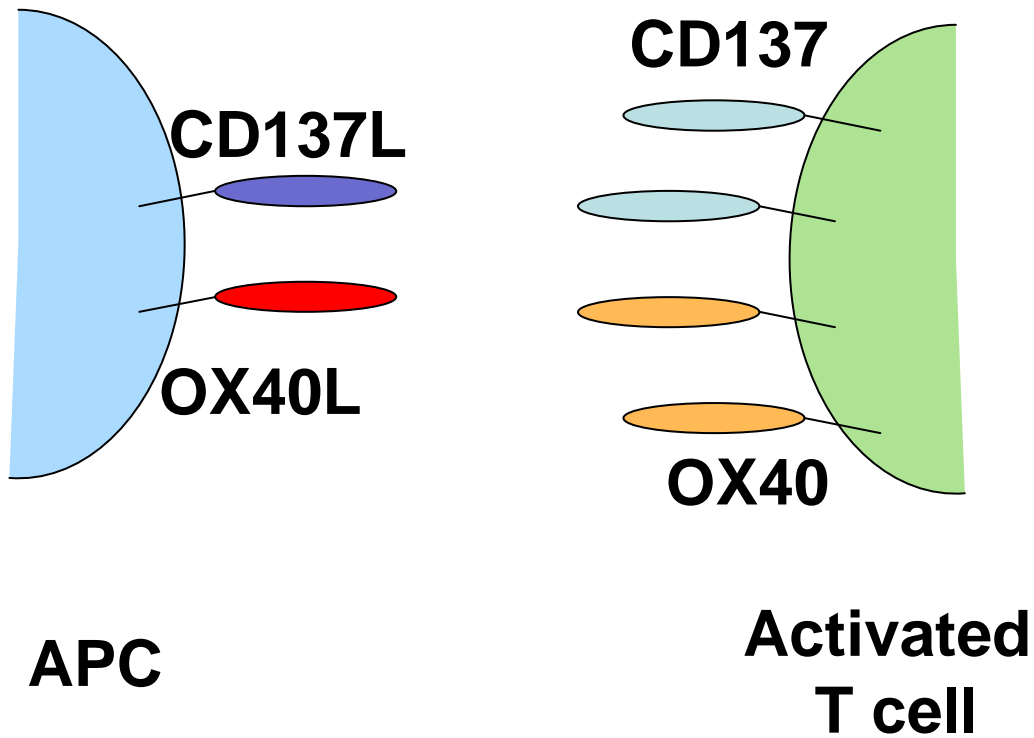
Aizea Morales-Kastresana

SITC 28th Annual Meeting, November 10th 2013

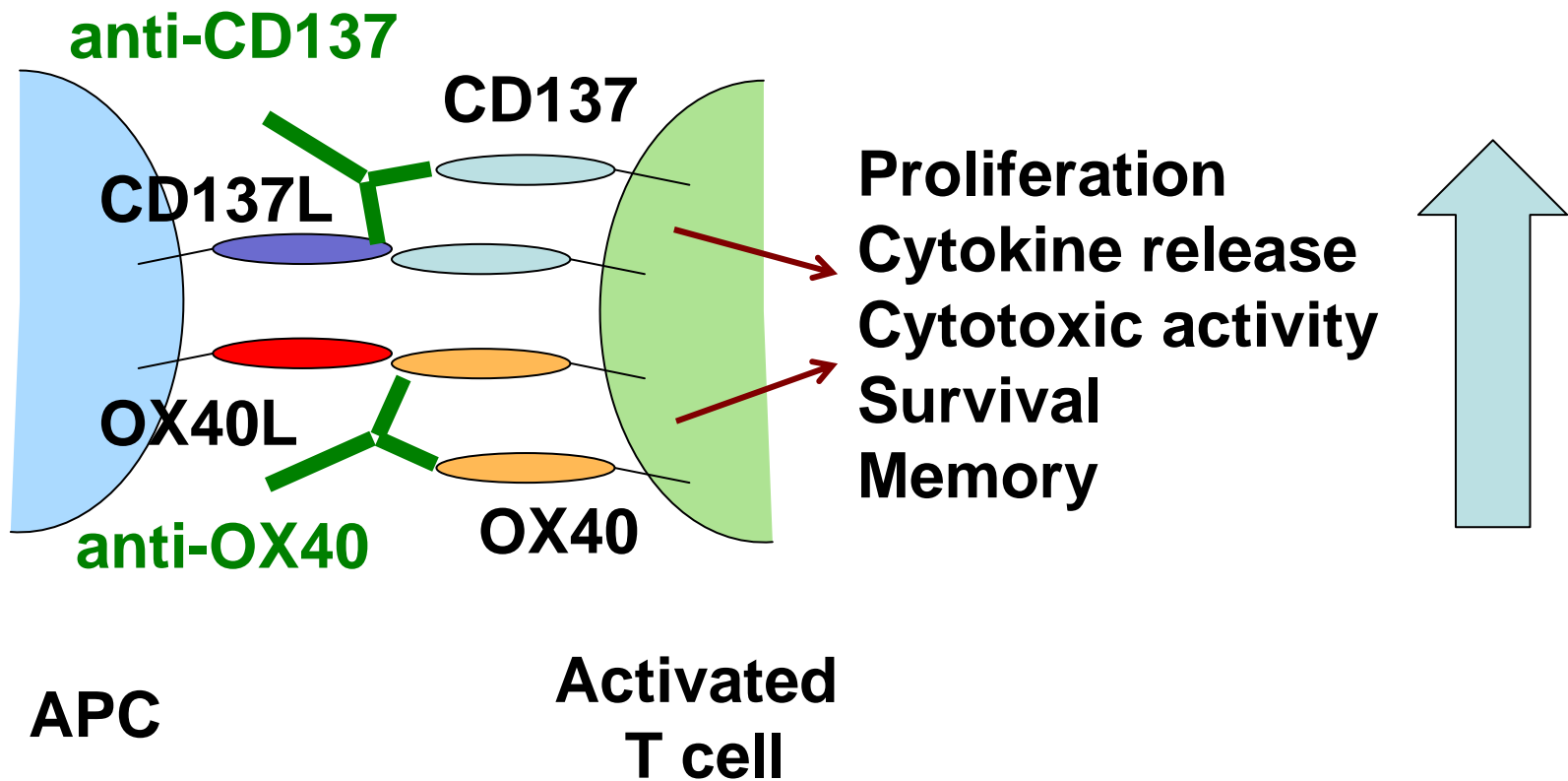
amoralesc@unav.es

No potential conflict of interests

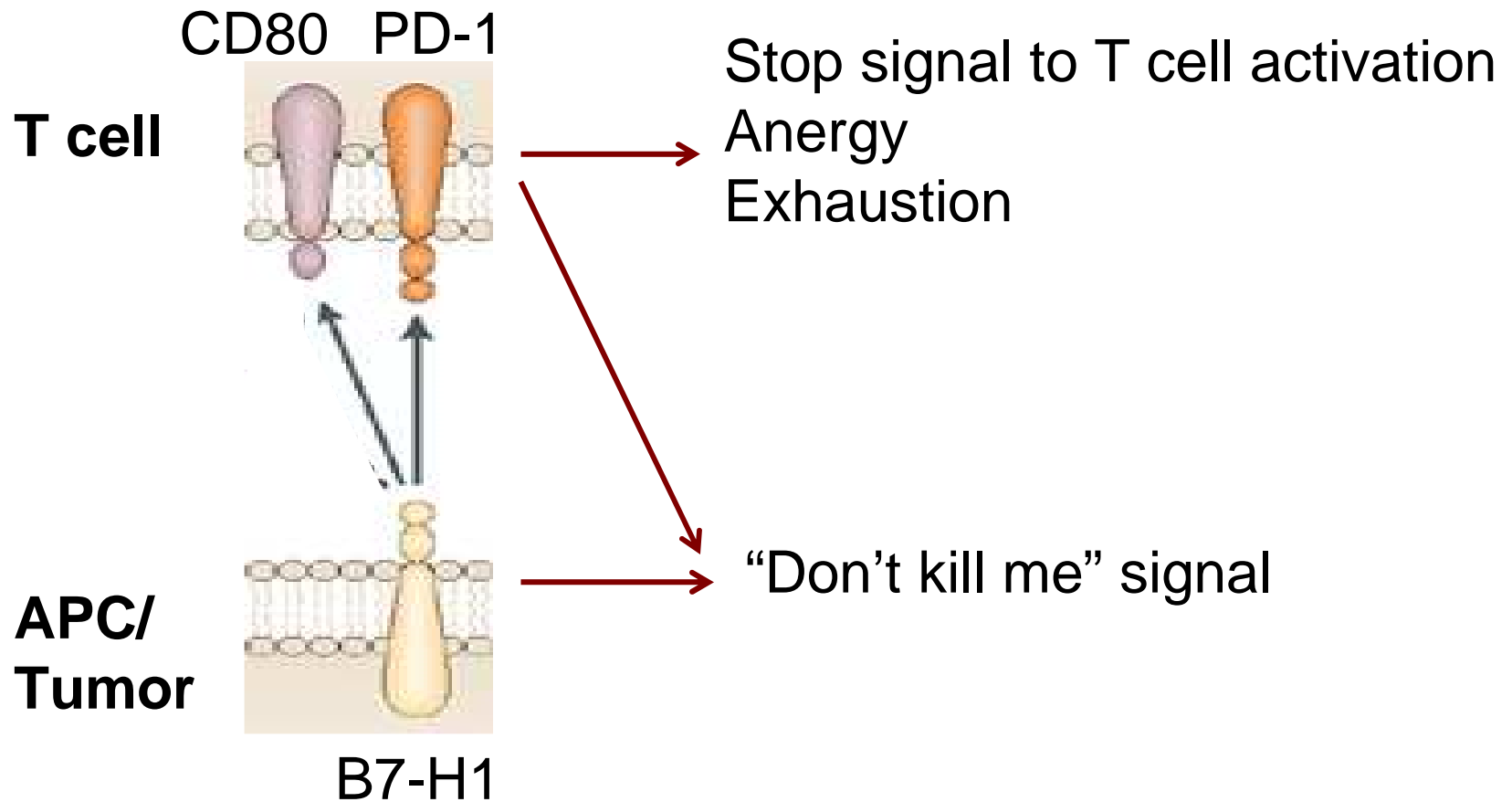
Activating signals: TNFRSF members CD137 and OX40



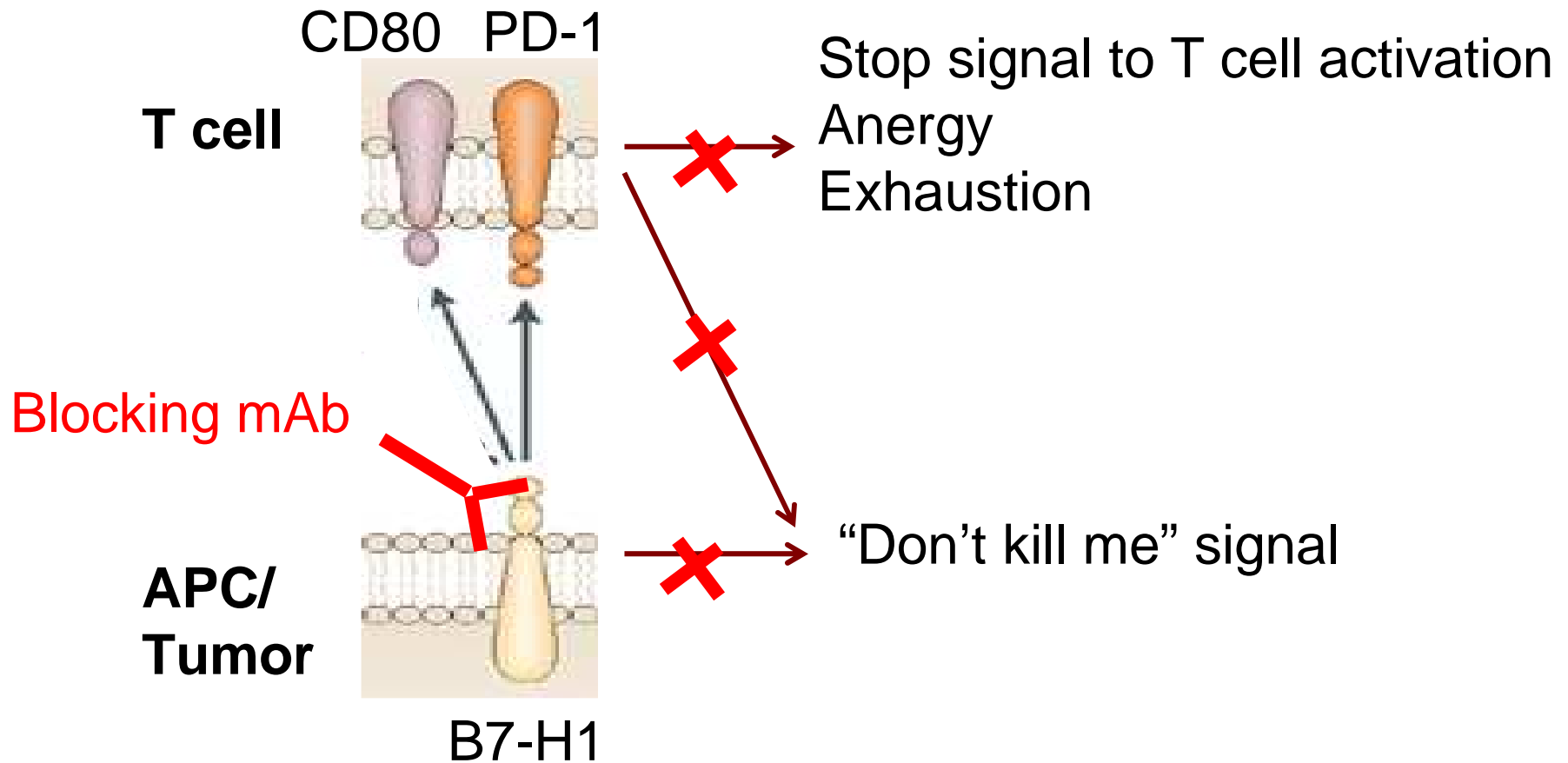
Activating signals: TNFRSF members CD137 and OX40



Inhibitory signals

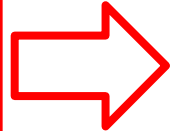


Inhibitory signals



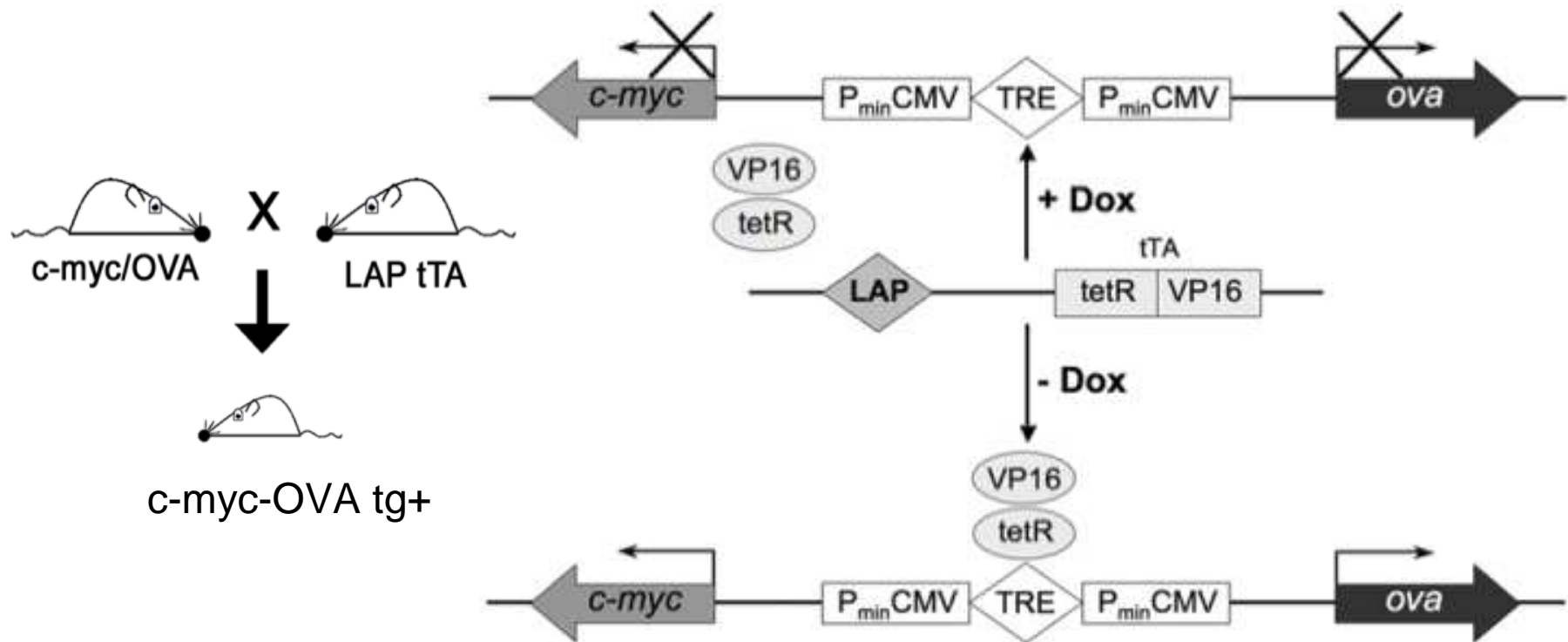
Combo3

anti-CD137
anti-OX40
anti-B7-H1



Transgenic mouse model of spontaneous hepatocarcinoma (c-myc-OVA tg+)

Inducible generation of HCC: Tet-off system

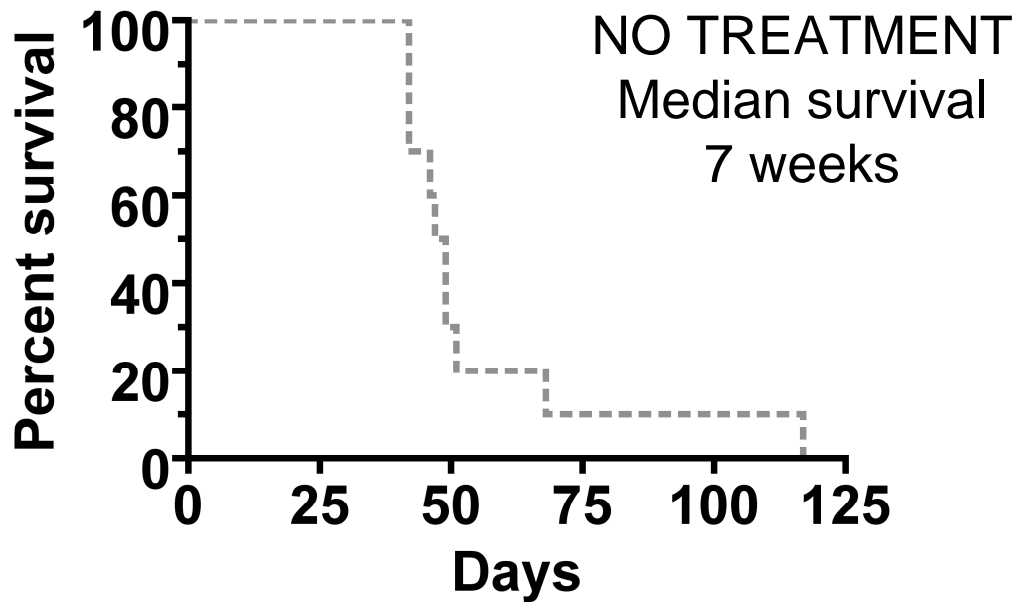


Doxycycline



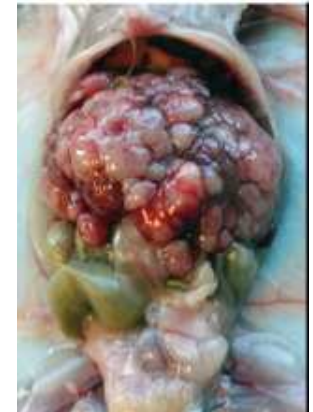
Breeding

Birth



Littermate

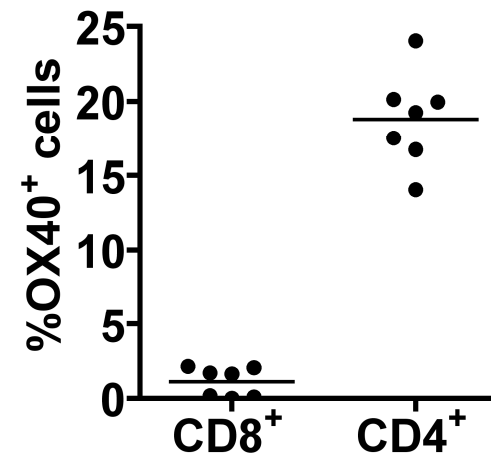
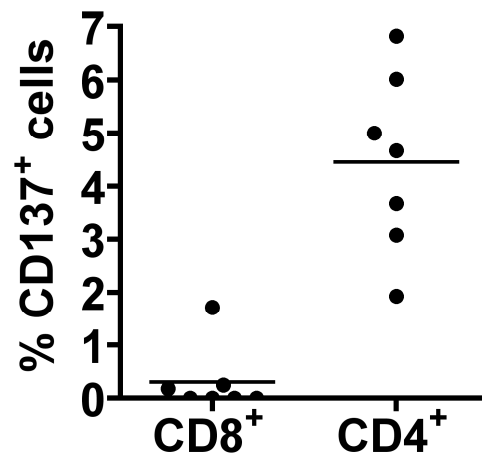
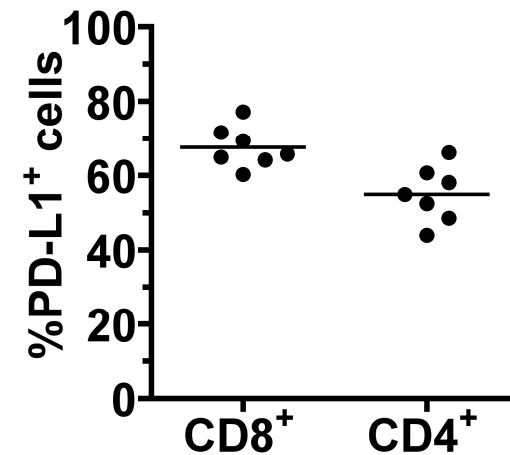
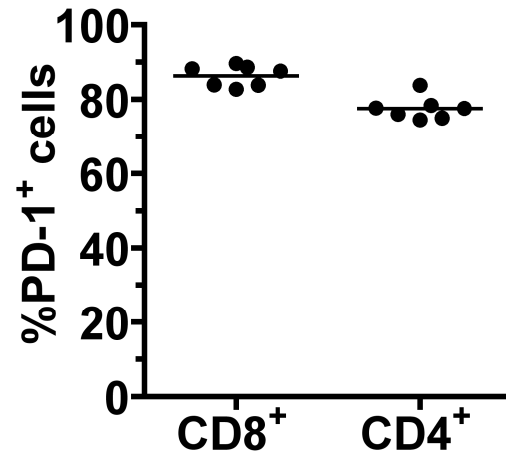
c-myc-OVA tg+



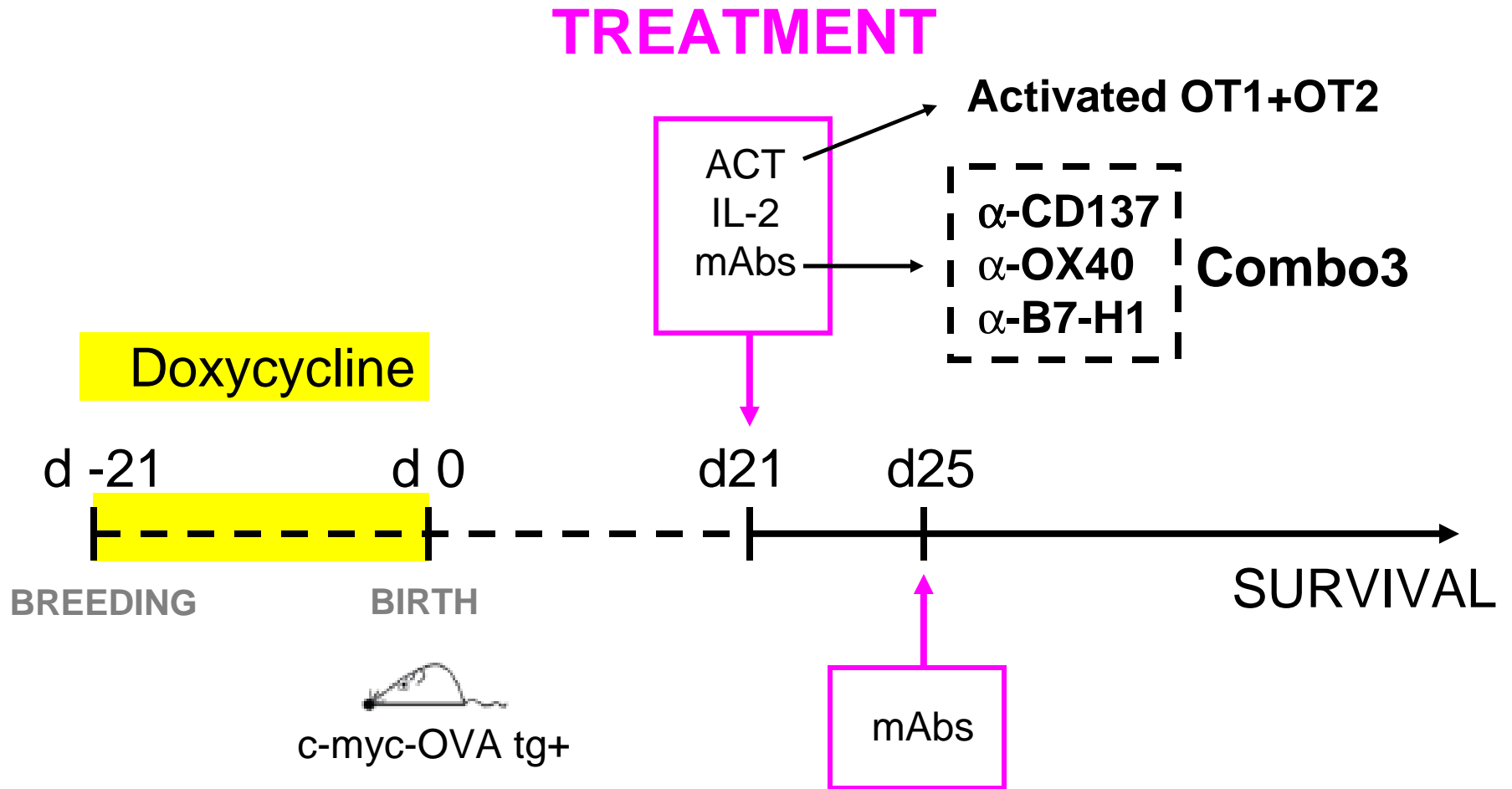
Ney et al. Hepatology 2009

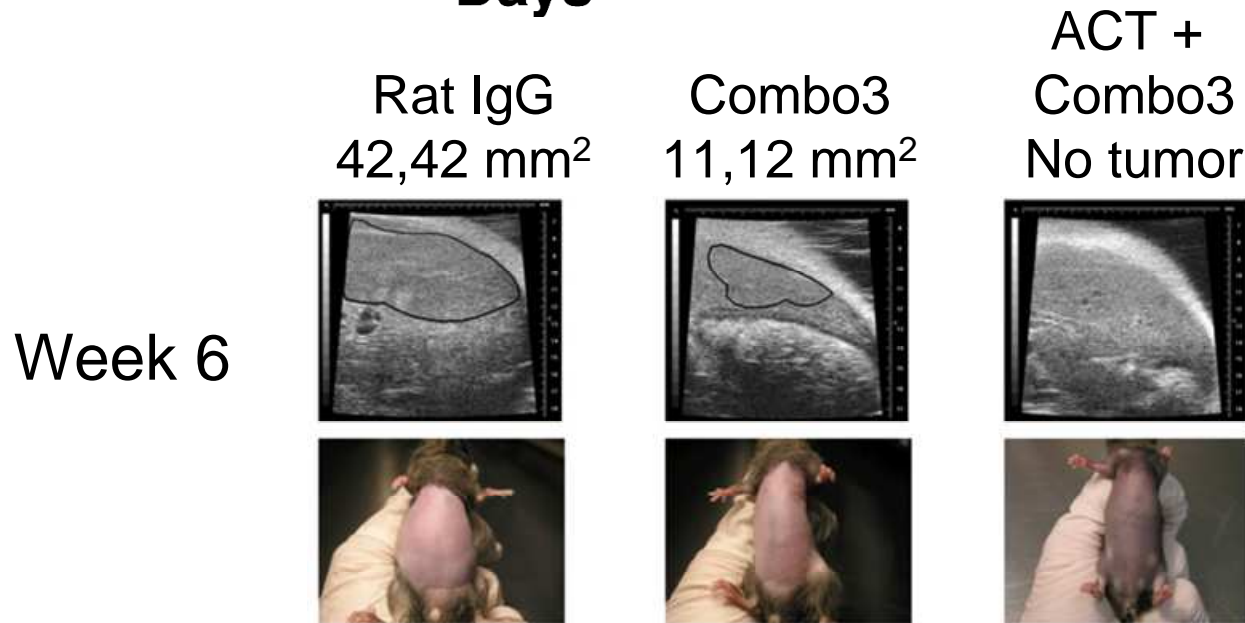
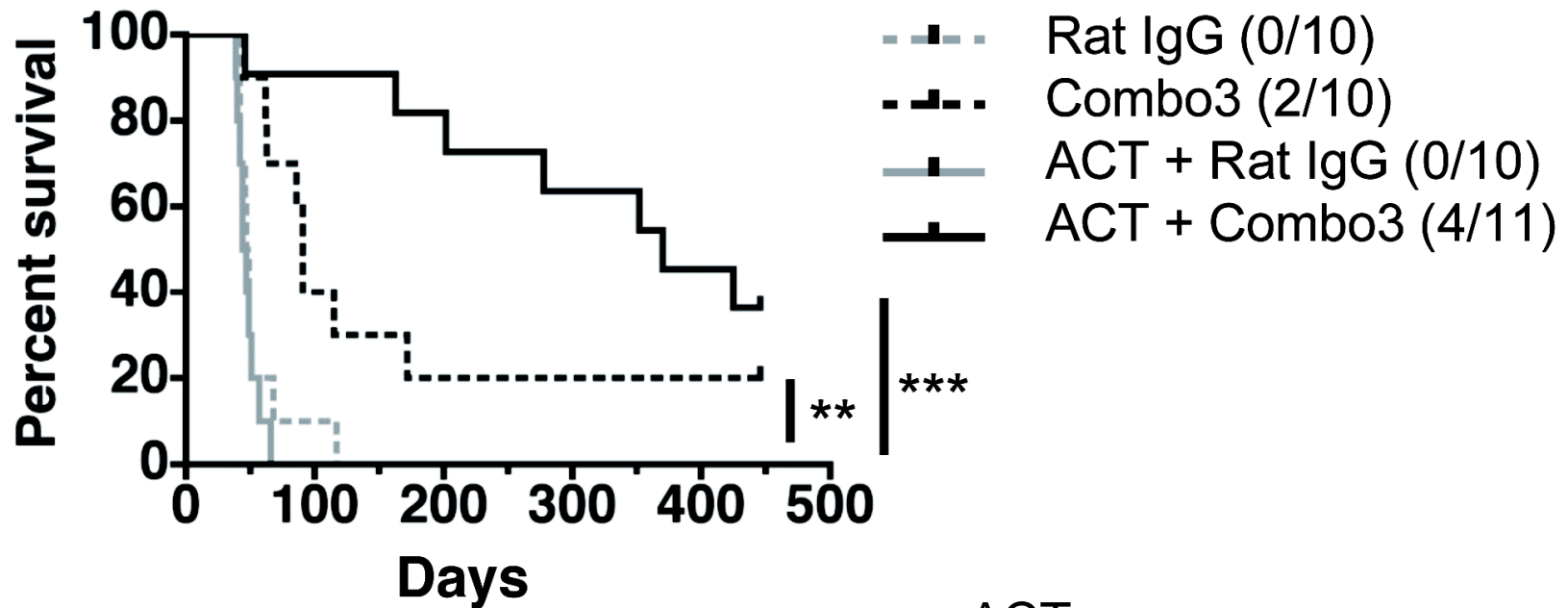
Targets for anti-CD137, anti-OX40 and anti-B7-H1 are expressed on TILs

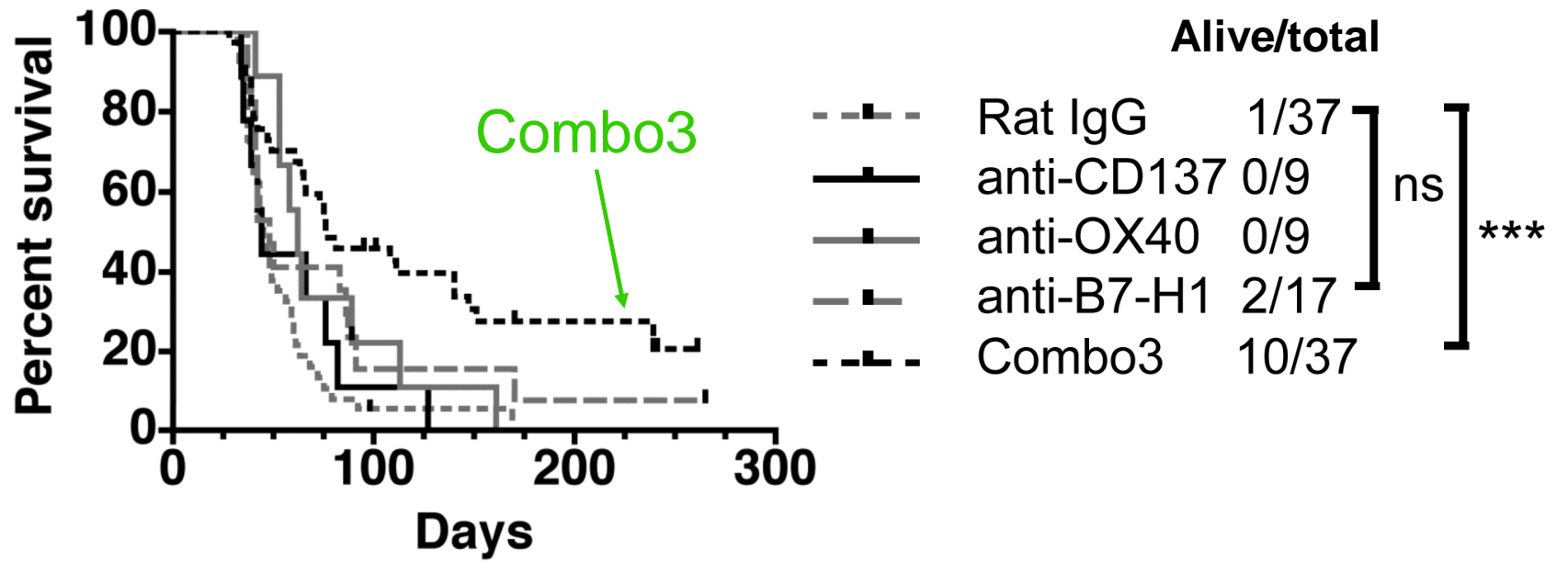
TILs in
3-week old
c-myc OVA tg+
mice



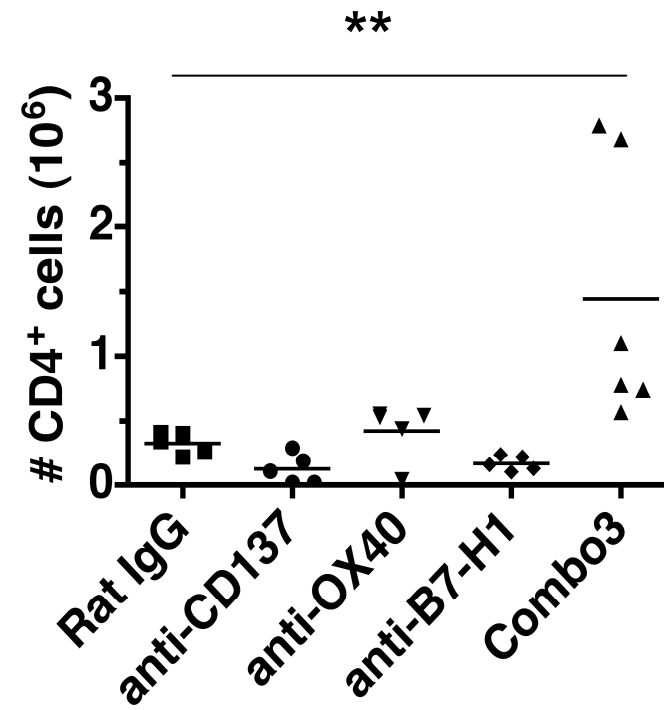
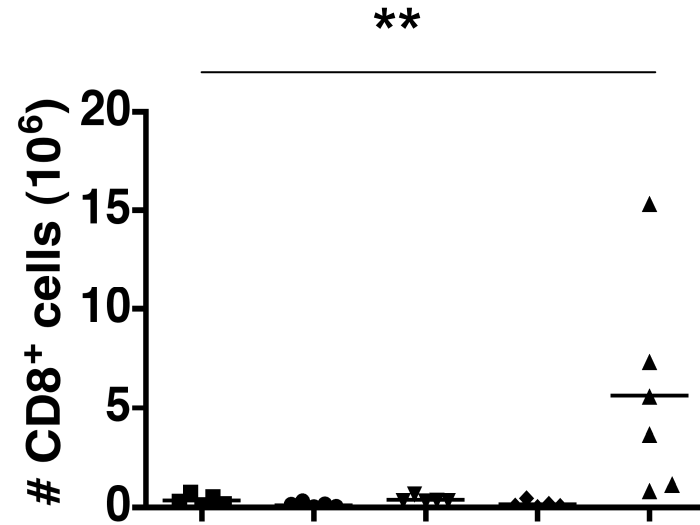
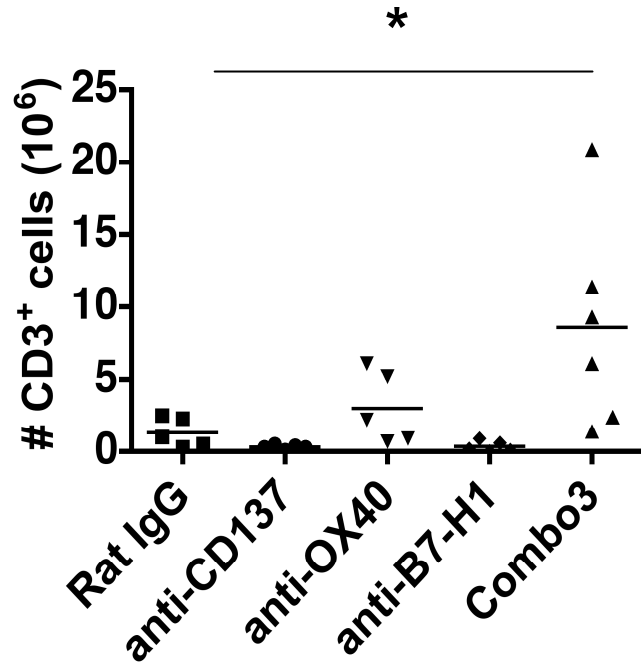
IMMUNOTHERAPY with mAbs + ACT

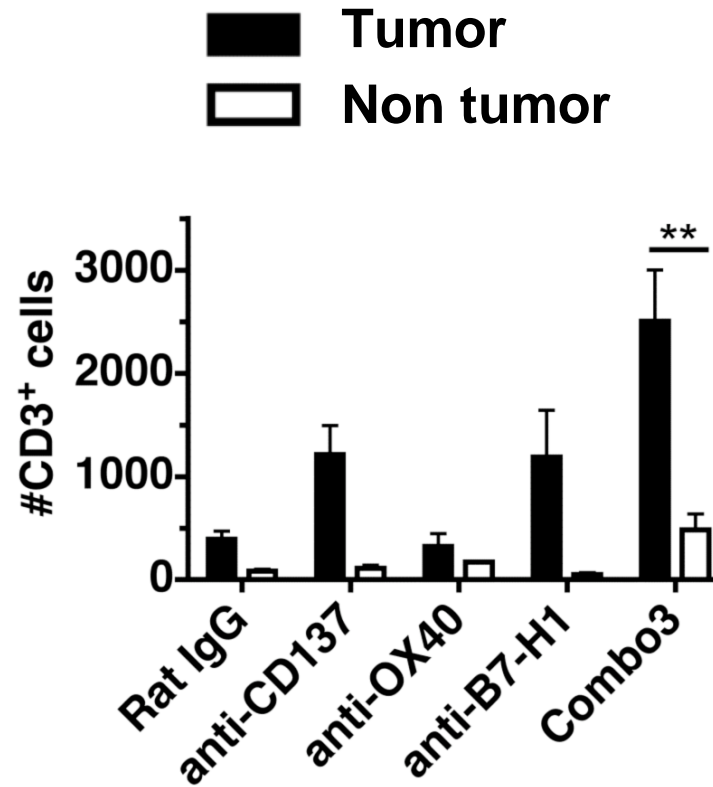
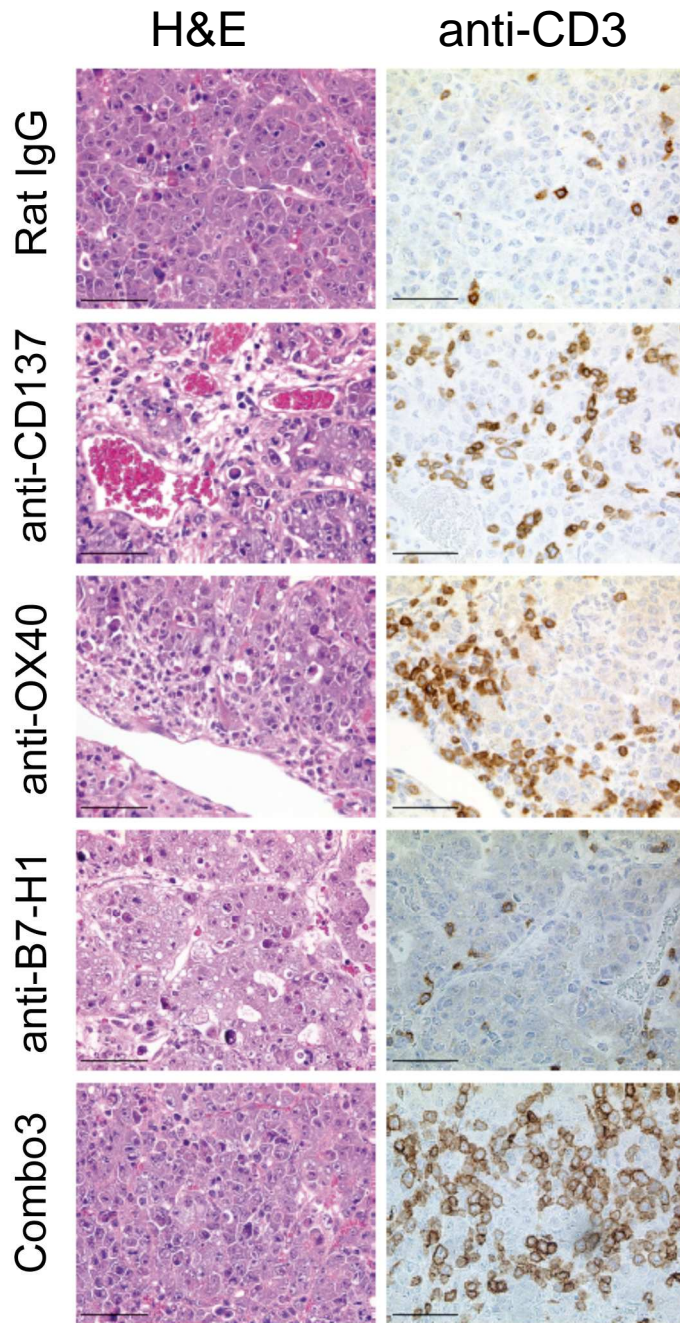




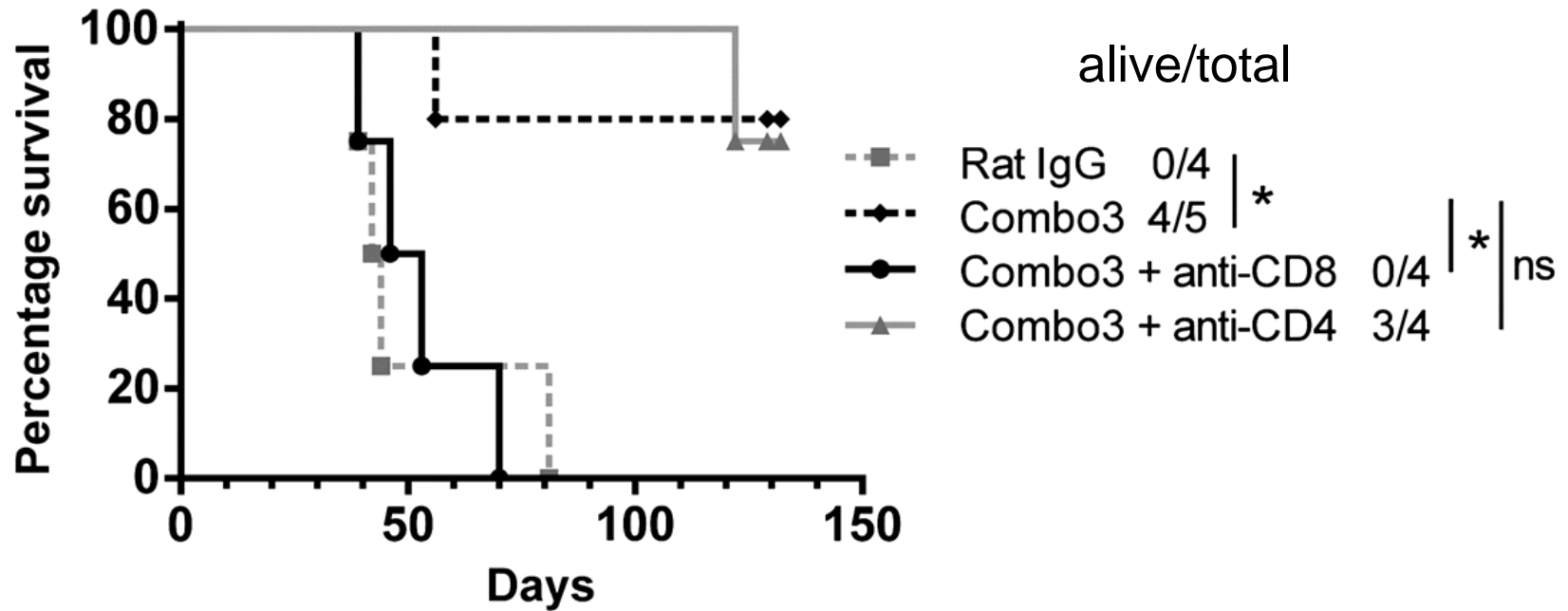


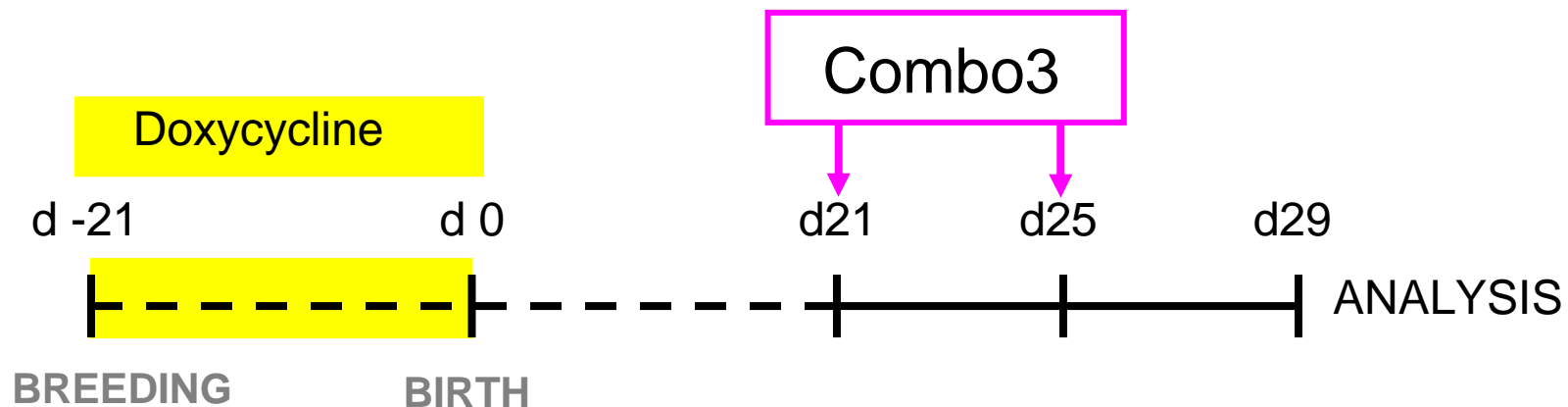
Increased T cell infiltrates upon Combo3 treatment



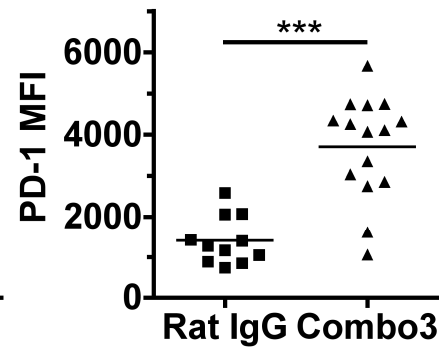
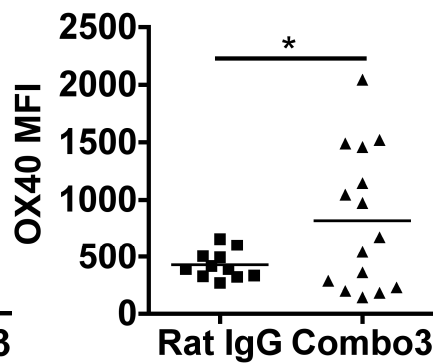
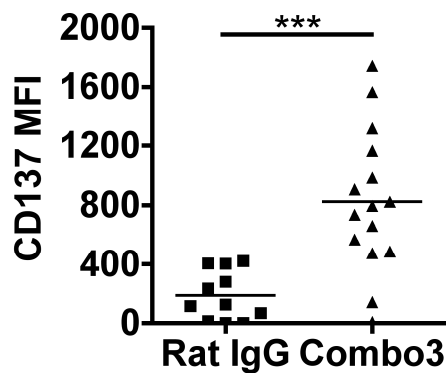
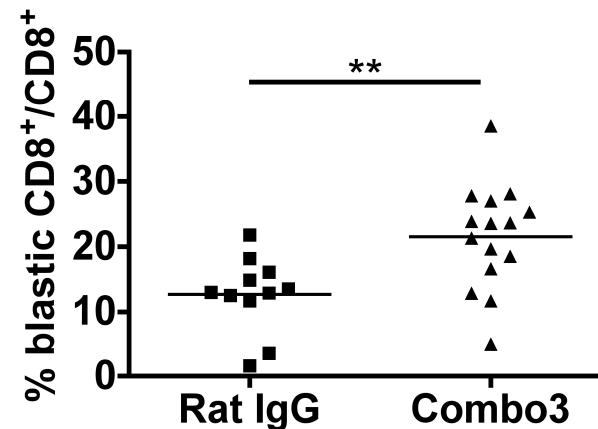
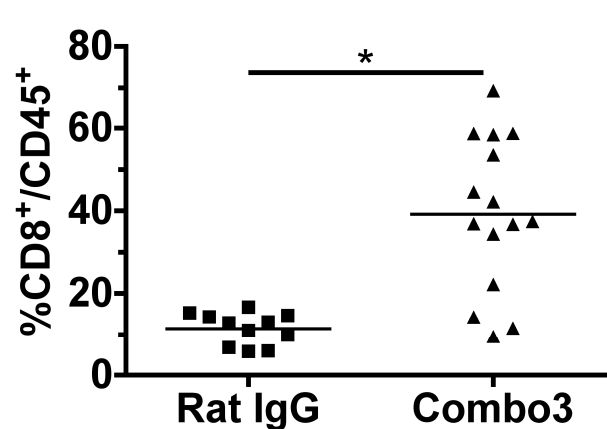


Combo3 efficacy is dependent on CD8⁺ T cells



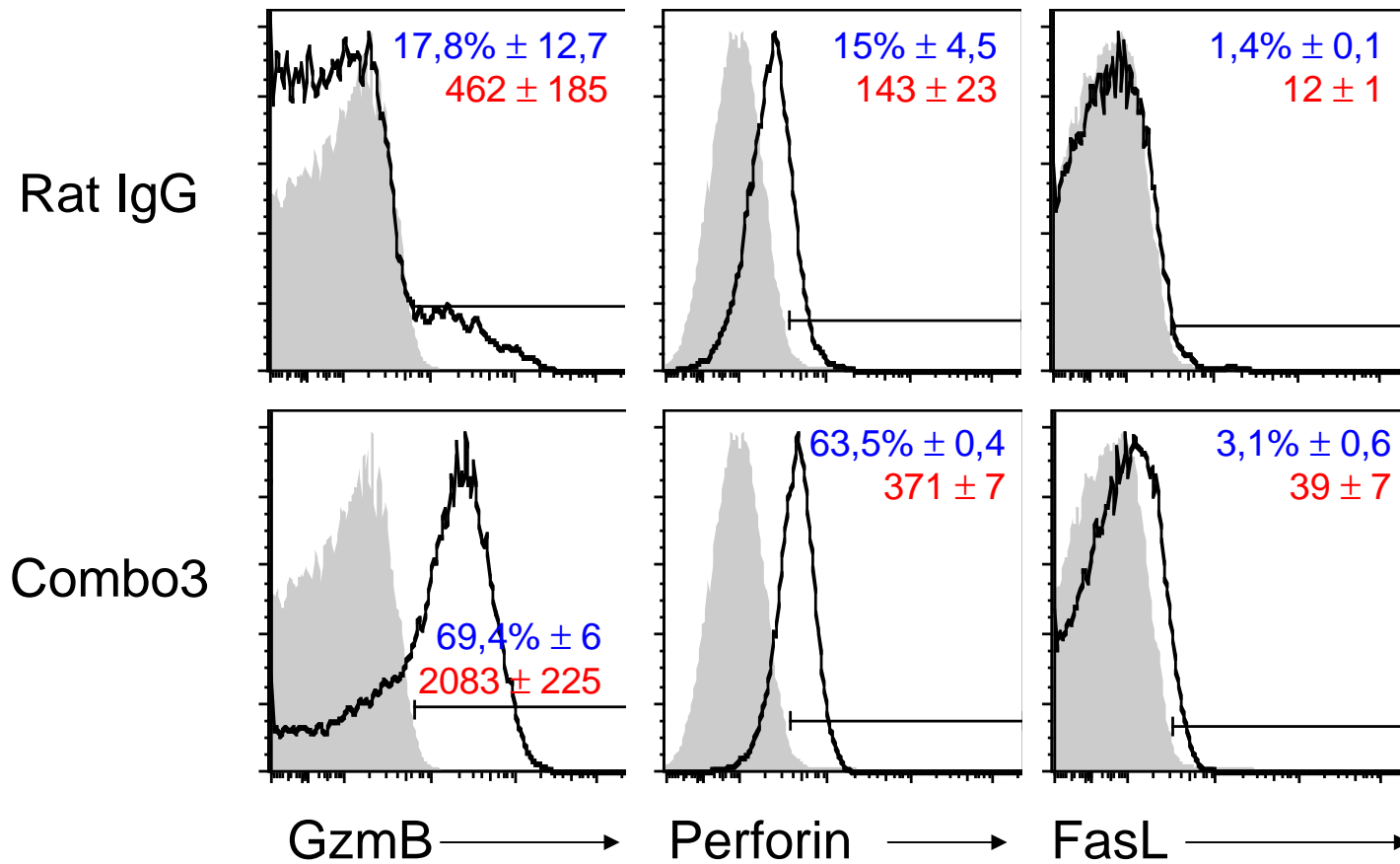


**CD8⁺
TILs**



Effector machinery is enhanced upon Combo3 Tx

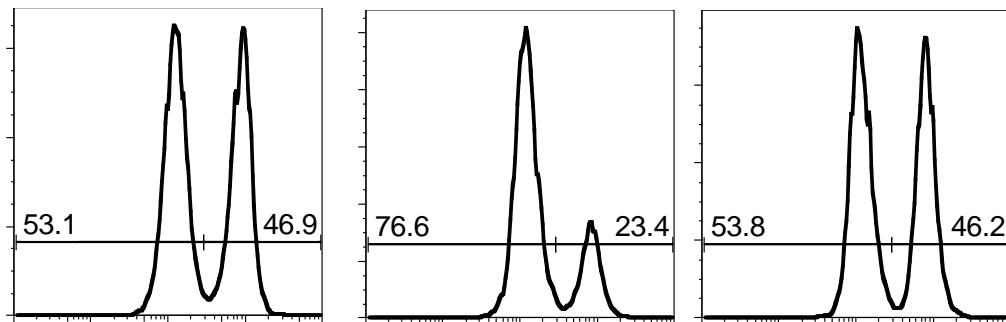
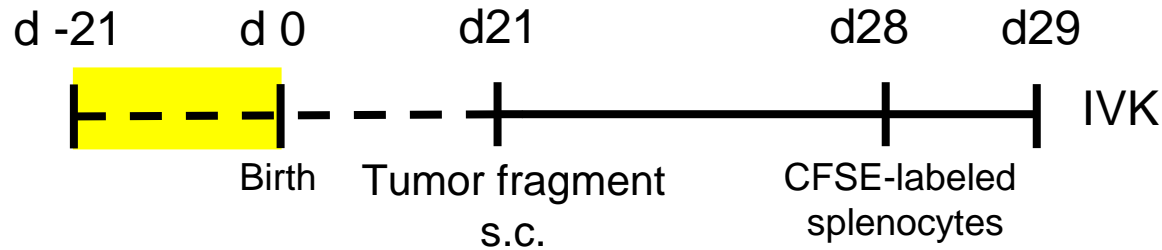
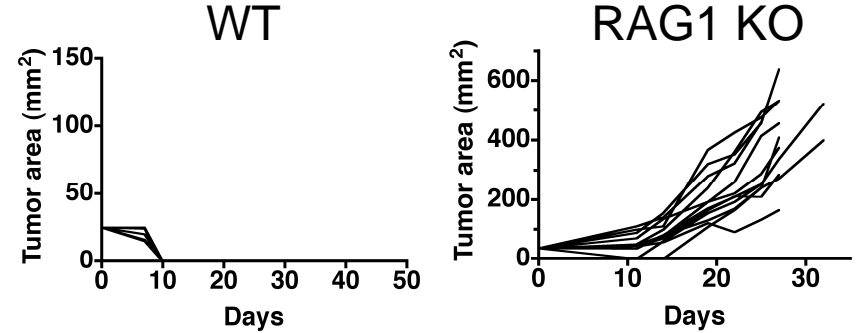
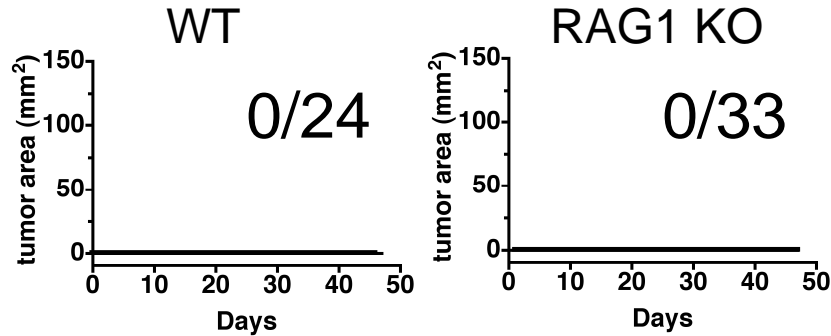
Gated on CD8 TILs



C-myc OVA tg+ mice are tolerized against SIINFEKL

JMJ cell line

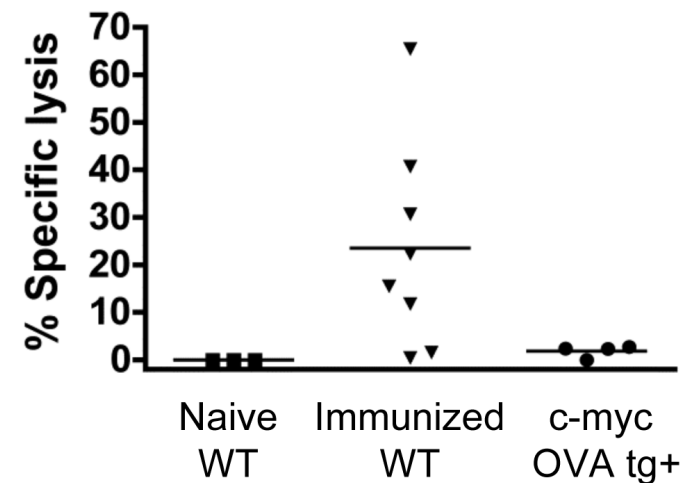
HCC tumor fragments



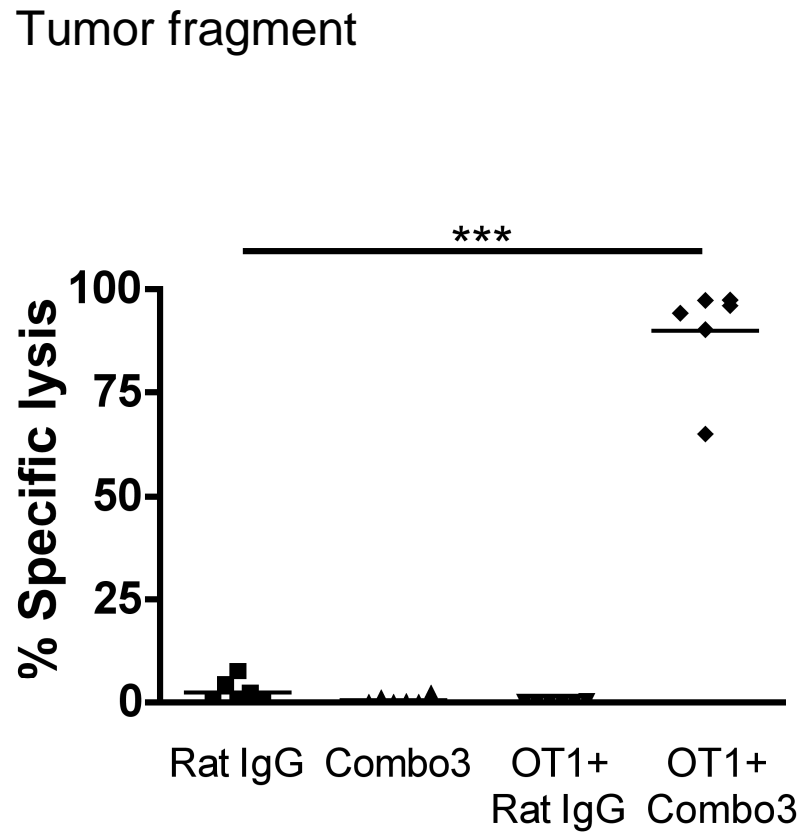
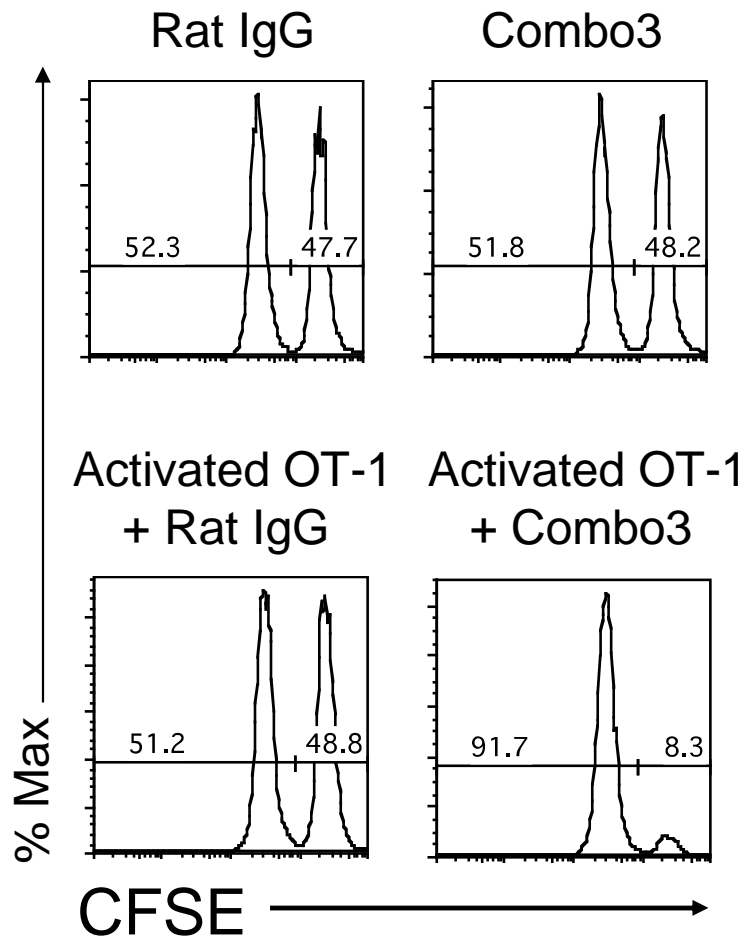
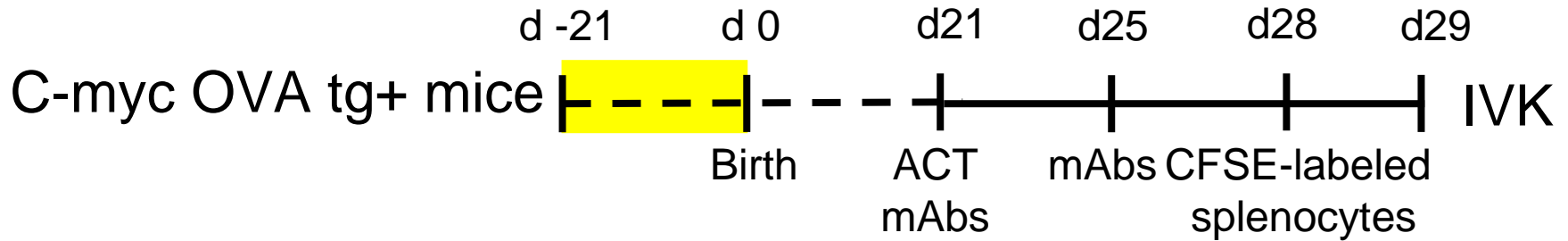
Naive WT

Immunized WT

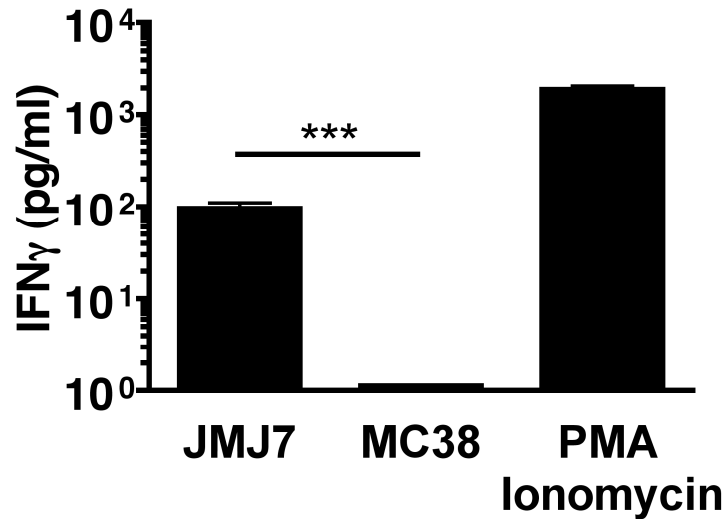
C-myc OVA tg+ mice



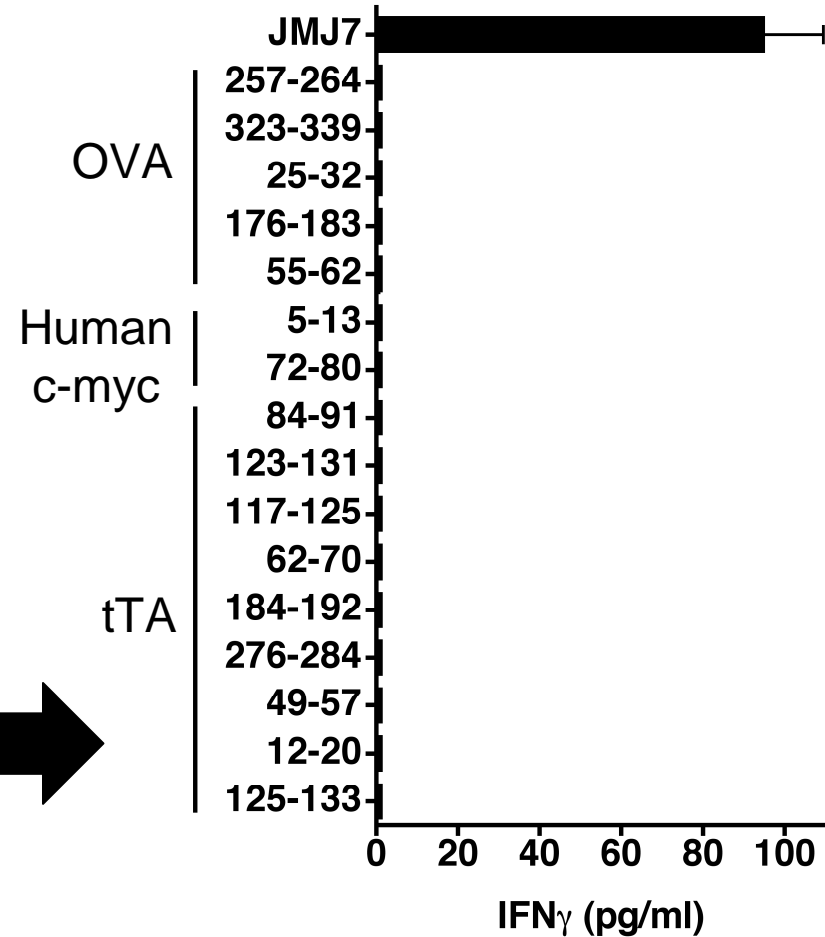
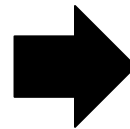
SIINFEKL does not drive Ag-specific T cell response



TILs recognize specific unknown peptides presented by JMJ cell line and secrete IFN γ



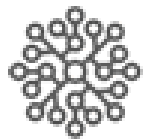
H-2K^b and D^b binding
feasible epitopes
(Immune Epitope Database)



CONCLUSIONS

- Combo3 prolongs the survival of c-myc OVA tg+ mice and synergizes with adoptive T cell therapy of activated OT-1 and OT-2 T cells, in a CD8⁺ T lymphocyte dependent fashion
- Combo3 increases CD3⁺ lymphocyte infiltrates in tumor nodules, but not healthy liver tissue
- CD8⁺ TILs are more blastic and show higher expression of Combo3 targets, allowing the readministration of Combo3
- Combo3 prevents the tolerization of transferred activated OT-1 T cells against SIINFEKL
- TILs from Combo3 treated mice recognize unknown epitopes on HCC-derived cell lines, but not SIINFEKL

AKNOWLEDGEMENTS



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José Medina
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Red Temática de
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"Una manera de hacer Europa"

Thanks for your attention
Questions?

LOOKING FOR POST-DOC!!

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