

Potent anti-tumor therapies based on OX40 engagement

Daniel Hirschhorn-Cymerman, PhD

Wolchok and Merghoub Laboratory

Ludwig Collaborative Laboratory
Memorial Sloan Kettering-Cancer Center

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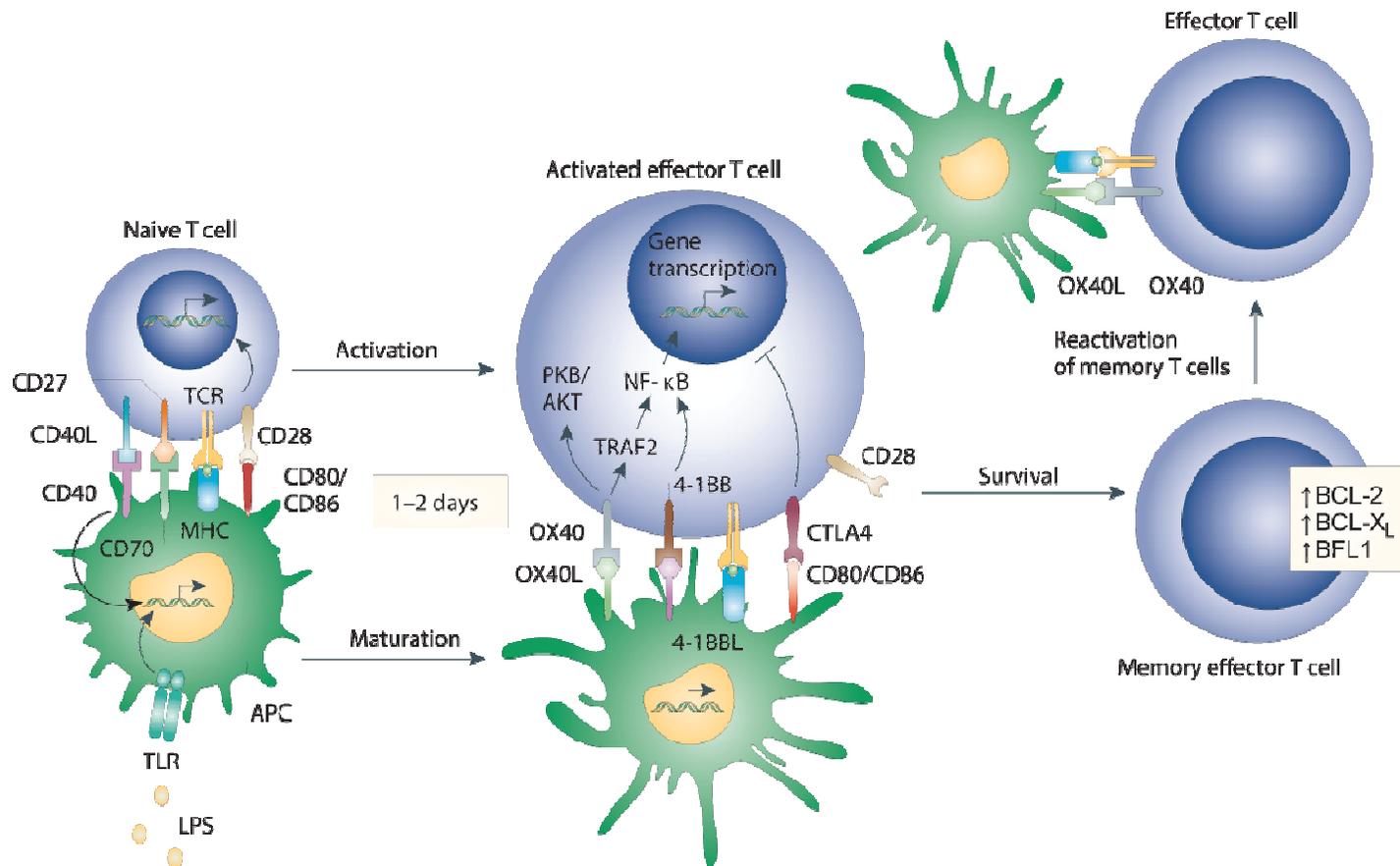
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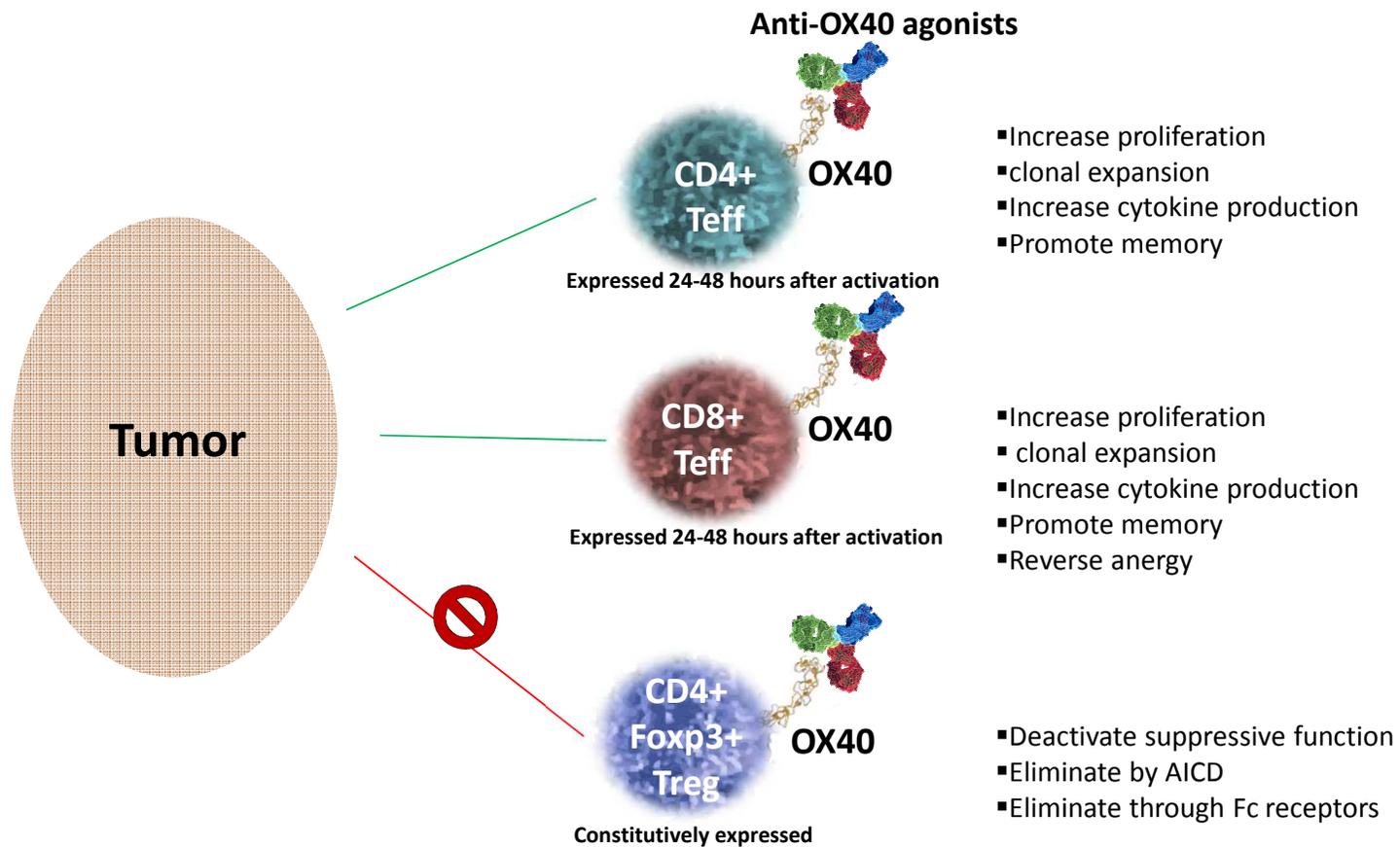
No relationship to disclose

Biological role of OX40-OX40L interaction in T-Cell function



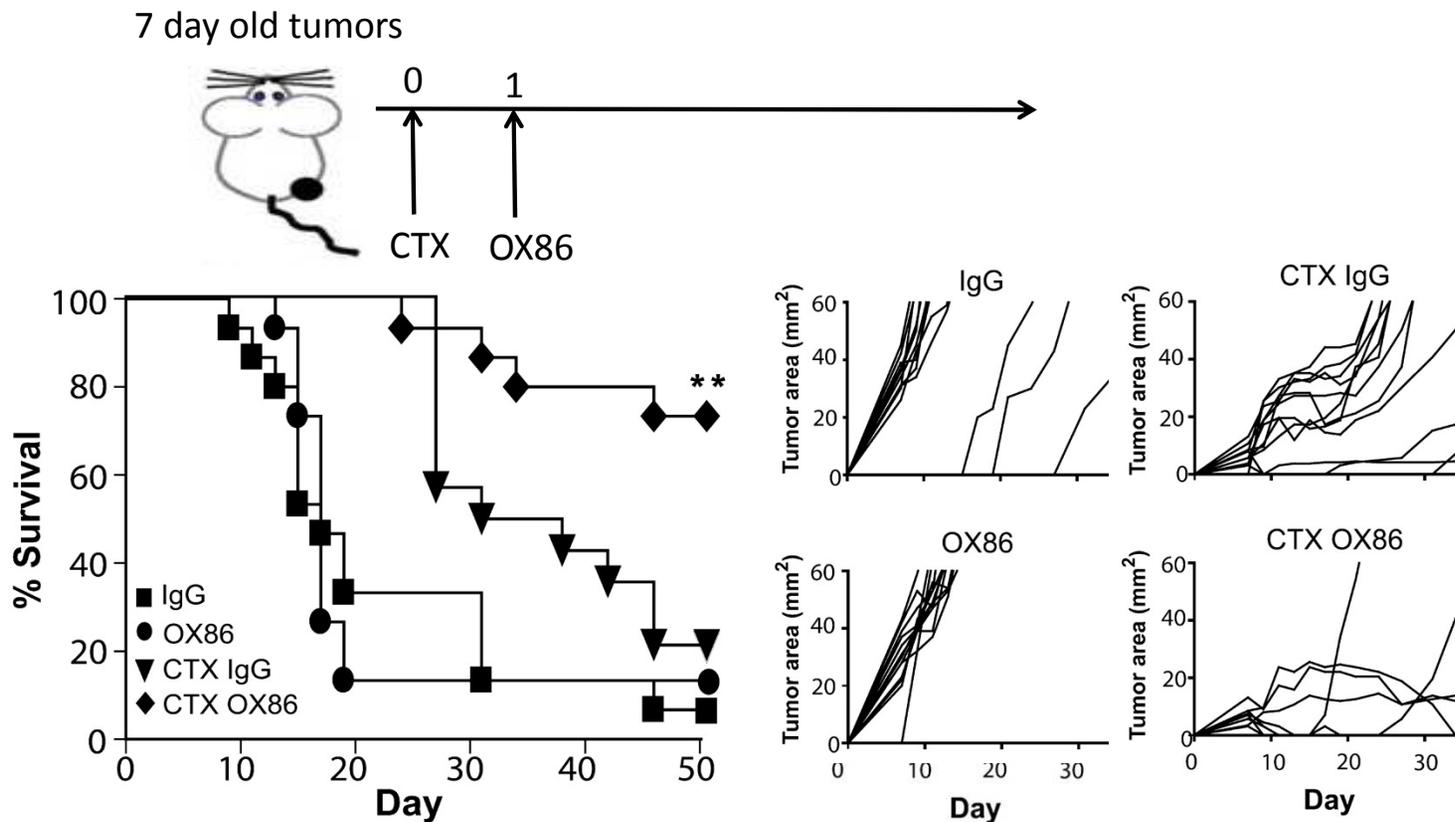
Nature Reviews Immunology 4, 420-431 (June 2004)

OX40 engagement as an effective tumor immunotherapy



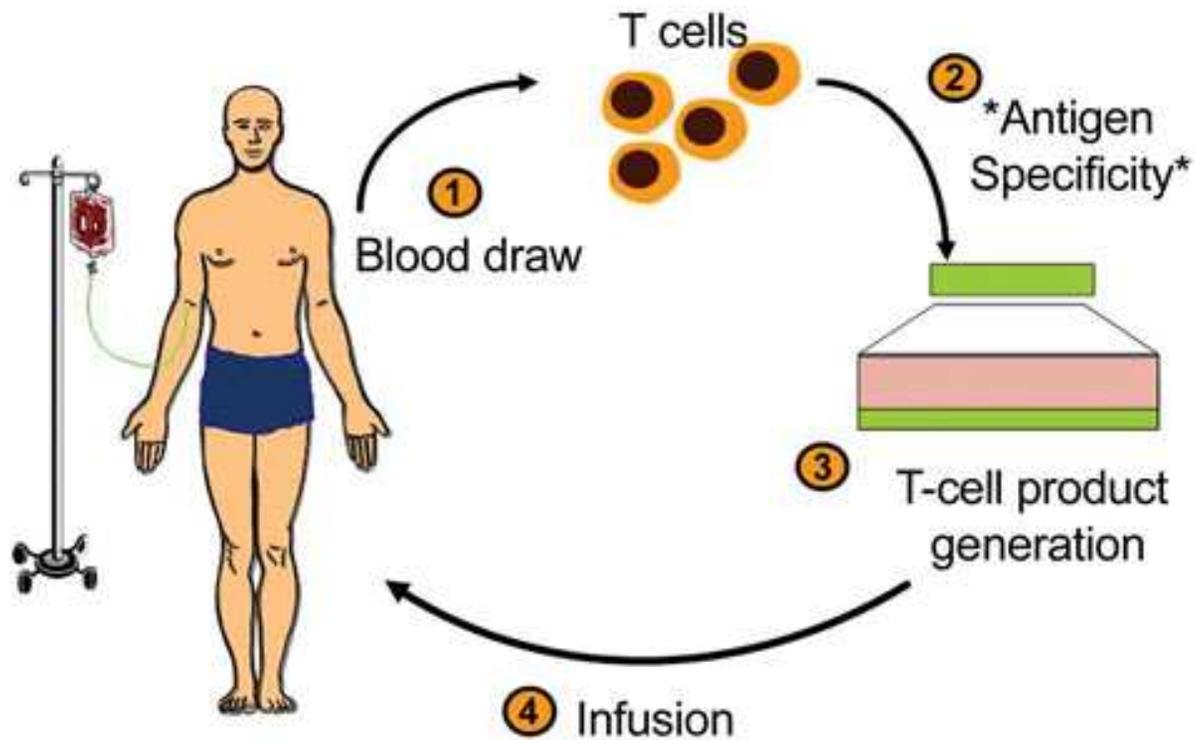
OX40 engagement as a monotherapy ineffective treating established poorly immunogenic tumors such as B16 melanoma

Combining chemotherapy (cyclophosphamide) and OX40 engagement regresses established B16 tumors



Problem: CTX and OX86 can cure small tumors only

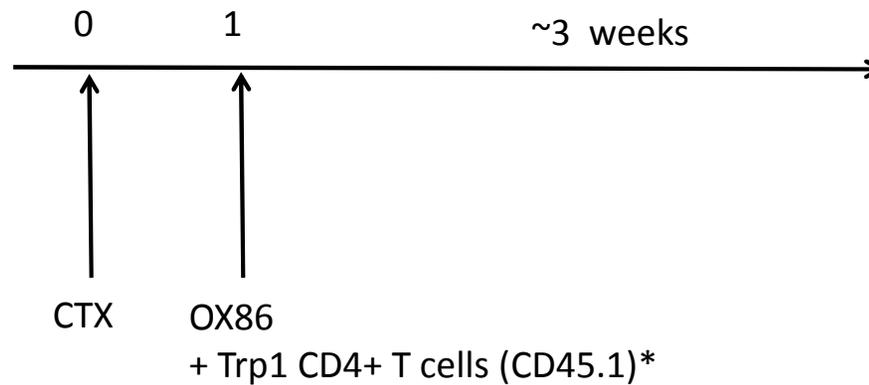
Adoptive T cell transfer of CD4+ T cells as a viable anti-tumor therapy



Adapted from Ronald Levy, MD

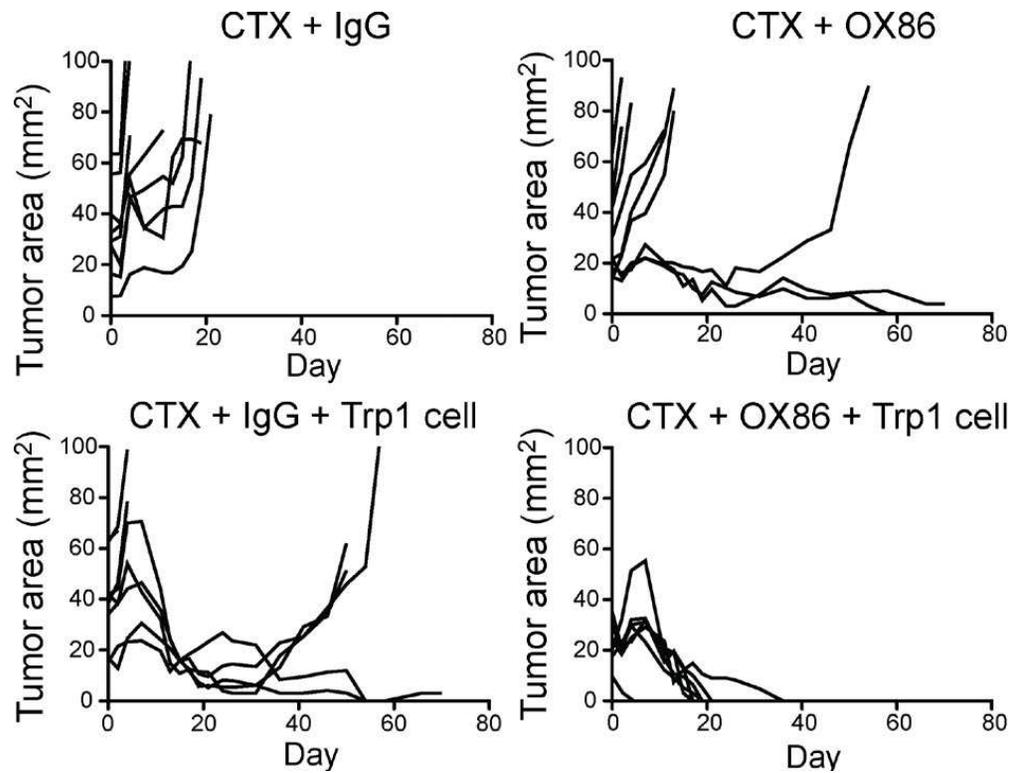
Melanoma-specific CD4+ T cells significantly enhances the potency of CTX + OX86 combination therapy

21 day old tumor

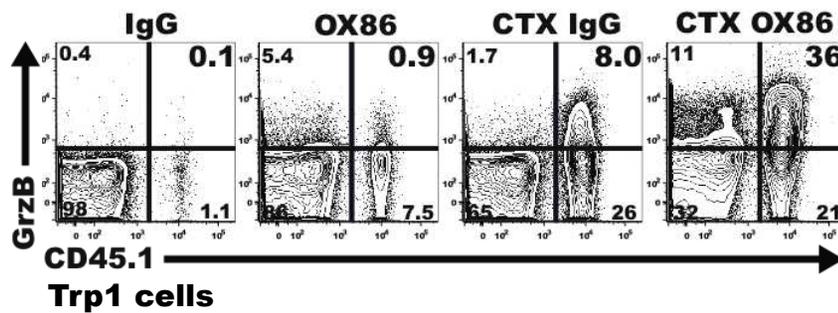


*Trp1 CD4+ T cells are purified from a TCR transgenic mouse (Muranski, Blood 2008)

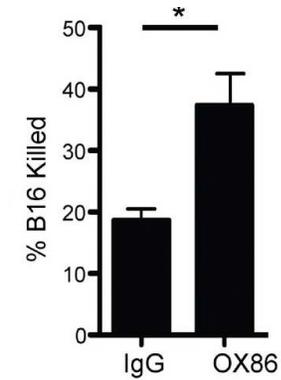
Trp1 cells synergize with OX86 and CTX to promote very large tumor regression



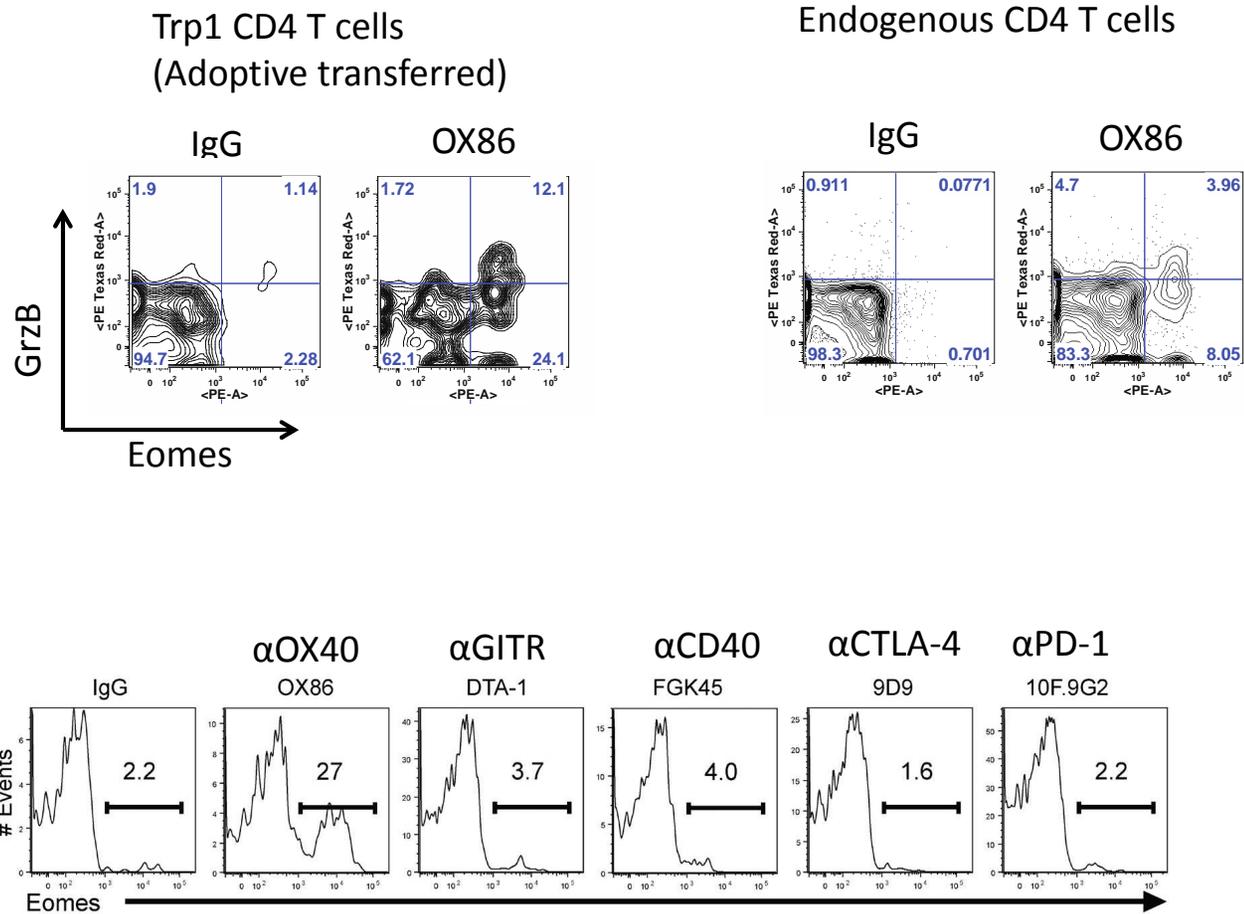
CTX and OX86 upregulate cytolytic granules on CD4+ T cells promoting tumoricidal function



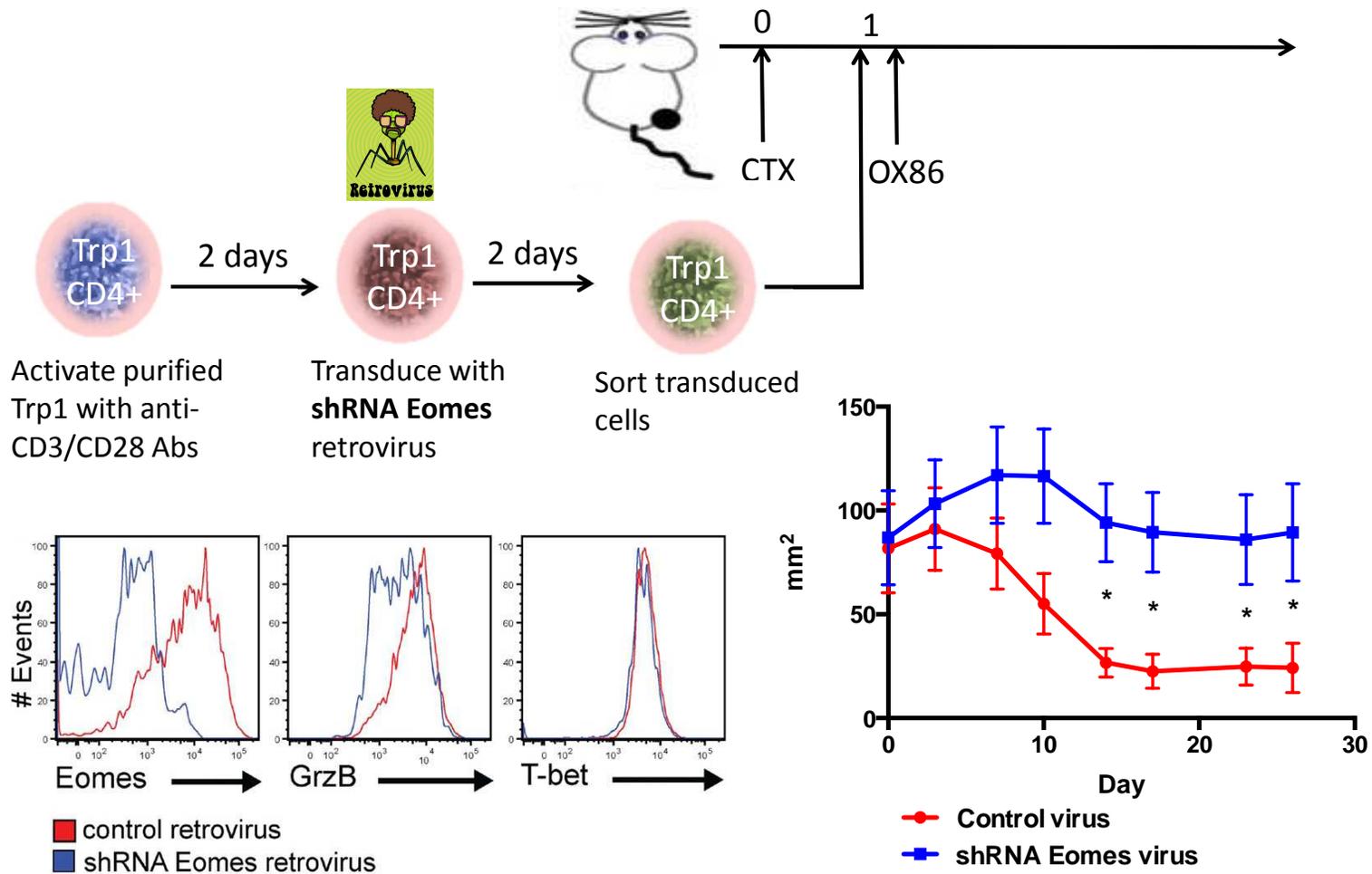
Sorted Trp1 cells from spleen of treated mice



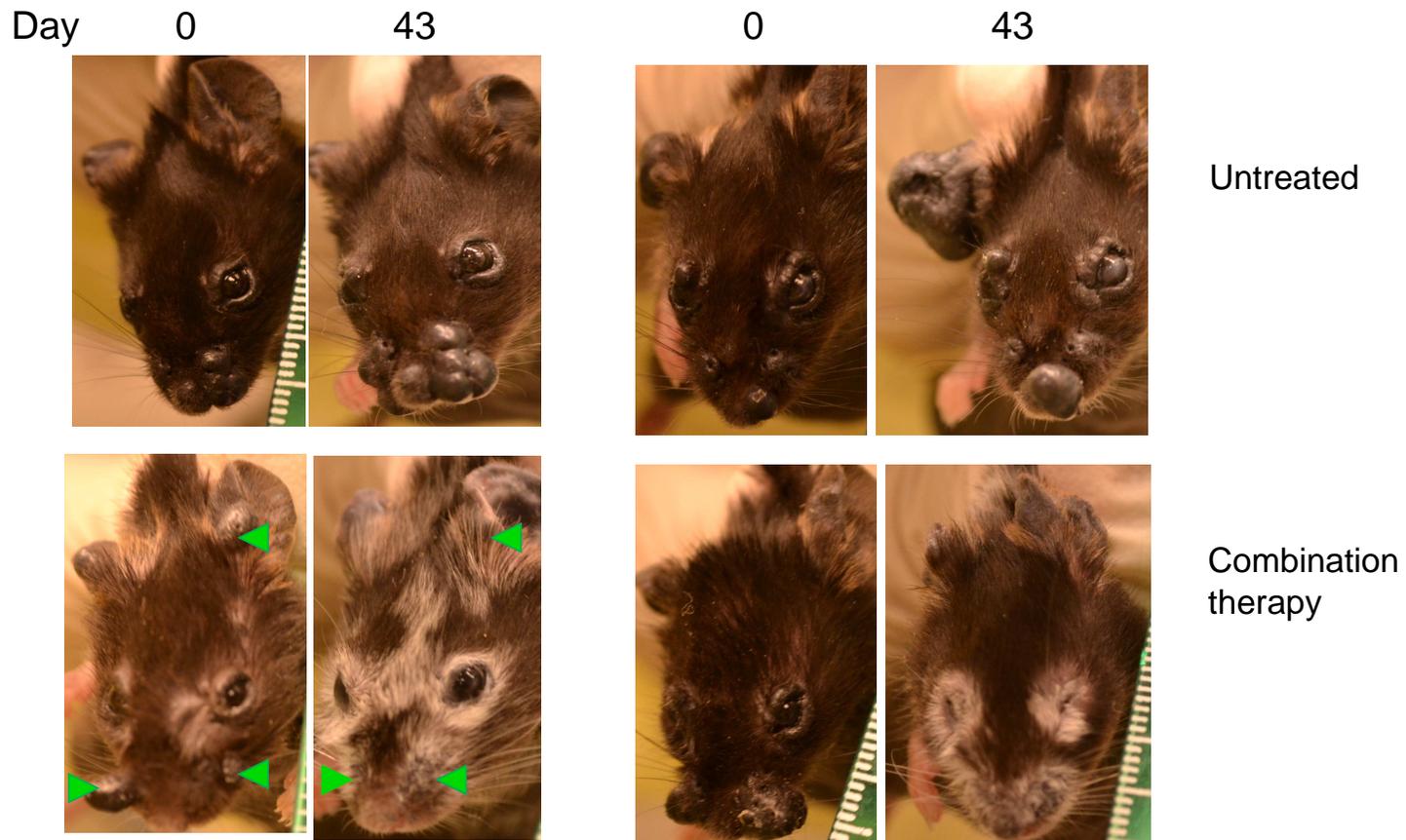
OX40 engagement promote cytotoxicity of CD4+ T cells phenotype by upregulating Eomes



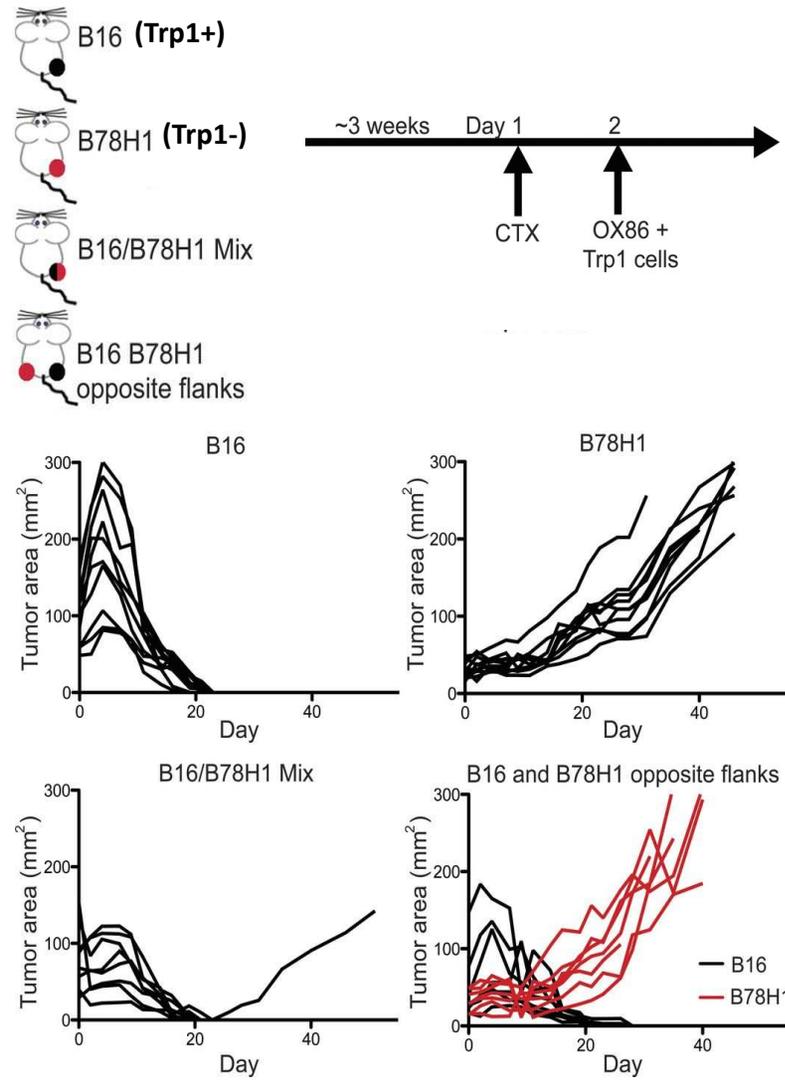
Eomes expression is partially necessary for the efficacy of the triple combination therapy



Triple combination therapy eradicate large established tumors: Spontaneous melanoma model (TG3)



Triple combination therapy promotes bystander tumour killing of antigen loss variants



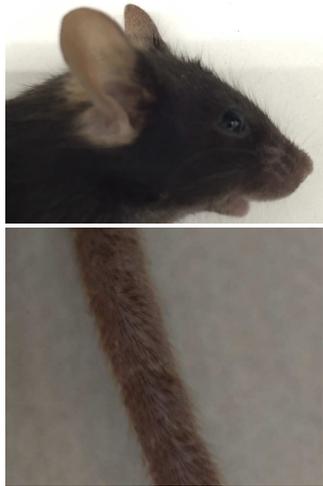
B78H1 is a B16 variant that does NOT express Trp1

Unusual immune-related adverse events of the triple combination therapy

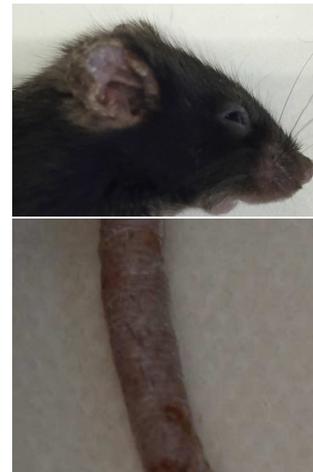


Autoimmune depigmentation is typical of anti-melanoma immune therapies

CTX + IgG + Trp1 cells



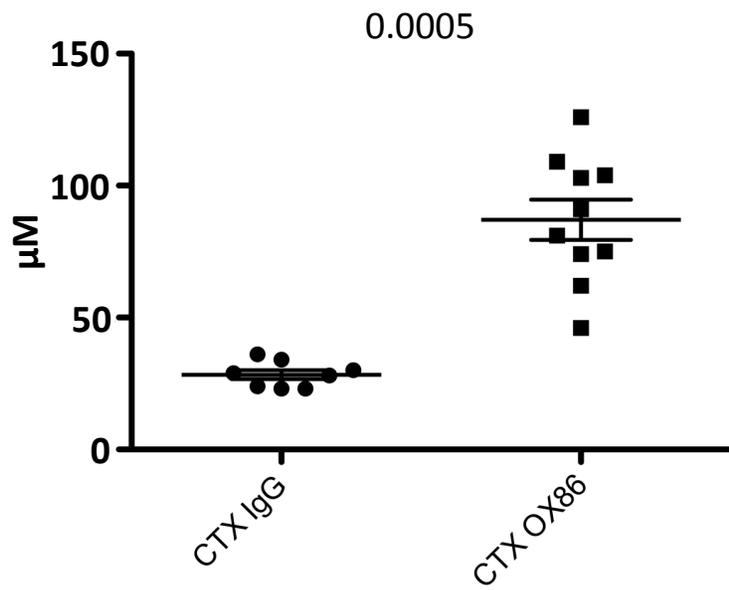
CTX + OX86 + Trp1 cells



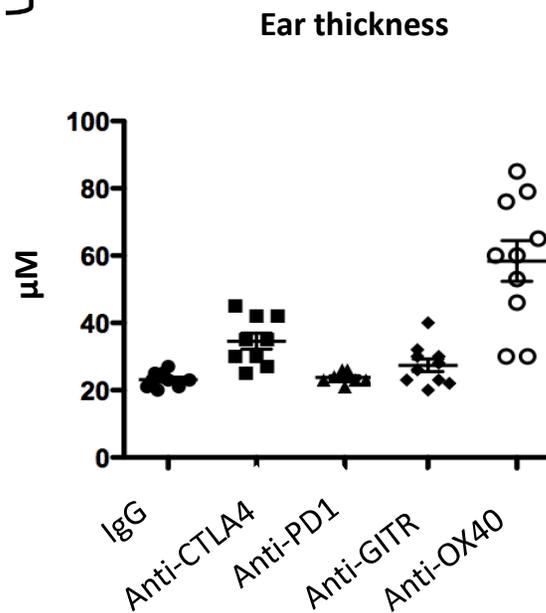
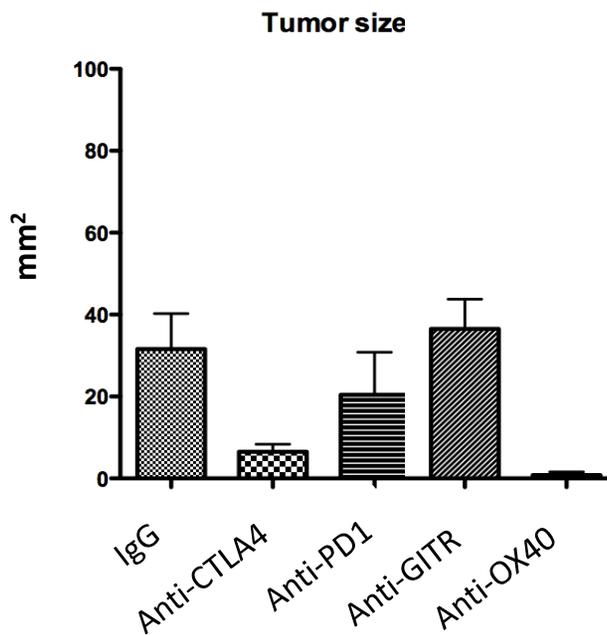
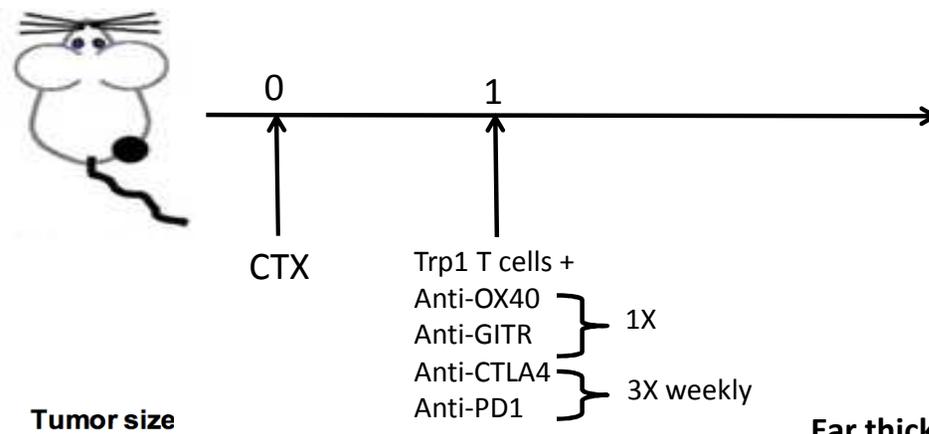
Swelling and destruction of tissues infiltrated with melanocytes such as the ears, tail, and snout (non hairy skin) ~ **3 weeks** after treatment

Thymic involution

Ear thickness as a quantifiable model for immune-related adverse events



Preferential induction of irAE by anti-OX40 in combination therapy

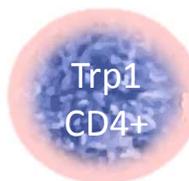


Trp1 from ear pinnae secrete Th1 and Th2 but not Th17 cytokines upon restimulation

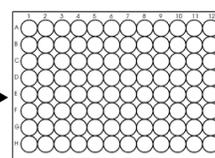
Ear of treated mice



Isolate Trp1 cells

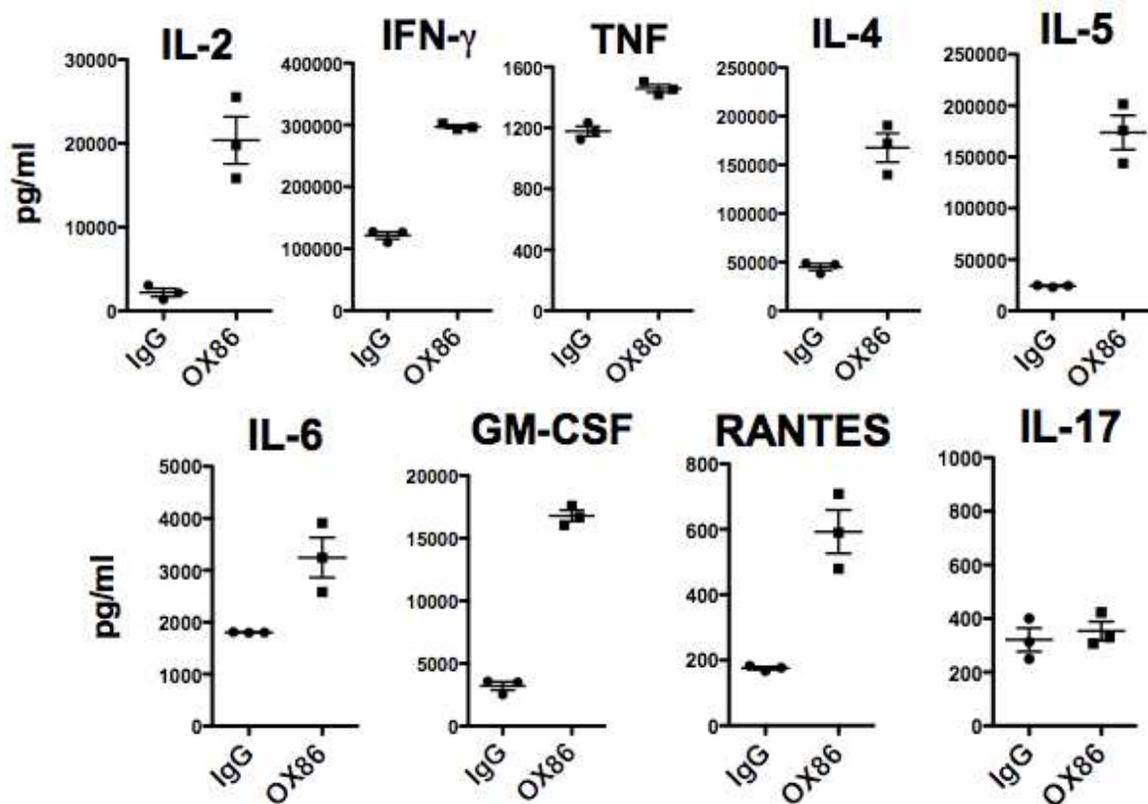


Incubate with APCs + peptide

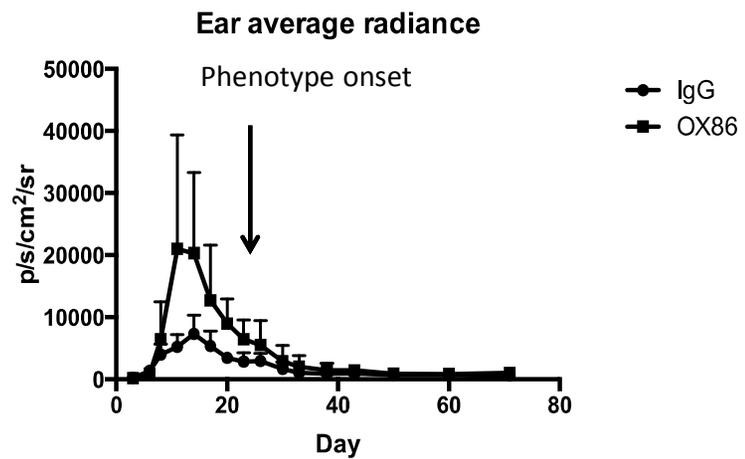


4 days

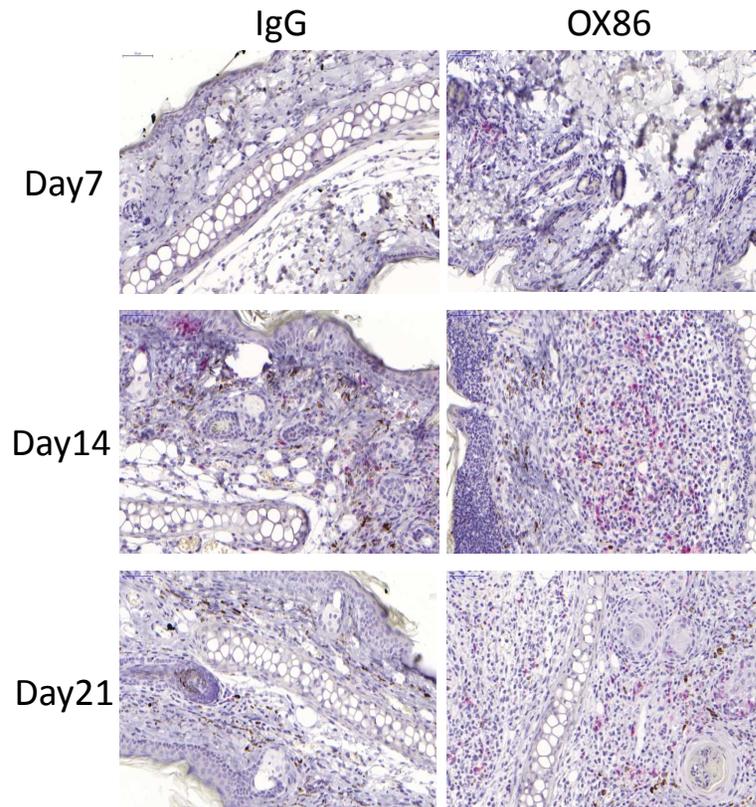
Measure cytokines



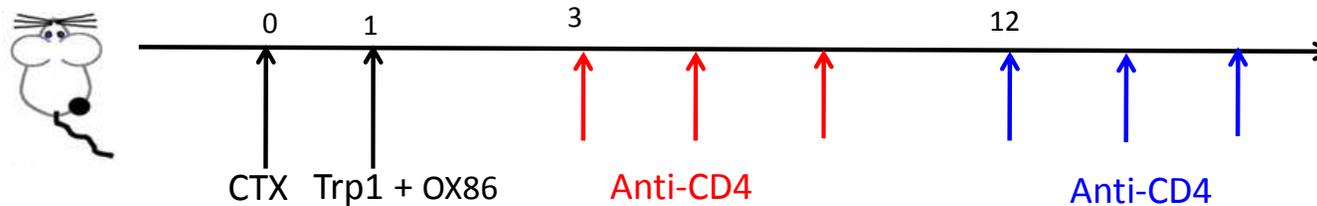
Kinetics of Trp1 cells infiltration tested by Trp1-Luciferase in vivo imaging does not correlate with irEA onset



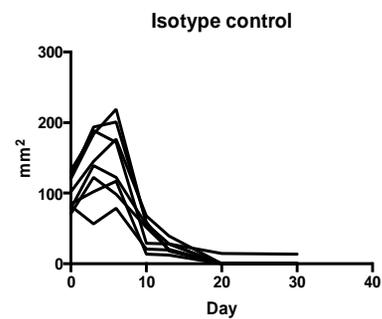
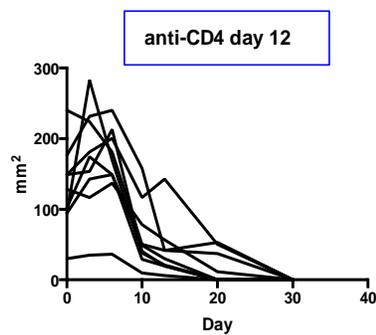
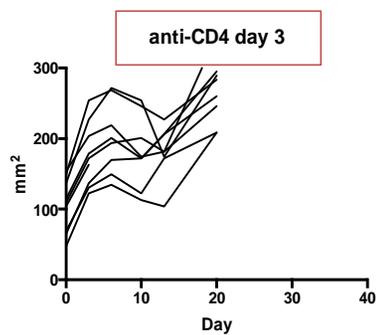
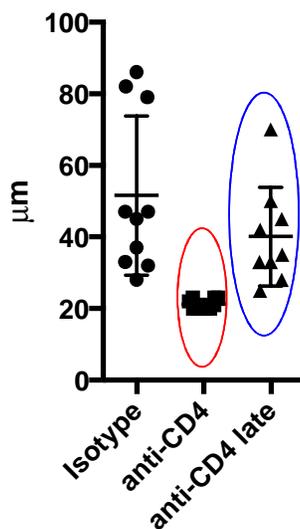
IHC of CD45.1 (Trp1) ear pinnae infiltration



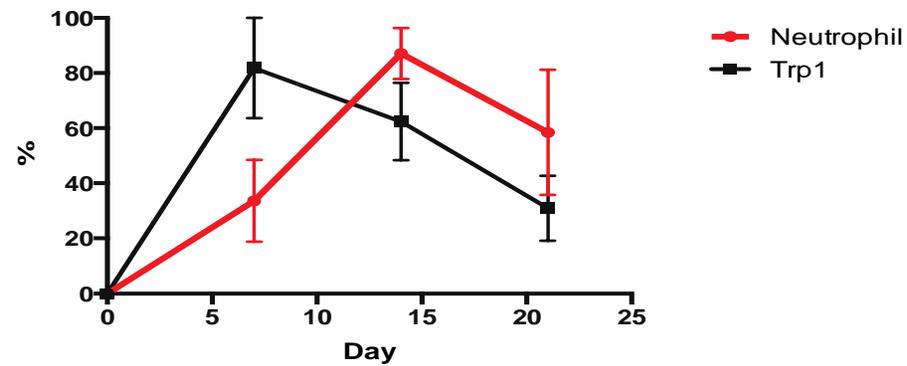
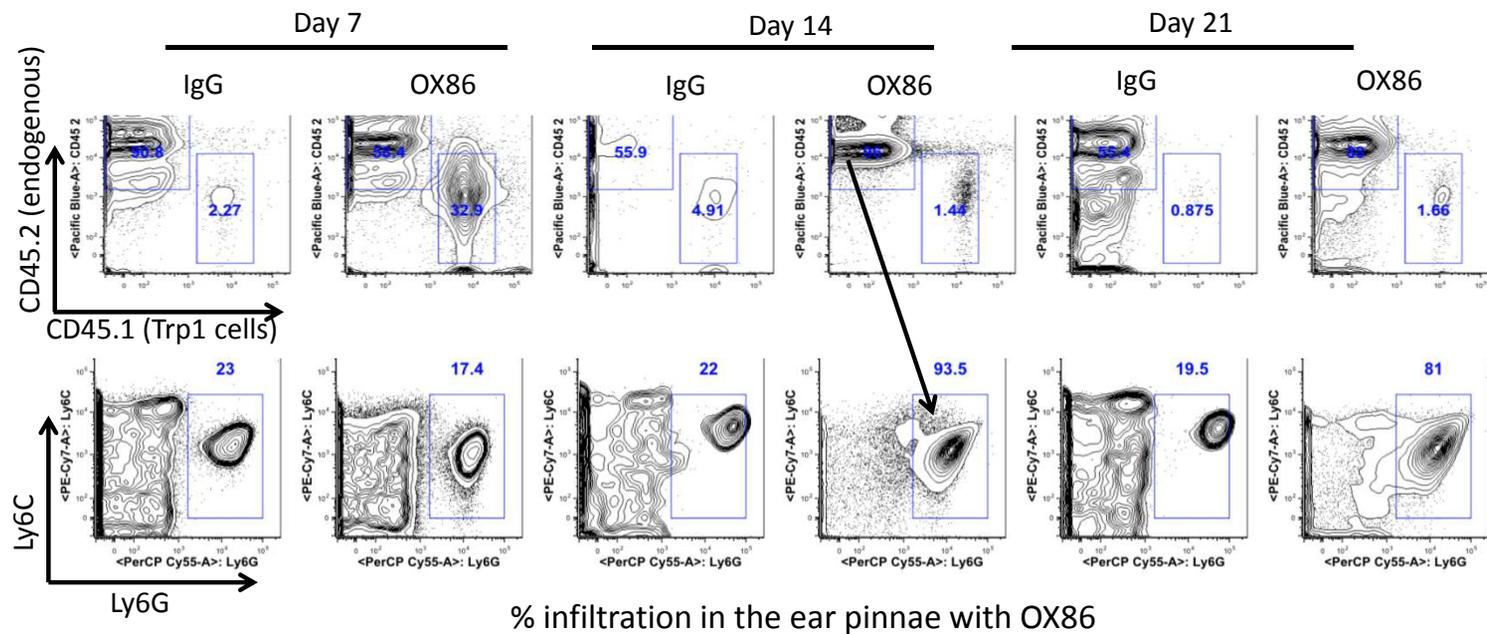
Late depletion of Trp1 cells does not affect irAE or anti-tumor immunity



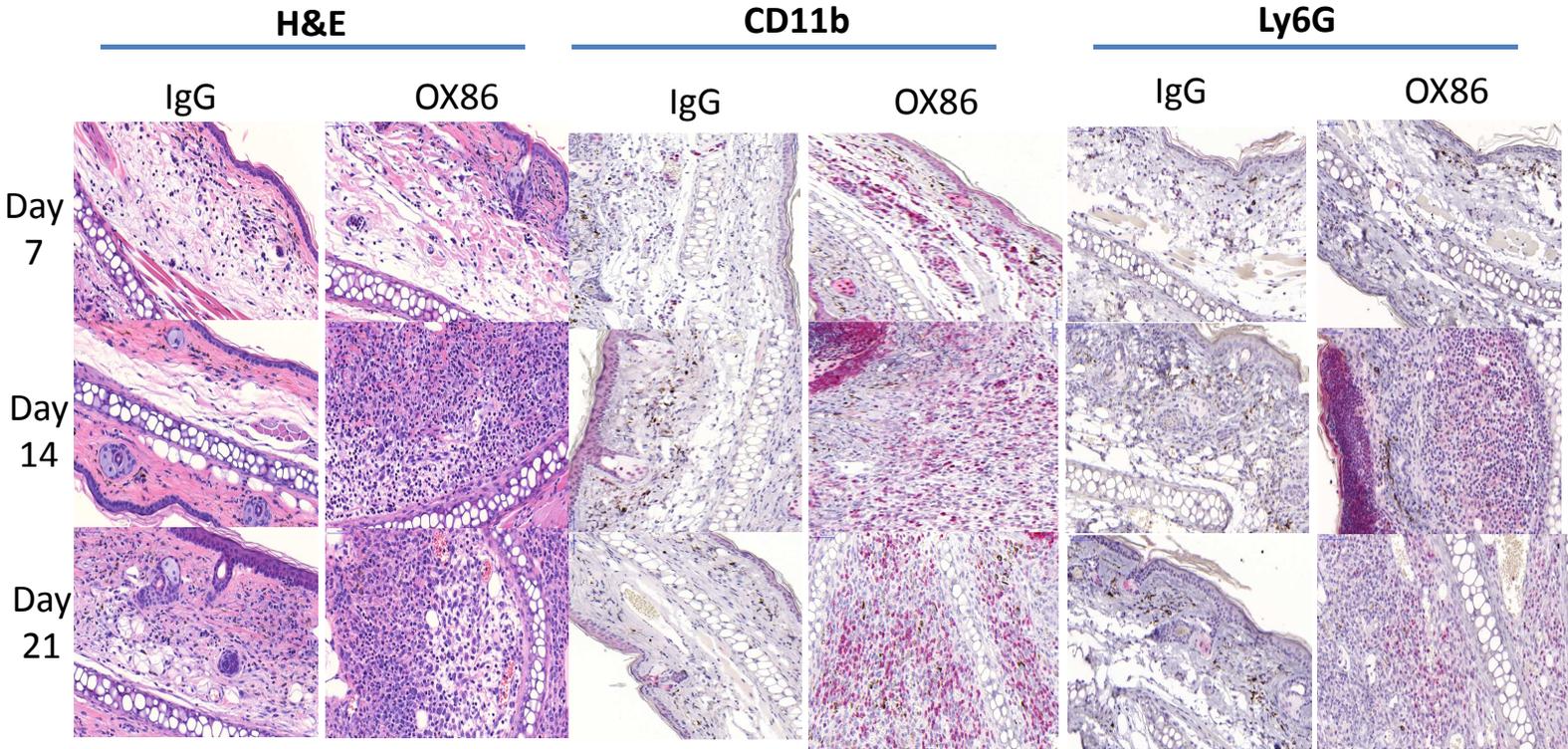
Ear thickness



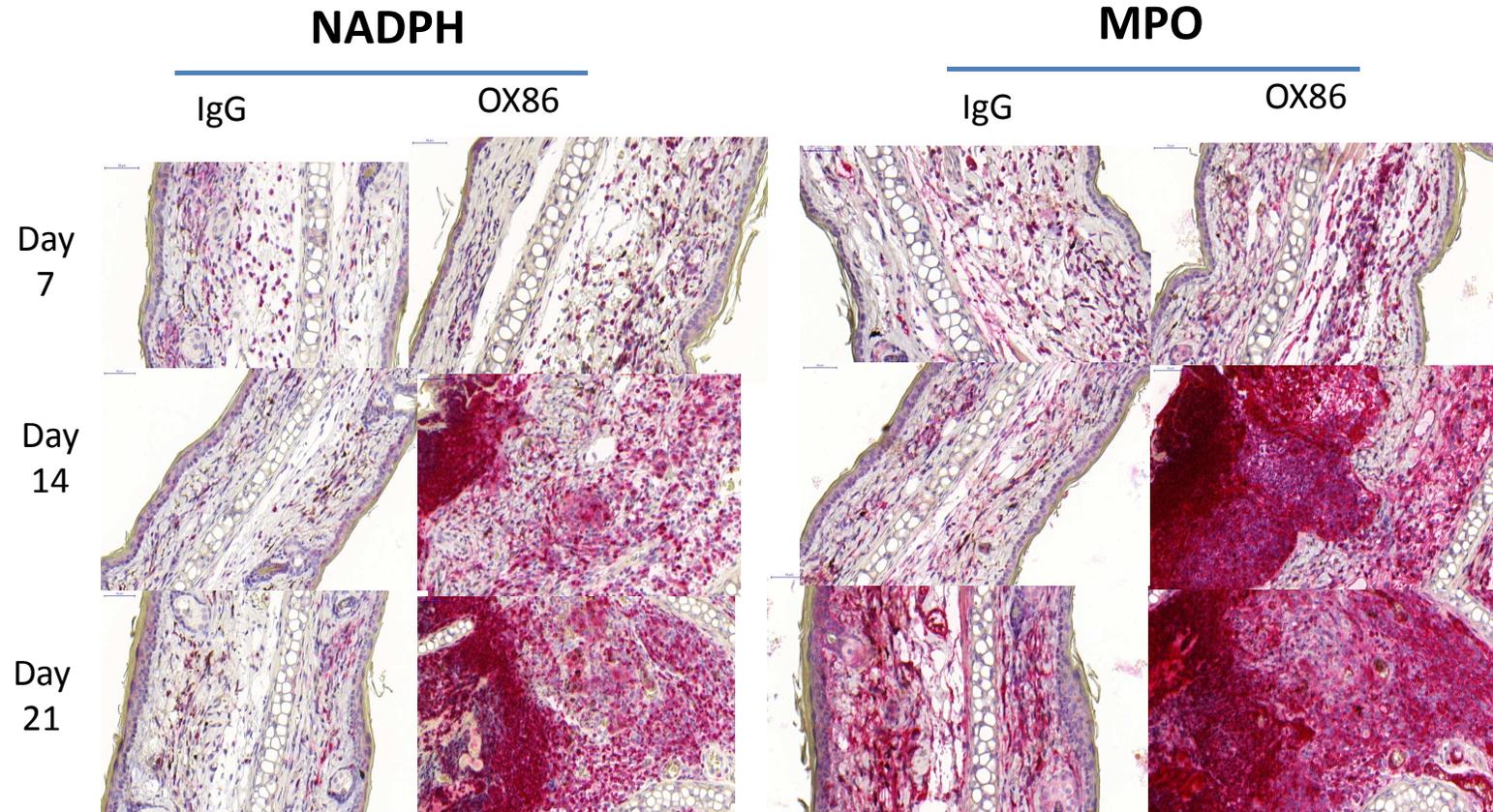
Progressive infiltration of neutrophils in the ear pinnae proceeds Trp1 decline



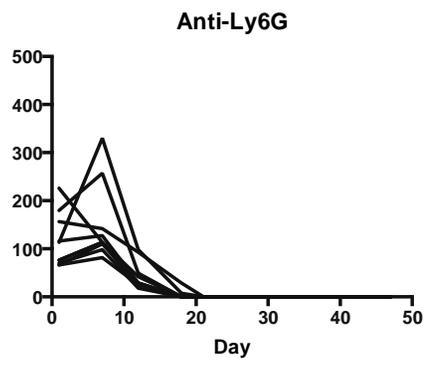
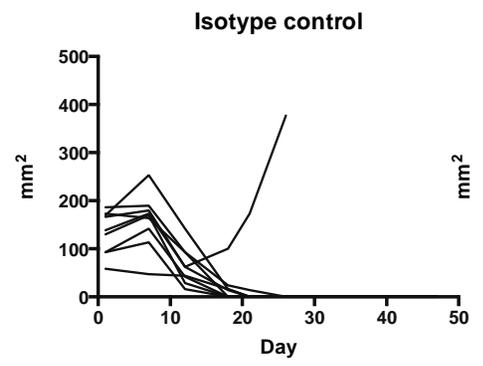
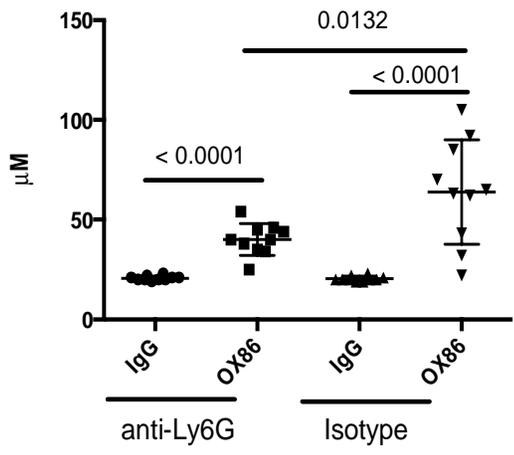
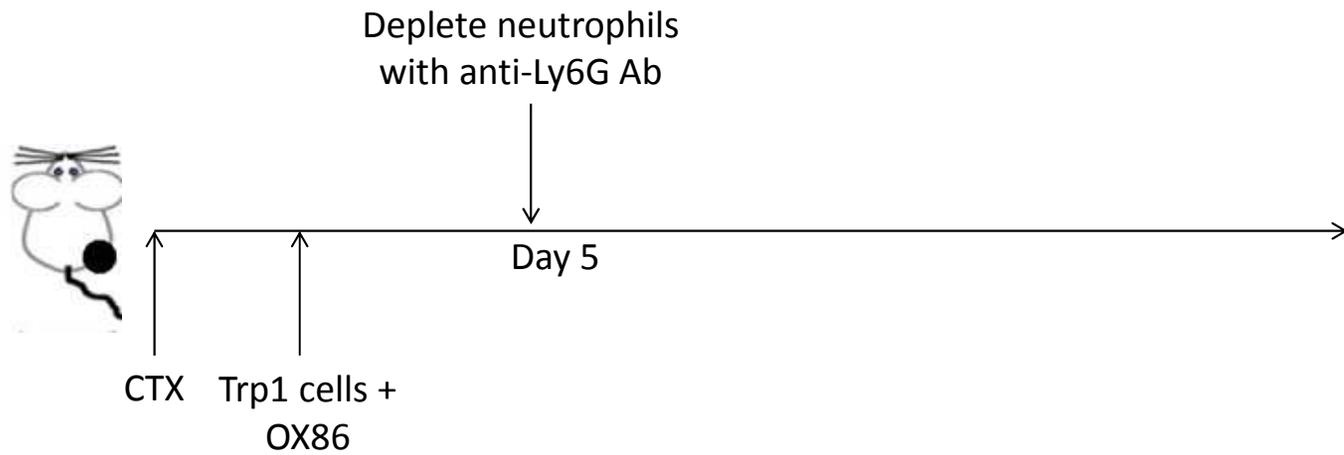
Innate cells (neutrophil) progressively infiltrate the ear pinnae



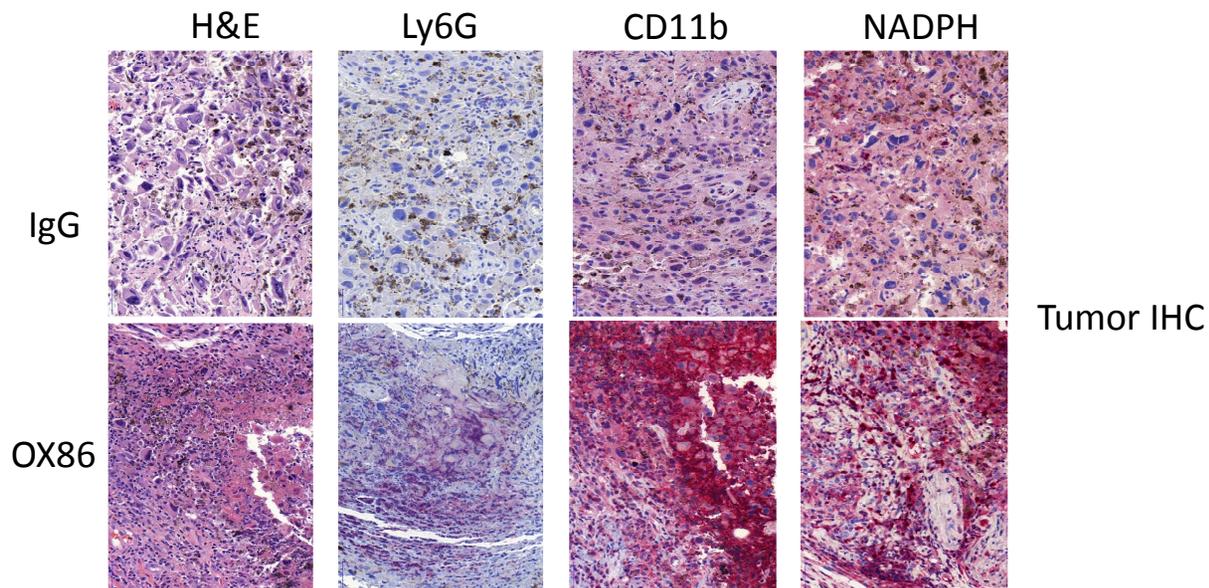
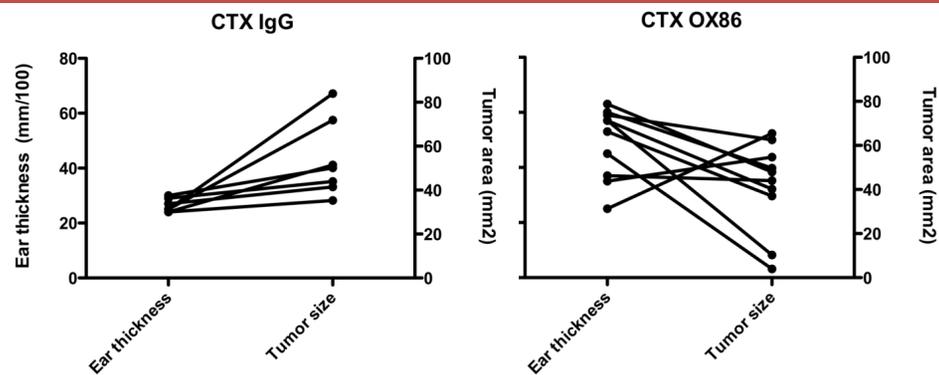
Progressive neutrophil degranulation in the ear pinnae



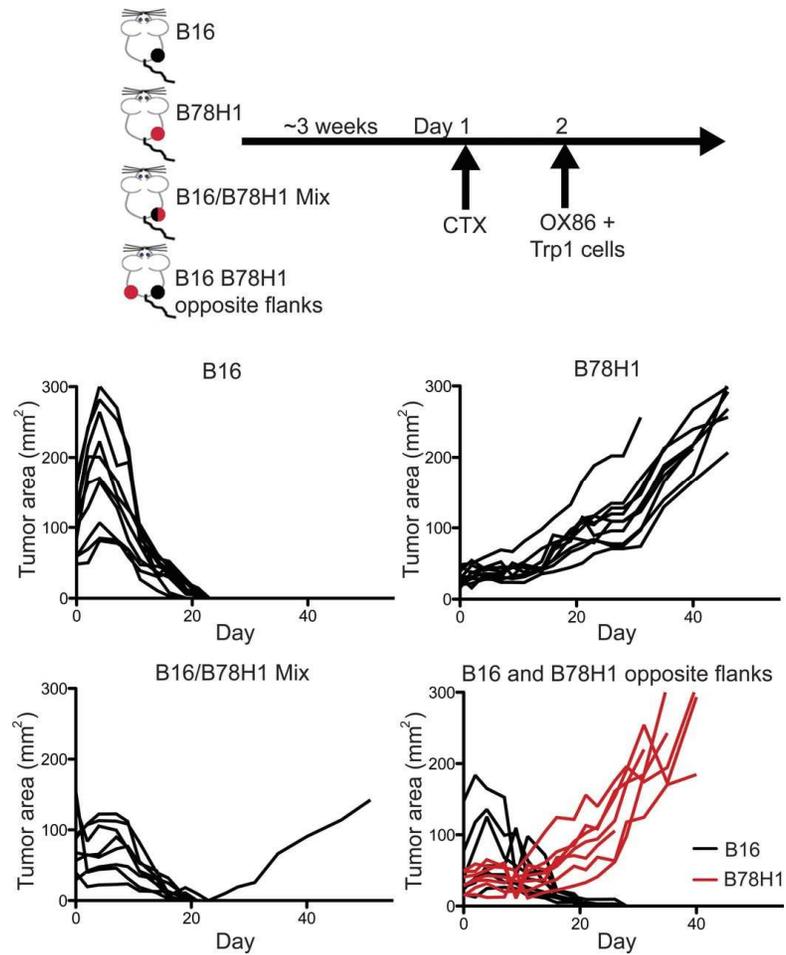
Are neutrophils necessary for Immune related adverse events?



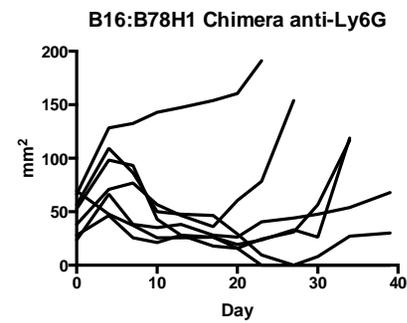
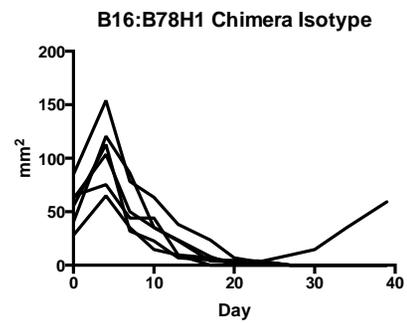
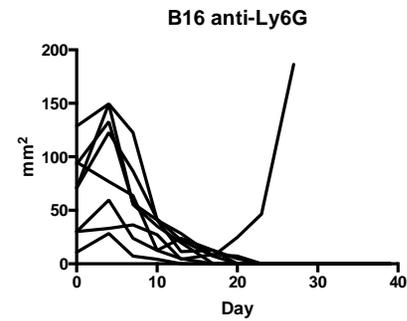
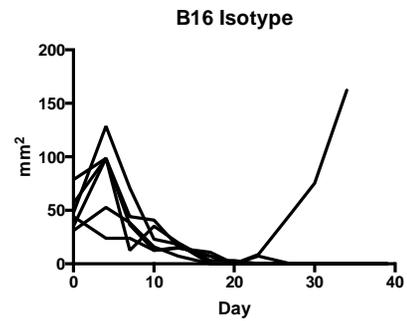
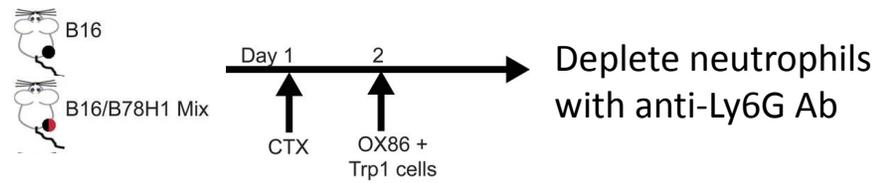
Direct correlation between ear phenotype and anti-tumor effects revealed similar mechanism



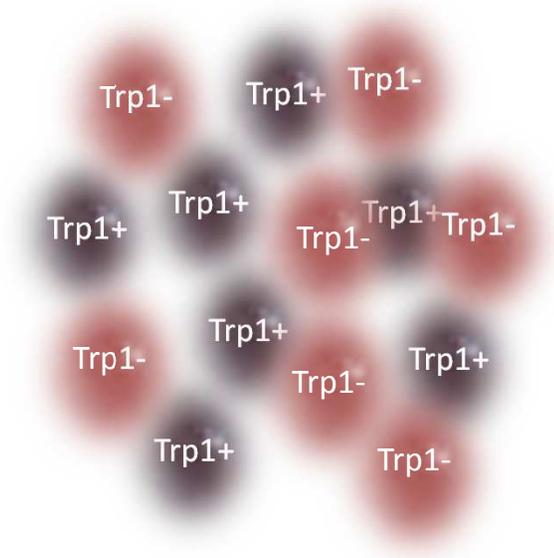
Antigen loss variant chimeric tumors is a more stringent model



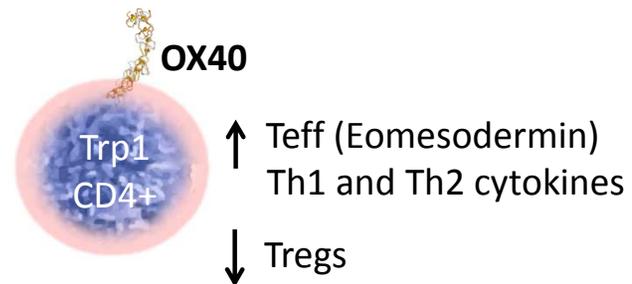
Neutrophils depletion prevents elimination of antigen loss variant chimeric tumors



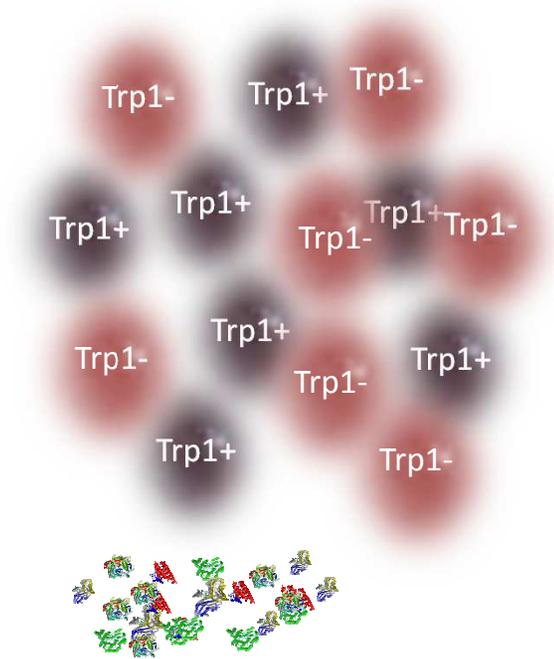
Tumor



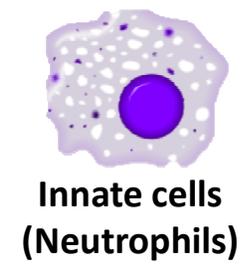
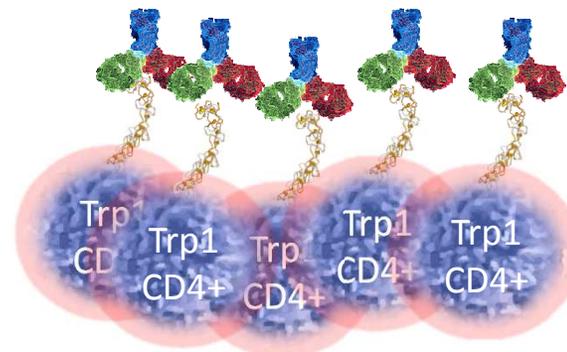
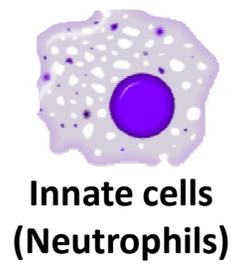
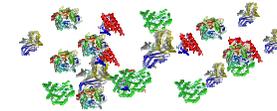
Tissue with melanocytes



Tumor



Tissue with melanocytes



Acknowledgements

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Yasin Senbabaoglu

E-mail: hirschhd@mskcc.org

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