

Chimeric Endocrine Receptor-Expressing T Cells Influenced by the Microbiota Delay Ovarian Cancer Progression by Boosting Pre-existing Anti-tumor Immunity



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Presenter Disclosure Information

Jose R Conejo-Garcia

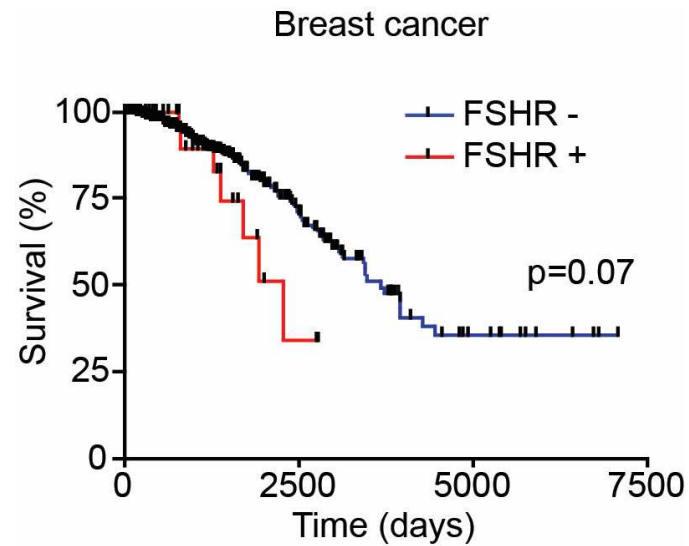
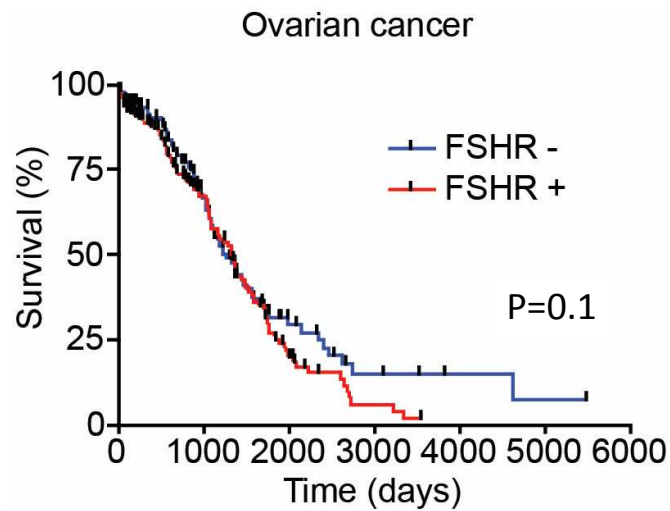
The following relationships exist related to this presentation:

CELDARA MEDICAL, SBIR application and research collaboration

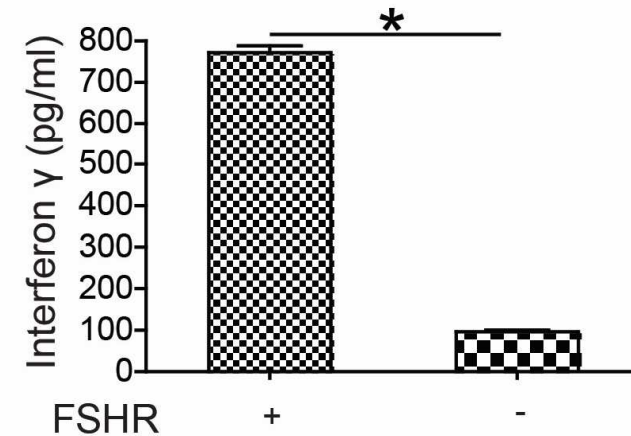
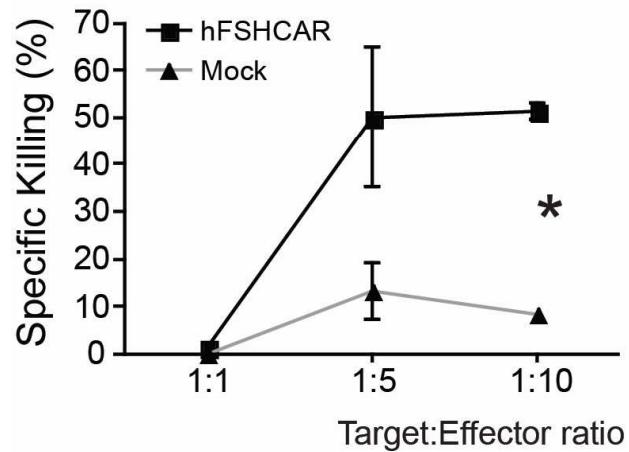
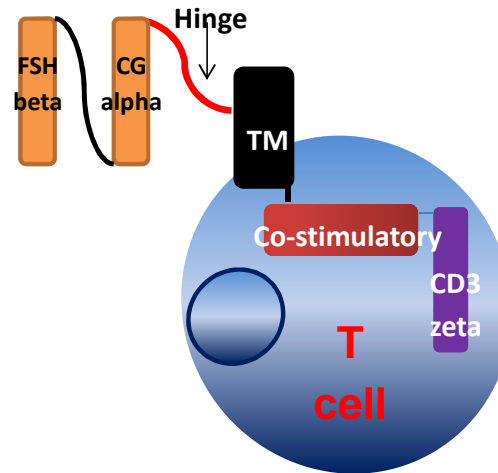
Aggressive epithelial ovarian tumors express FSHR

56% of advanced human
serous ovarian cancers

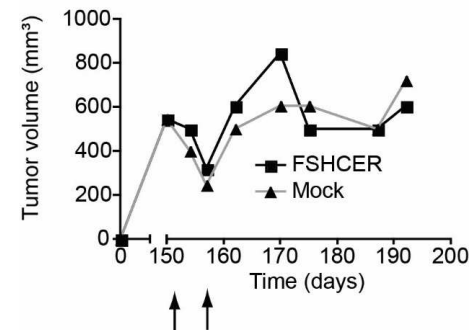
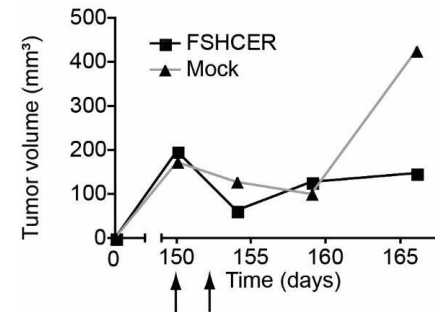
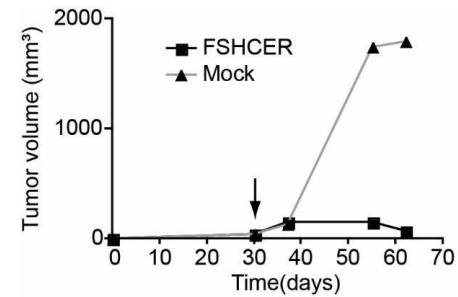
4% of breast cancers



Human FSHR+ tumors elicit effector responses on human FSH-targeted primary T cells

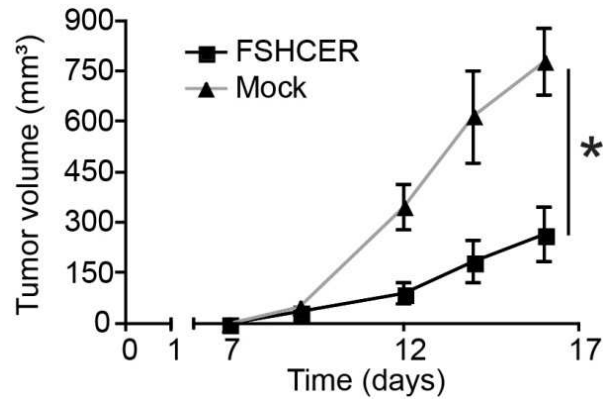


FSH-targeted CAR T cells abrogate the growth of established patient-derived ovarian carcinomas

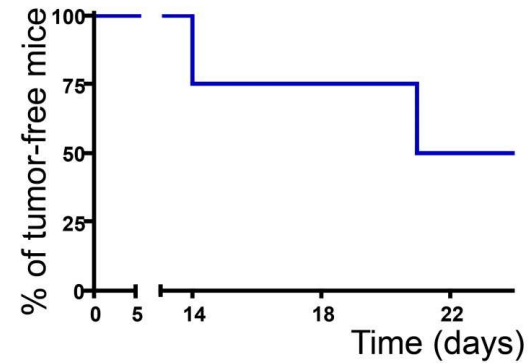


Dr. A. Perales-Puchalt, Unpublished data

FSH-targeted CAR T cells abrogate the growth of established p53-driven breast tumors

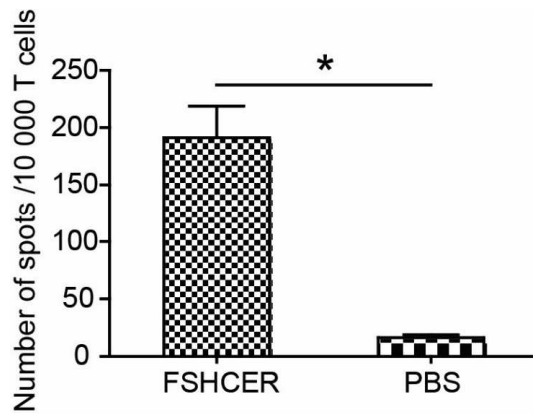


I.V. administration (X2)



I.T. administration (X2)

Syngeneic FSH-targeted CER T cells boost **endogenous**, pre-existing T cell-dependent, **protective** anti-tumor immunity

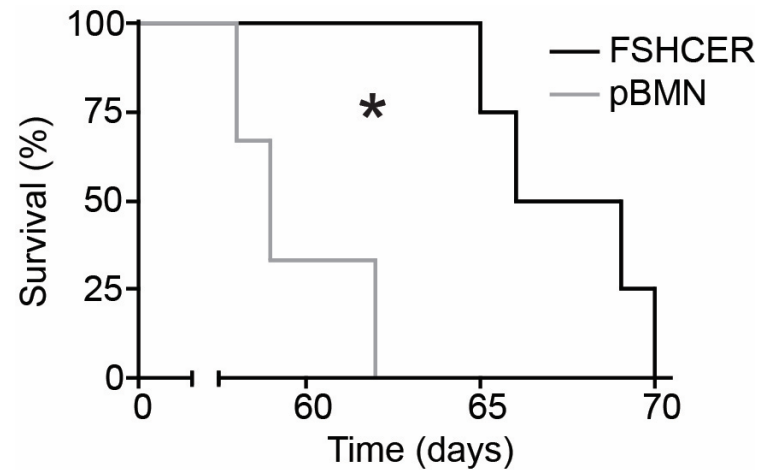


Dr. A. Perales-Puchalt, Unpublished data

FSH-targeted CER T cells exert significant but limited therapeutic benefits in an aggressive model of ovarian cancer ascites

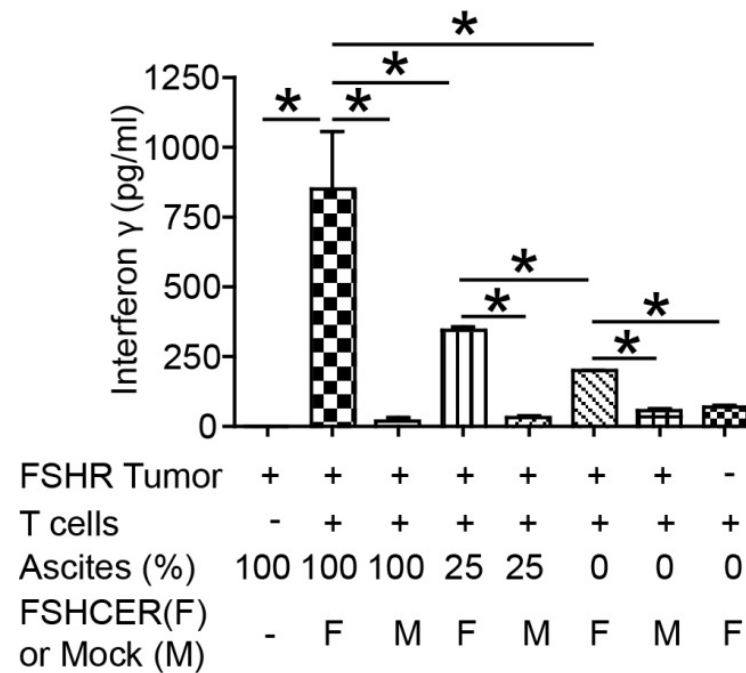


**ID8-Defb29-
VEGF-a-mFSHR**

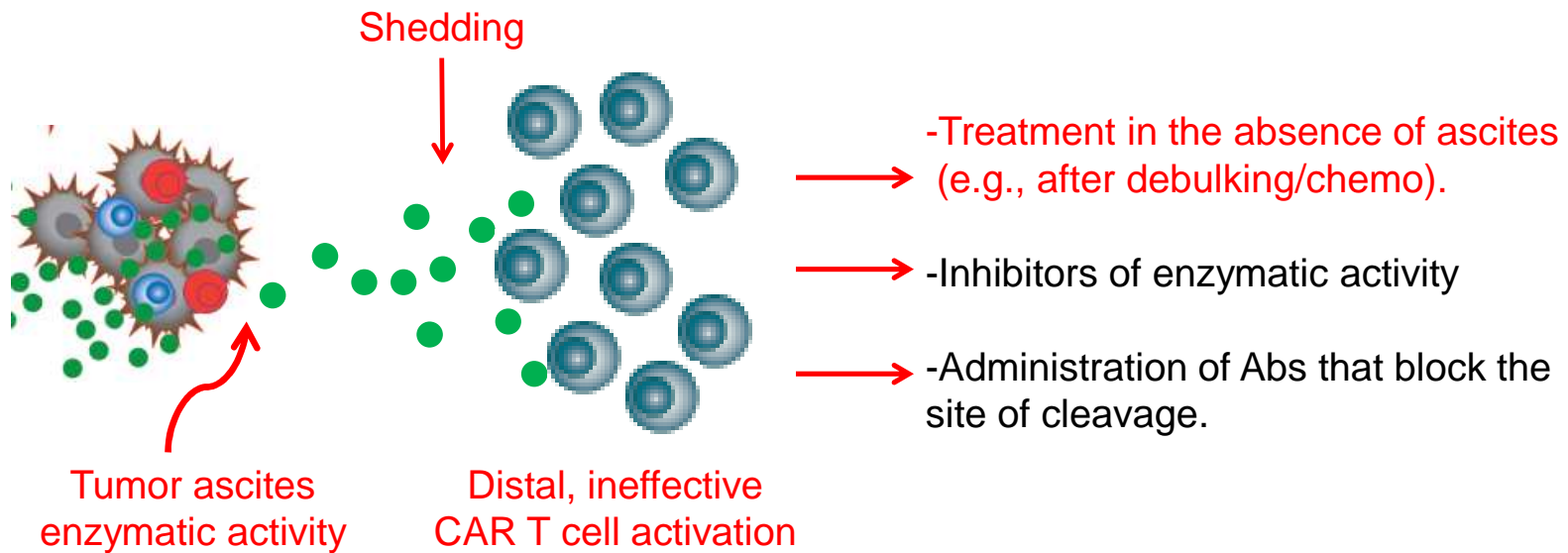


**2 treatments of 10e6 CAR T
cells; days 7 and 14**

Tumor ascites increases the reactivity of FSHCER T-cells against their cognate target

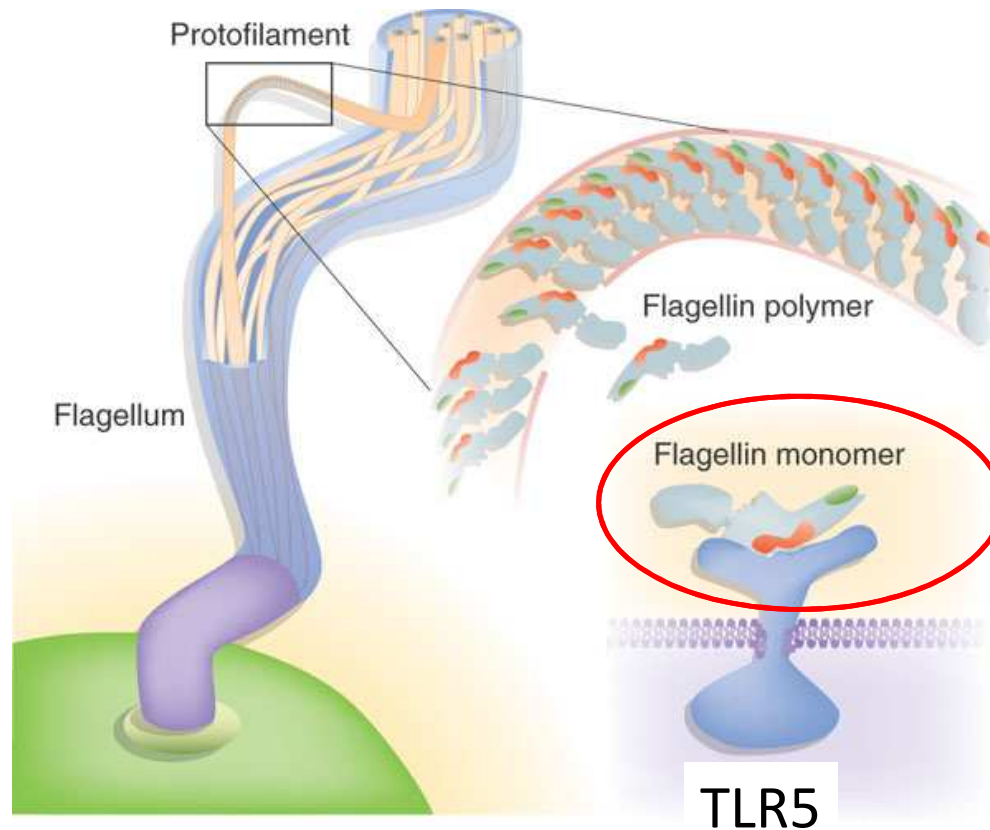


Tumor ascites in the absence of fresh FSHR+ tumor cells induces significantly weaker responses



What else influences immunotherapeutic effectiveness?

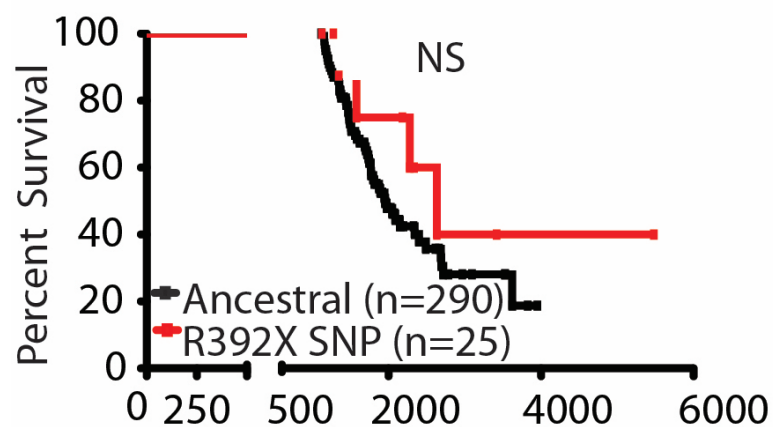
TLR5



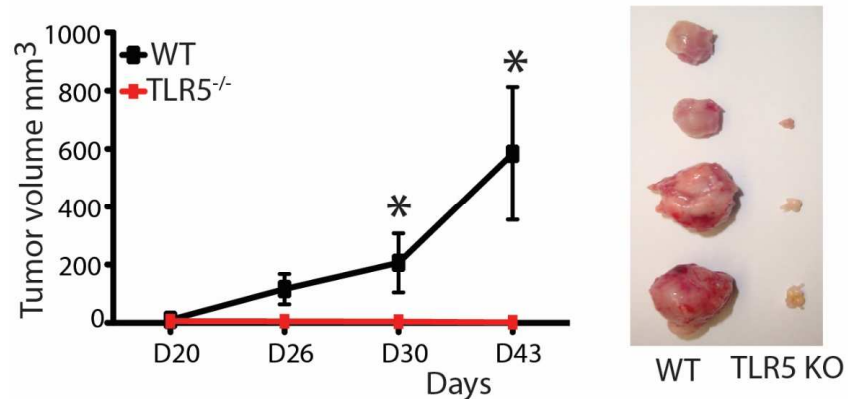
Nature Immunology **4**, 1159 - 1160

**7-10% of the general population are functional TLR5 KOs
(R392X dominant negative).**

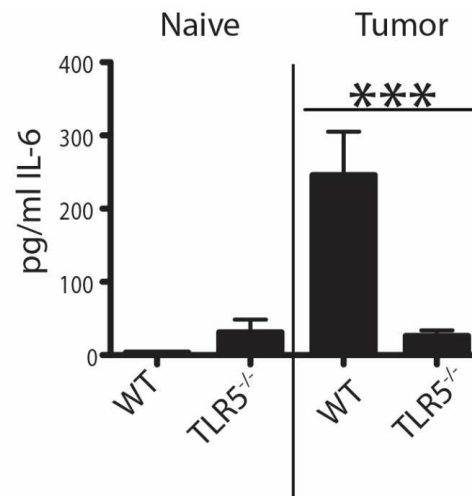
Proportions of long-term (>6 year) ovarian cancer survivors is higher in patients with a functional polymorphism in TLR5 (R392STOP)



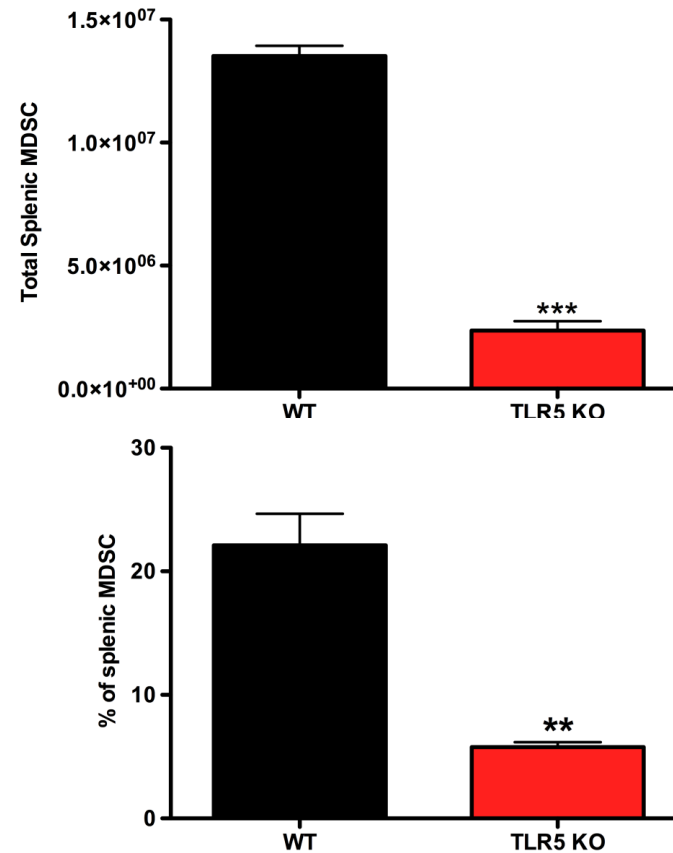
Delayed progression of orthotopic syngeneic ovarian tumors in TLR5 KO individuals



Systemic up-regulation of IL-6 in tumor-bearing hosts is TLR5-dependent

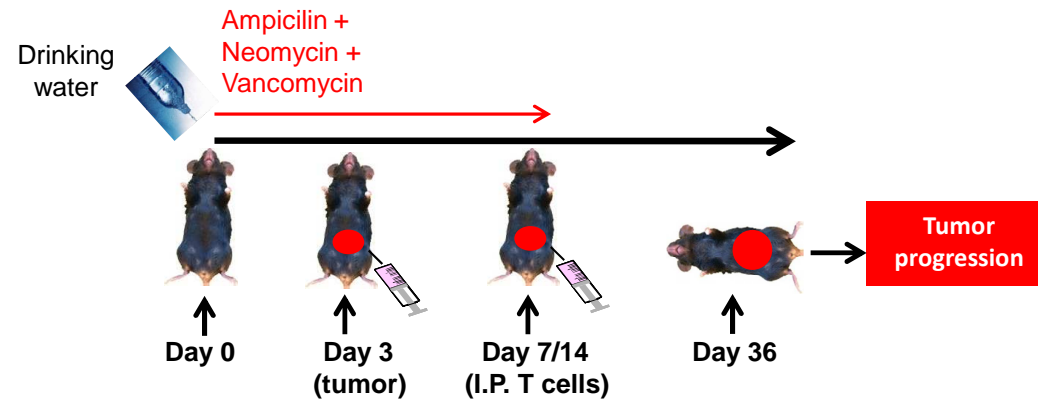


TLR5 KO mice mobilize less immunosuppressive MDSCs than WT mice with comparable tumor burden



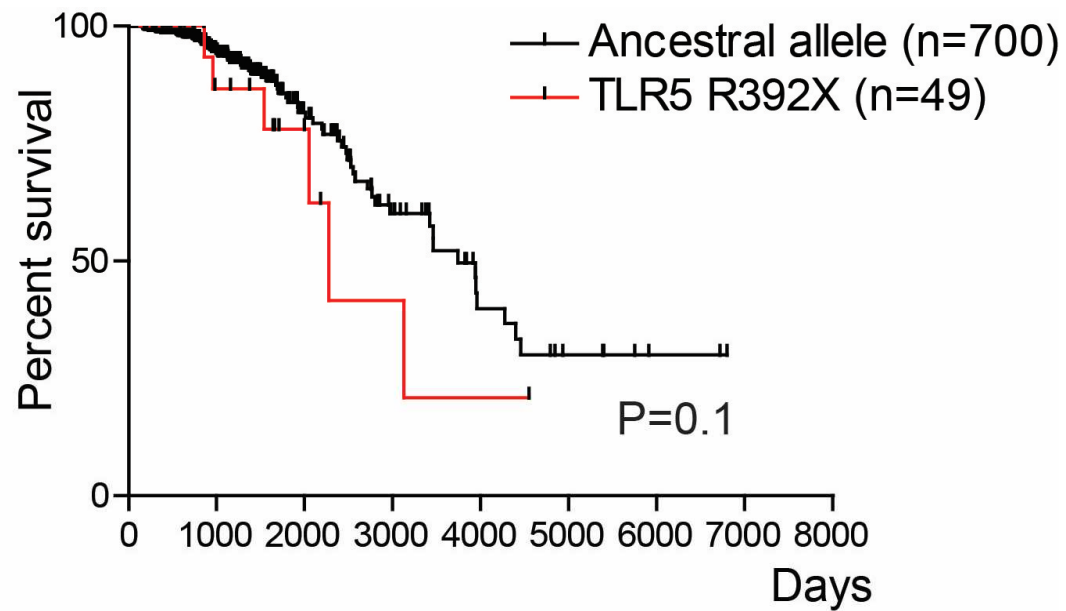
MDSC=GR1^{high}CD11b⁺

Commensal bacteria influence the effectiveness of FSH-targeted T cells against FSHR+ tumors

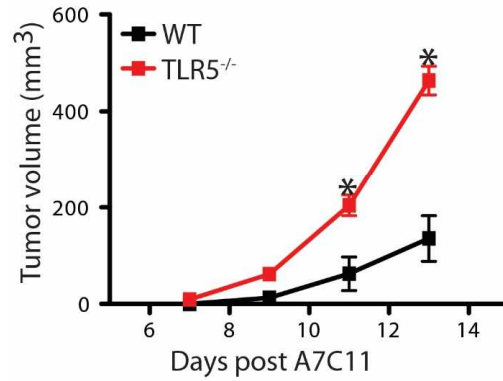


What about breast adenocarcinomas?

Luminal breast cancer carriers of the R392X SNP exhibit worse outcome

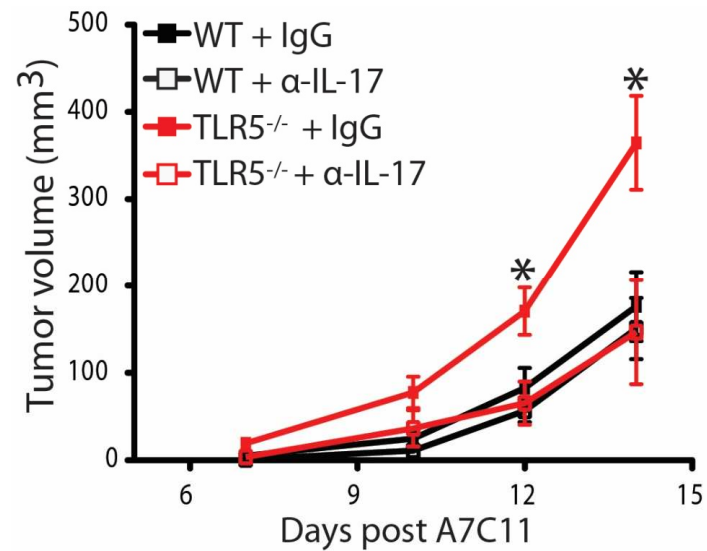


IL-6-resistant syngeneic breast tumor cells grow faster in the absence of TLR5 signaling, with lower systemic IL-6



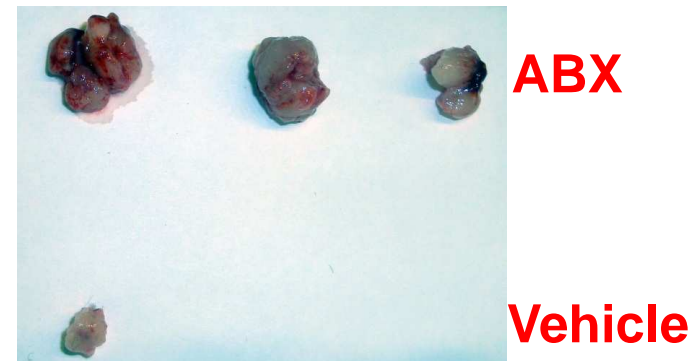
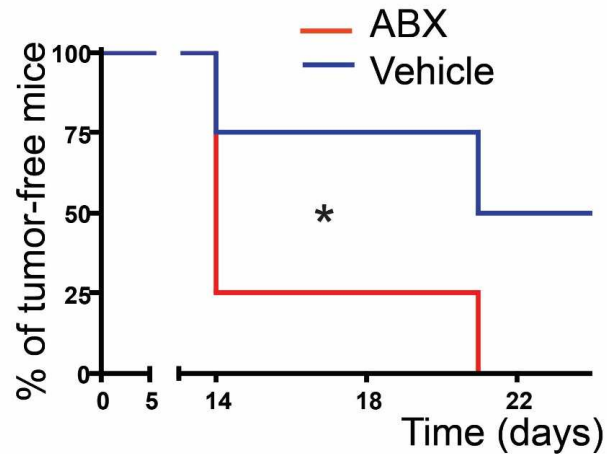
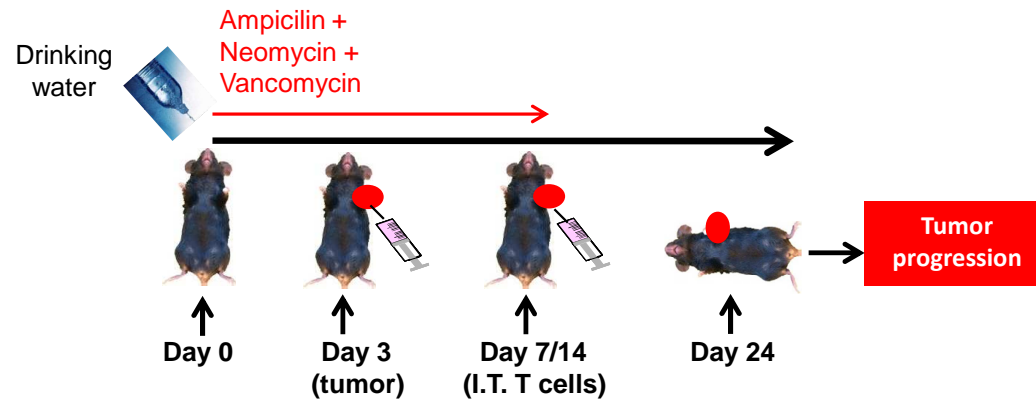
IL-17 drives breast cancer (but no other tumors) progression in TLR5 KO individuals

Decreased tumor growth in
TLR5-deficient hosts



IL-17 neutralization

Commensal bacteria influence the effectiveness of FSH-targeted T cells against FSHR+ tumors



Dr. A. Perales-Puchalt, Unpublished data

Lessons and Take Home Messages

- Key points:**

- Ovarian and breast cancers express targetable hormone receptors.
- Full-length hormones effectively and specifically re-direct the cytotoxic activity of T cells towards tumor cells.
- FSH-targeted CAR T cells do not induce any obvious toxicity.
- FSH-targeted T cells persist in the host until end-stage disease.
- However, tumor ascites induces shedding of FSHR and limits the effectiveness of FSH-targeted CAR T cells.

- Potential impact on the field:**

- We report novel mechanisms of activity and modulating factors influencing the effectiveness of a T cell-based immunotherapeutic approach for specific and safe targeting of ovarian carcinoma

- Lessons learned:**

The growth of primary tumors, metastatic spreading and the effectiveness of immunotherapies are significantly influenced by commensal bacteria, which regulates tumor-promoting inflammation.

Collaborators
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