

Presenter Disclosure Information

David D. Roberts

The following relationships exist related to this presentation:

No Relationships to Disclose

CD47 limits cooperation between adaptive tumor immunity and radiation therapy

David Roberts, Ph.D.

Laboratory of Pathology, CCR

Current

David Soto-Pantoja
Sukhbir Kaur



Alumni

Justin Maxhimer
Jeff Isenberg

Collaborators

Laboratory of Pathology, NCI

Arunima Ghosh

Radiation Biology Branch, NCI

David Wink

Lisa Ridnour

William DeGraff

Vaccine Branch, NCI

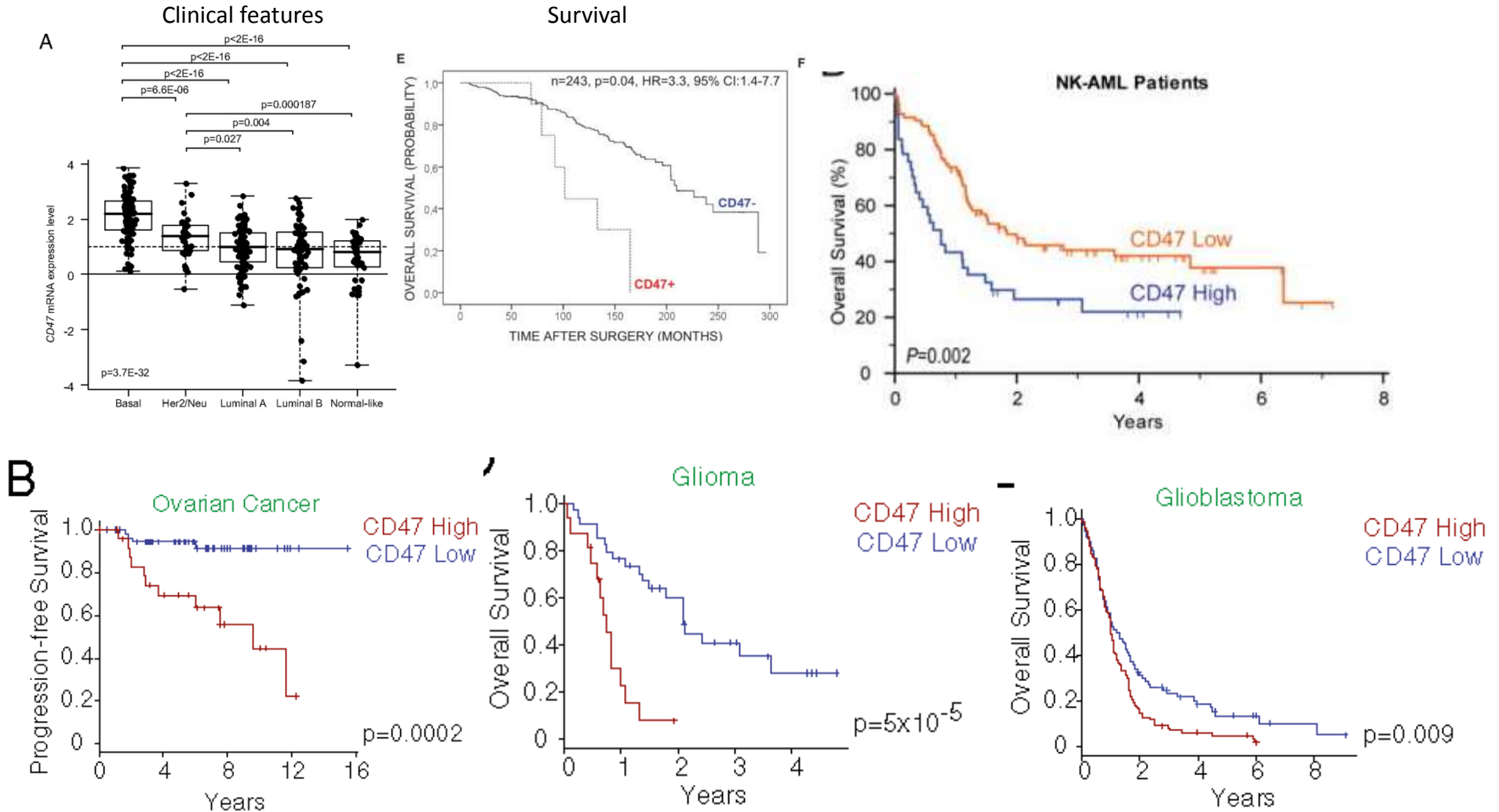
Masaki Terabe

Jay A. Berzofsky

High CD47 expression in human cancers correlates with poor prognosis

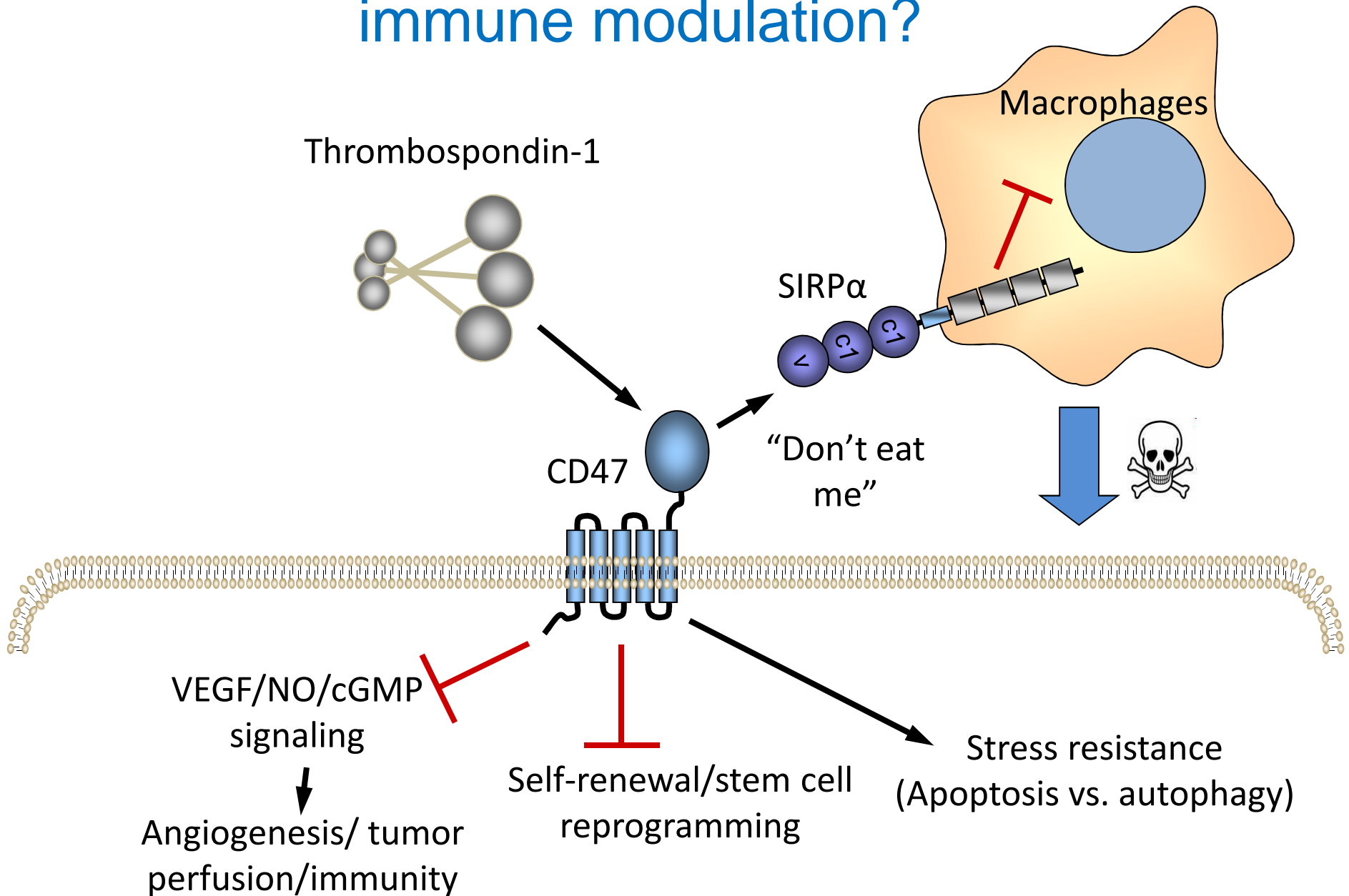
Breast Cancer

Leukemia



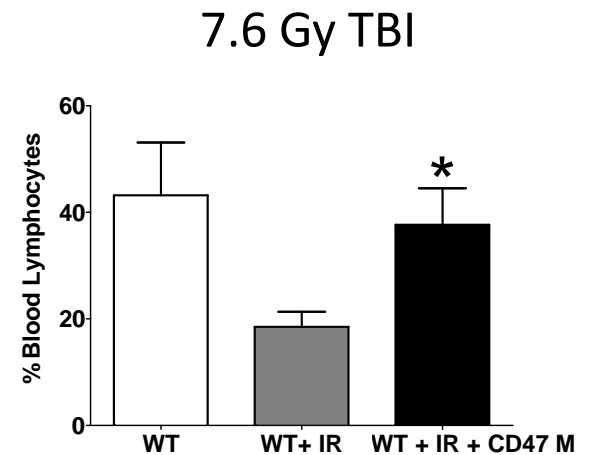
Zhao PNAS 2011; Majeti Cell 2009; Willingham PNAS 2012; Baccelli Oncotarget 2014

Role of CD47 in cancer: signaling versus immune modulation?



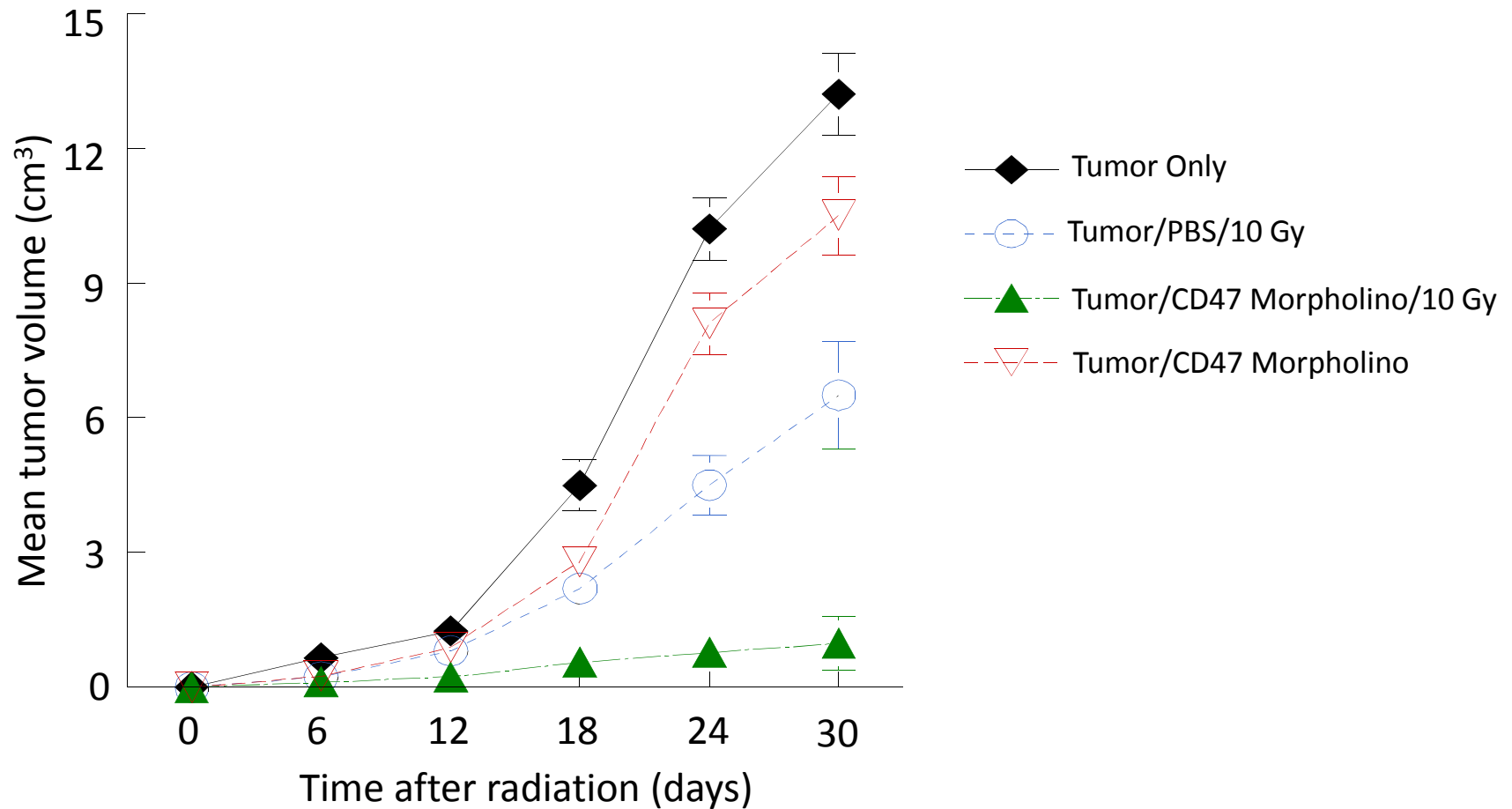
CD47 limits cell and tissue radioresistance

- Mice lacking CD47 or its ligand thrombospondin-1 are radioresistant
- Therapeutic blockade of CD47 using an antisense morpholino protects mice from local and total body irradiation
- CD47 blockade protects bone marrow hematopoietic function
- Circulating lymphocytes are preserved
- Radioprotection is cell-autonomous and mediated by a protective autophagy response

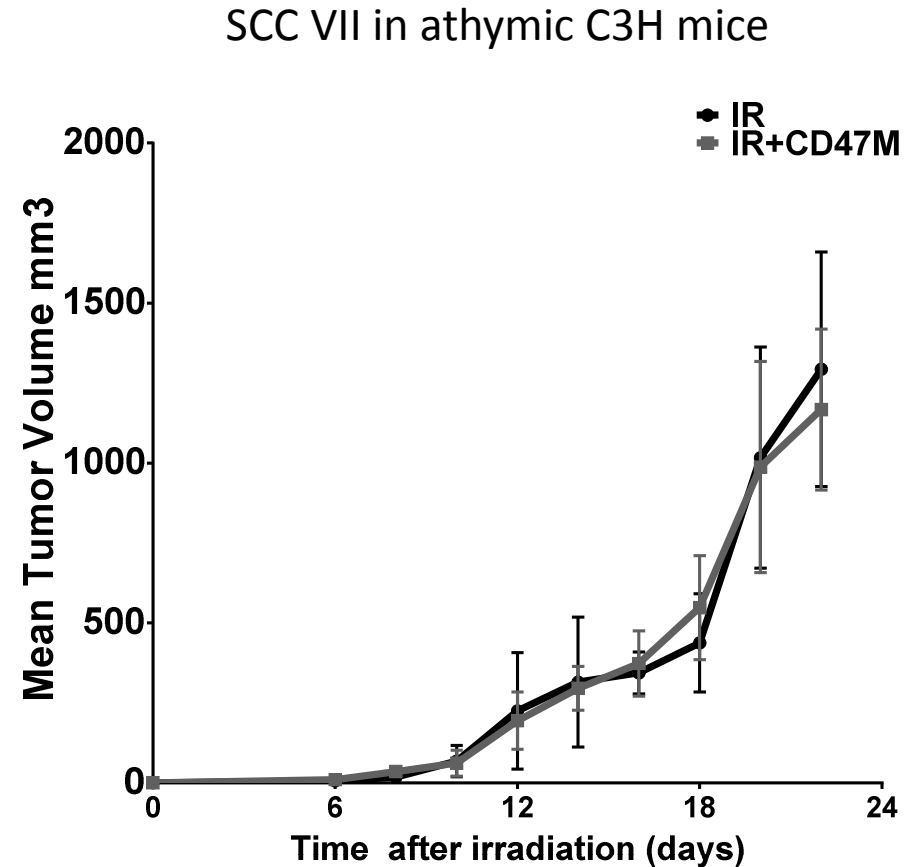
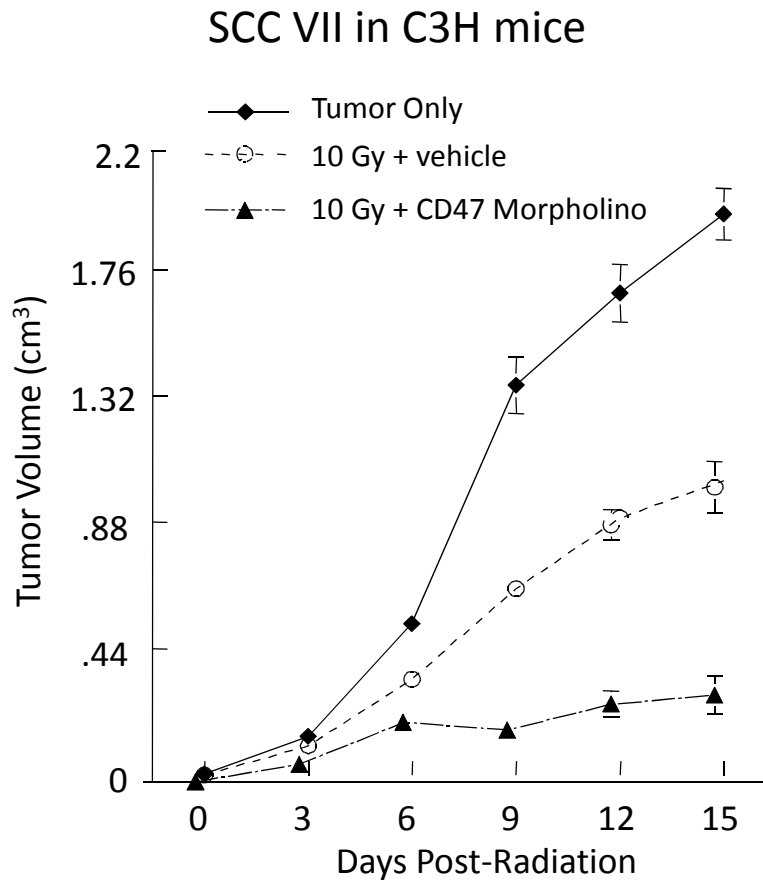


Isenberg, *Am J Pathol* 2008; Maxhimer, *Science Transl Med* 2009; Soto-Pantoja, *Autophagy* 2012; Soto-Pantoja *Sci Rep* 2013

Suppression of CD47 enhances the radiation-induced delay in B16 melanoma growth in C57Bl/6 mice

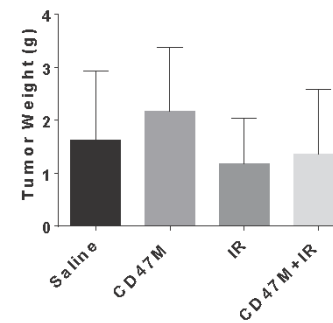
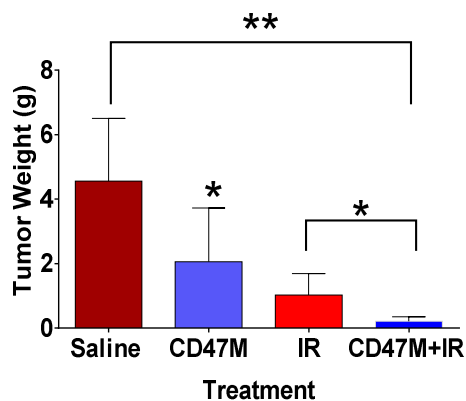
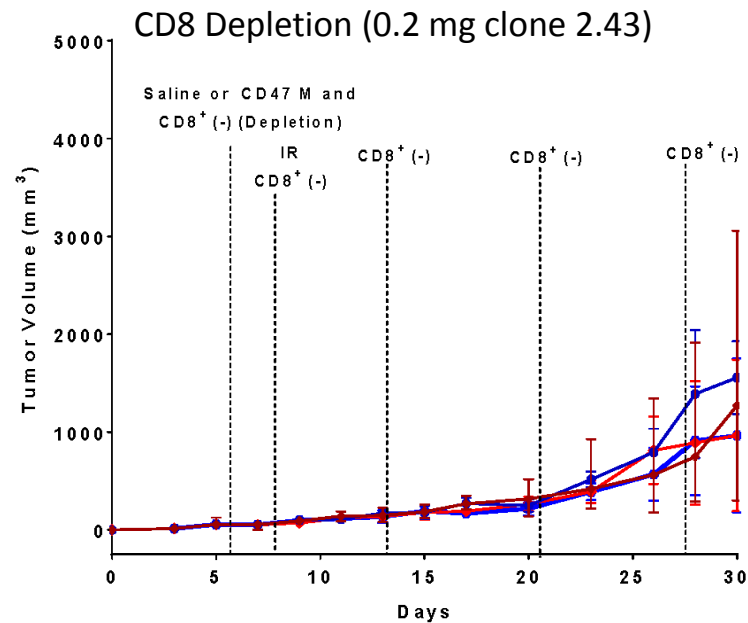
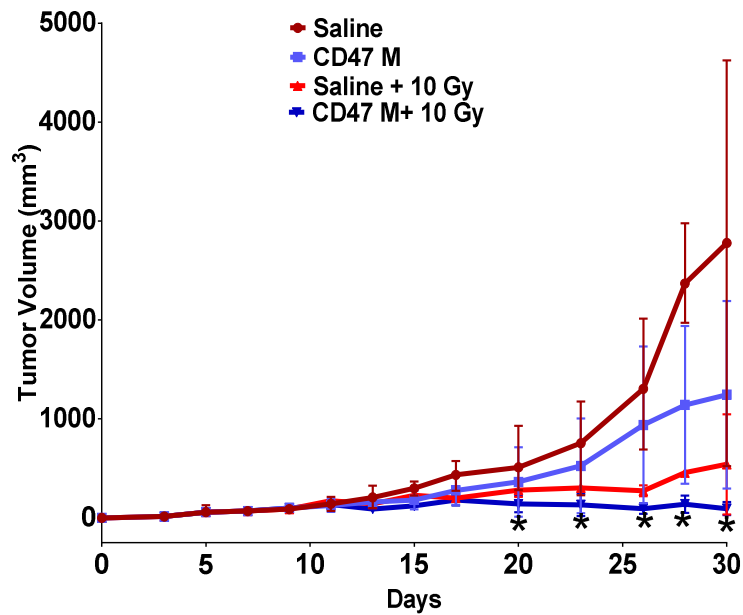


Synergism between CD47 blockade and radiation therapy requires T cells



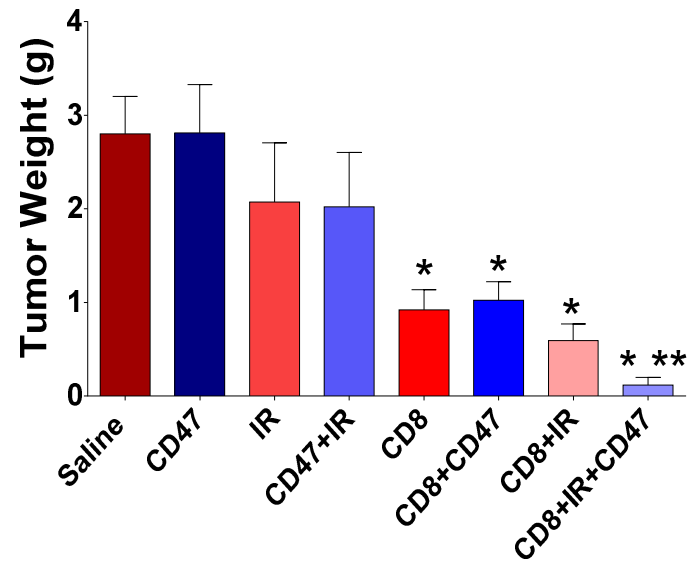
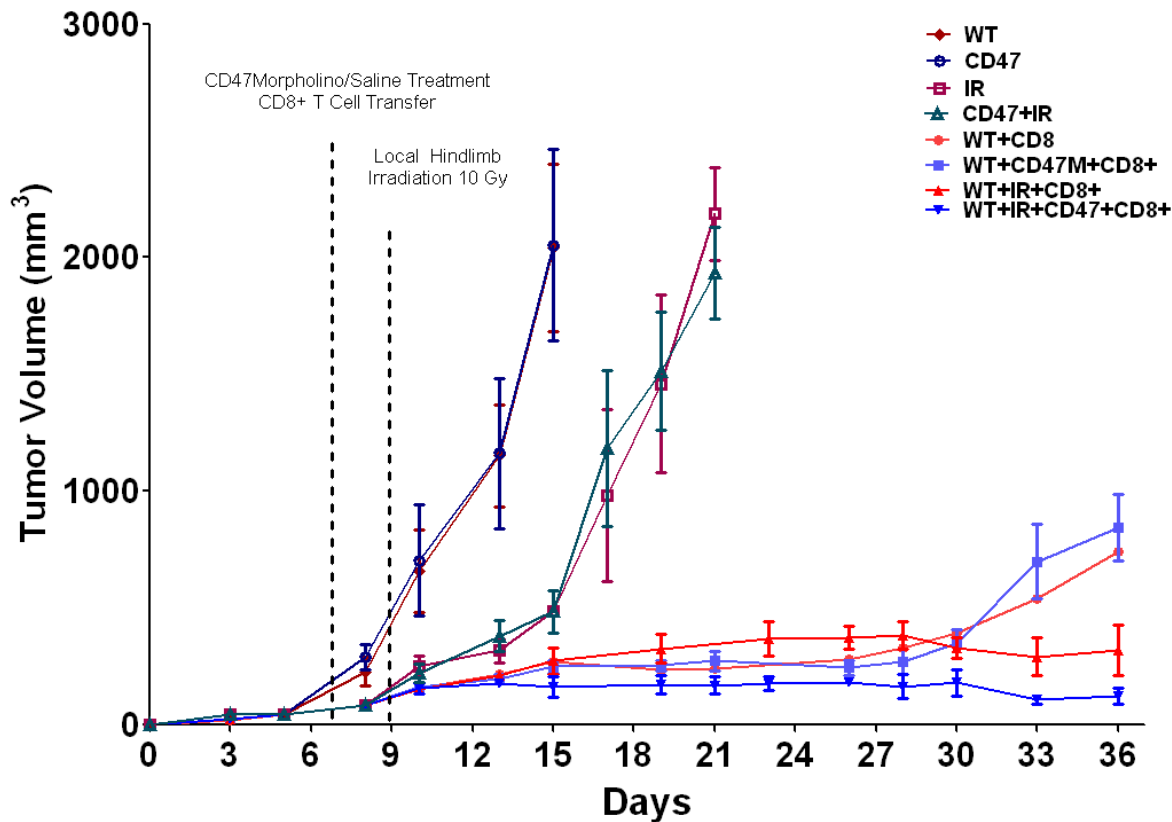
Maxhimer, *Science Transl Med* 2009; Soto-Pantoja, *Cancer Res* 2014

Enhancement by CD47 blockade of radiation growth delay for 15-12RM fibrosarcoma in BALB/c mice requires CD8⁺ T cells

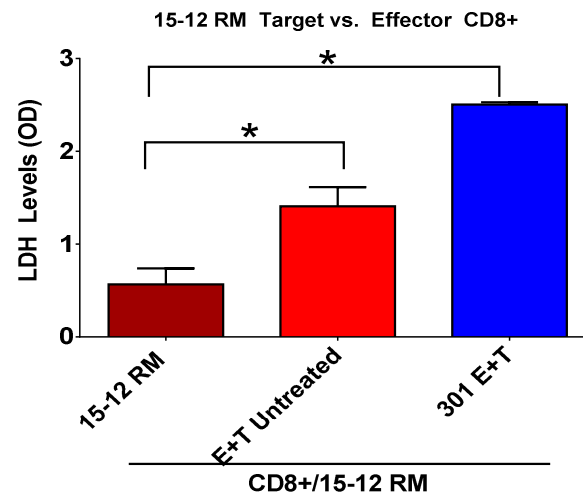
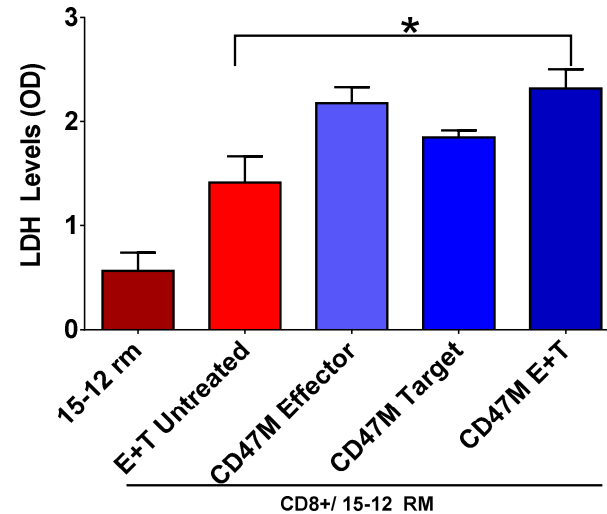
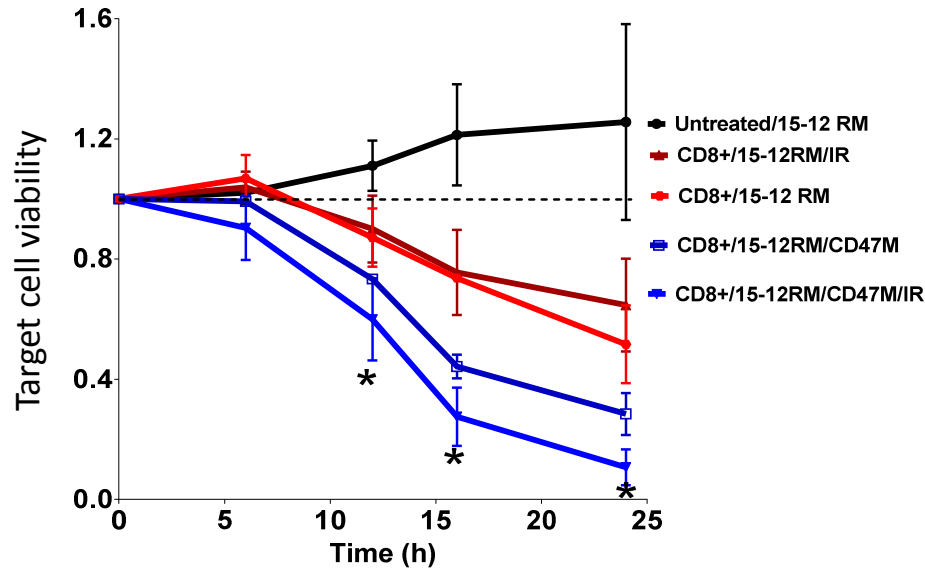


Synergism between CD47 blockade, adoptive CD8 T cell immunotherapy, and irradiation

15 -12 RM Fibrosarcoma Tumor Growth in athymic nu/nu BALB/c mice



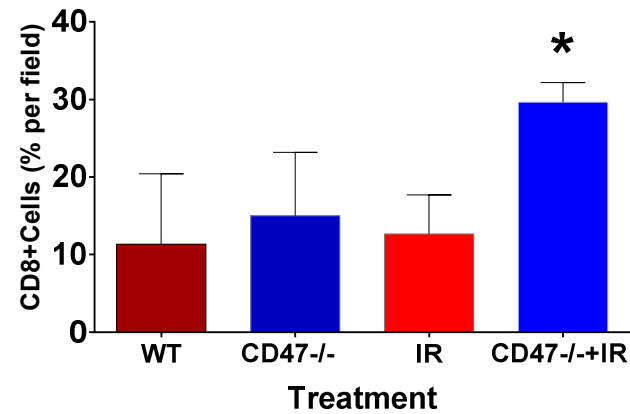
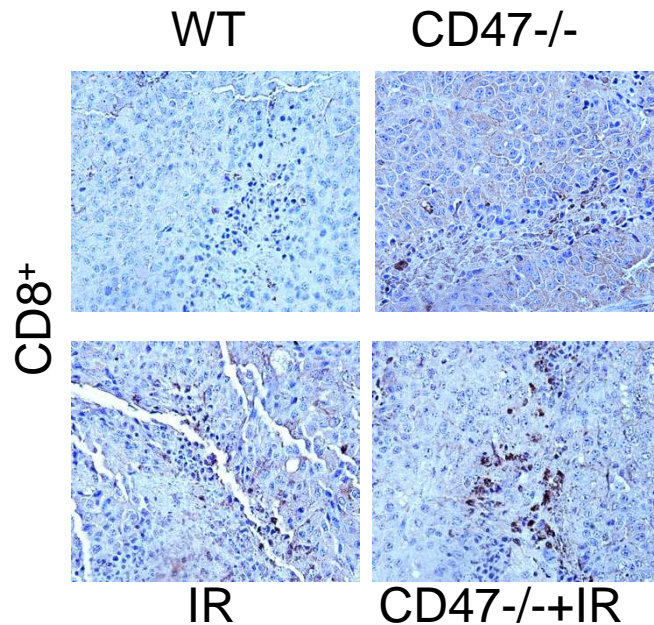
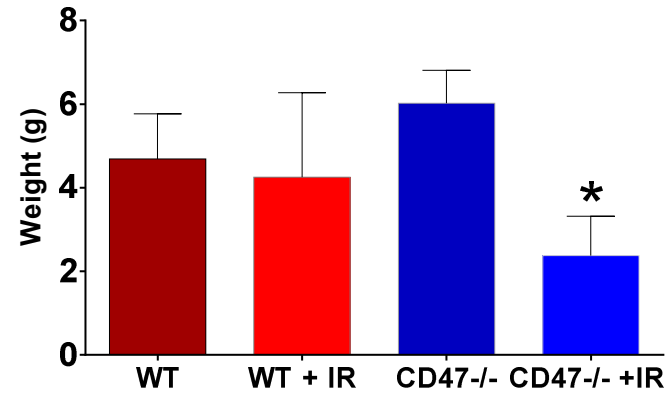
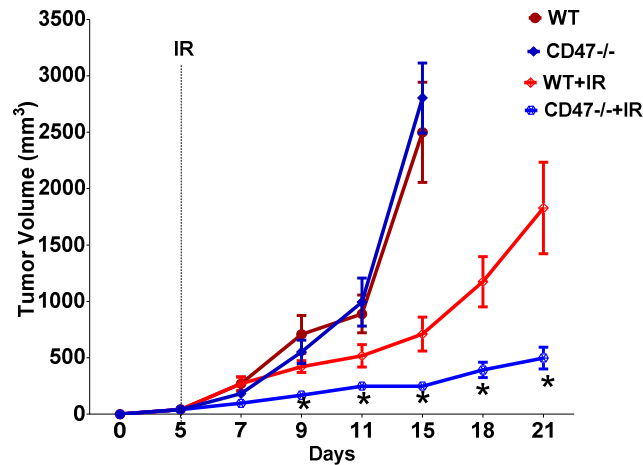
CD47 blockade increases CD8 CTL activity in vitro



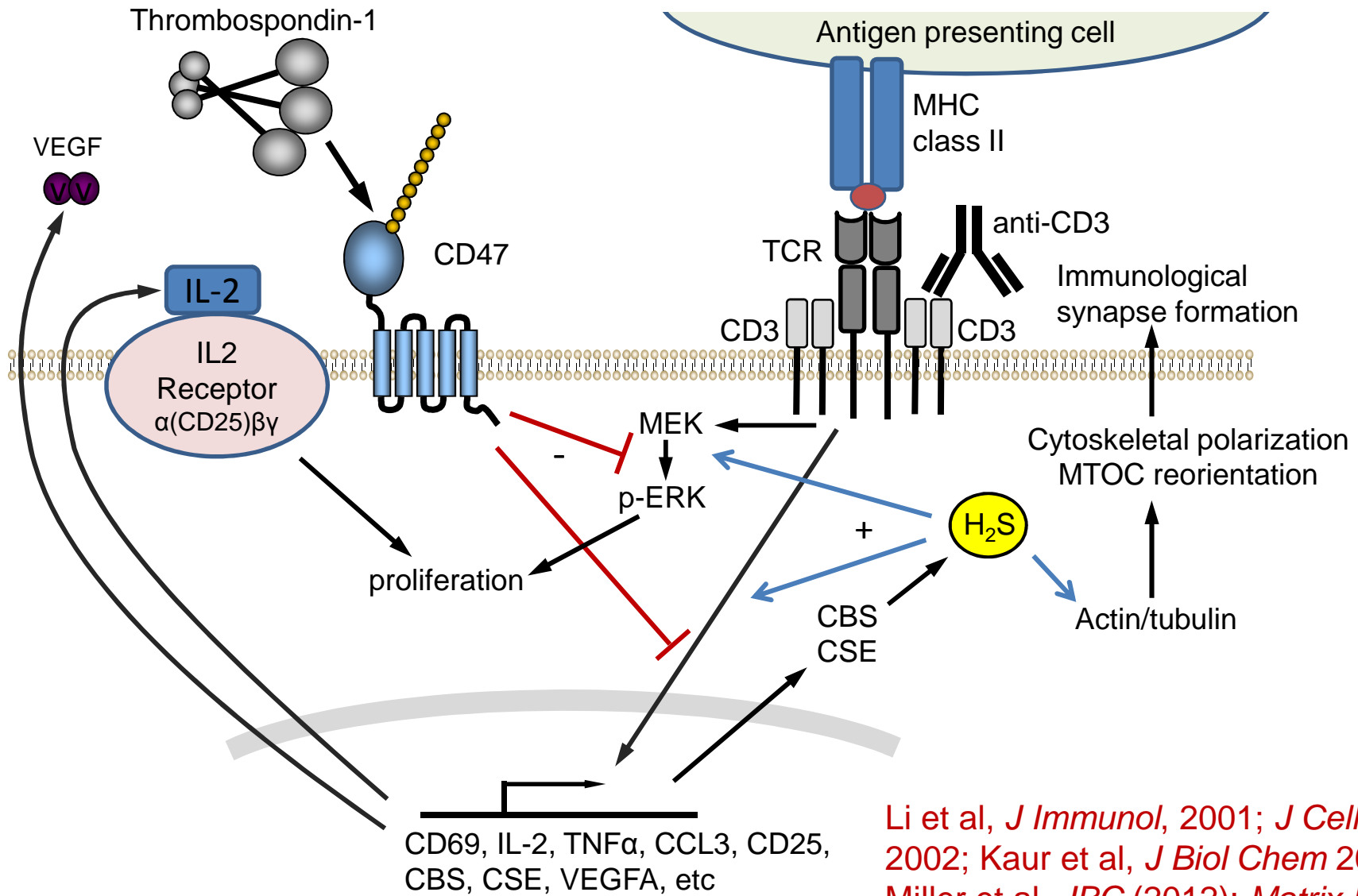
301: murine
CD47 blocking
antibody

Eliminating CD47 in the tumor microenvironment is sufficient to enhance tumor radiation response

B16 melanoma in WT versus CD47-null C57Bl/6 mice



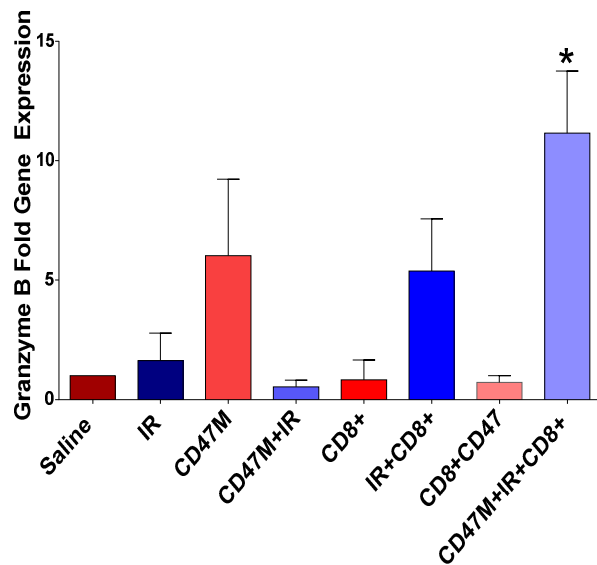
CD47 signaling limits T cell activation



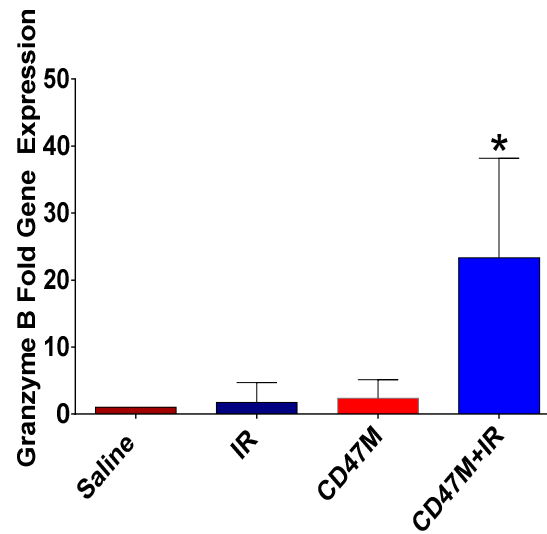
Li et al, *J Immunol*, 2001; *J Cell Biol* 2002; Kaur et al, *J Biol Chem* 2011; Miller et al. *JBC* (2012); *Matrix Biol* 2013; Kaur, et al *J. Immunol.* 2014

CD47 blockade synergizes with radiation to increase granzyme B expression

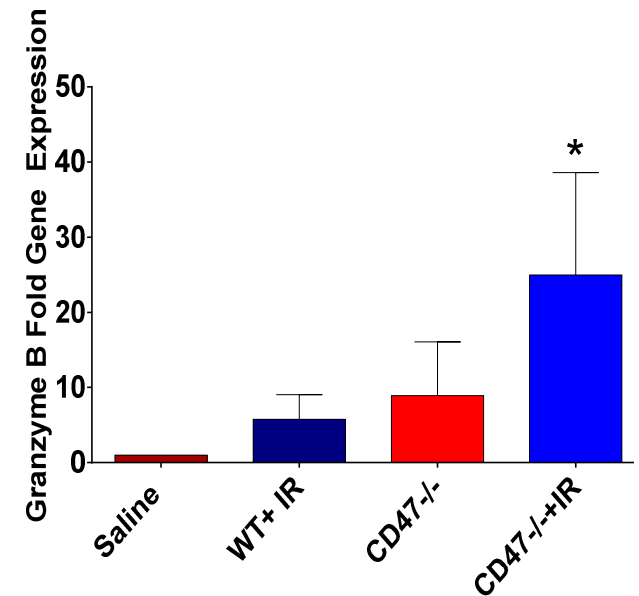
15-12RM Fibrosarcoma adoptive transfer model



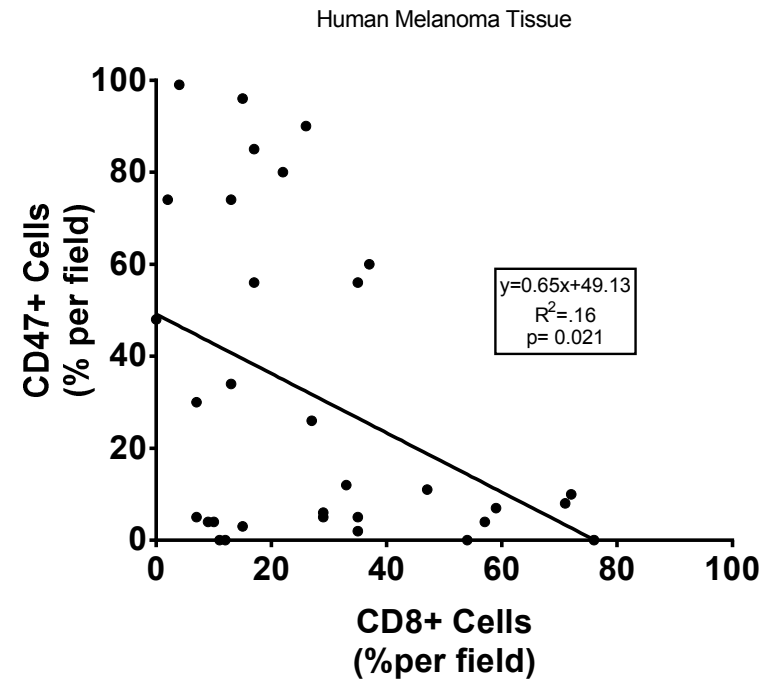
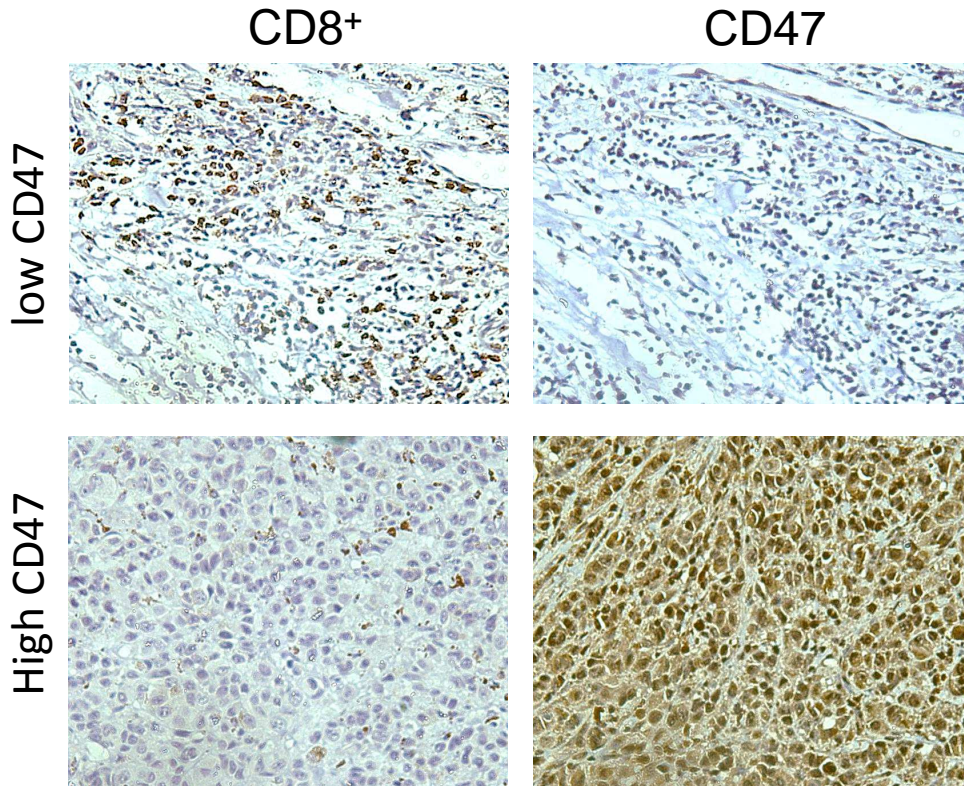
15-12RM Fibrosarcoma in immune-competent mice



B16 melanoma model



CD8⁺ T cell infiltration inversely correlates with CD47 expression in human melanomas

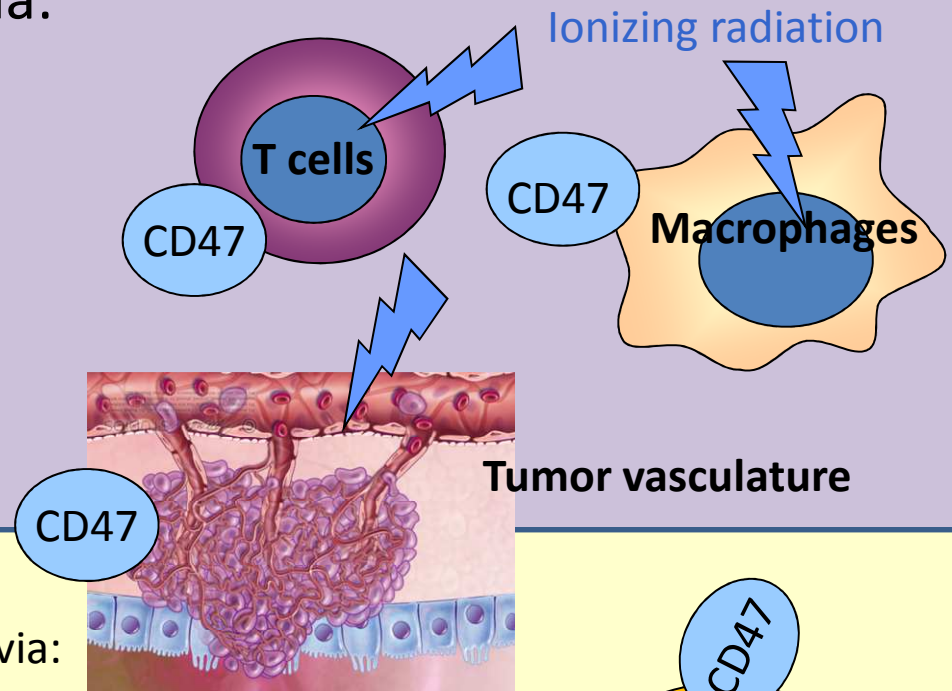


Differential effects of CD47 signaling blockade on tumor vs. stromal cells

Healthy tissues and tumor stroma:

CD47 blockade increases stromal cell survival via:

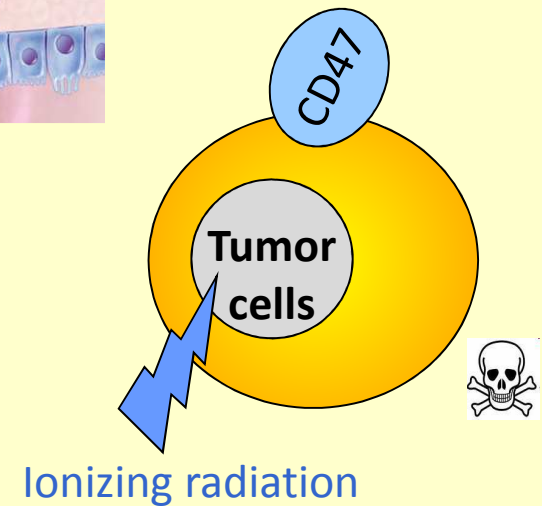
- Nitric oxide and VEGF signaling
- Enhanced autophagy
- Inducing c-Myc and other stem cell factors



Tumor cells:

CD47 blockade increases tumor cell death via:

- Decreasing protective autophagy
- Resistance to c-Myc regulation
- Decreased resistance to innate immunity
- Enhanced CTL killing of tumor cells



Lessons and Take Home Messages

•Key points

- Suppression of CD47 in the tumor microenvironment enhances radiation growth delay in syngeneic fibrosarcoma and melanoma models.
- Synergism between CD47 blockade and radiation to delay tumor growth requires CD8⁺ T cells.
- Blockade of CD47 on either target or effector cells enhances antigen-dependent CD8⁺ CTL-mediated killing of tumor cells in vitro and the efficacy of adoptive CD8⁺ T cell transfer in vivo.
- Enhanced T cell mediated killing following CD47 blockade is associated with increased granzyme B expression.

•Potential impact on the field

- Therapeutics targeting CD47 could improve the efficacy of radiation therapy alone and in combination with adoptive T cell immunotherapy

•Lessons learned

- CD47 is an immune checkpoint inhibitor for T cells