Functional reprogramming of the tumor stroma by IL-12 Engineered T cells is required for anti-tumor immunity

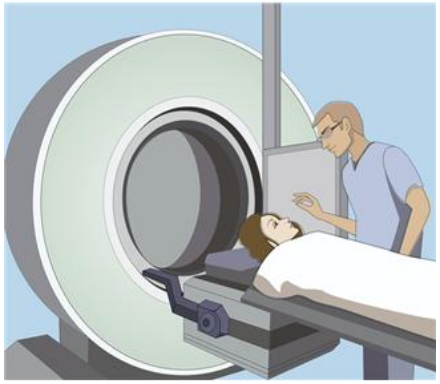
Sid Kerkar, M.D.

Cancer Therapies

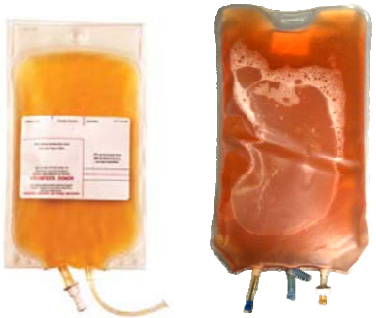
Surgery

Chemotherapy

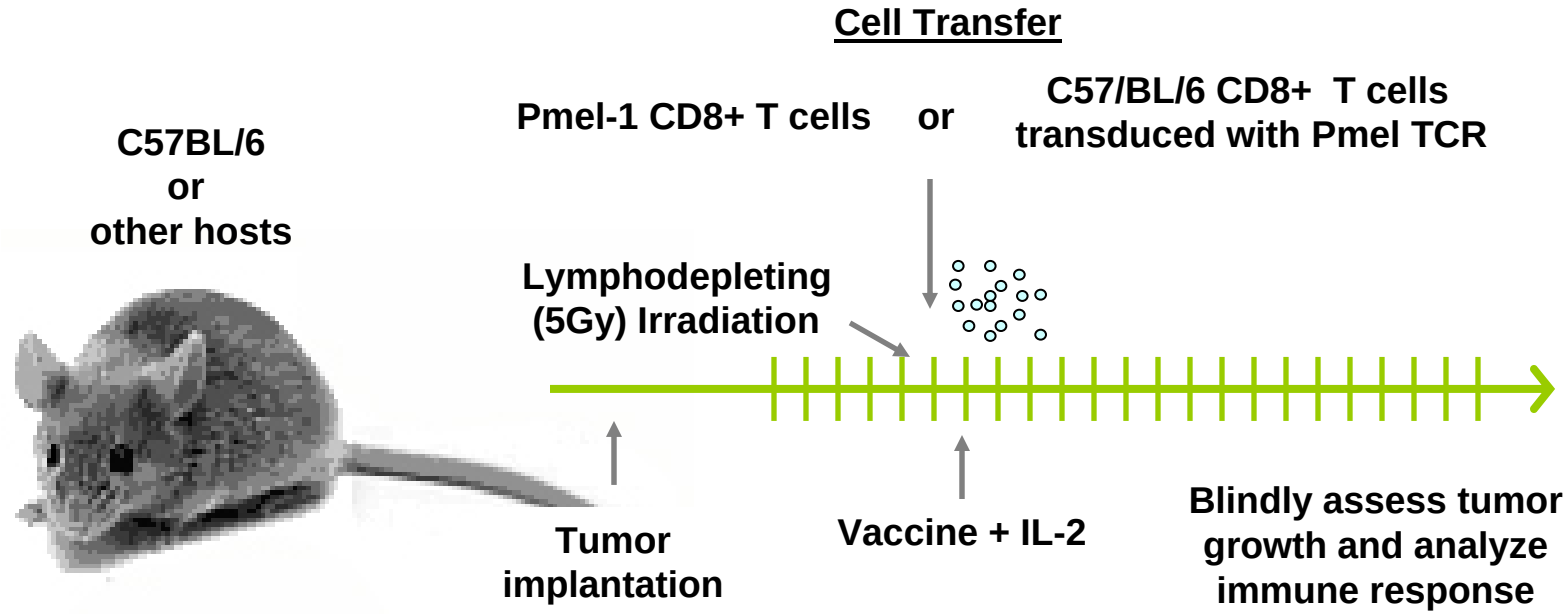
Radiation



Emerging Cell Based Therapy



Mouse B16/Melanoma Model of Adoptive Cell Transfer



A tripartite regimen is effective:

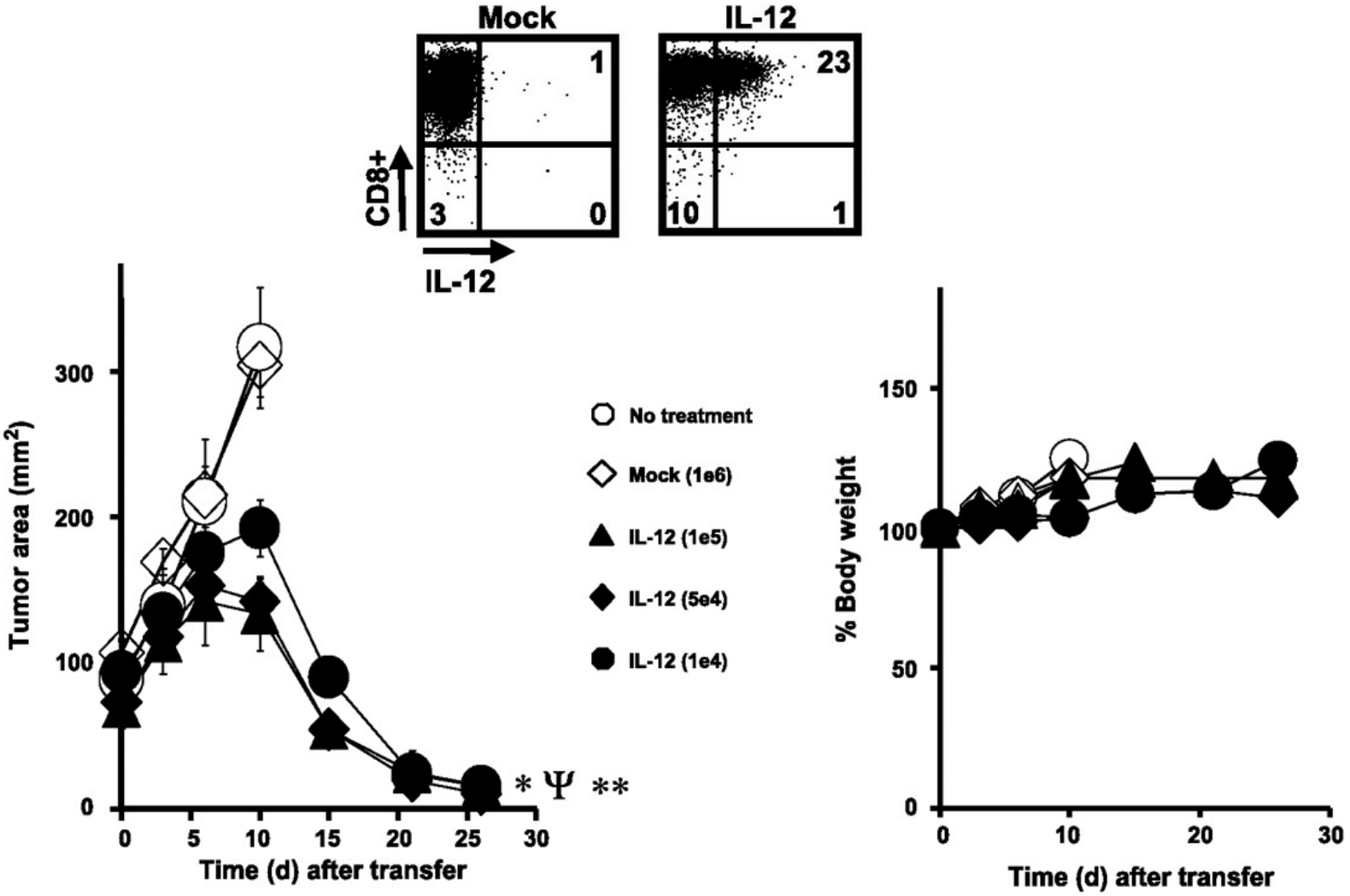
i) 1 million Pmel-1 CD8+ cells

ii) 2 x 10^7 plaque-forming units of rVV encoding hgp100

iii) administration of high-dose IL-2: 600,000 IU BID for 3 days

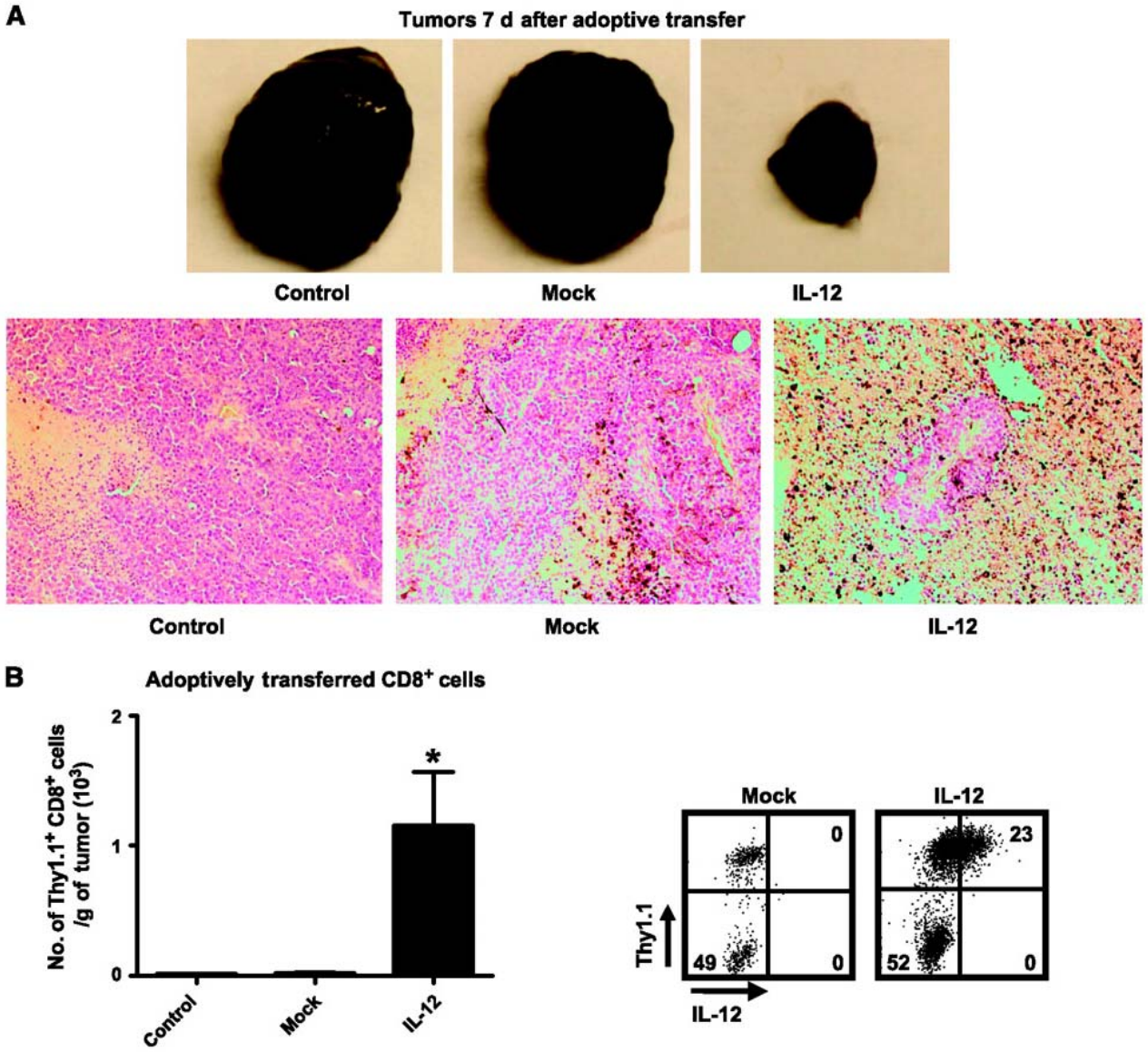
Overwijk WW et al. J Exp Med. 2003 Aug 18;198(4):569-80

Tumor-Specific CD8+ T Cells Expressing Interleukin-12 eradicate established B16 melanomas with 10,000 cells and no IL-2 or Vaccine



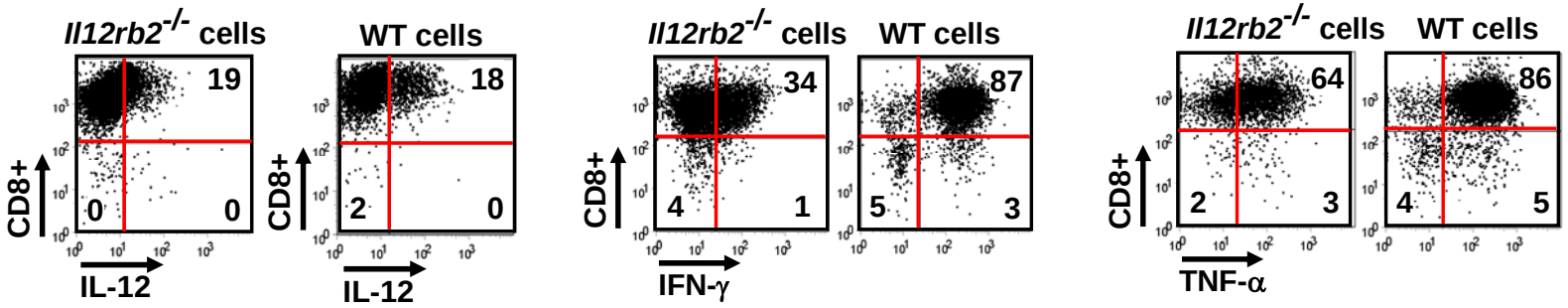
Kerkar SP et al. Cancer Res. 2010 Sept. 1st, 70;6725

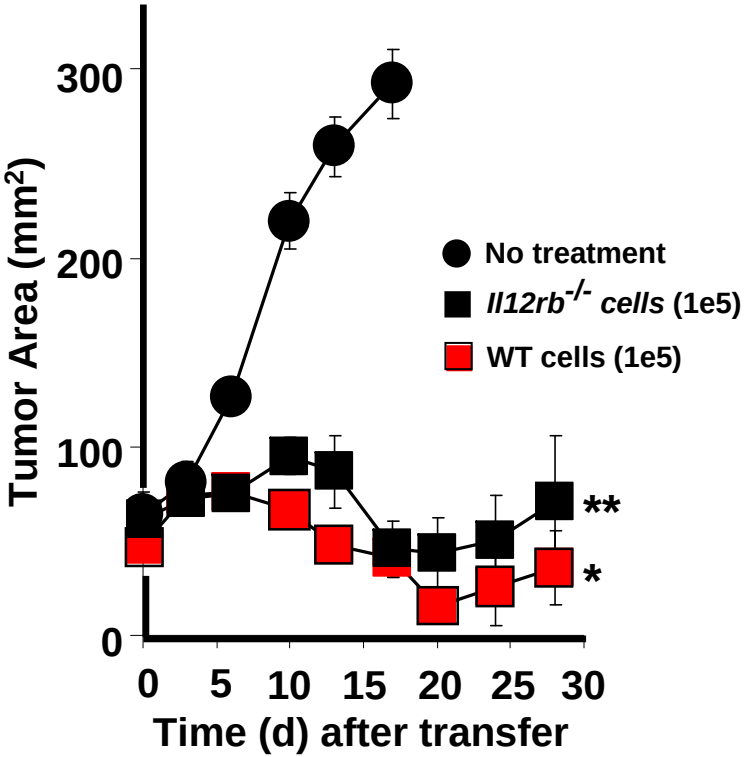
Treatment with IL-12 engineered CD8+ T cells leads to increased tumor infiltration of adoptively transferred cells stably expressing IL-12

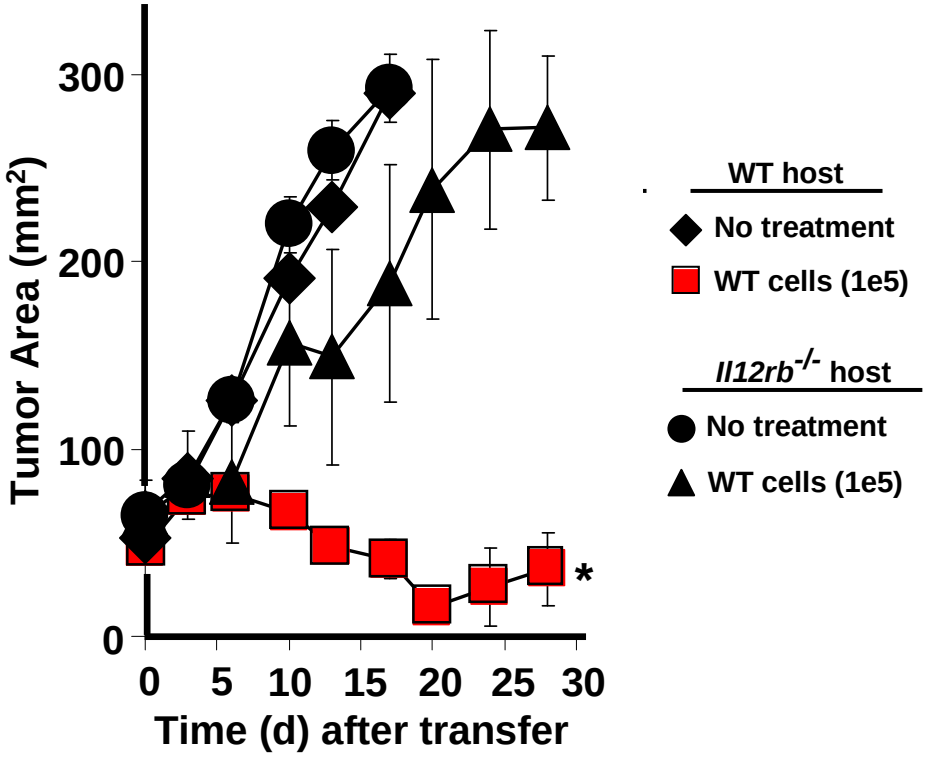


Kerkar SP et al. Cancer Res. 2010 Sept. 1st, 70;6725

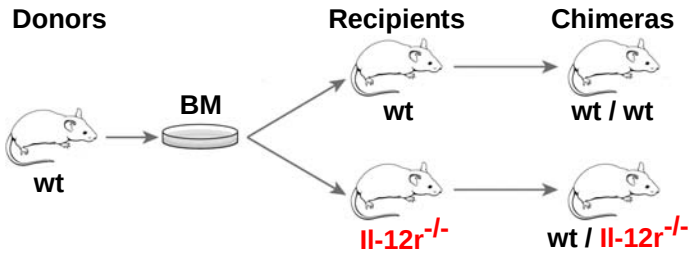
IL-12 based anti-tumor immunity is dependent on endogenous factors

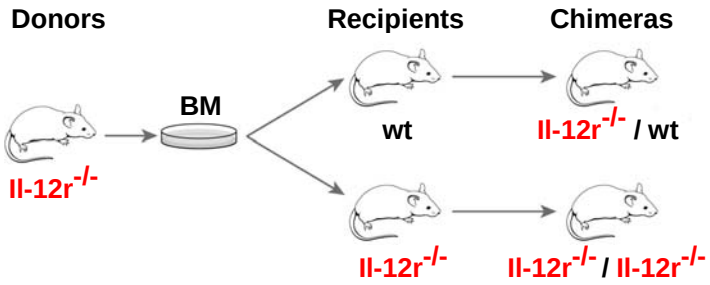


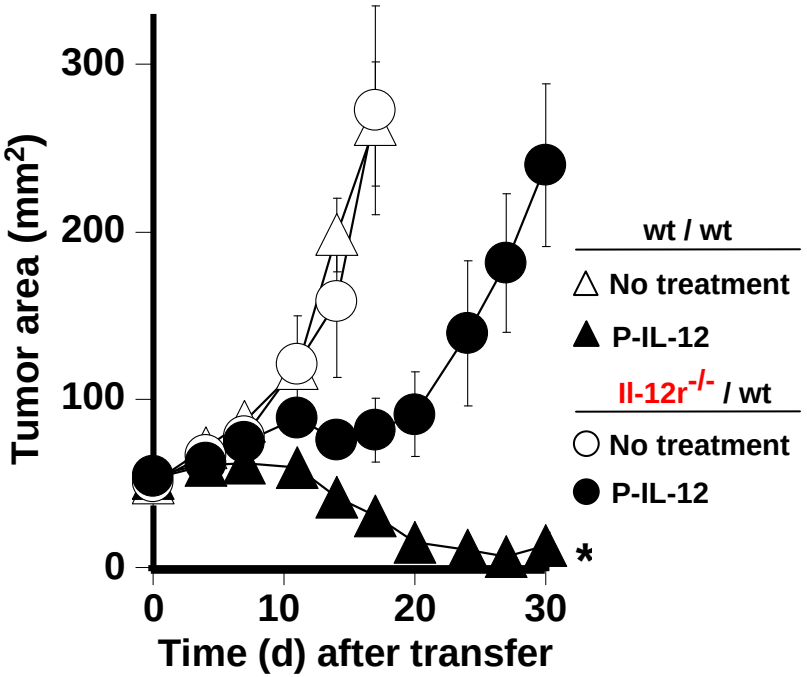


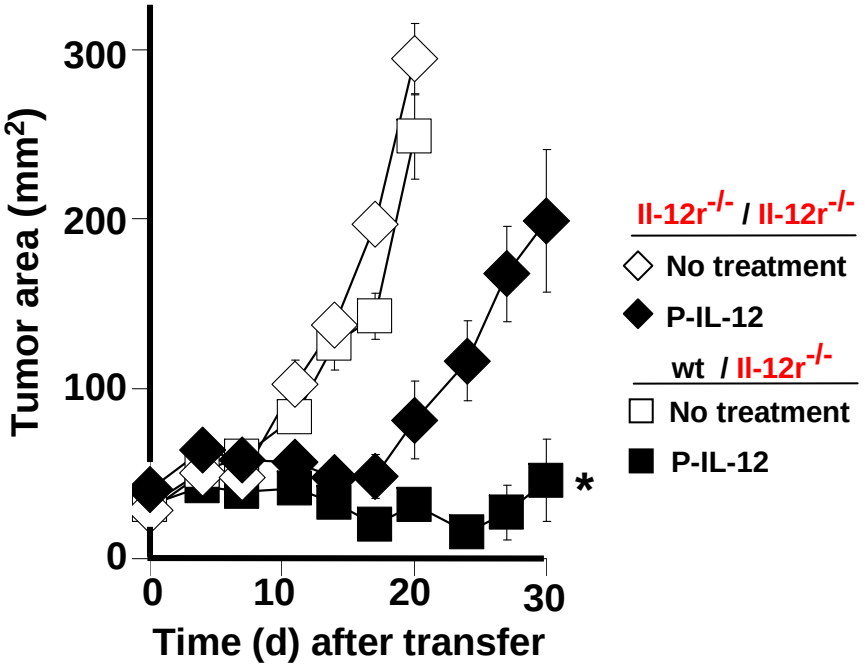


IL-12 based anti-tumor immunity is dependent specifically on host bone marrow derived cells

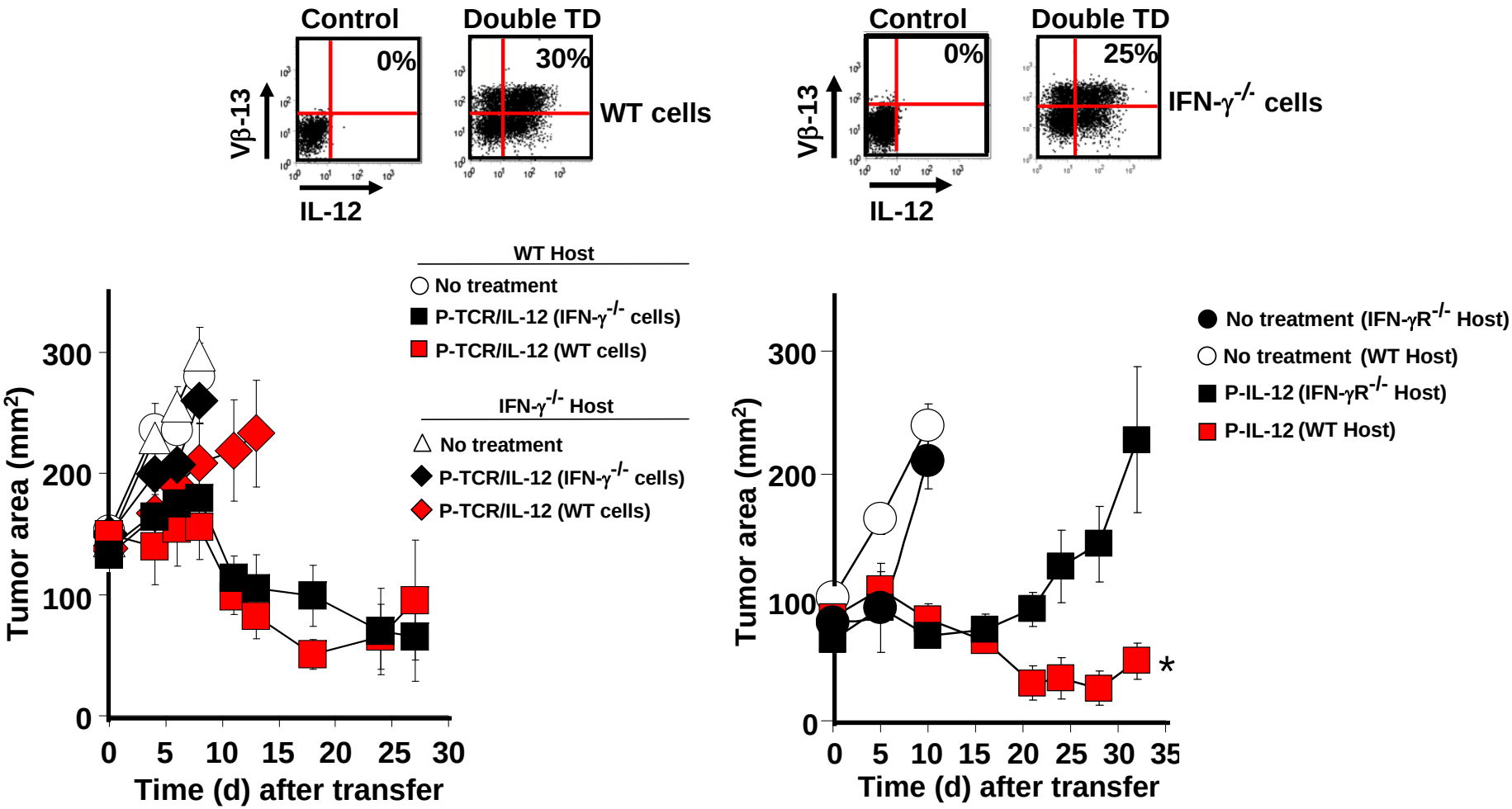




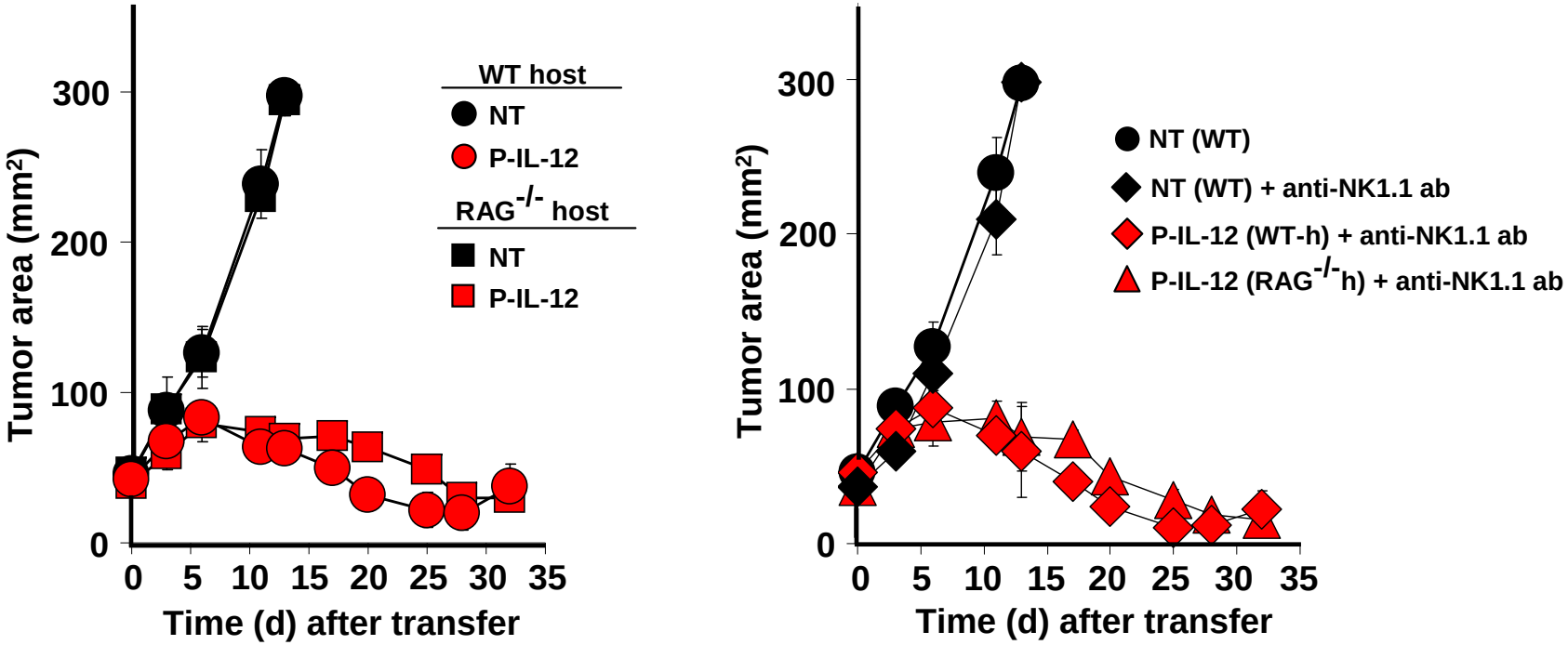




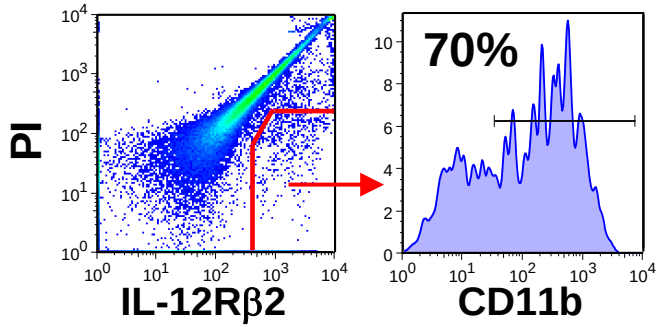
IFN-γ expression and sensitization through host cells is critical for successful treatment

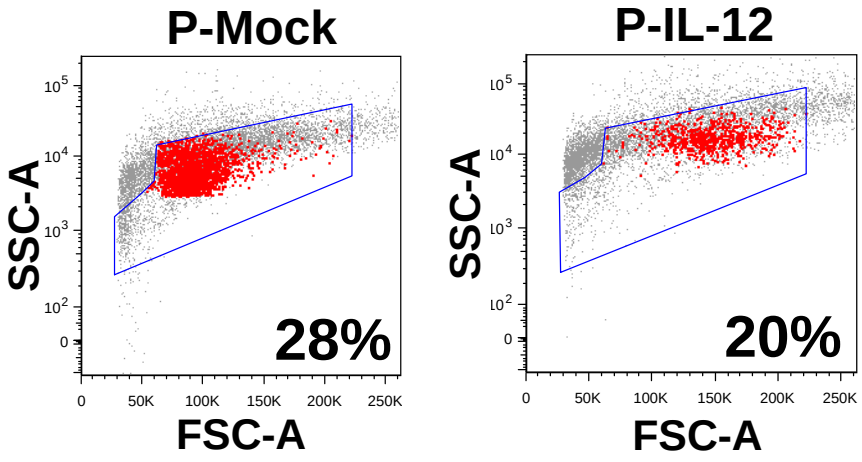


Host NK, T and B cells are not necessary for tumor rejection



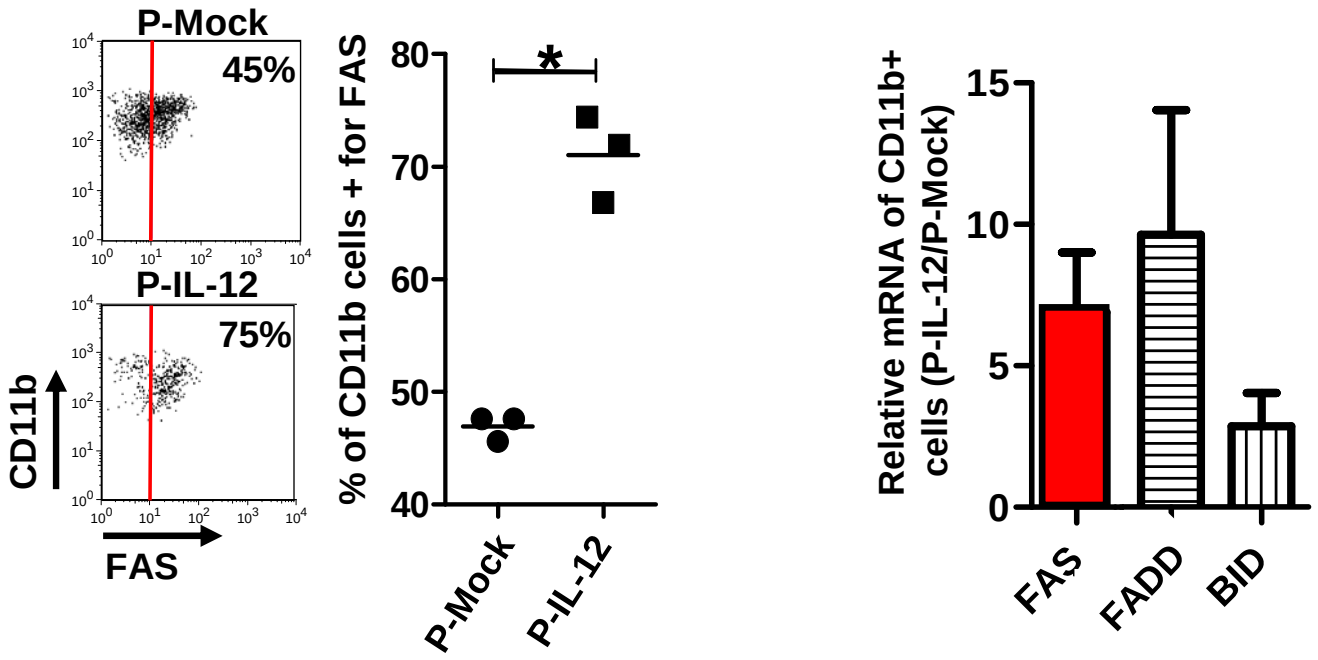
Majority of cells expressing IL-12Rβ2 within the tumor are CD11b+ myeloid derived cells



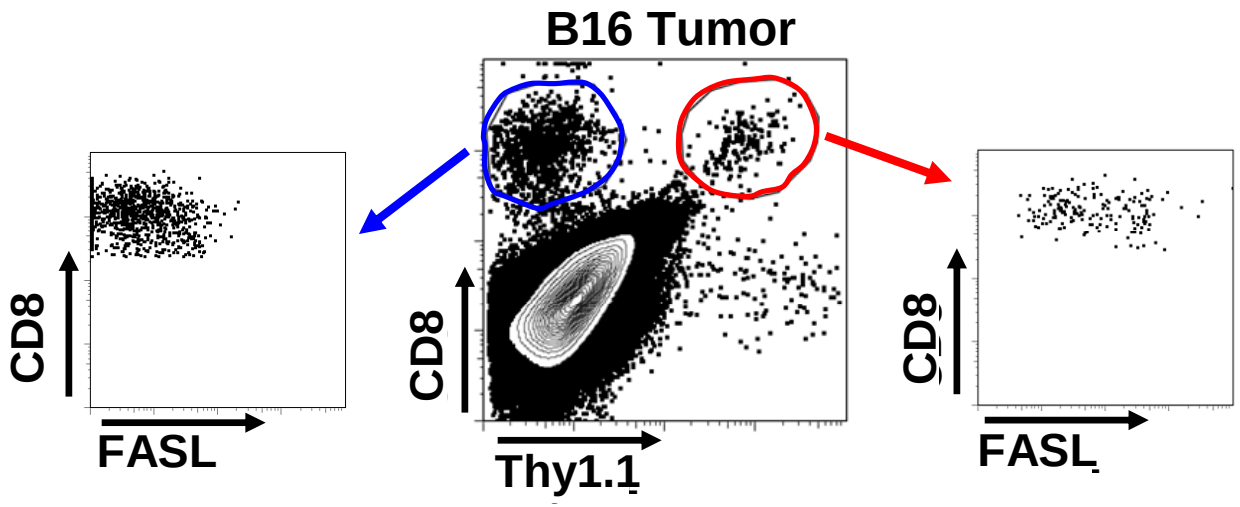


PI-, CD3-, NK1.1-, B220- CD11b+

CD11b+ Myeloid Cells within tumors of IL-12 treated mice have higher expression of FAS (CD95)



Adoptively transferred CD8+ T cells within the tumor have high FASL expression



Pmel Thy1.1+ cells expressing IL-12 were transferred into C56/BL6 mice

Summary

- **Small numbers of tumor specific T cells overproducing IL-12 within the tumor microenvironment can eradicate large established tumors**
- **Anti-tumor immunity is dependant on IL-12 and IFN-γ dependent sensitization of host bone marrow derived myeloid cells**
- **IL-12 engineered T cells induce functional changes in the myeloid population residing within tumors**
- **Anti-tumor immunity is largely dependent on the ability of endogenous cells to cross-present tumor antigens in vivo**

Clinical Applicability

- **Clinical grade inducible vector designed by Ling Zhang and Richard Morgan**

- **Phase I/II Study of Metastatic Melanoma Using Lymphodepleting Conditioning Followed by Infusion of CD8 Enriched Tumor Infiltrating Lymphocytes Genetically Engineered to Express IL-12**

Principal Investigator

Steven A. Rosenberg, M.D. Ph.D.

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NICHOLAS P. RESTIFO **GIORGIO TRINCHIERI**