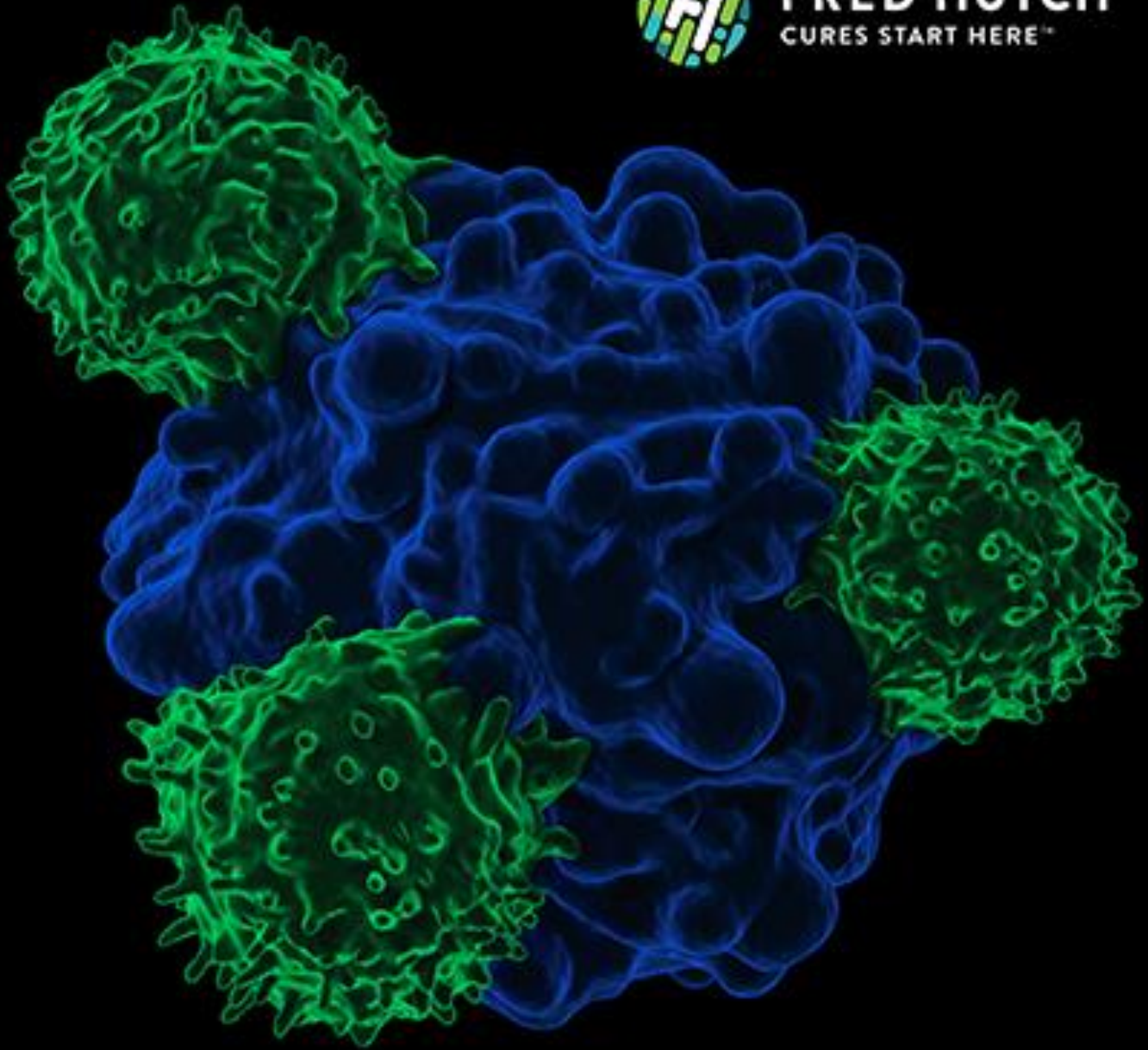




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Engineering adoptive T cell therapy to overcome immune suppression in ovarian cancer

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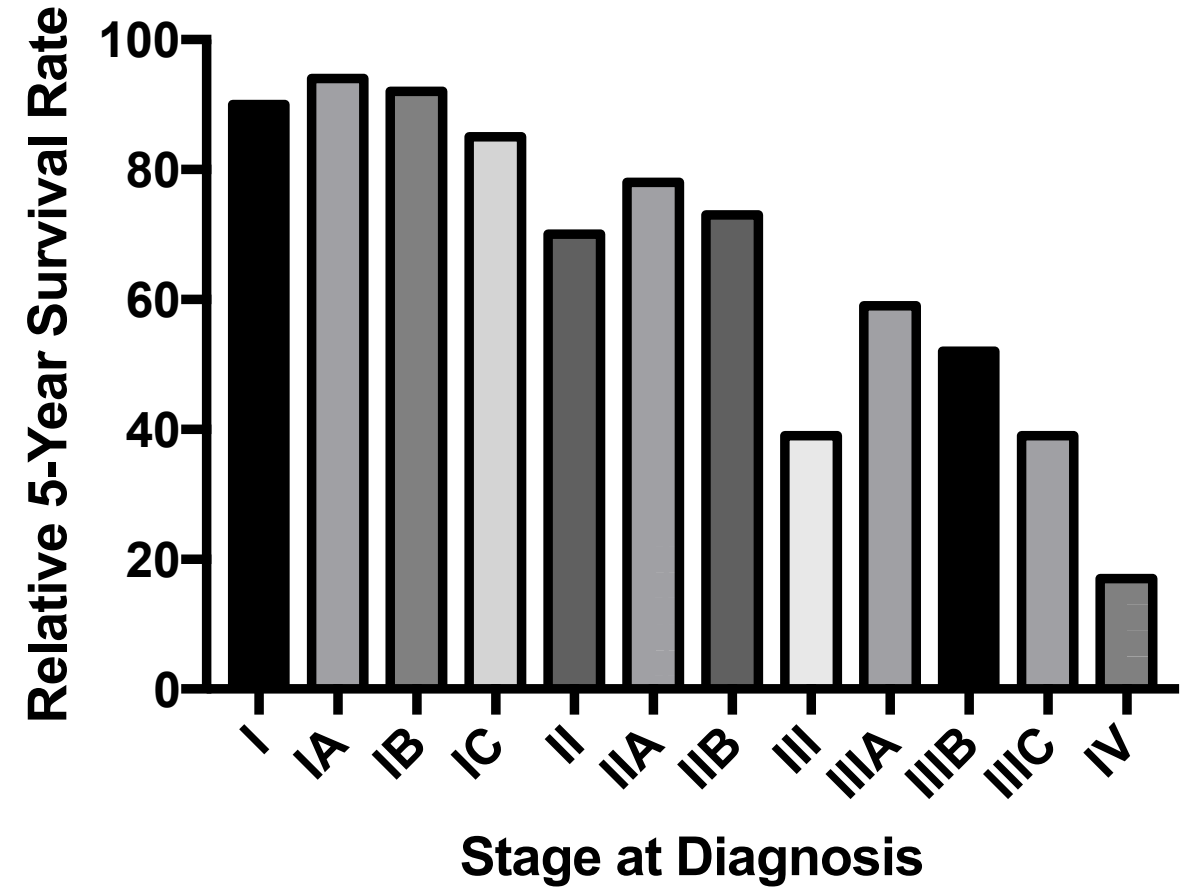
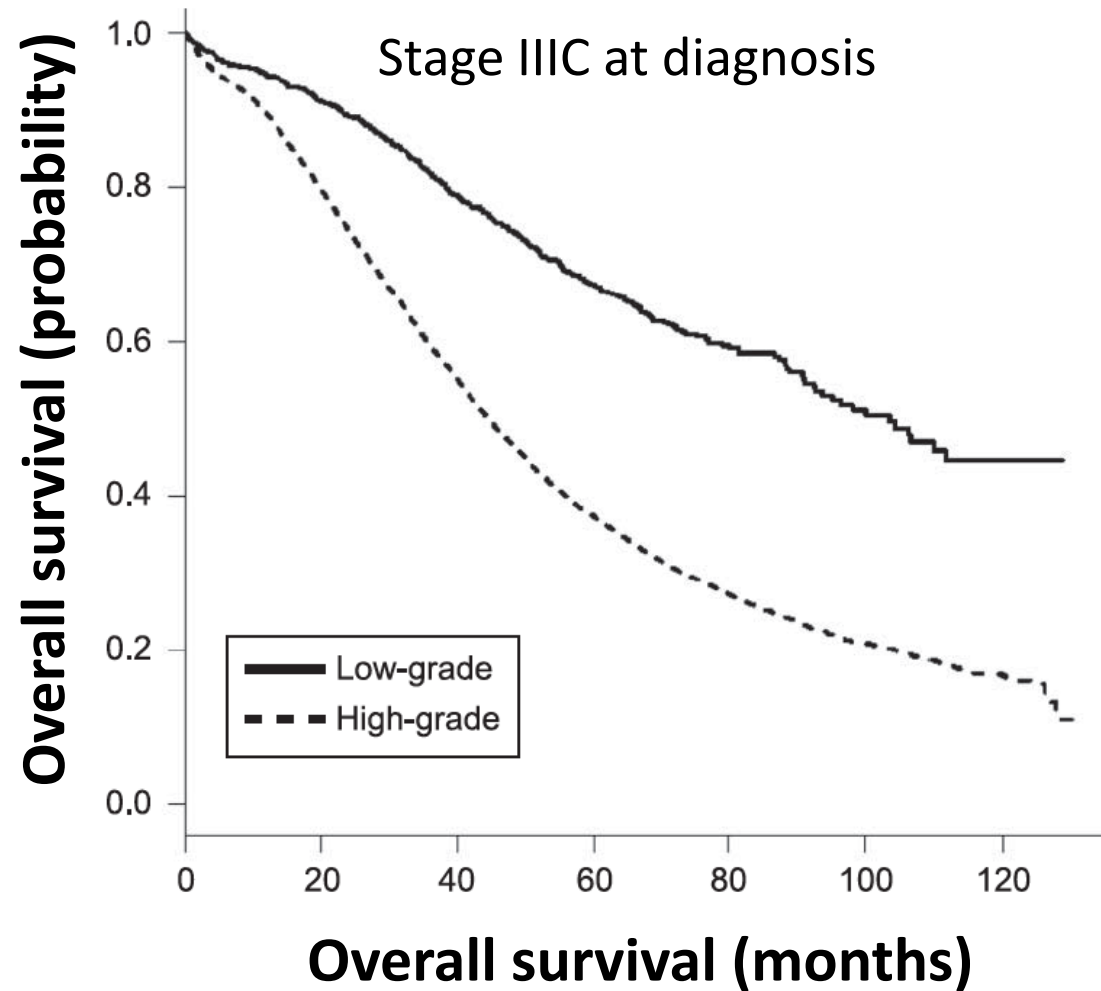
Disclosure Information

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Dr. Kristin G. Anderson

I have no financial relationships to disclose in relation to the content of this activity.

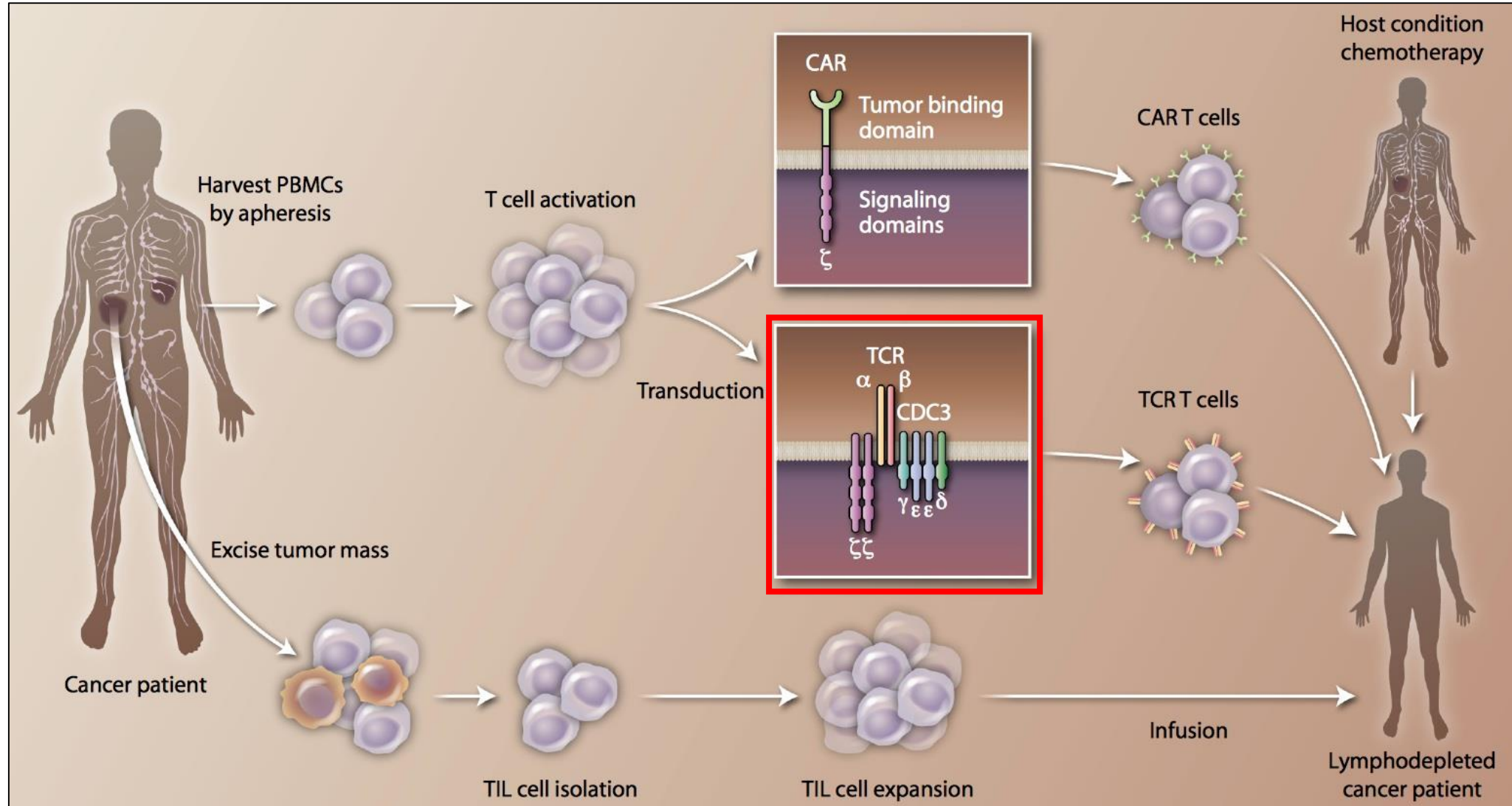
The overall 5-year survival rate for advanced stage high grade serous ovarian cancer patients is less than 50%



Gockley *et al.* Obstetrics and Gynecology (2017)

Generated from data available at: <https://www.cancer.org/cancer/ovarian-cancer/detection-diagnosis-staging/survival-rates.html>

Adoptive T cell therapy is currently used in the clinic to treat malignancies

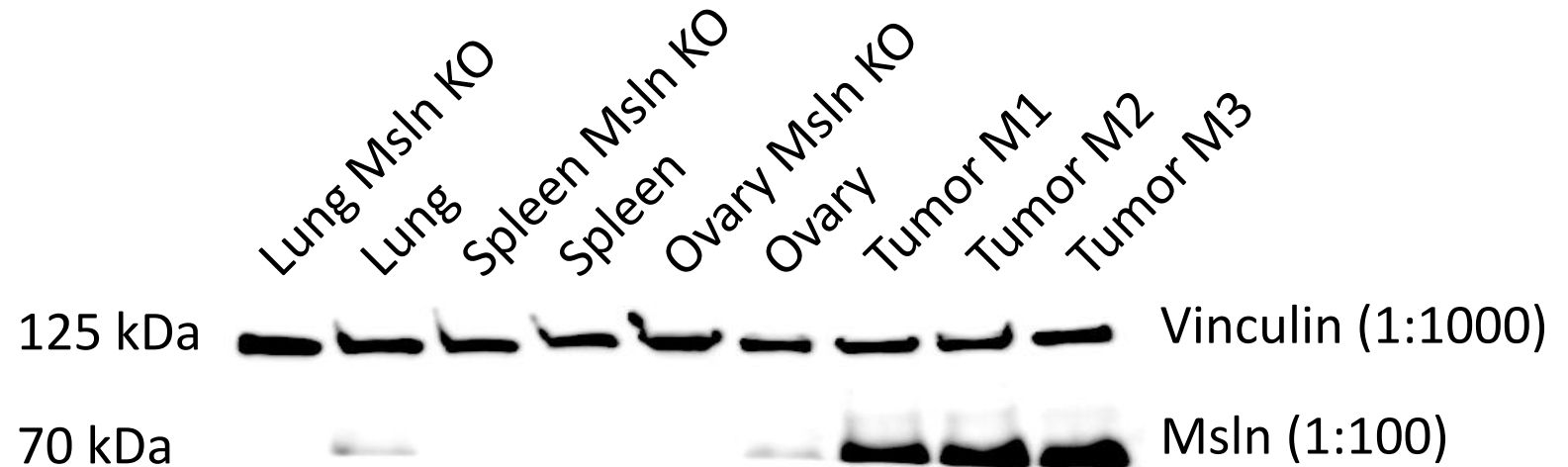
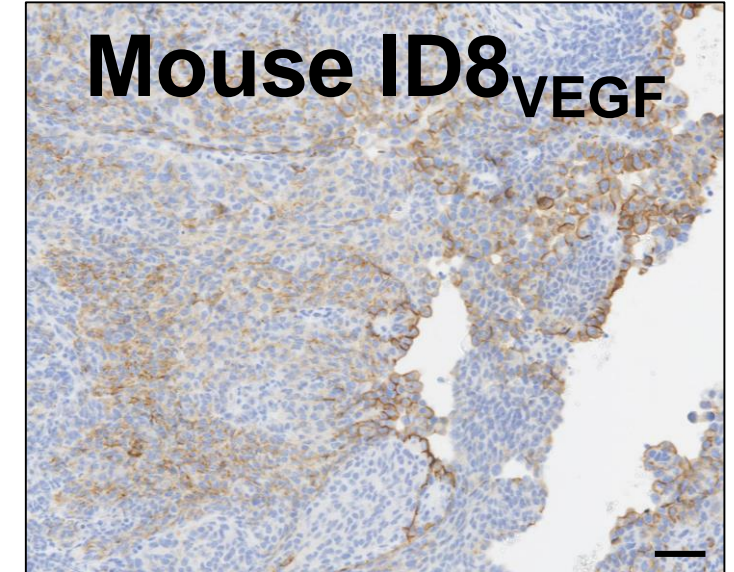
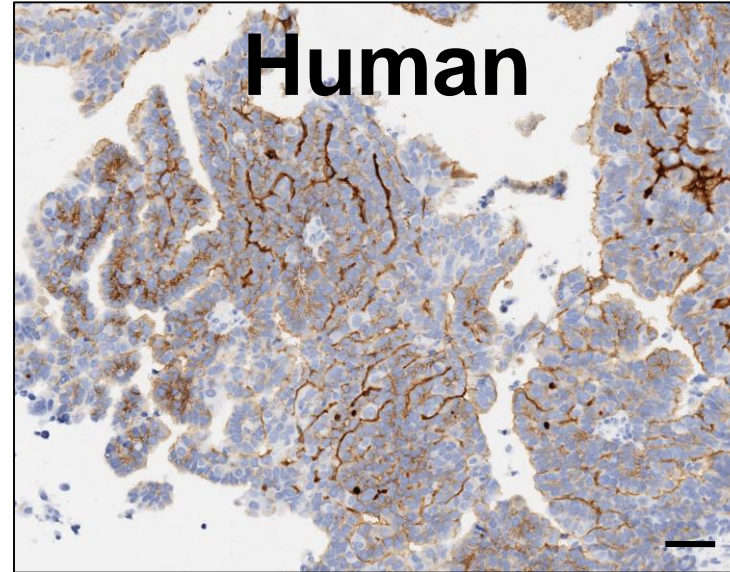
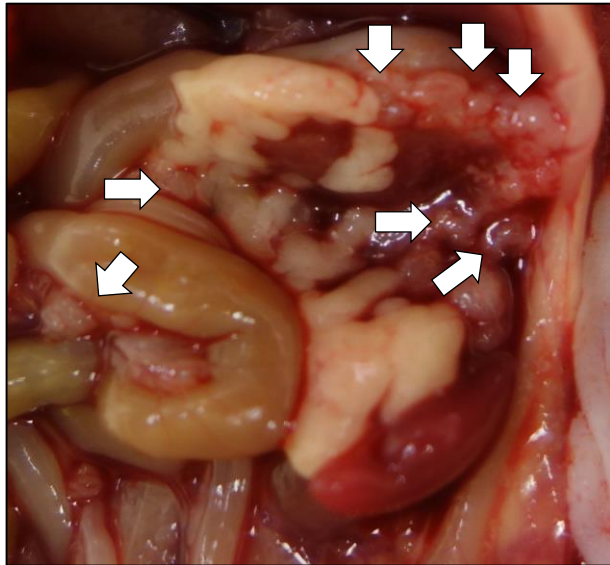
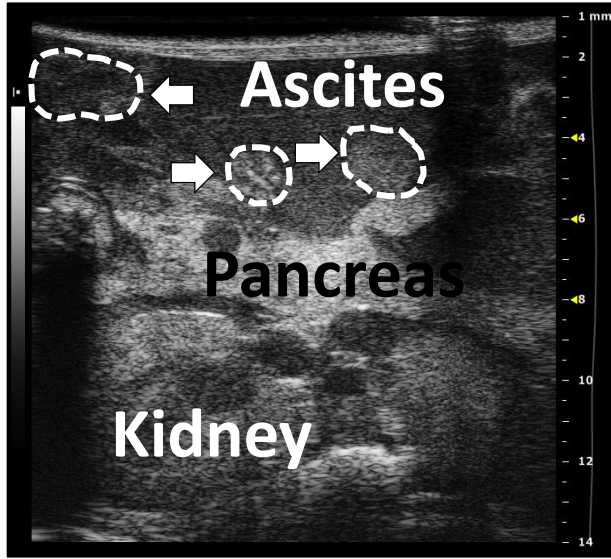


Adapted from: June, Riddell, and Schumacher, *Sci Transl Med*. 2015

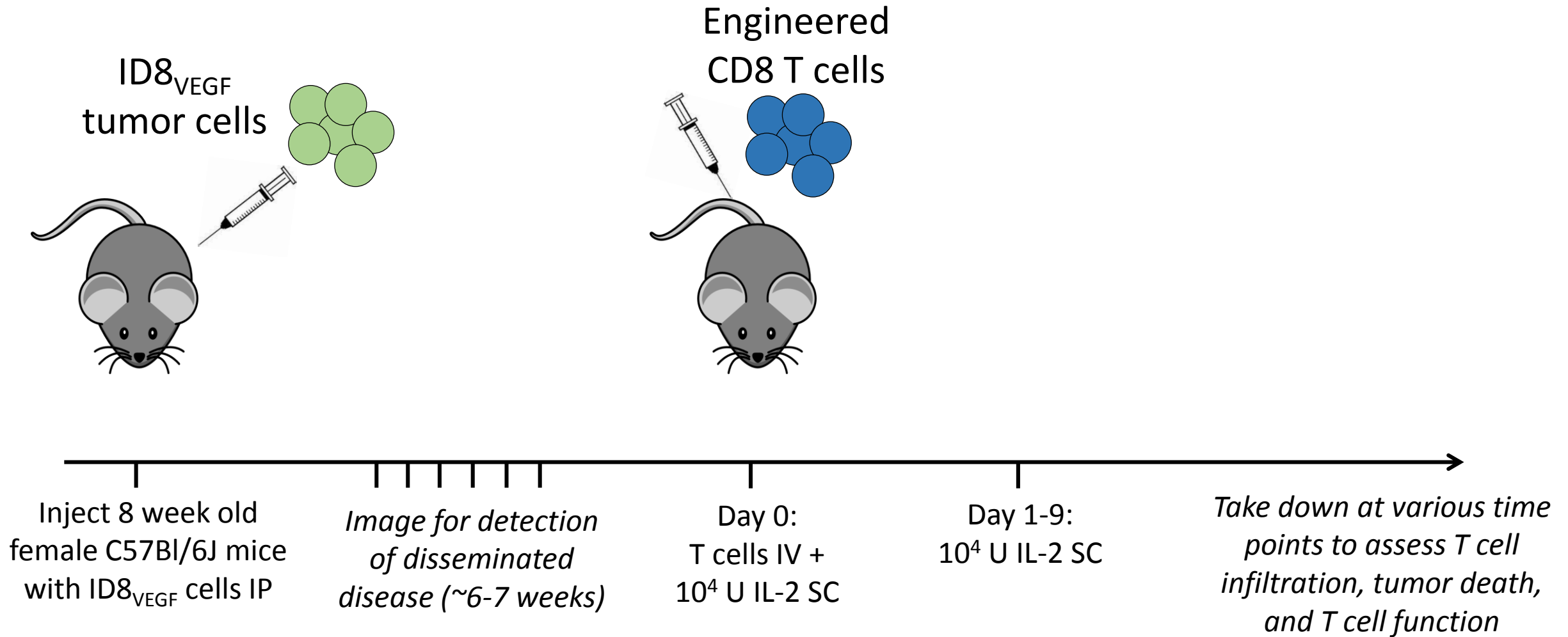
Hypothesis:

CD8 T cells engineered to express a high-affinity T cell receptor specific for an ovarian cancer antigen will slow tumor growth and prolong survival

The ID8_{VEGF} tumor model recapitulates characteristics of human ovarian cancer

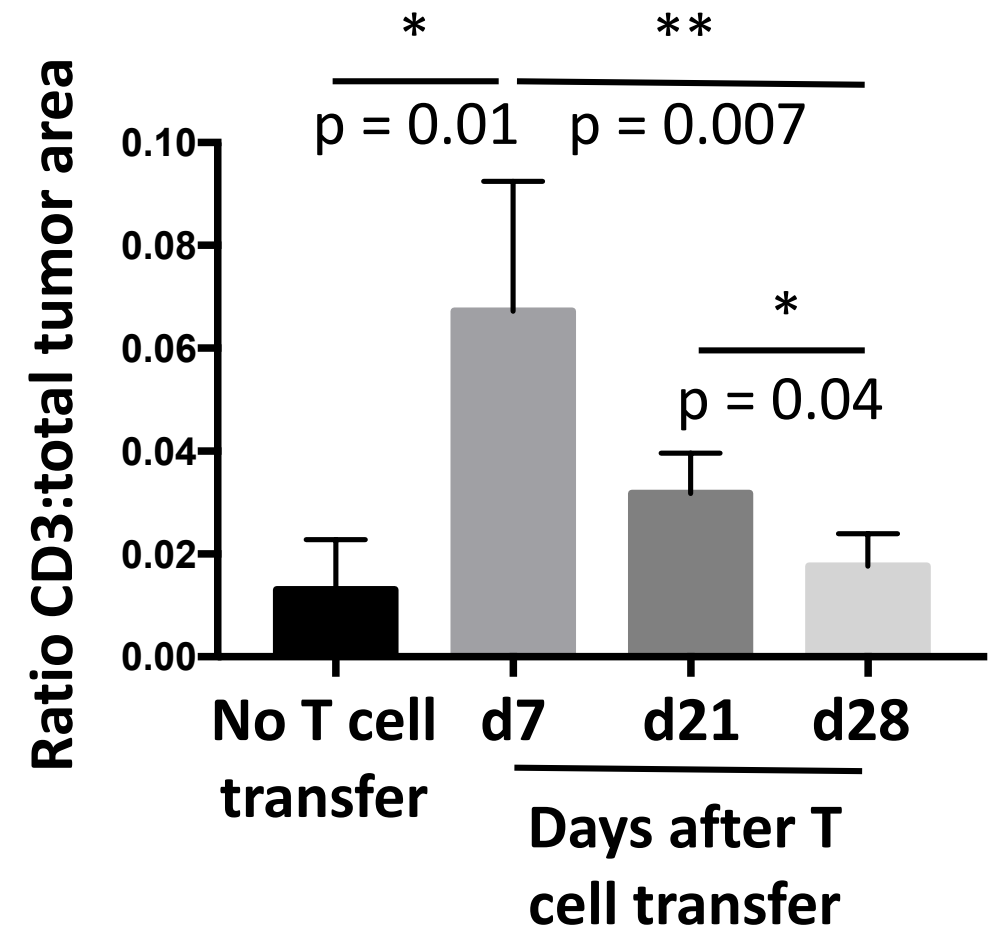
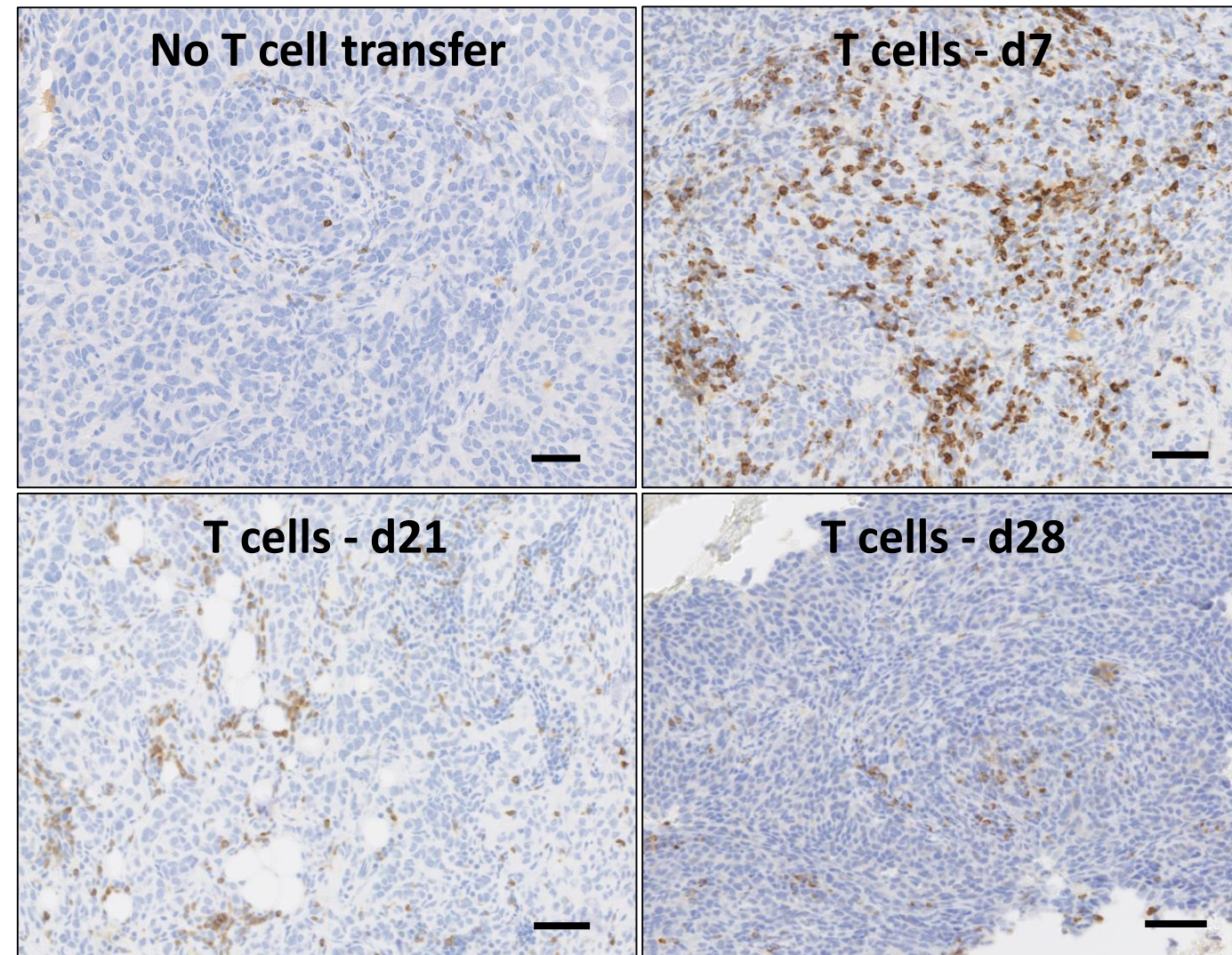


Initial strategy to evaluate engineered T cell therapy in advanced stage ovarian cancer

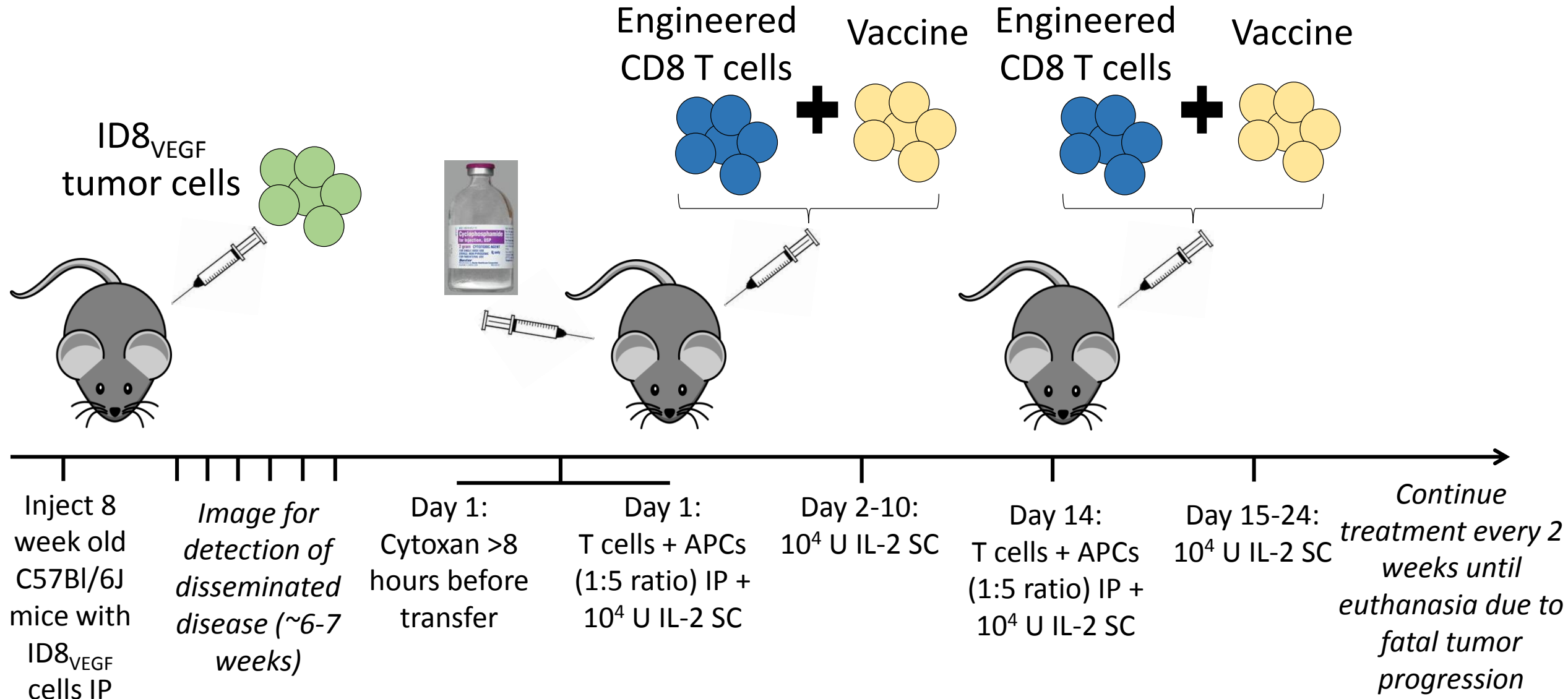


Engineered mesothelin-specific T cells infiltrate ID8_{VEGF} tumors but do not persist

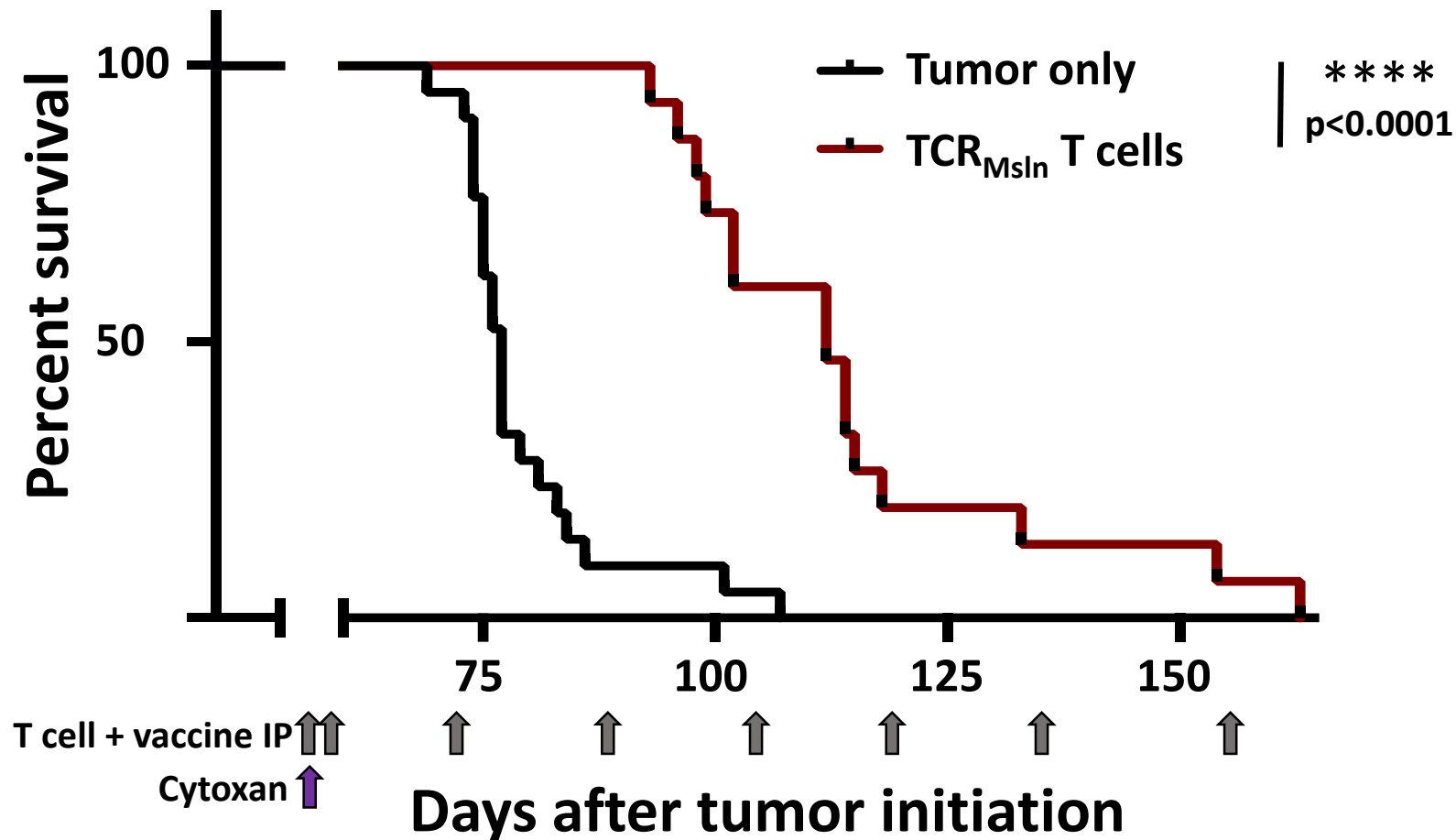
CD3



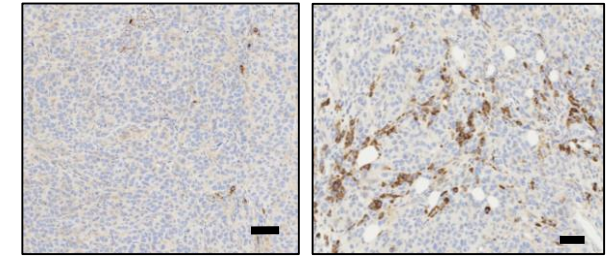
Initial strategy to achieve antitumor activity with engineered T cells



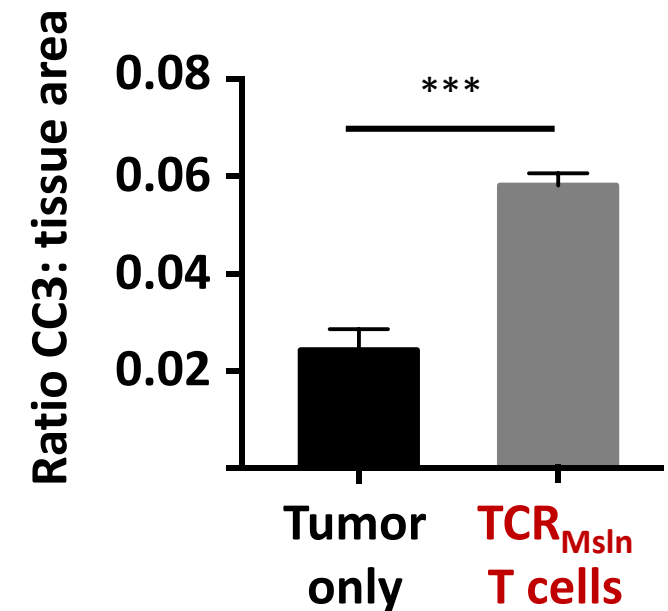
Treatment of ID8_{VEGF} tumor-bearing mice with Msln-specific T cells prolongs survival



Cleaved Caspase 3+



Tumor only TCR_{Msln} T cells

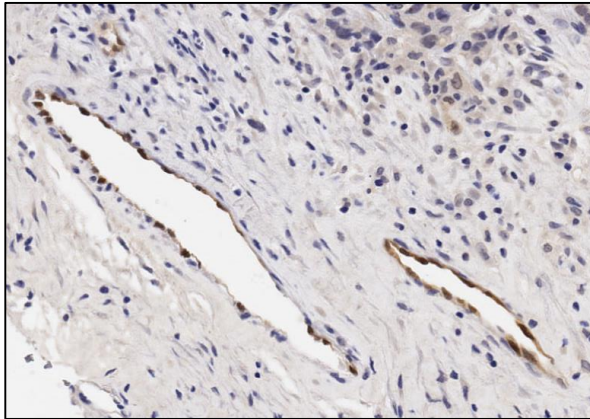


Engineered Fas Immunomodulatory Fusion Proteins may overcome induced T cell death and promote cell proliferation/survival

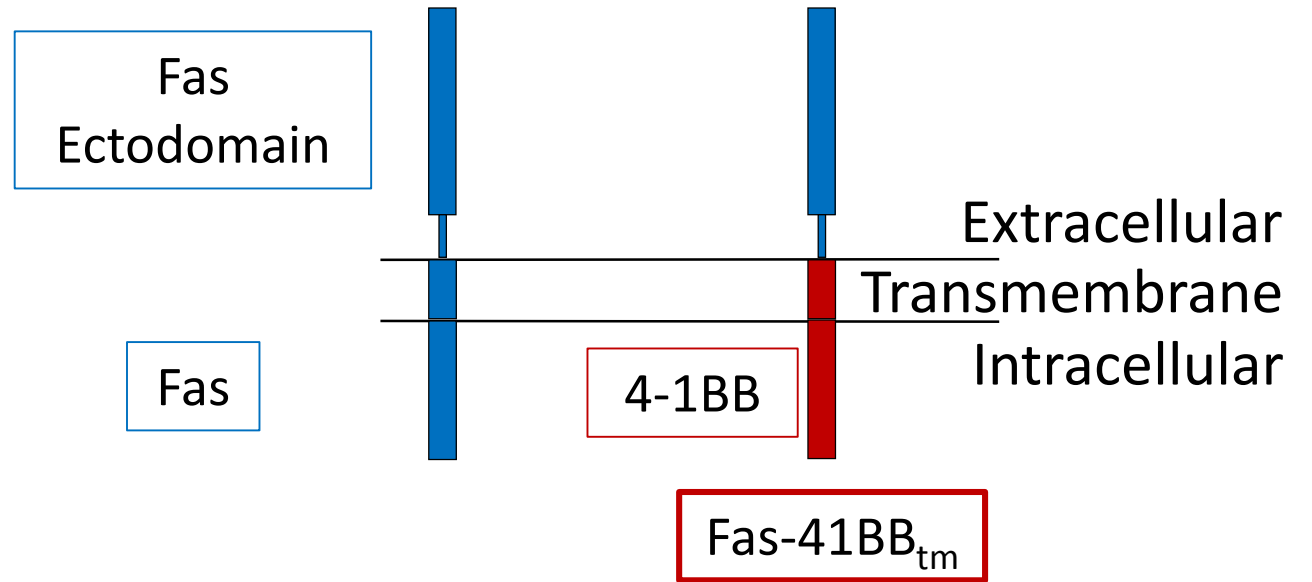
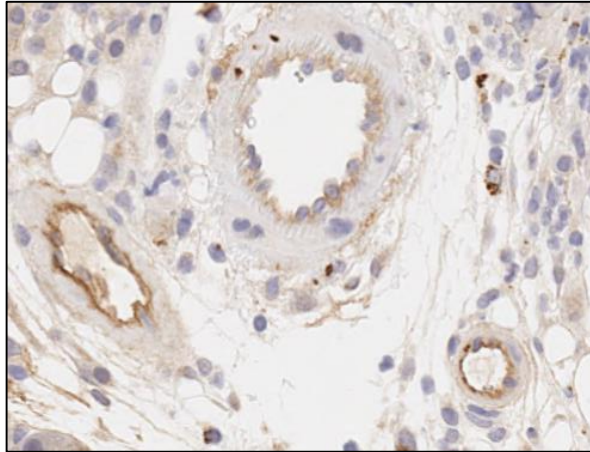
Altered Trafficking/Survival

Human

Fas Ligand

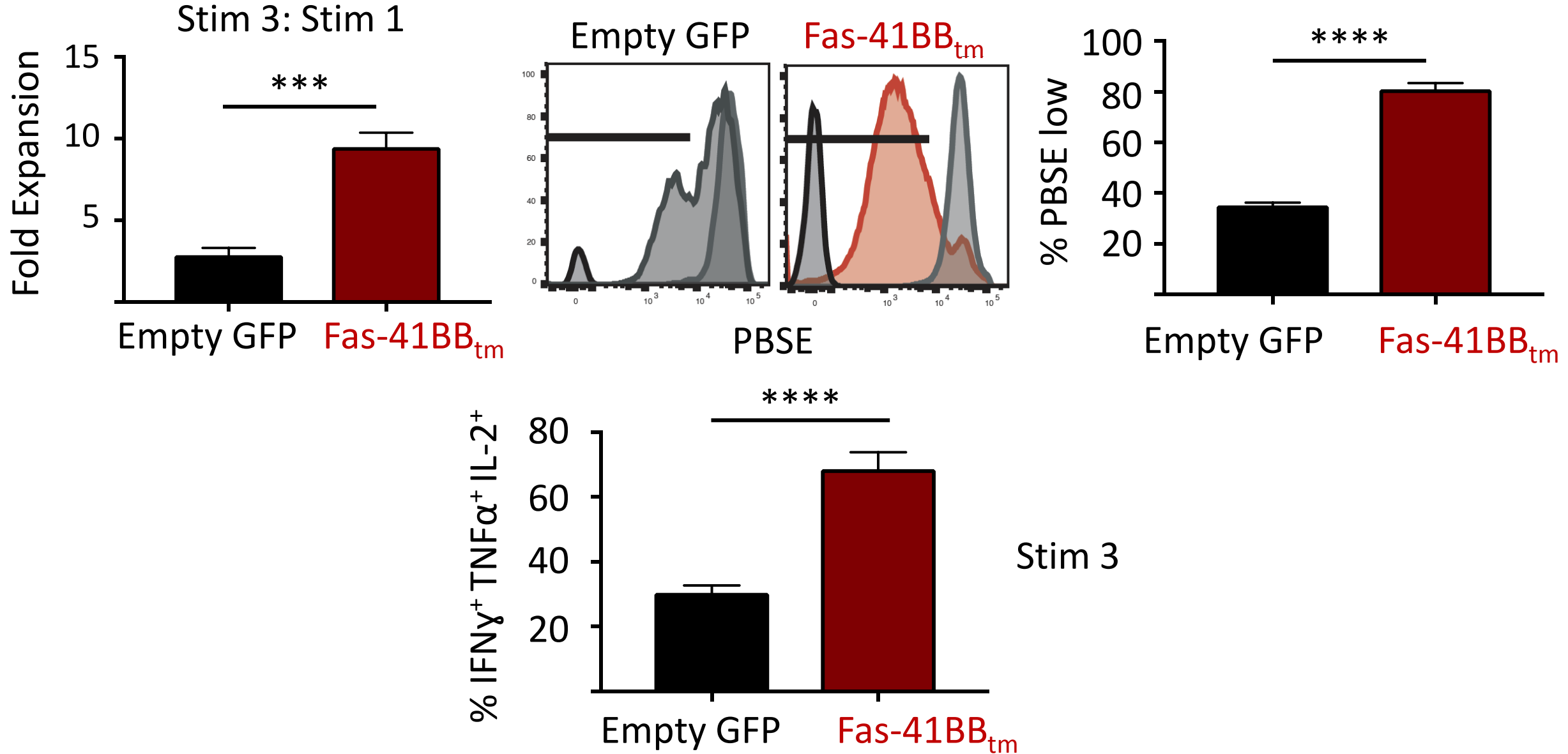


**Mouse
ID8_{VEGF}**

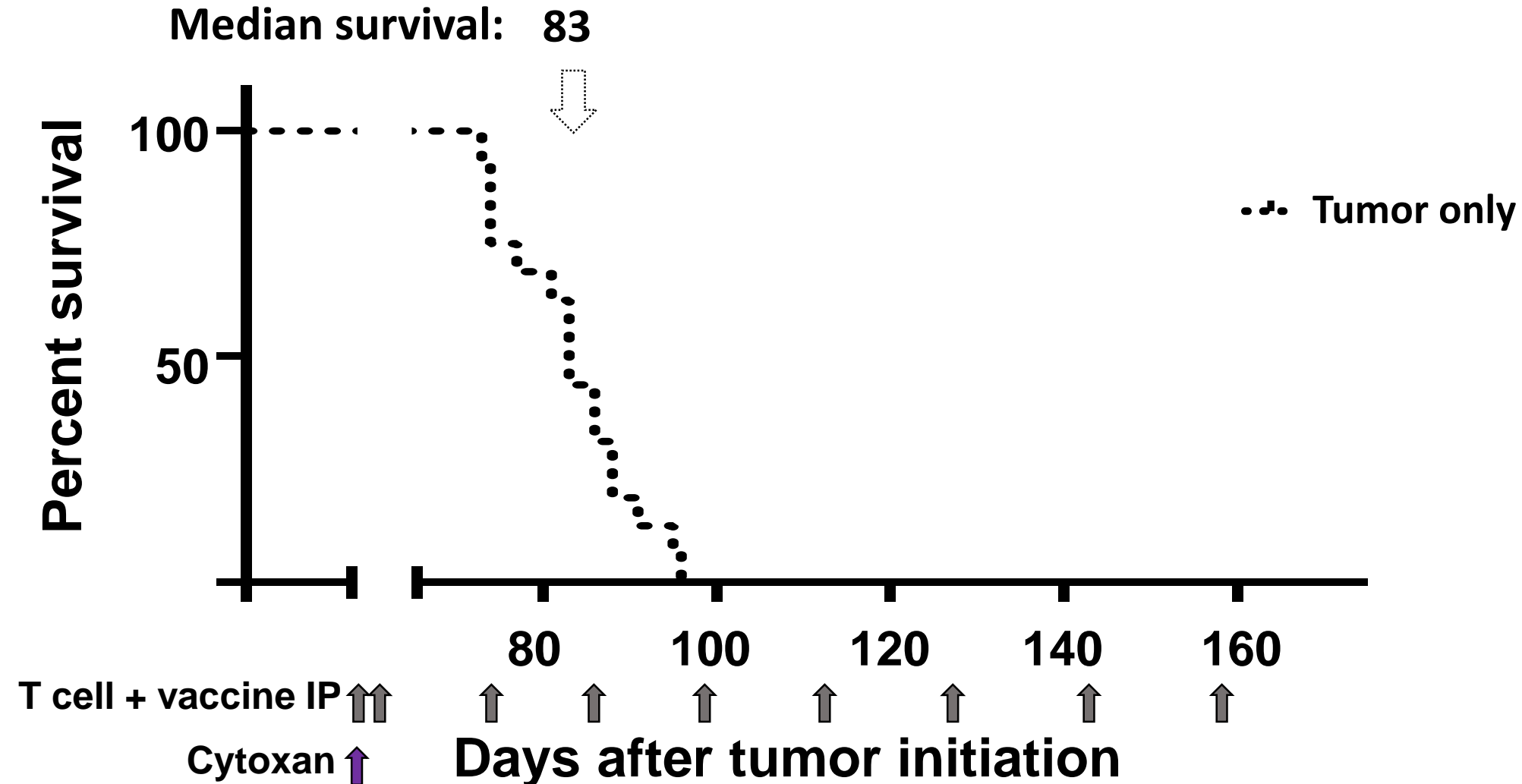


Shannon Oda, PhD

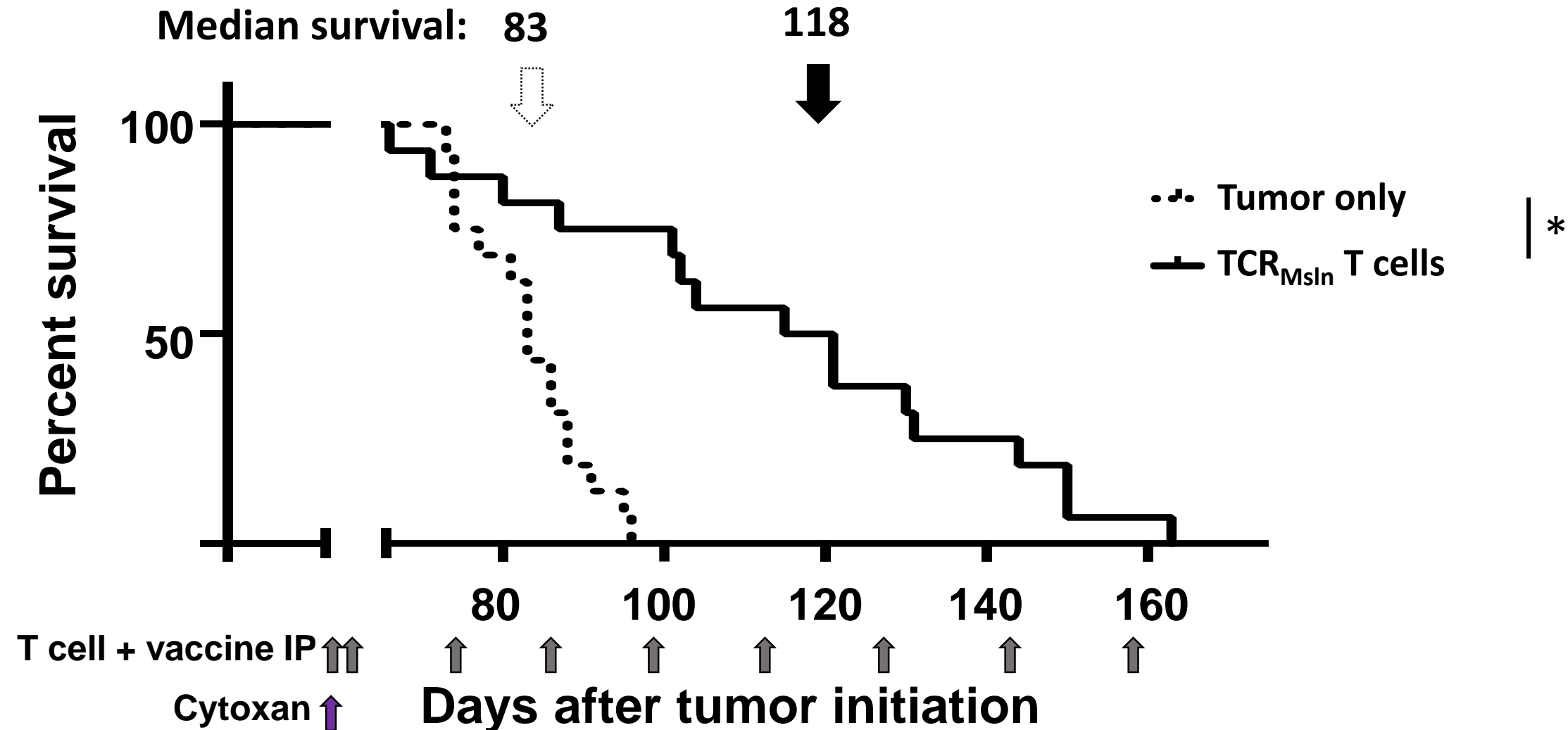
T cells expressing Fas-4-1BB IFPs have enhanced proliferative ability and cytokine production



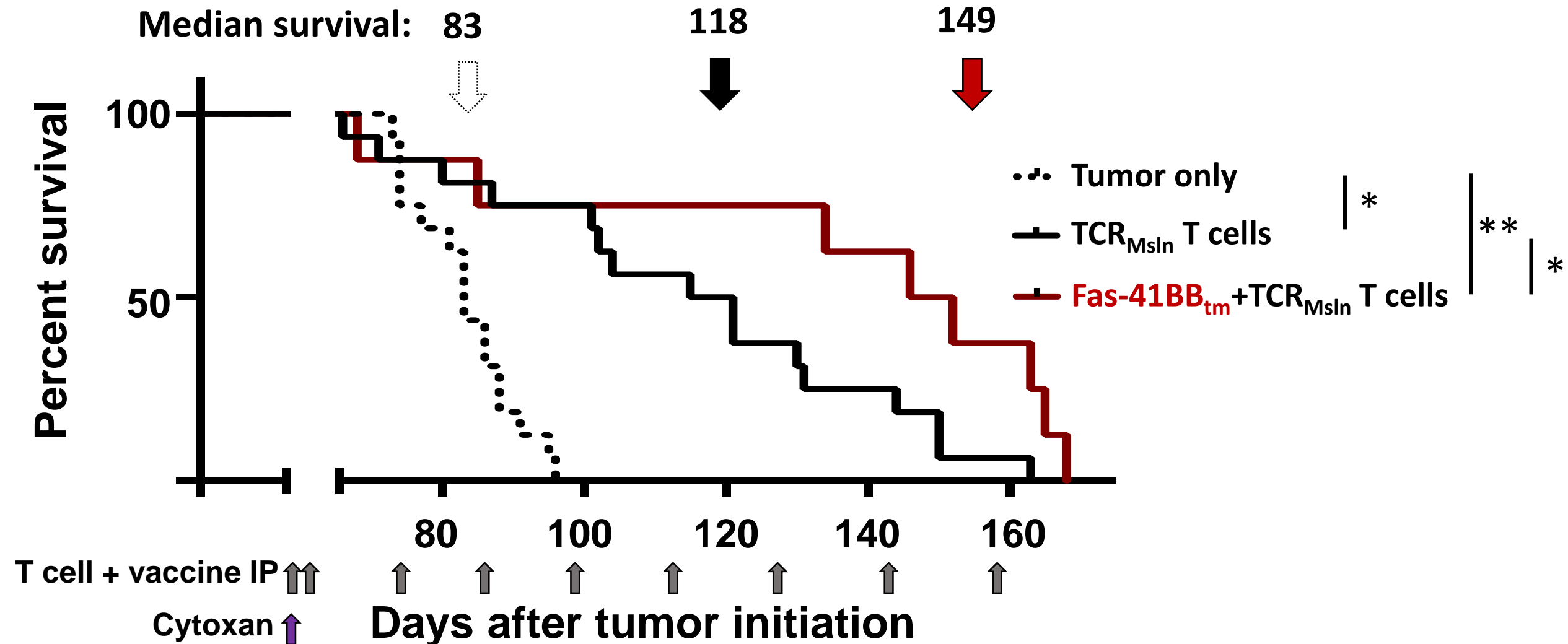
ID8_{VEGF} tumor-bearing mice treated with Msln-specific T cells expressing a Fas IFP have prolonged survival relative to mice treated with Msln-specific T cells



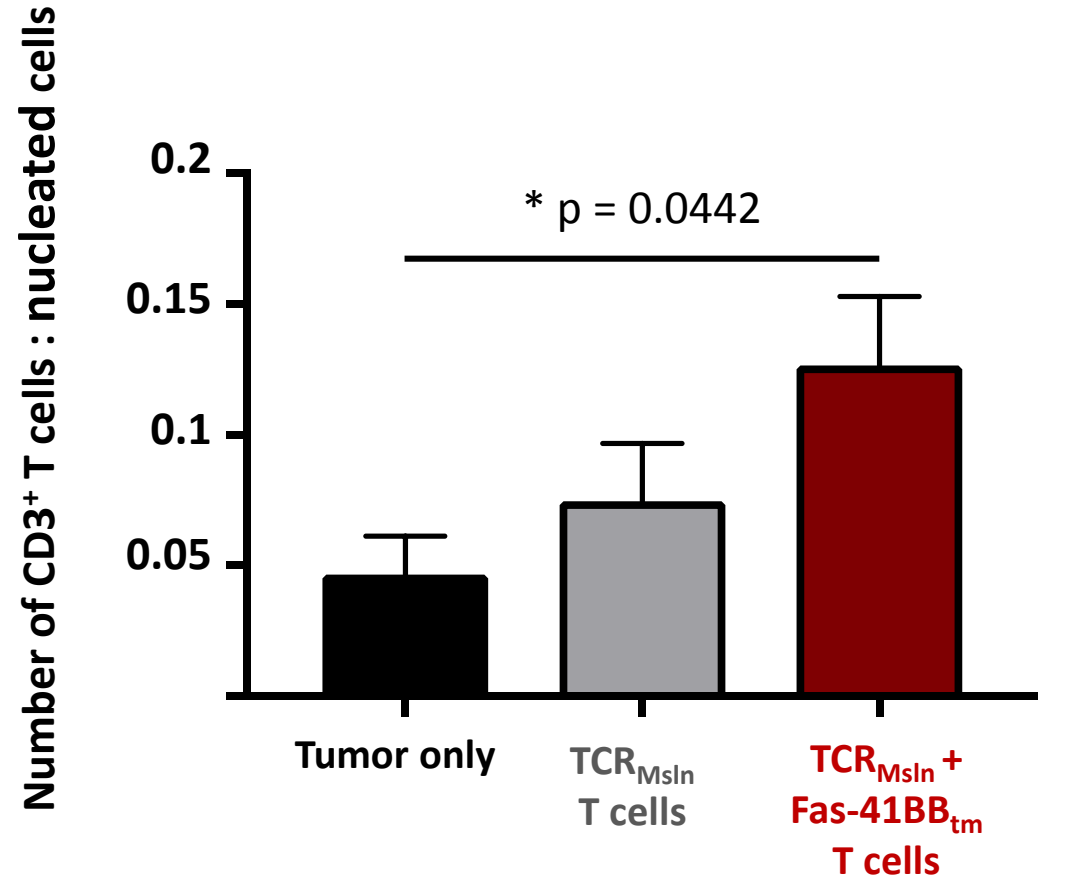
ID8_{VEGF} tumor-bearing mice treated with Msln-specific T cells expressing a Fas IFP have prolonged survival relative to mice treated with Msln-specific T cells



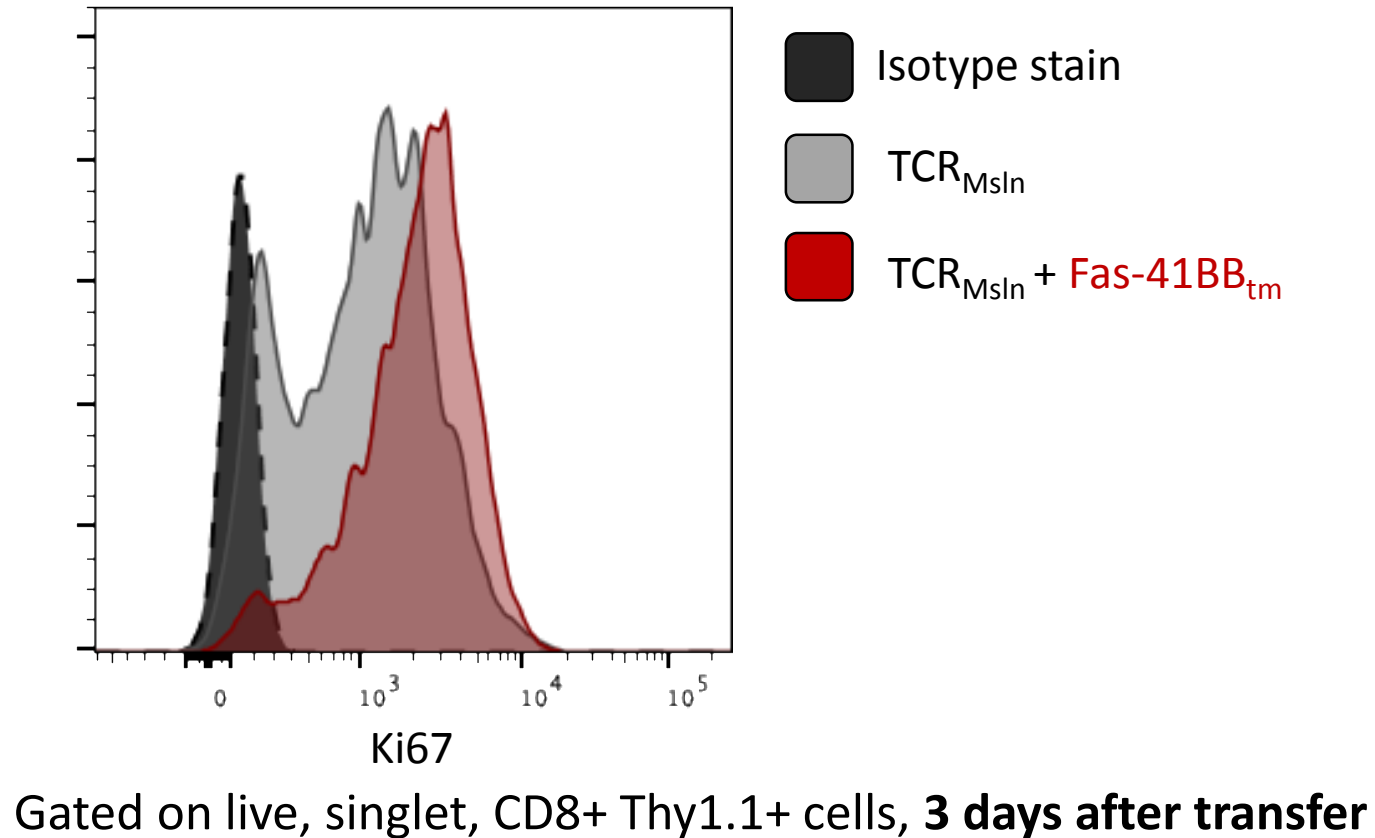
ID8_{VEGF} tumor-bearing mice treated with Msln-specific T cells expressing a Fas IFP have prolonged survival relative to mice treated with Msln-specific T cells



T cells expressing Fas-4-1BB IFPs are enriched in ID8_{VEGF} tumors and have greater proliferative potential



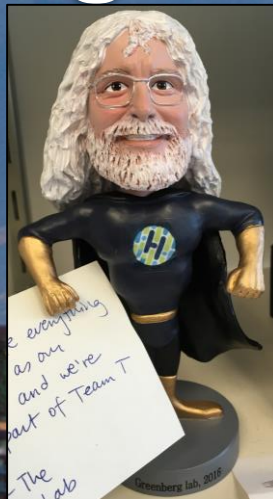
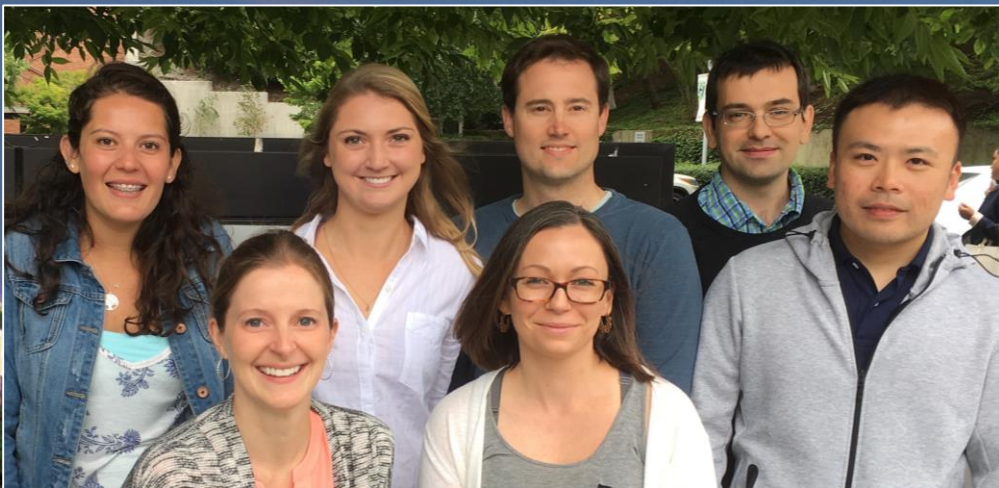
Quantified using IHC, 21 days after T cell transfer



Take home messages:

- The ID8_{VEGF} mouse model mimics features of human ovarian cancer:
 - metastatic lesions, terminal ascites, over-expression of Mesothelin.
- Engineered T cells infiltrate but do not persist in ID8_{VEGF} tumors.
- Adoptive transfer of high-affinity MSLN-specific T cells prolongs survival of tumor-bearing mice.
- The addition of an IFP to co-opt Fas-mediated signaling in CD8 T cells enhances the efficacy of engineered T cell therapy.

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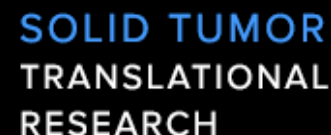
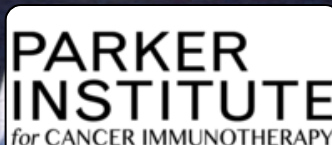
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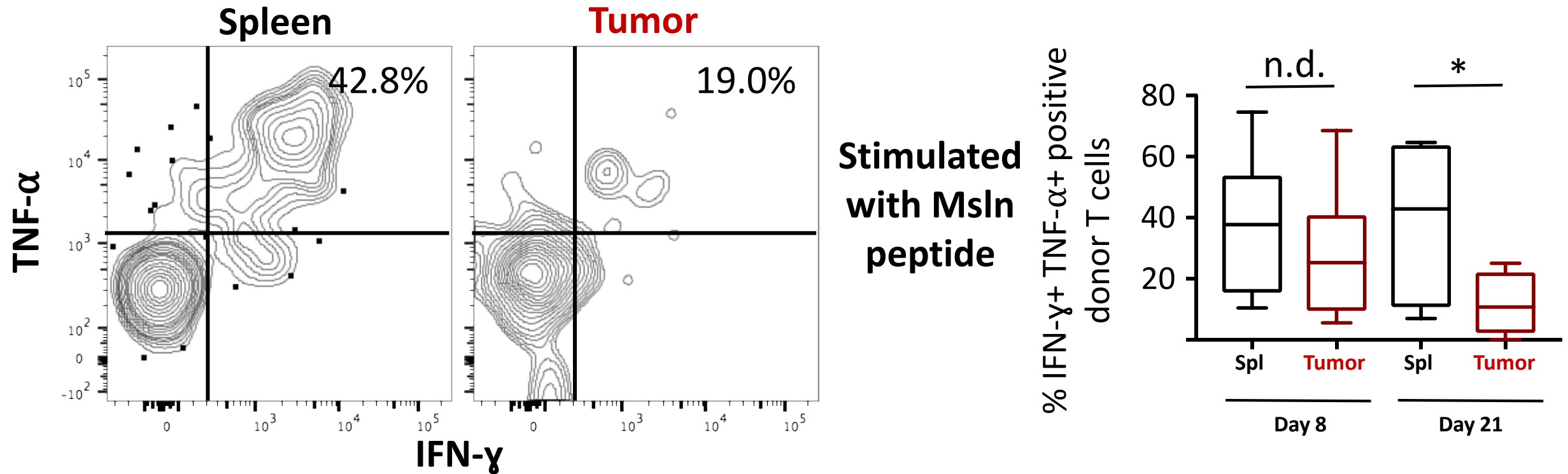
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Msln-specific T cells have reduced function after prolonged antigen experience within ID8_{VEGF} tumors

T cell cytokines with anti-tumor activity



Gated on lymphocytes, live, CD8+, Thy1.1+ cells, **21 days after T cell transfer**