



Genetically-modified T cells for solid tumors



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Disclosure

- Patents and patent applications in the fields of T-cell & Gene therapy for cancer
- TESSA Therapeutics: Research collaboration
- DSMB Member: Immatics



Outline

- HER2-CAR T cells: clinical experience for sarcoma
- Genetic modifications to enhance CAR T-cell function
 - IL15
 - TLR signaling

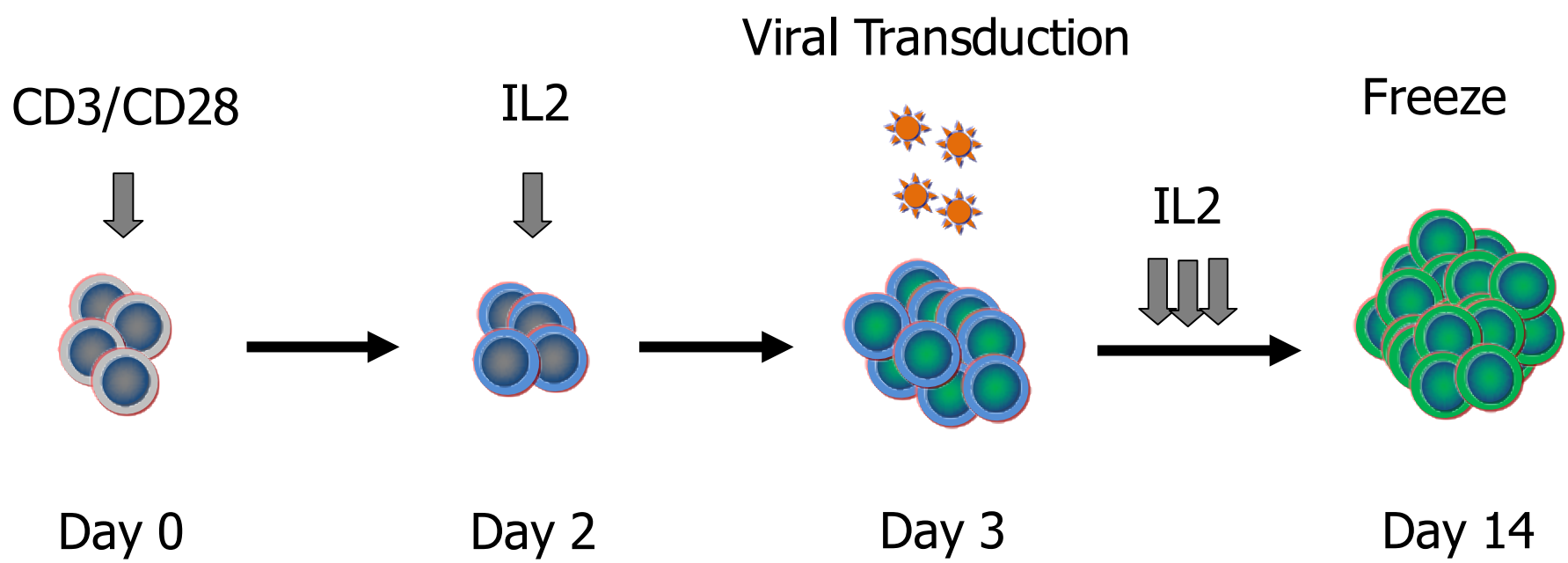
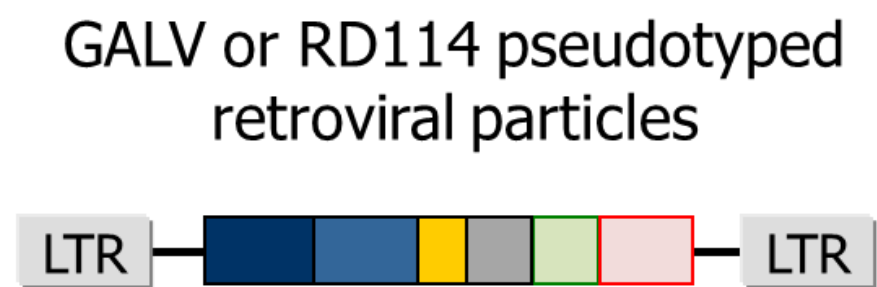
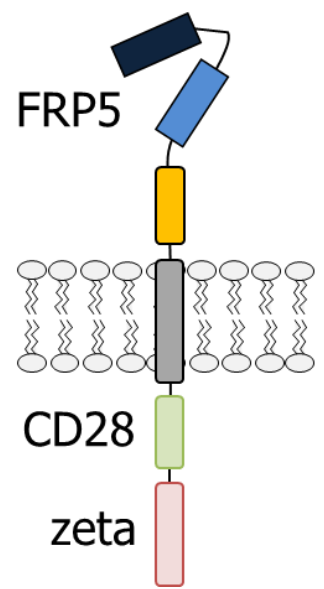


Human Epidermal Growth Factor 2 (HER2; HER2/neu; ERBB2)

- EGFR family of tyrosine kinase receptors
 - Orphan receptor
- Gene amplified in 20 to 25% of breast cancer
 - HER2 antibodies and tyrosine kinase inhibitors effective
- Overexpressed in broad range of malignancies at low levels
 - Brain tumors, sarcomas, 20 – 30% of breast cancer, lung cancer
 - HER2 antibodies and tyrosine kinase inhibitors **ineffective**



2nd Generation HER2-CARTs



(Moritz et al, PNAS 1994; Ahmed et al, Mol Thr 2009)



FRP5-scFV-based HER2-CAR Ts: Preclinical studies

- Recognize and kill
 - 'none gene-amplified' HER2+ cancer cells
 - tumor initiating cells
- Potent antitumor activity in preclinical models
 - Osteosarcoma
 - Medulloblastoma, GBM



T-cell Therapy for HER2+ Sarcoma

- T-cell product: HER2-CARTs
- Dose level: 1×10^5 to 1×10^8 cells/m²
- Patient characteristics
 - 16 OS, 2 EWS, 1 DSRCT
 - metastatic disease
 - had failed multiple lines (>3) of salvage therapy



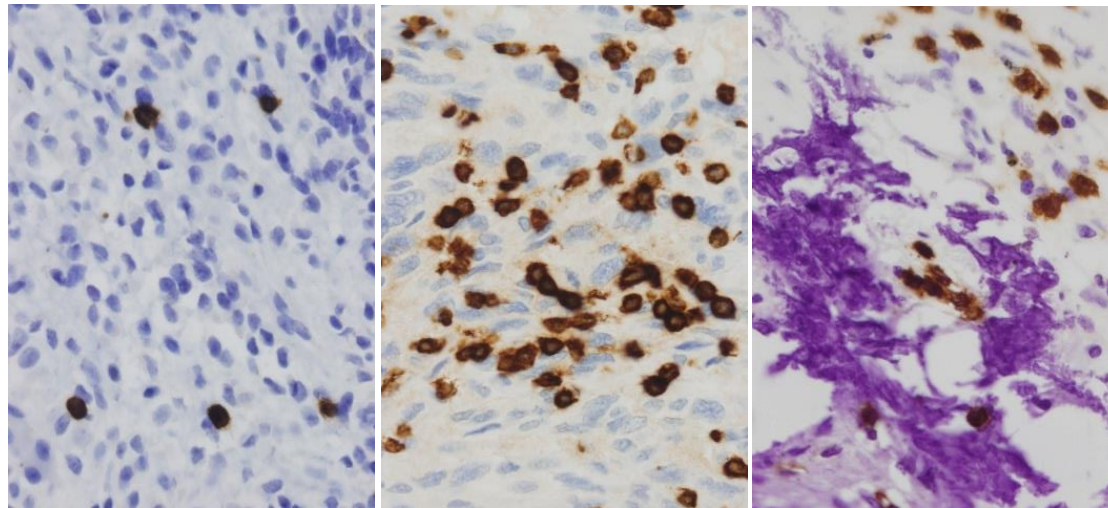
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- Figure 1: Viral titers of DL7 and DL8. The graph shows viral titers (copies per μg DNA) for DL7 (red lines) and DL8 (blue lines) over time post-infusion (3hr, 1wk, 2wk, 4wk, 6wk). DL7 titers start around 6-22 copies at 3hr and drop to near zero by 1wk. DL8 titers start very high (off-scale) and drop sharply to around 8-24 copies at 1wk, then gradually decline to near zero by 6wk.



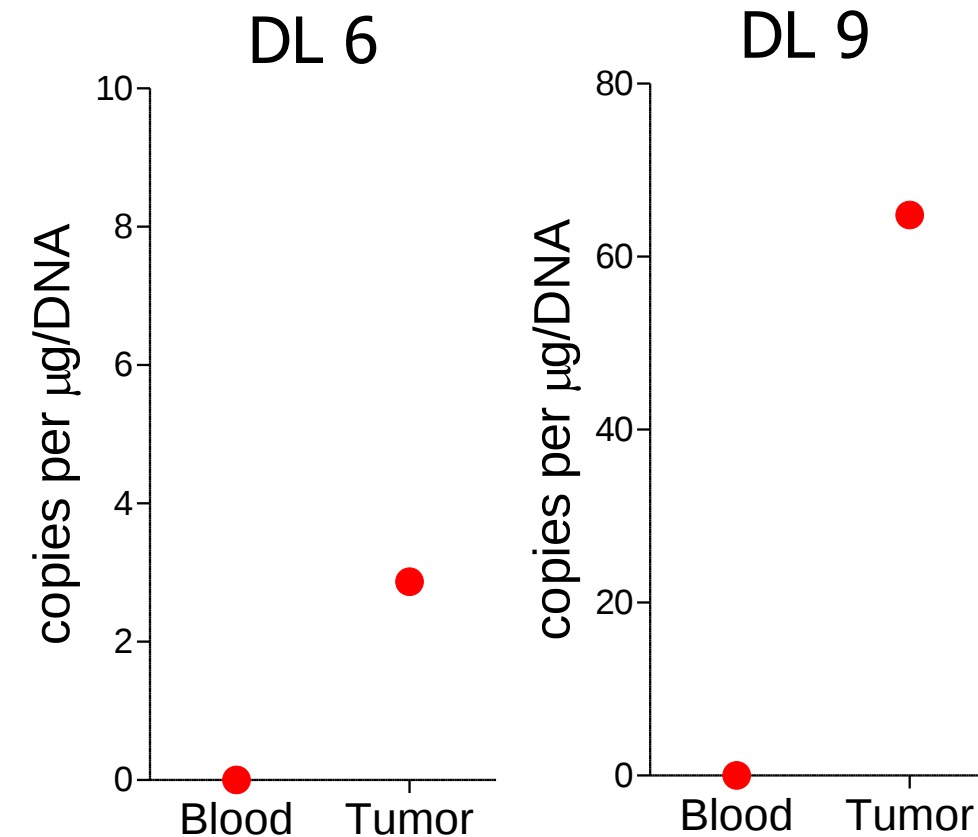


HER2-CARTs traffic to tumor sites

CD3+ T cells
at tumor site



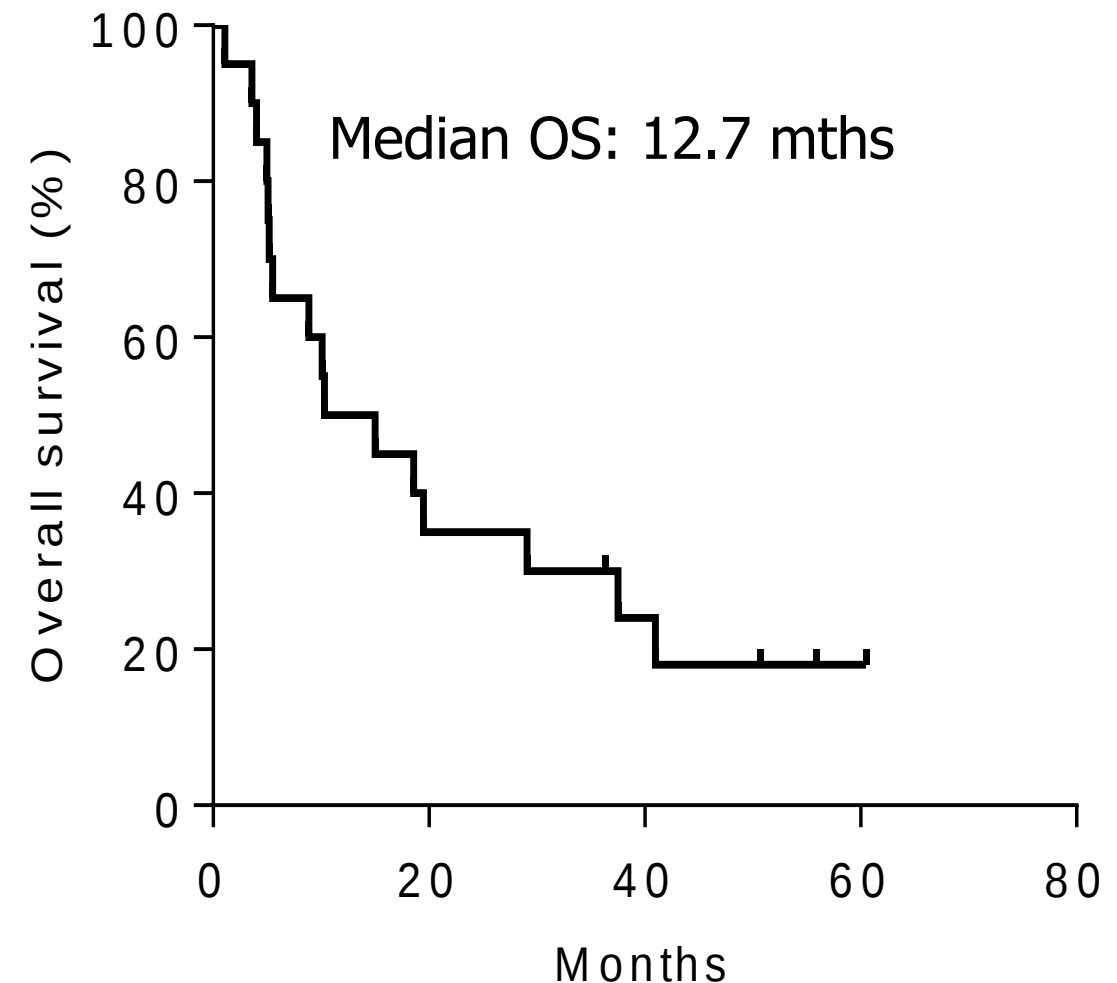
HER2-CARTs at
tumor site





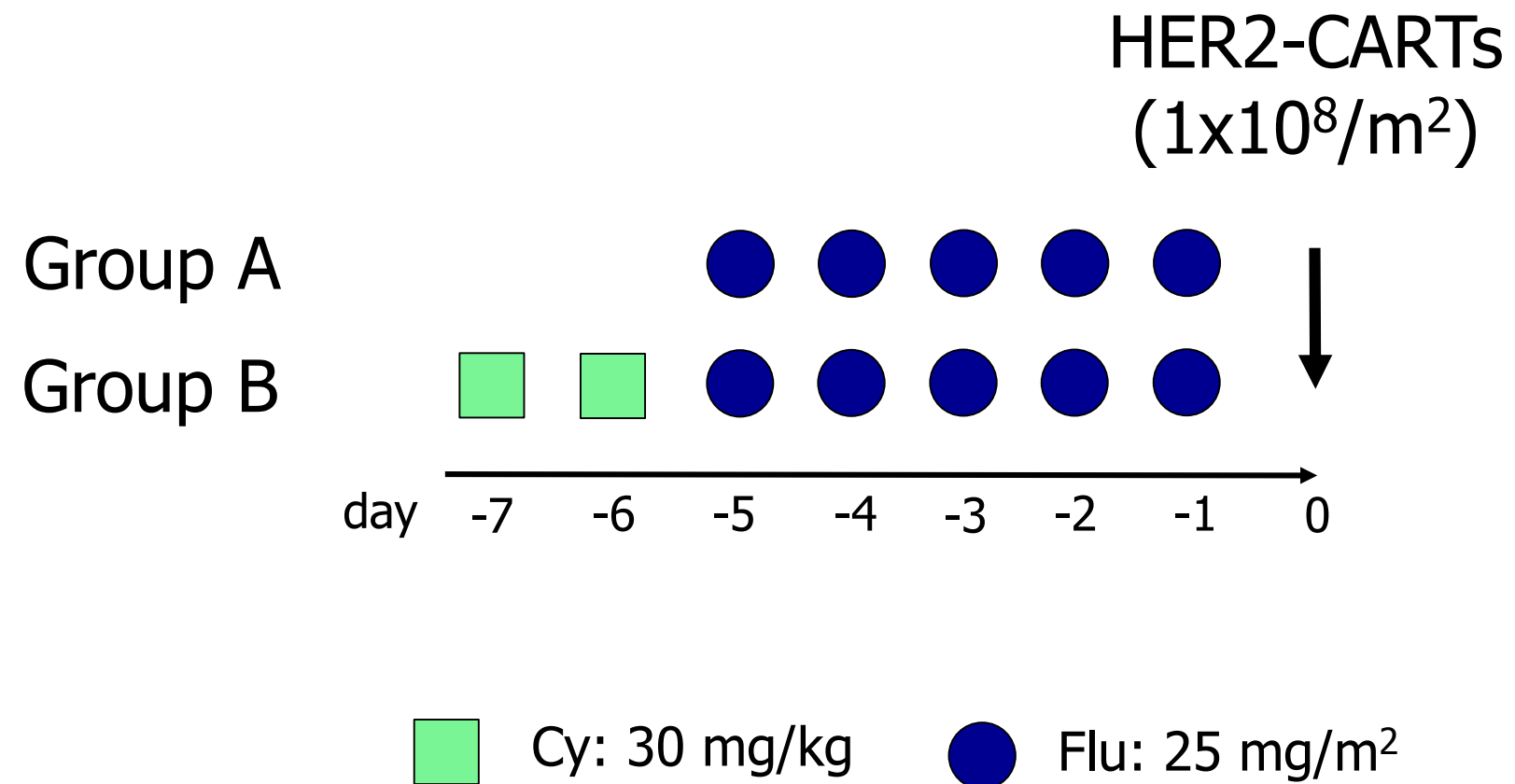
Clinical Outcome

- 4 patients: stable disease for 12 wks to 14 mths
 - 3 patients
 - tumor removed (1 tumor: >90% necrosis)
 - all alive with no disease (4 to 5 years)
- 13 patients with progressive disease
 - 1 patient
 - surgery
 - one dose of CARTs: no disease (3 years)





Lymphodepletion prior HER2-CART infusion



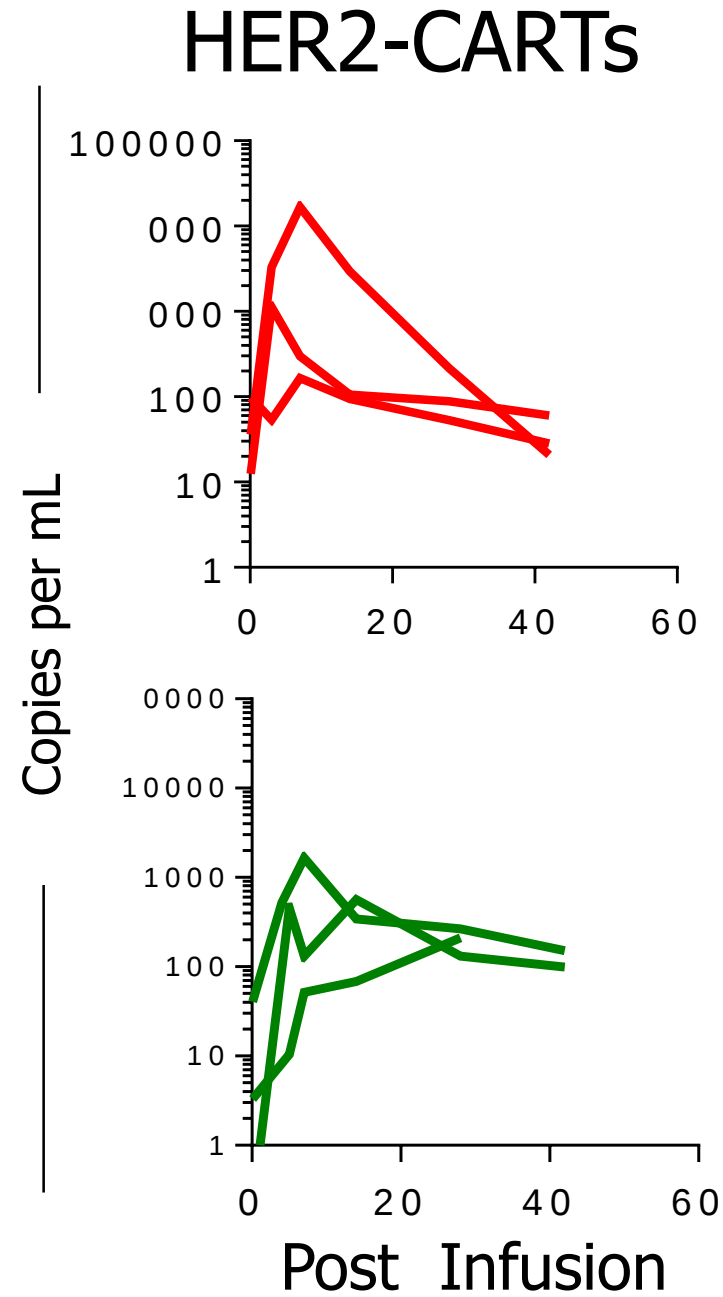
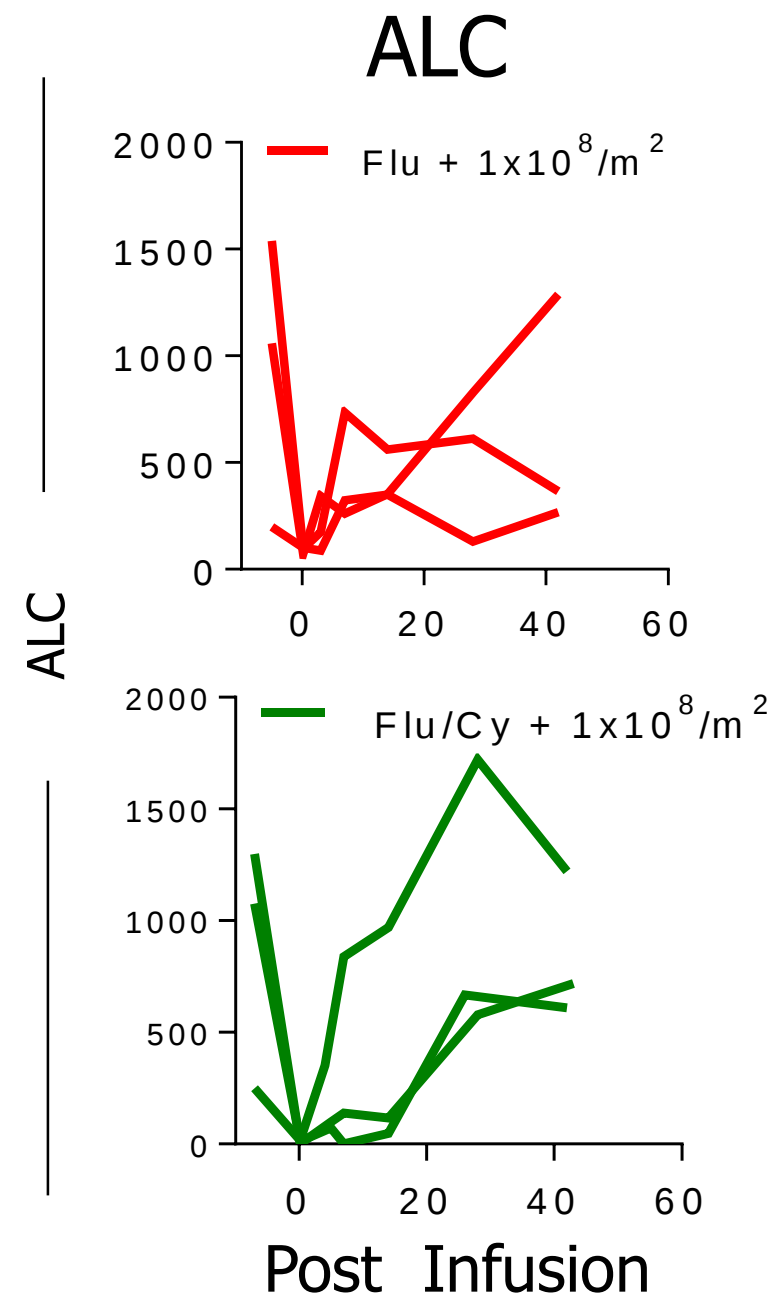


Lymphodepletion: Safety

- 2 patient: no symptoms
- 3 patients: CRS grade 1
 - fever: 12 to 72 hours post T-cell infusion
 - CRP: up to 8.9
- 1 patient: CRS grade 2
 - fever: 12 to 72 hours post T-cell infusion
 - CRP: up to 7.2
 - hypotension (low dose dopamine for ~ 36 hours)
 - transient oxygen requirement



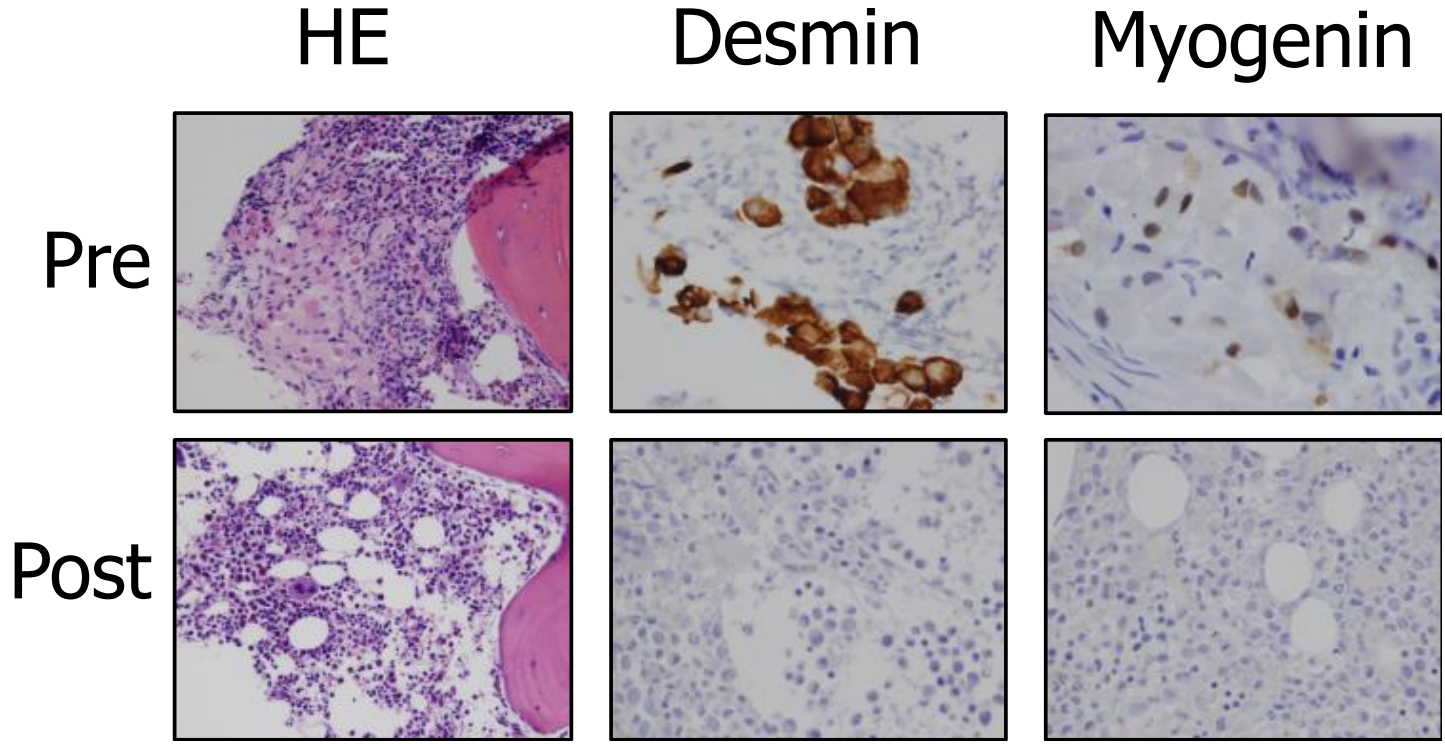
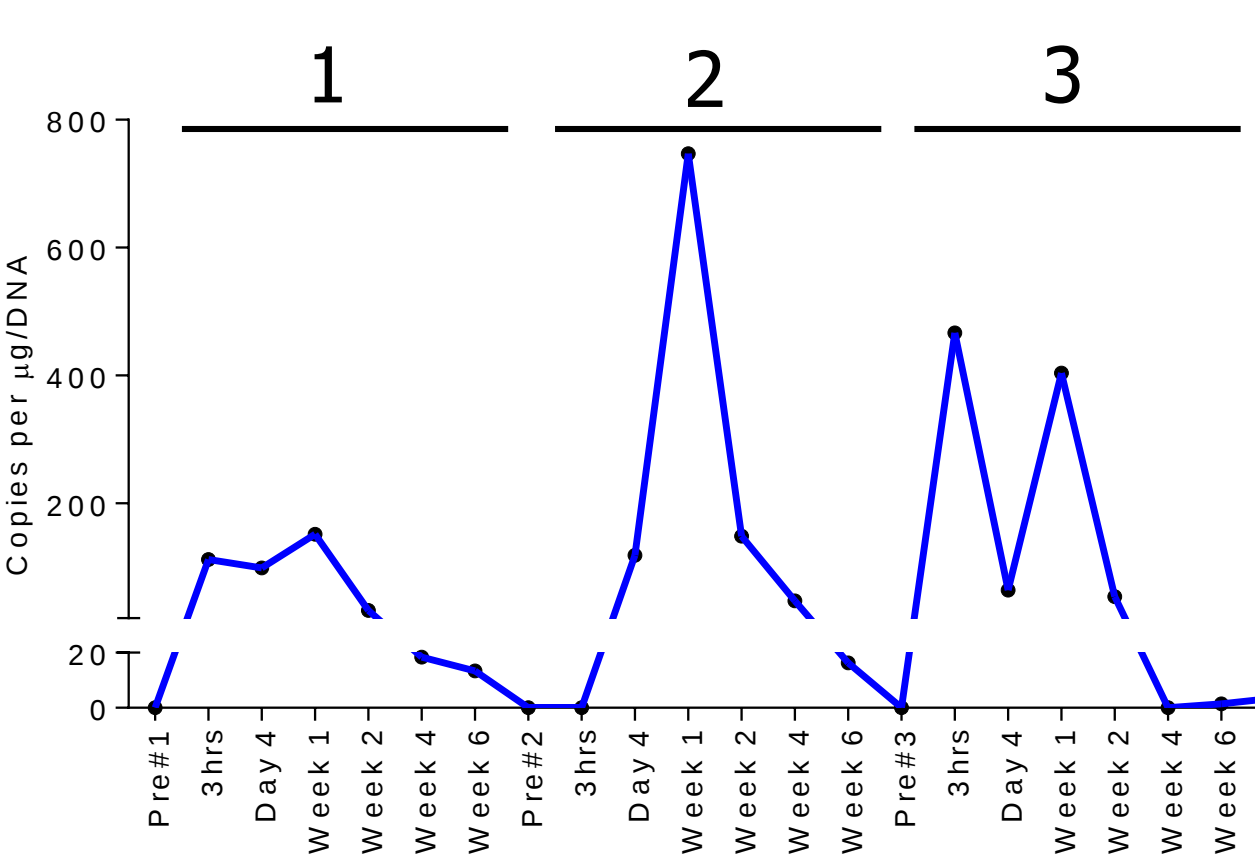
ALC and HER2-CARTS post Flu or Flu/Cy





Recurrent/refractory Rhabdomyosarcoma: CR post HER2-CAR Ts

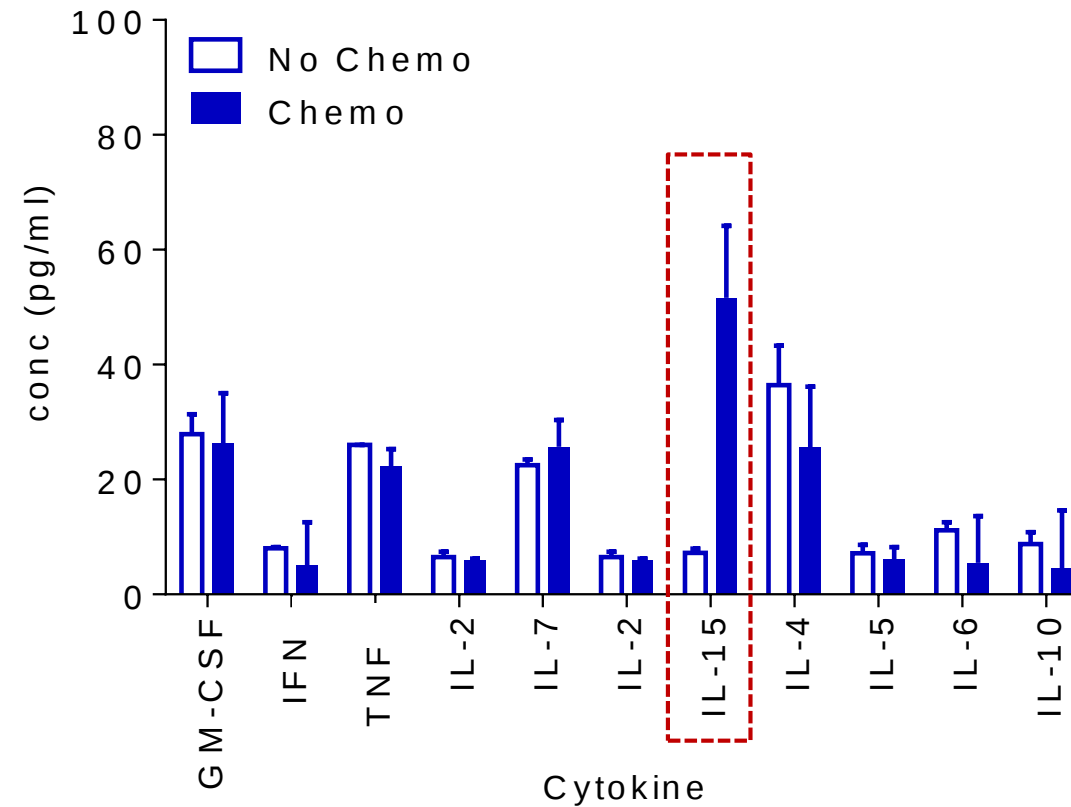
Chemo + CART



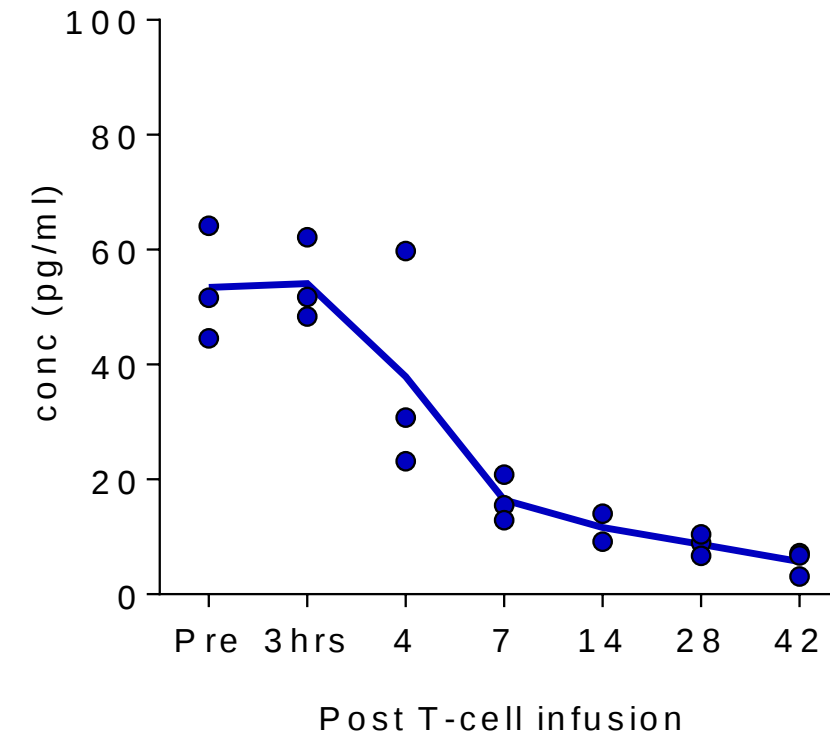


Post chemotherapy: Increase in IL15

Post chemo/Pre CART



IL15 post
Chemo + CART



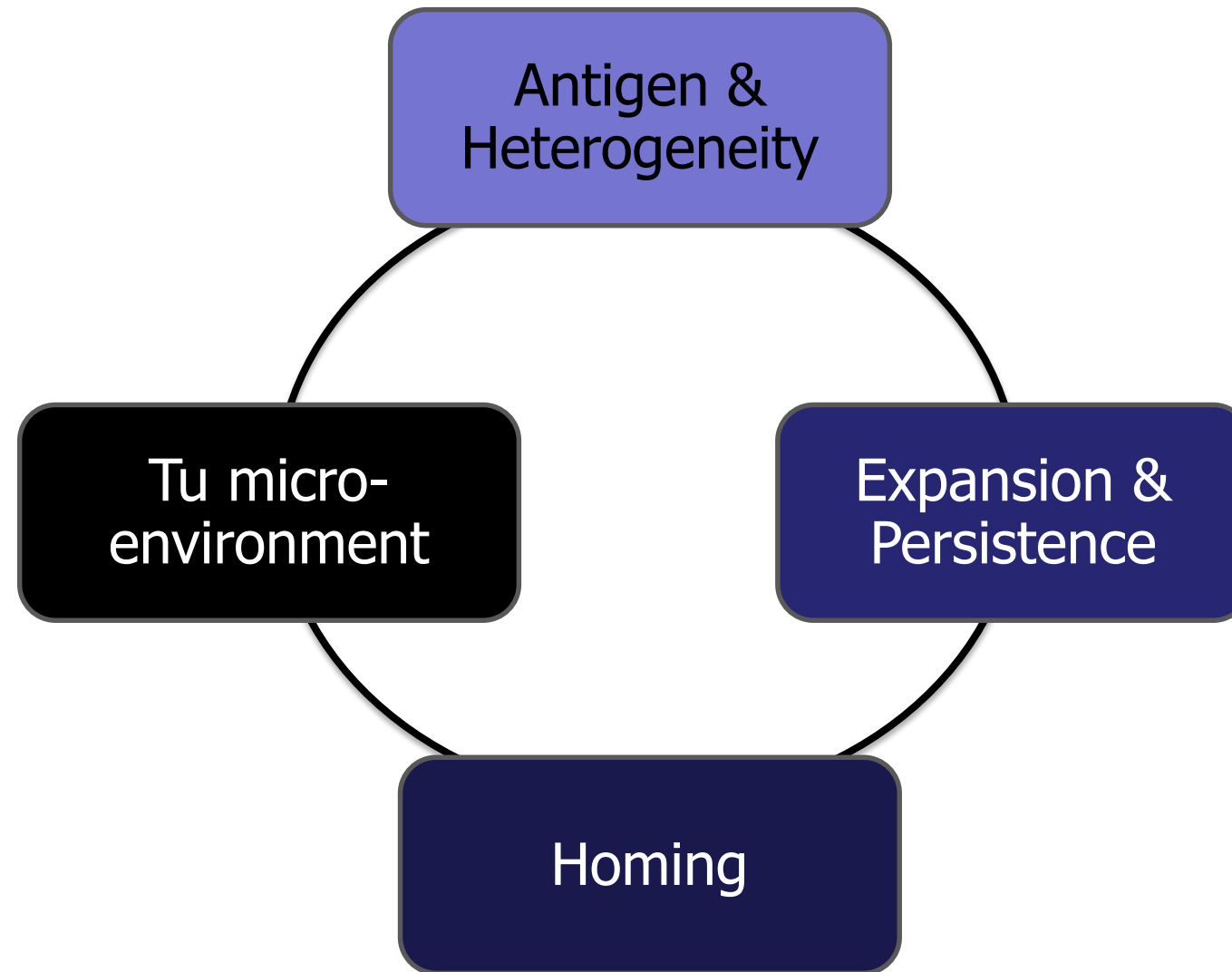


Published Clinical CART Studies: Brain & Solid Tumors

Target	Disease	Outcome
IL13R α 2	GBM	2/3 transient response (Clin Can Res, 2015) 1 impressive regression (NEJM, 2016)
HER2	GBM	1/17 PR & 7/17 SD (JAMA Onc, 2017)
EGFRvIII	GBM	1/10 SD (AACR/ASGT, abstract)
CAIX	Renal Cancer	On target/Off cancer tox (JCO, 2006)
FR	Ovarian Cancer	No activity (Clin Can Res, 2006)
CD171	Neuroblastoma	1/6 PR (Mol Ther, 2007)
GD2	Neuroblastoma	3/11 CR (Nat Med, 2008)
HER2	Colon Ca	1 Death (Mol Ther, 2010)
HER2	Sarcoma	4/17 SD (JCO, 2015)

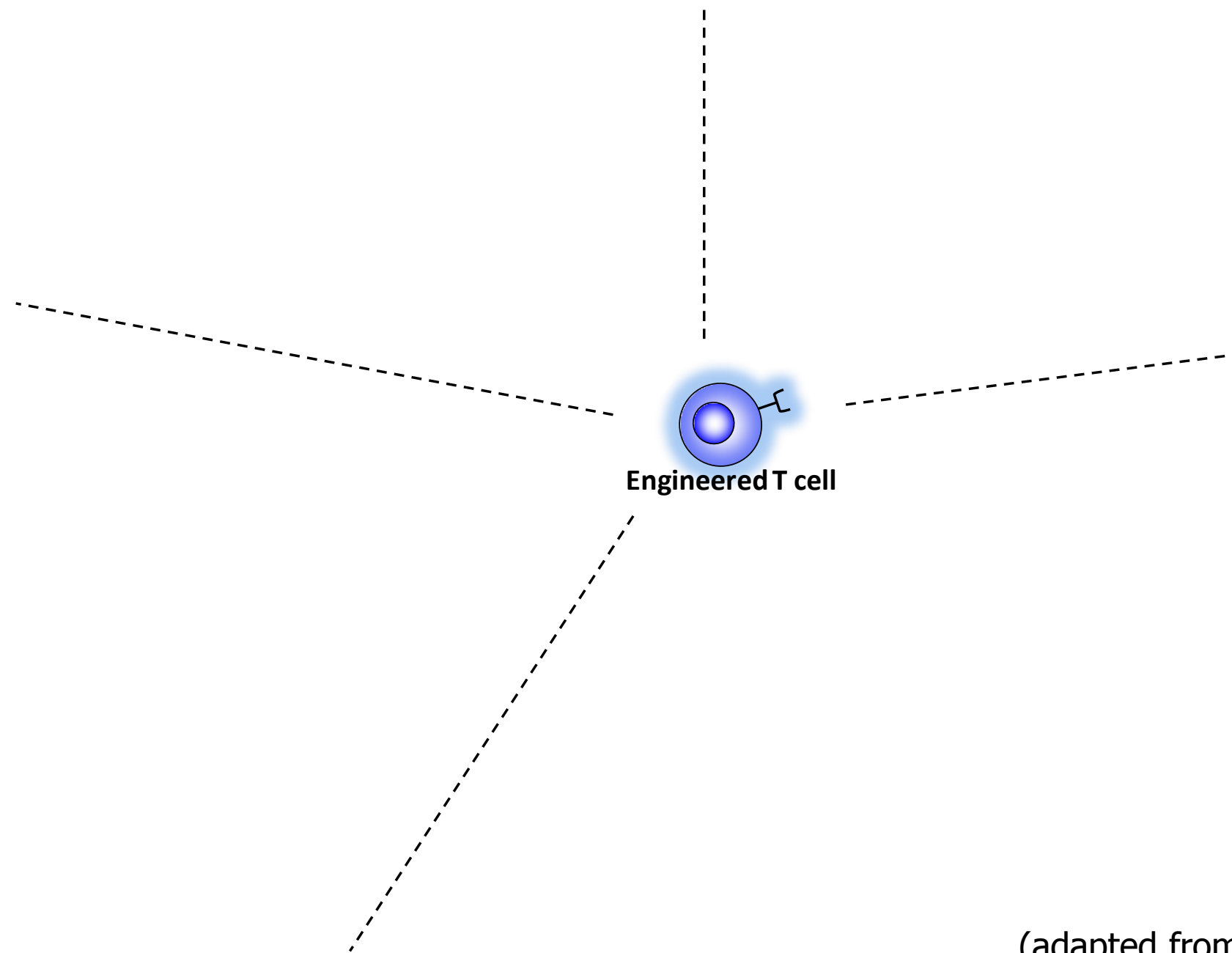


T-cell Therapy for solid & brain tumors: Challenges





Genetic modification to enhance CART function



(adapted from Vera et al. Lancet Onc; 2013)



Does expression of IL15 enhance
antitumor activity of CARTs?

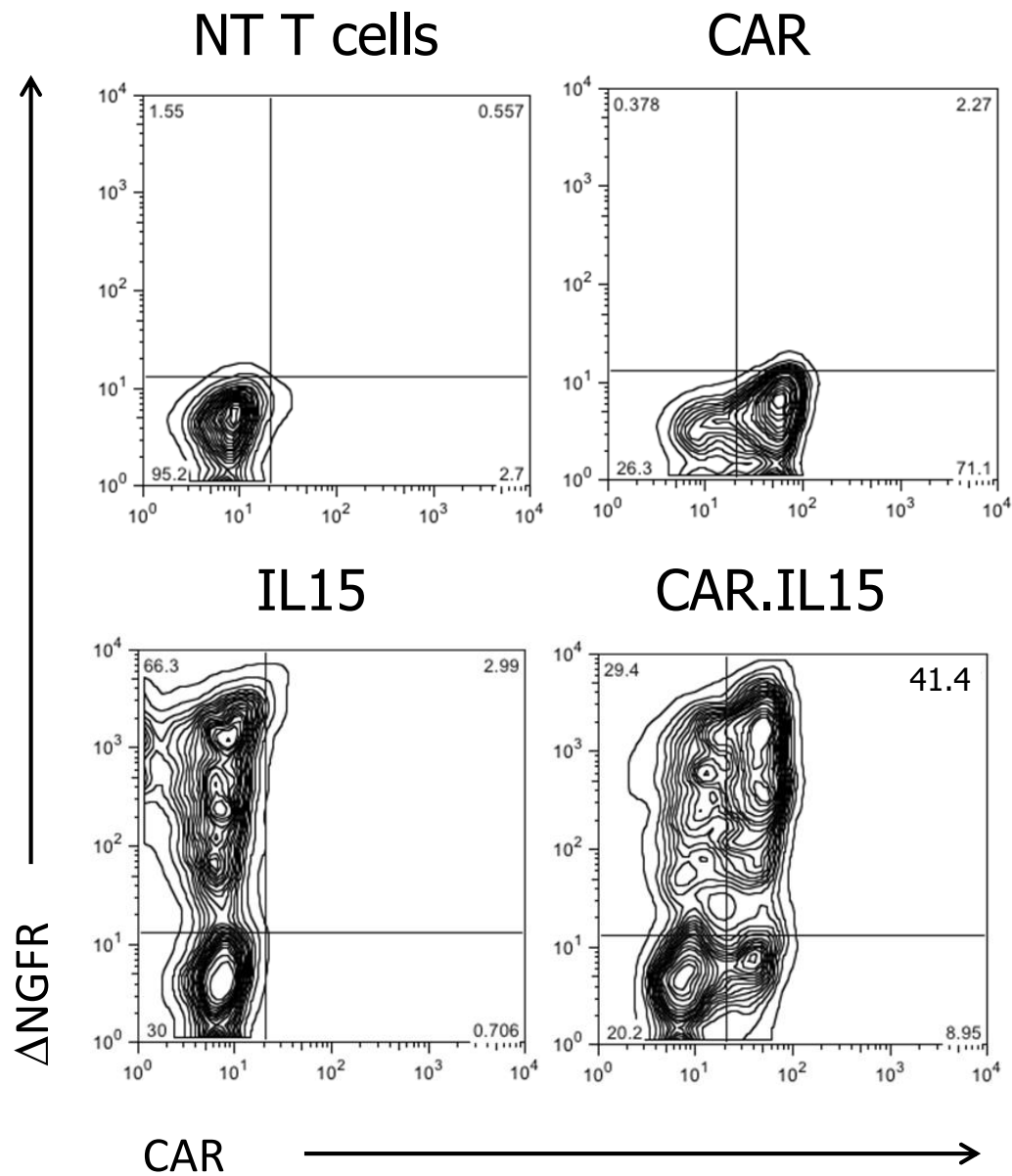


Generation of CAR.IL15 T cells

IL13Ra2.CAR



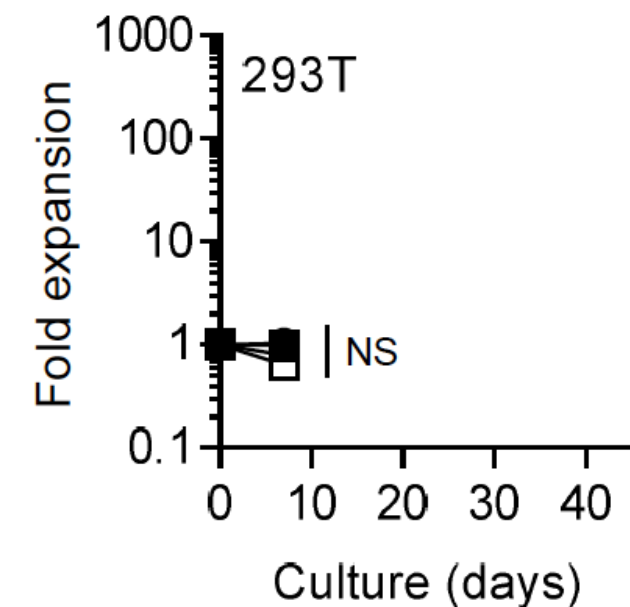
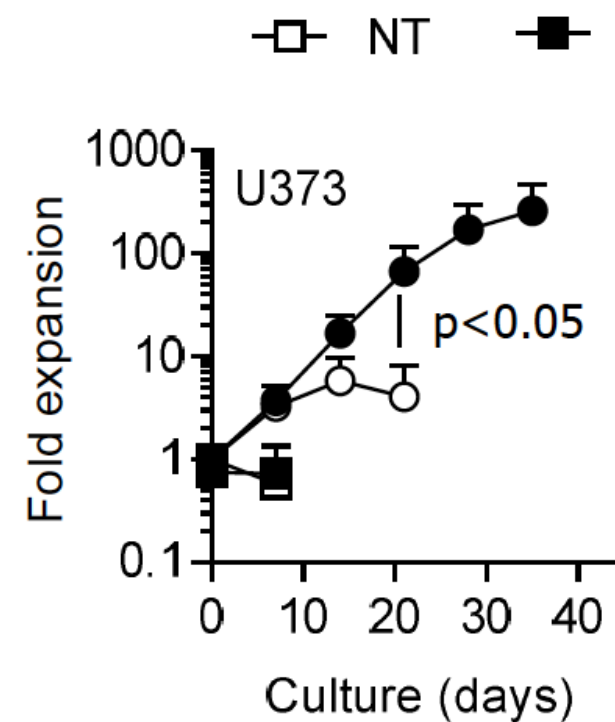
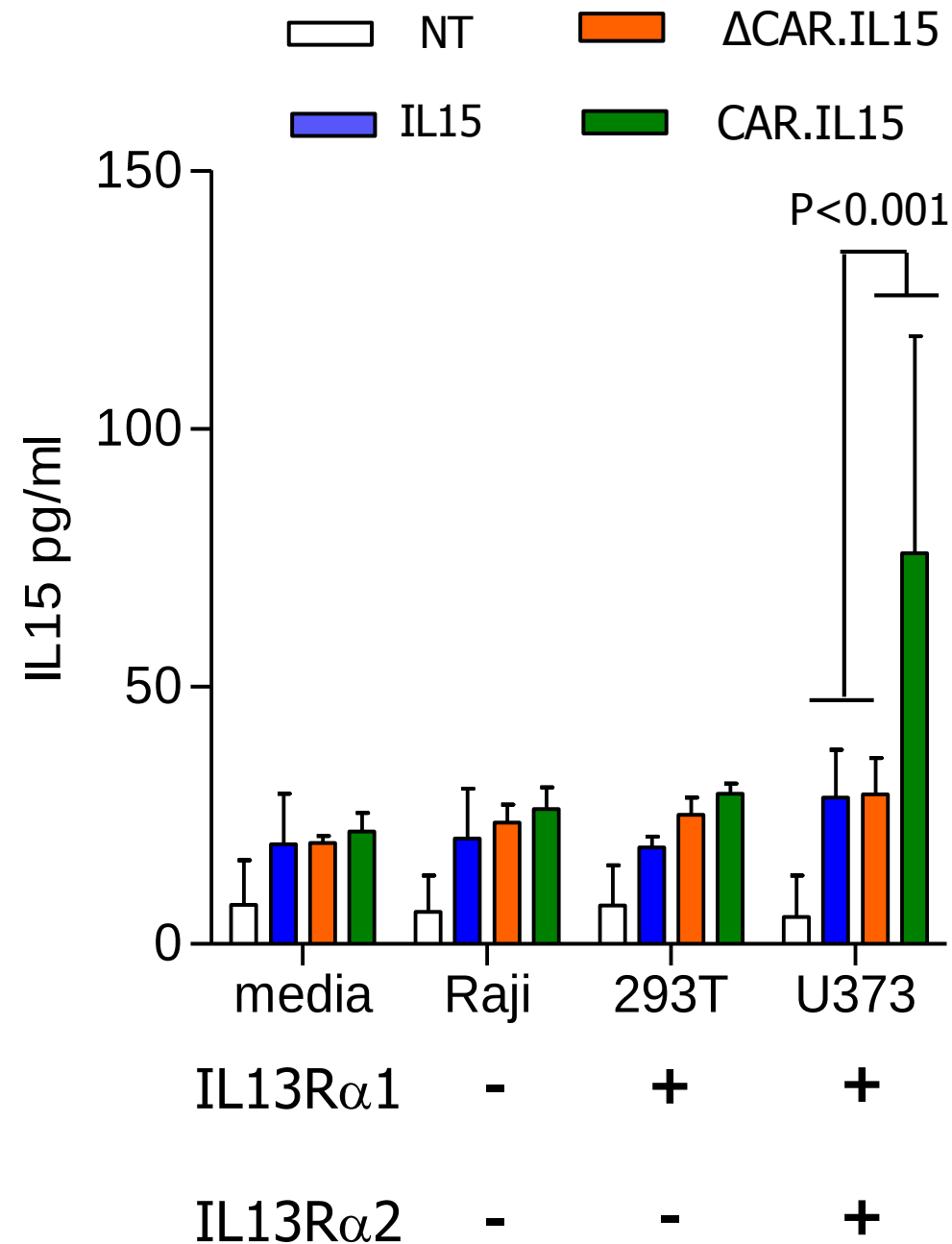
IL15 retroviral vector





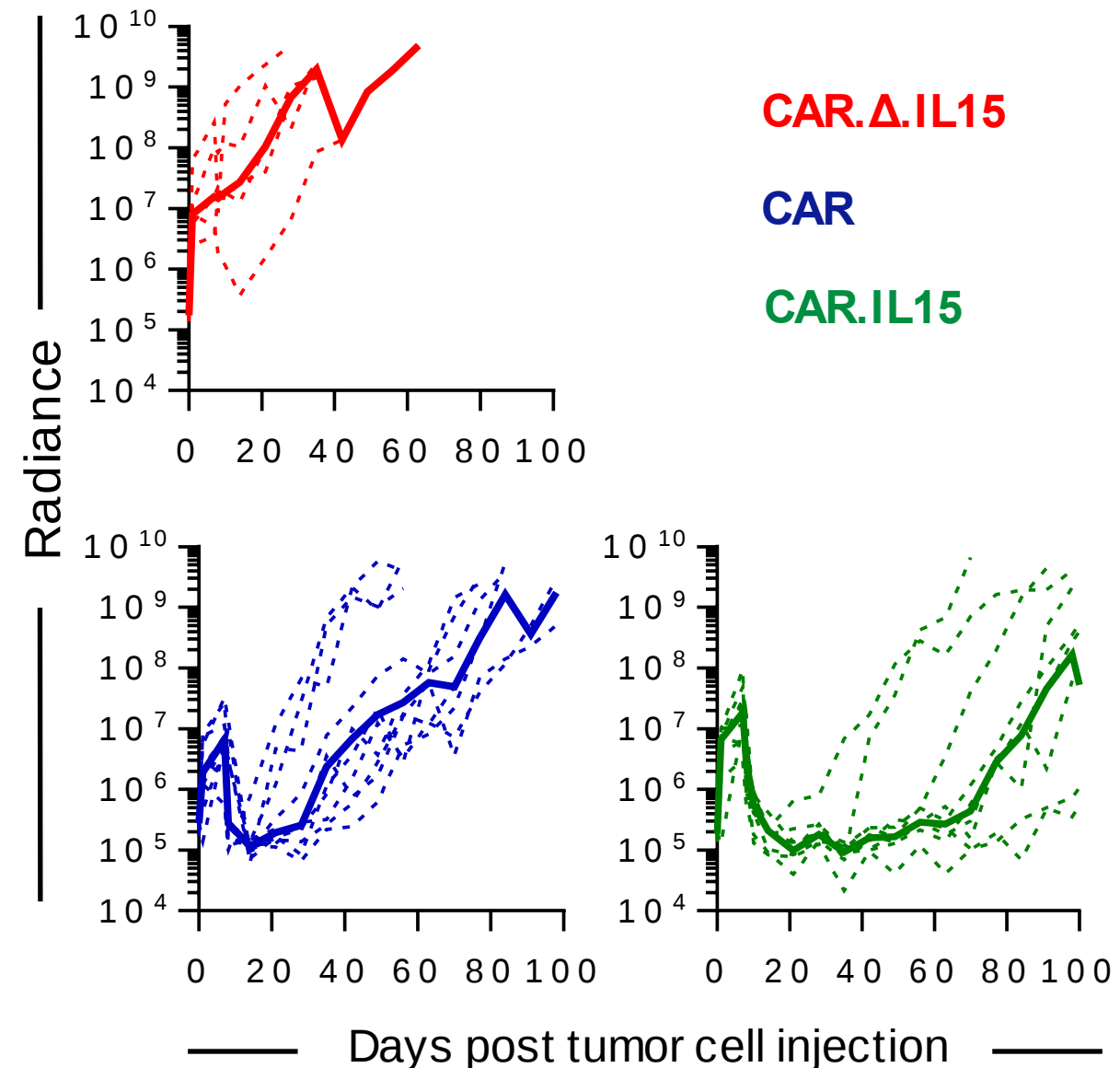
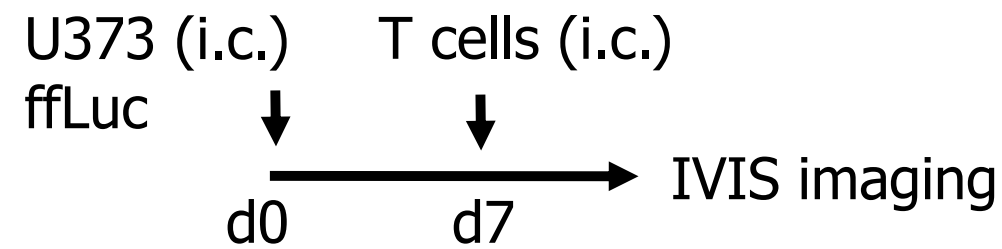
CAR.IL15 T cells:

Activation dependent IL15 secretion & expansion



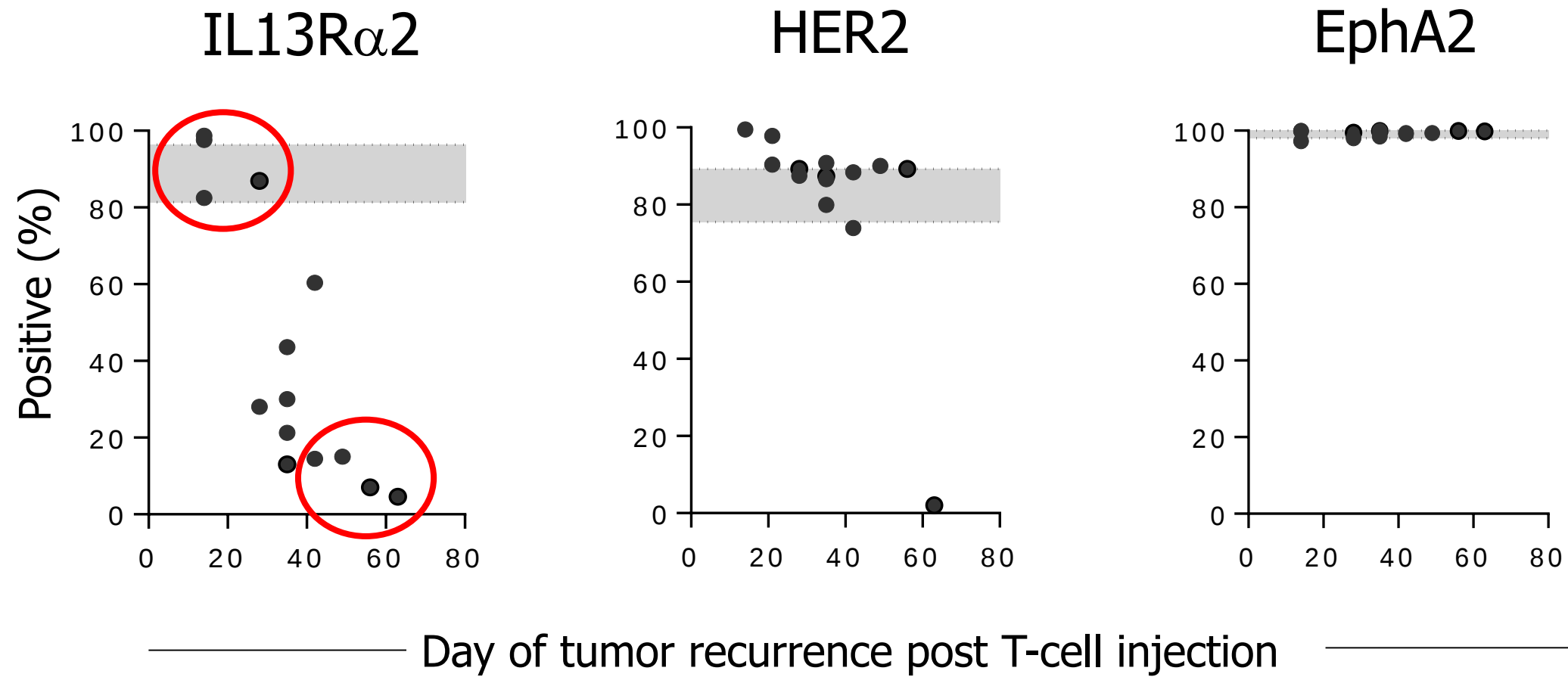


CAR.IL15 T cells: Improved antitumor activity





Late recurrences: uniform loss of IL13R α 2 expression

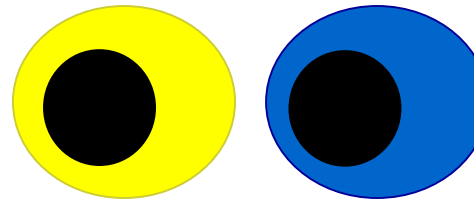




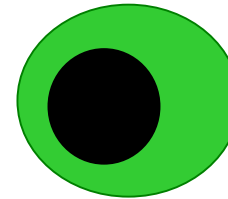
How to prevent antigen loss variants?

- Target multiple antigens

CART pool



Bispecific CARTs



- 2 CARs
- bispecific CARs
 - Tandem CAR
 - Leaf CAR
 -

- Induce antigen spreading



Does activation of TLR signaling in
CARTs enhance antitumor activity?



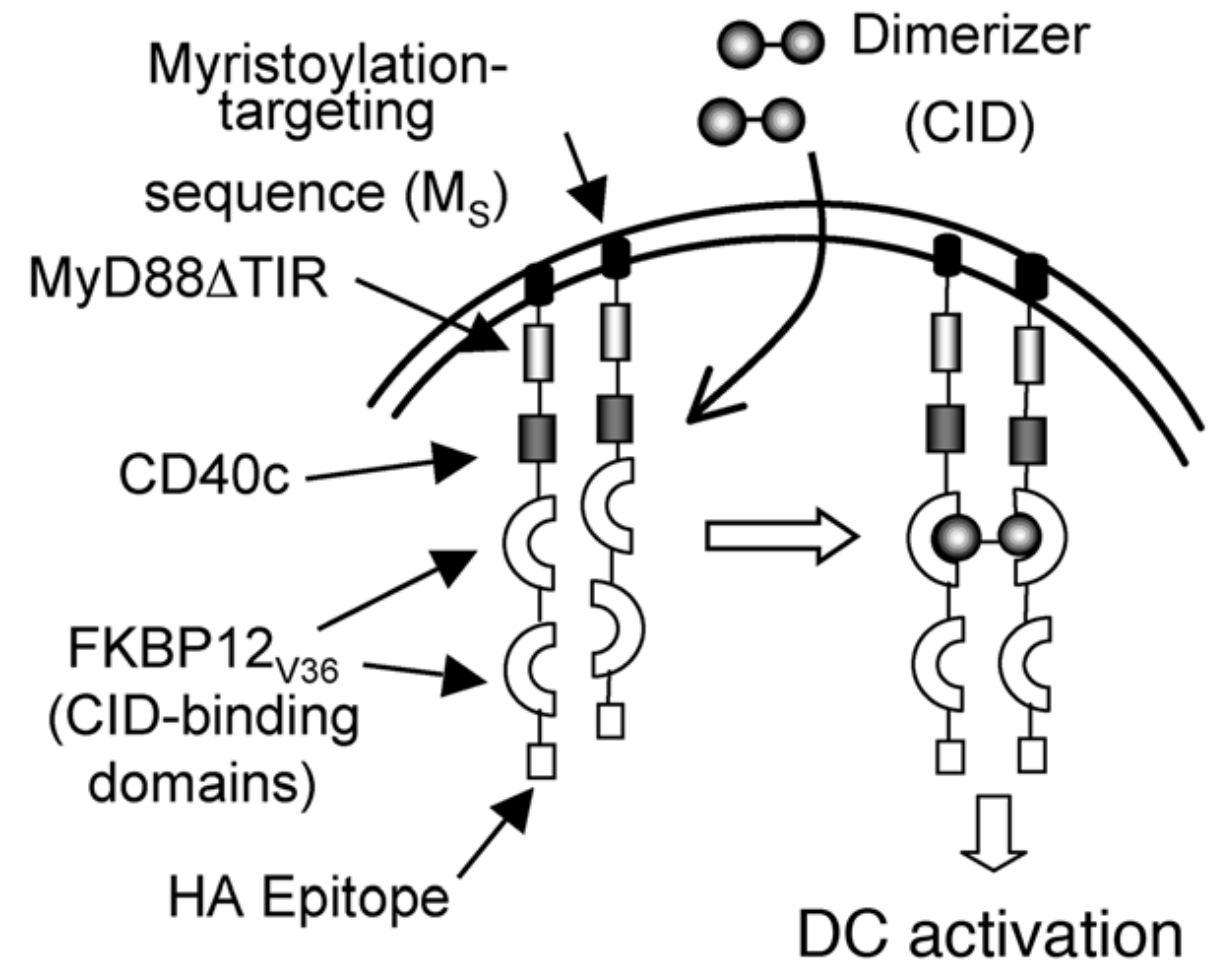
MyD88 and CD40: Alternative costim molecules in T cells

MyD88

- Intracellular adapter protein involved in TLR and IL-1 family signaling
- Modulates T-cell effector function

CD40

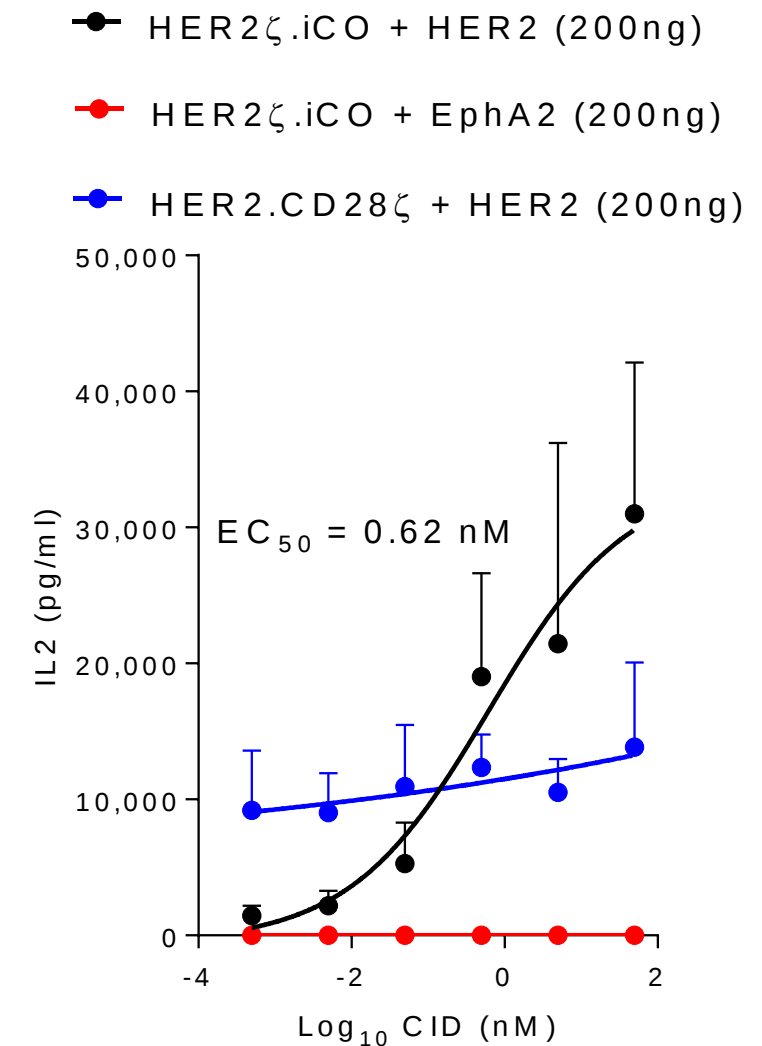
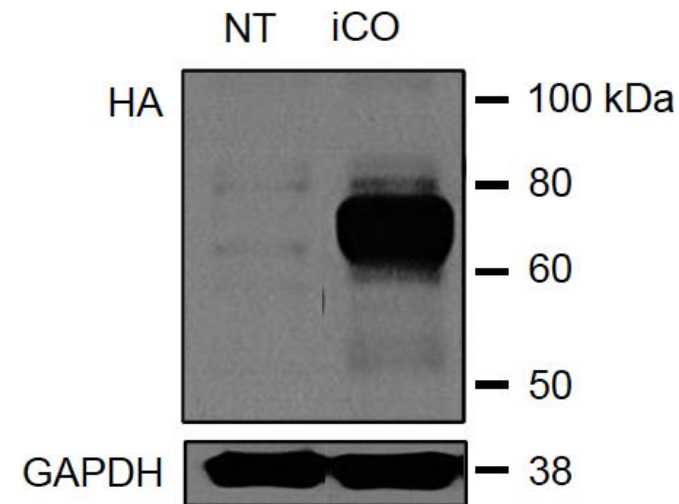
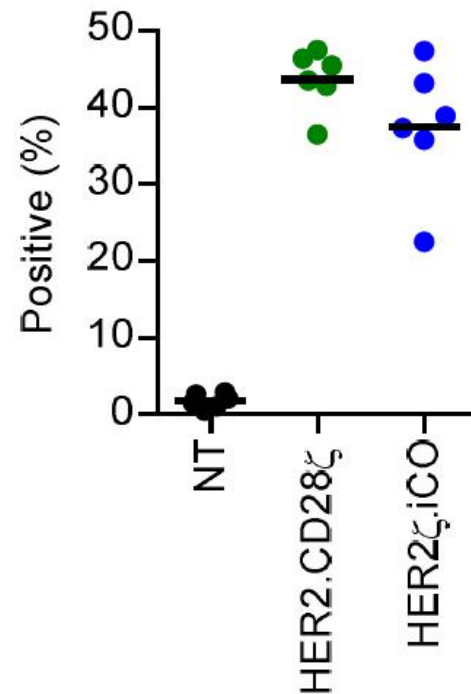
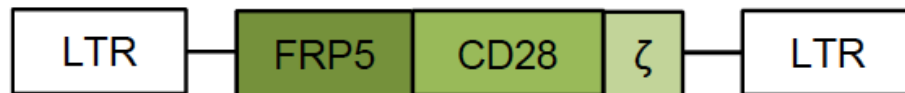
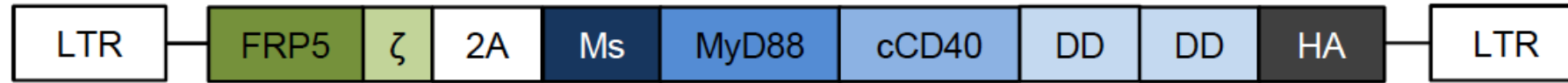
- Mainly expressed on APCs but also T cells
- Costim effects



(Narayanan et al JCI 2011)

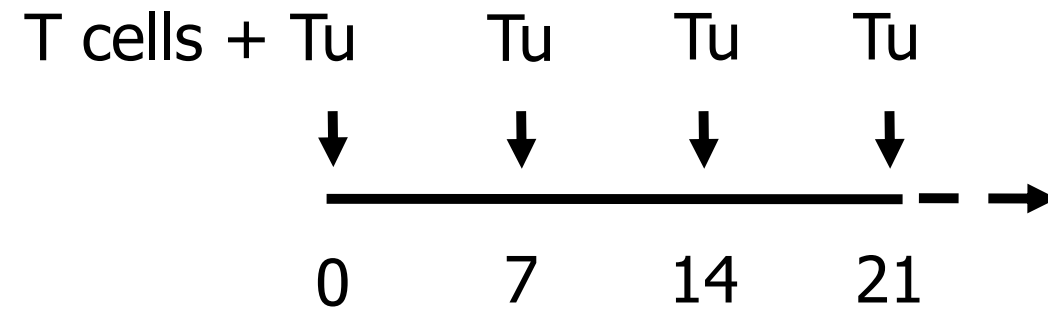


Characterization of CAR.iCO T cells

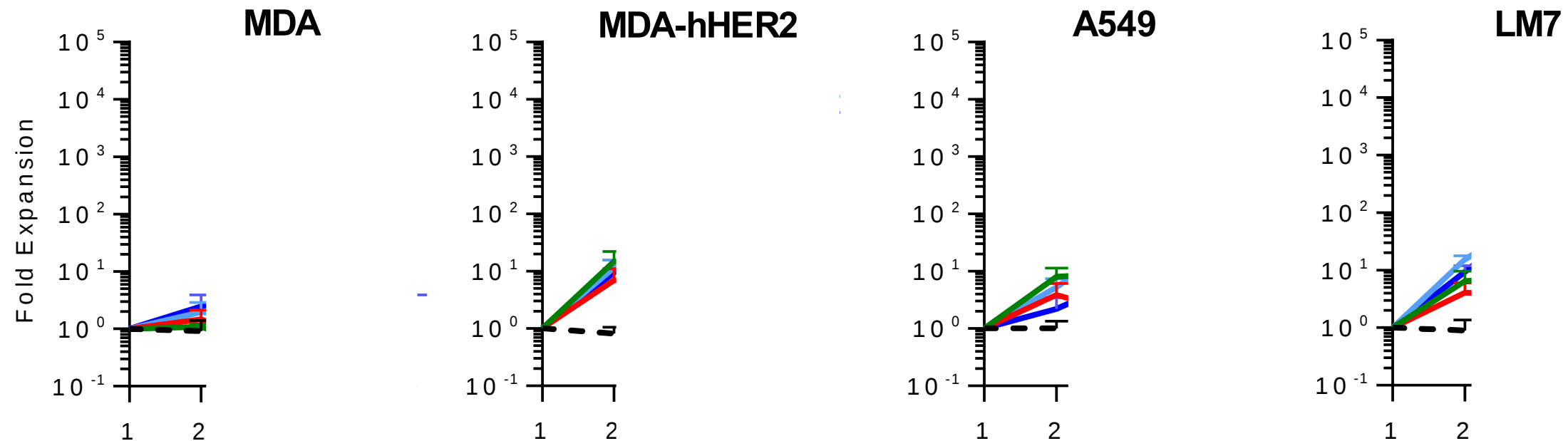




CAR.iCo T cells: improved T-cell expansion



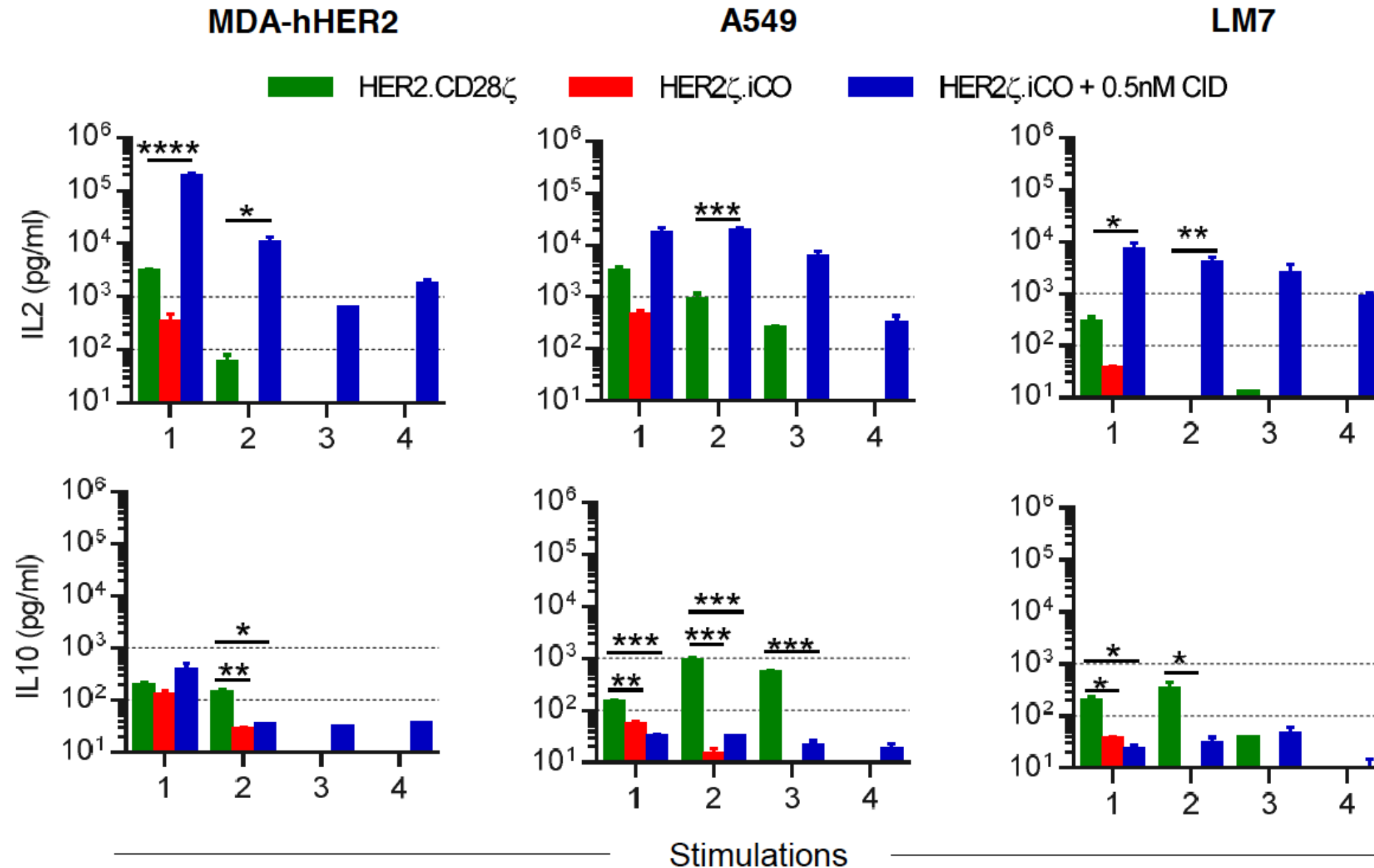
-- NT — HER2.CD28ζ — HER2ζ.iCo — HER2ζ.iCo + 0.5nM CID — HER2ζ.iCo + 5nM CID



Stimulations

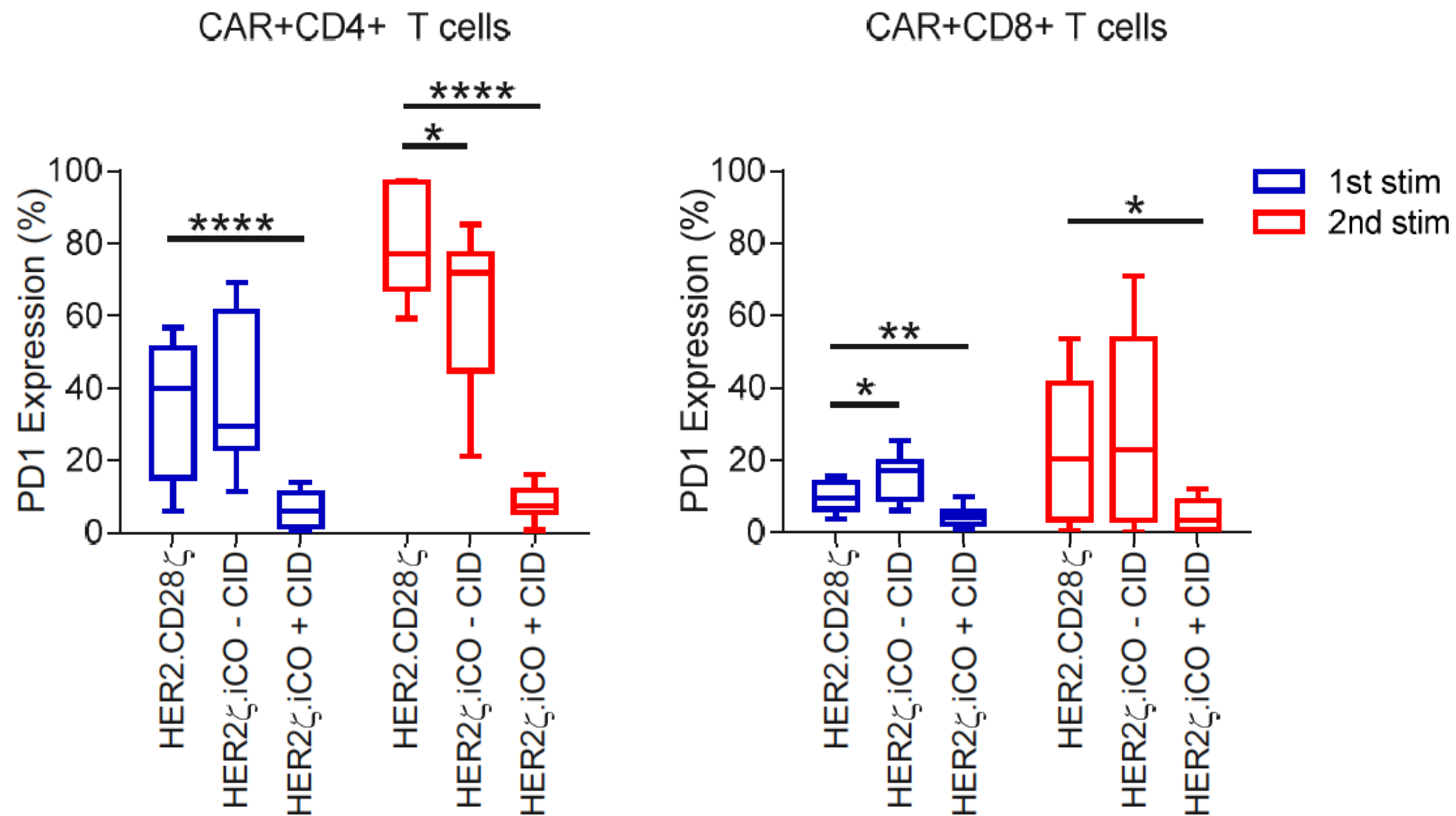


CAR.iCo Ts: improved TH1-cytokine production



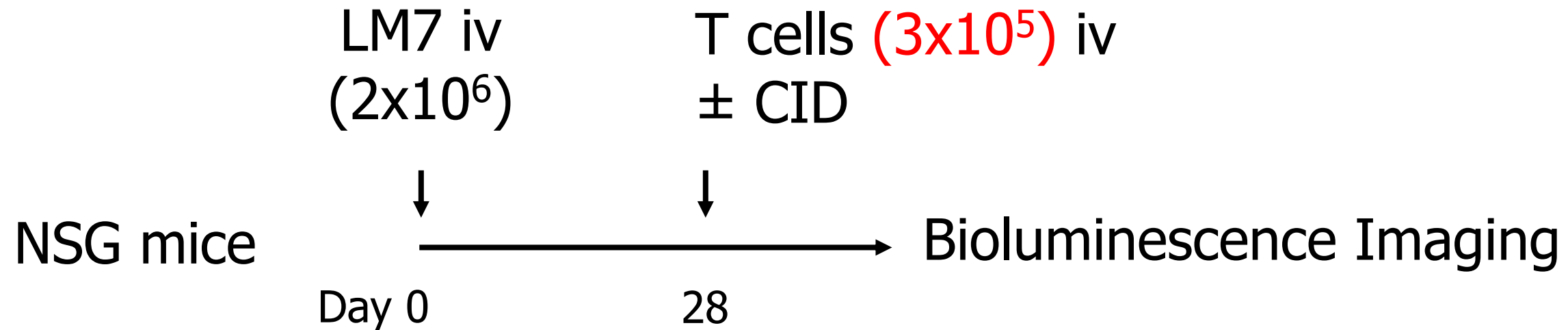


CAR.iCo T cells: decreased PD-1 expression



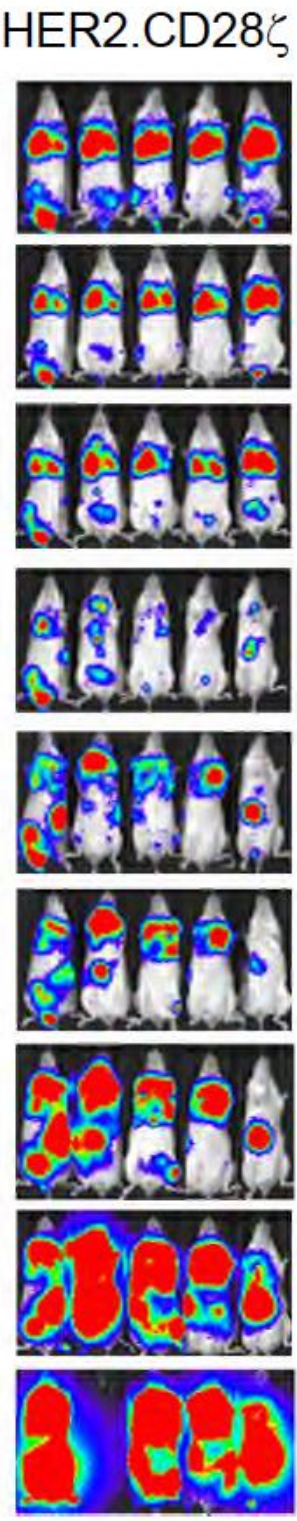
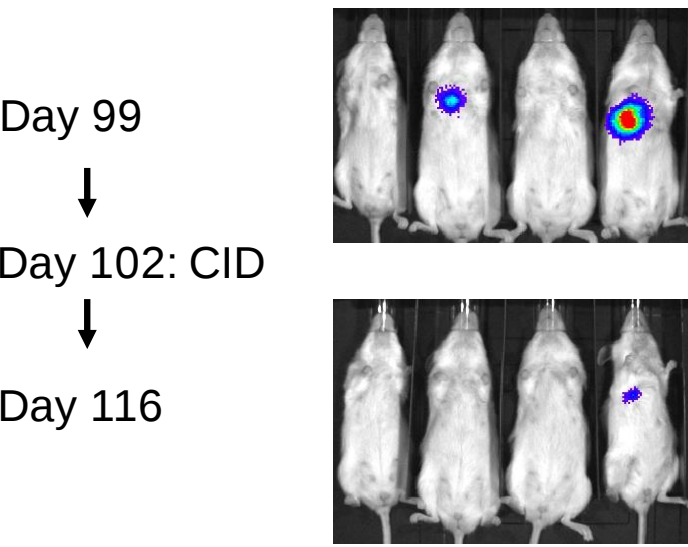
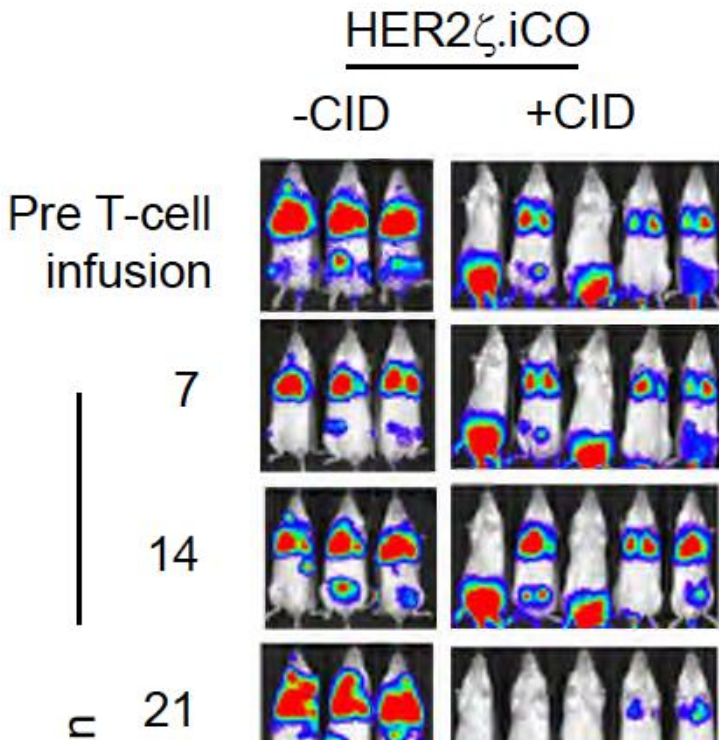
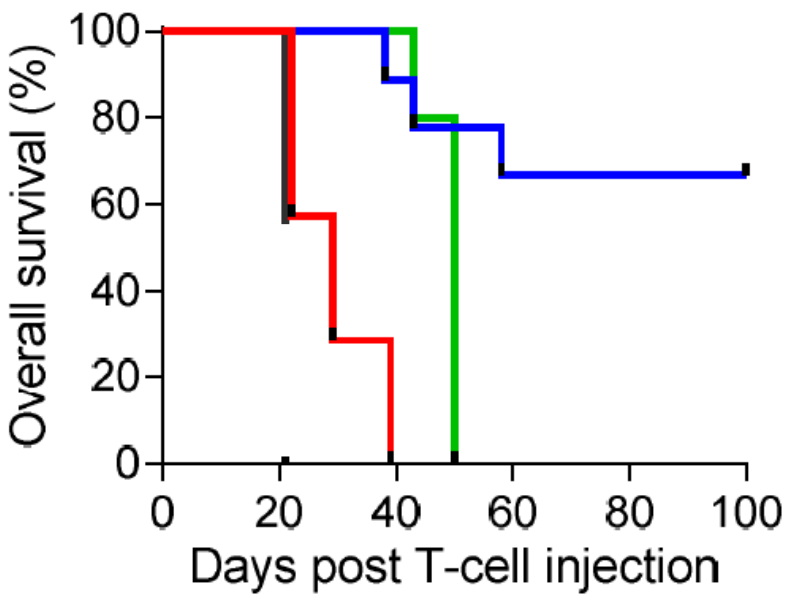
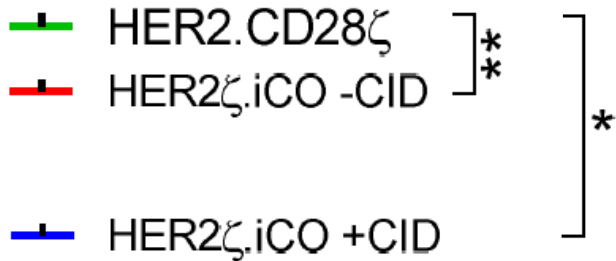


Do CAR.iCO T cells have improved antitumor activity *in vivo*?





Antitumor activity





Conclusions

- CARTs for solid tumors
 - Limited antitumor activity in early phase clinical studies
- Strategies to improve antitumor activity
 - 2nd genetic modification/other treatment modalities
 - Improved efficacy in preclinical models
 - **BUT** clinical experience so far limited



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