Addressing Relapse after CART Cell Therapy for ALL

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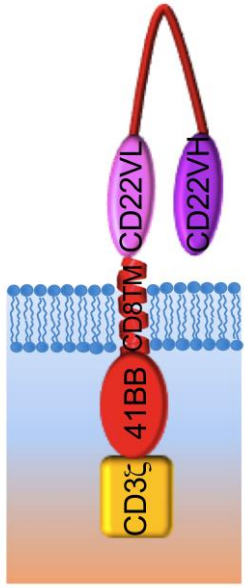
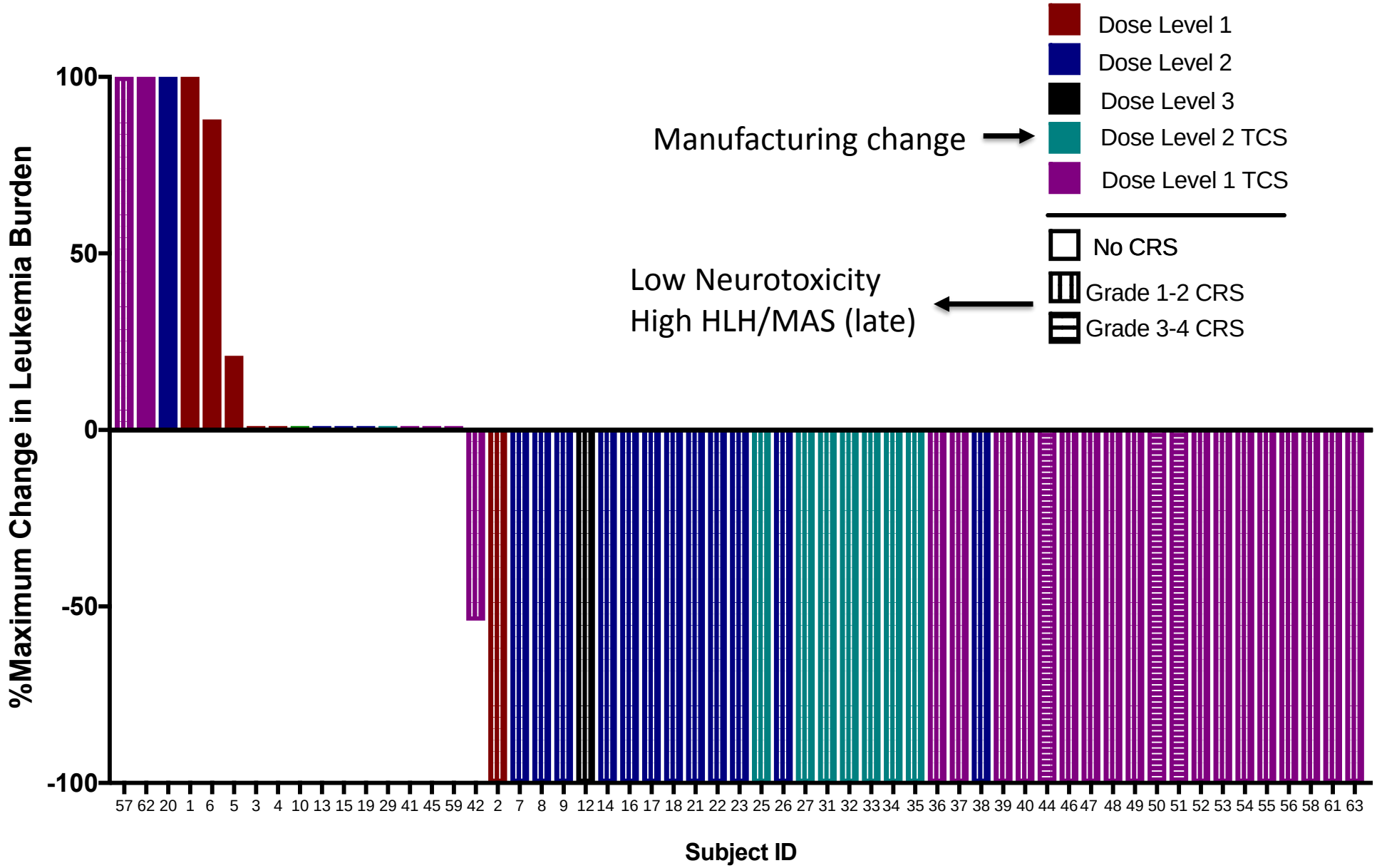
Initiative and Director of Cancer Immunotherapy

Disclosures

- I have no actual or potential conflict of interest in relation to this presentation.

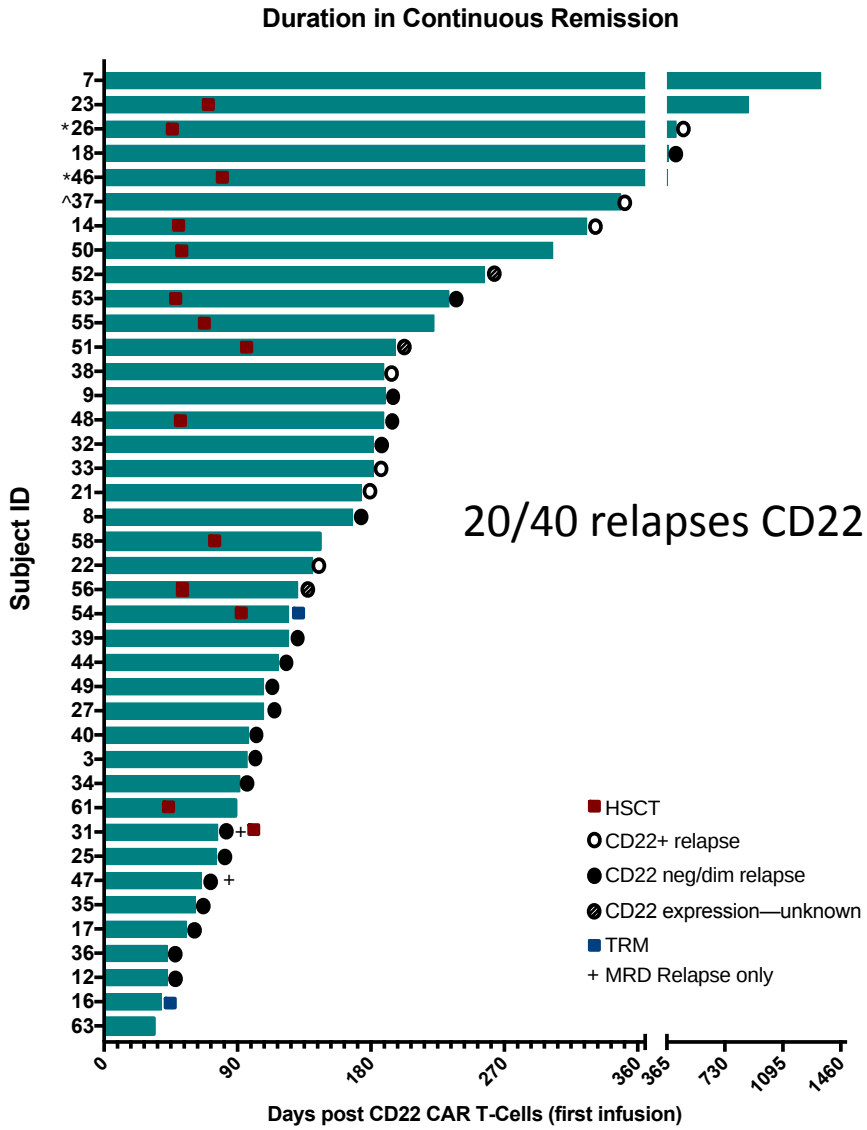
The CD22 CAR Experience: Lessons Learned from a First in Human Trial



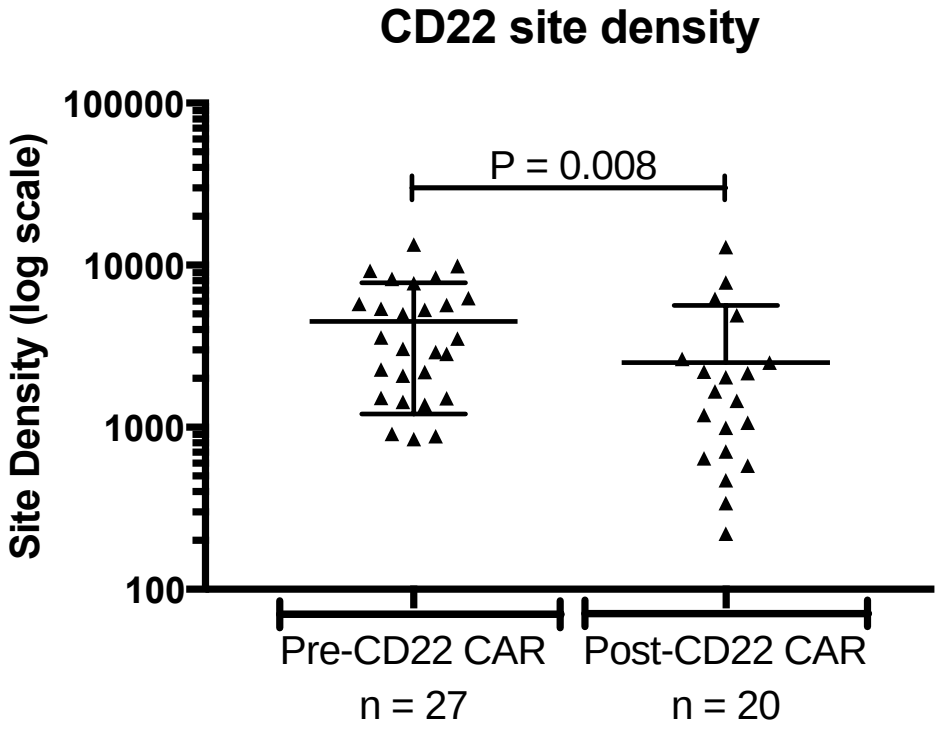


Haso…Orentas, *Blood* 2013
Haso….Fry, *ASH* 2013
Fry/Shah et al., *Nature Medicine 2017*

CD22 BBz CAR:
Relapse associated with CD22 modulation

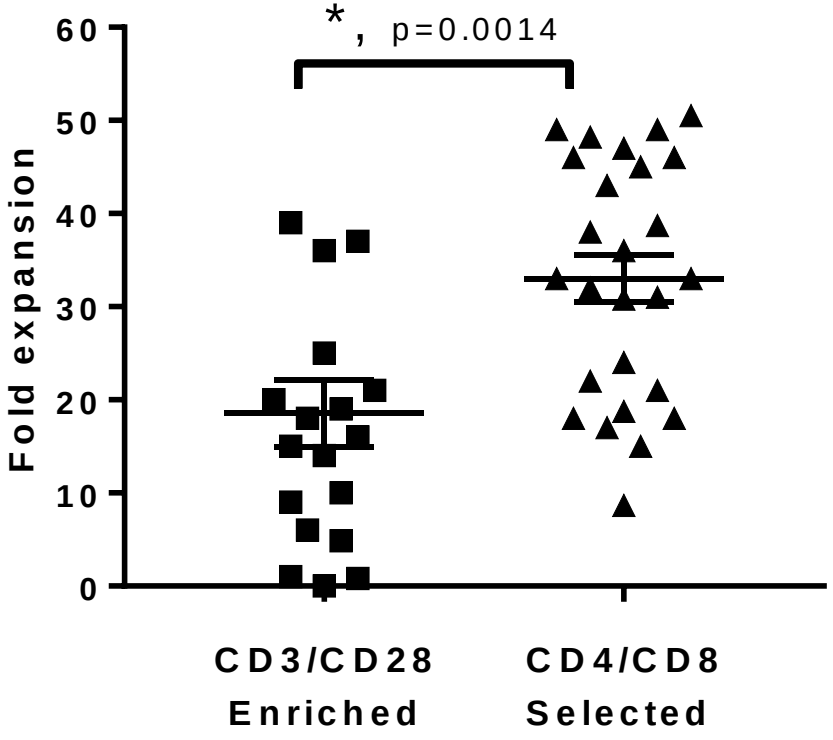


20/40 relapses CD22 dim/neg

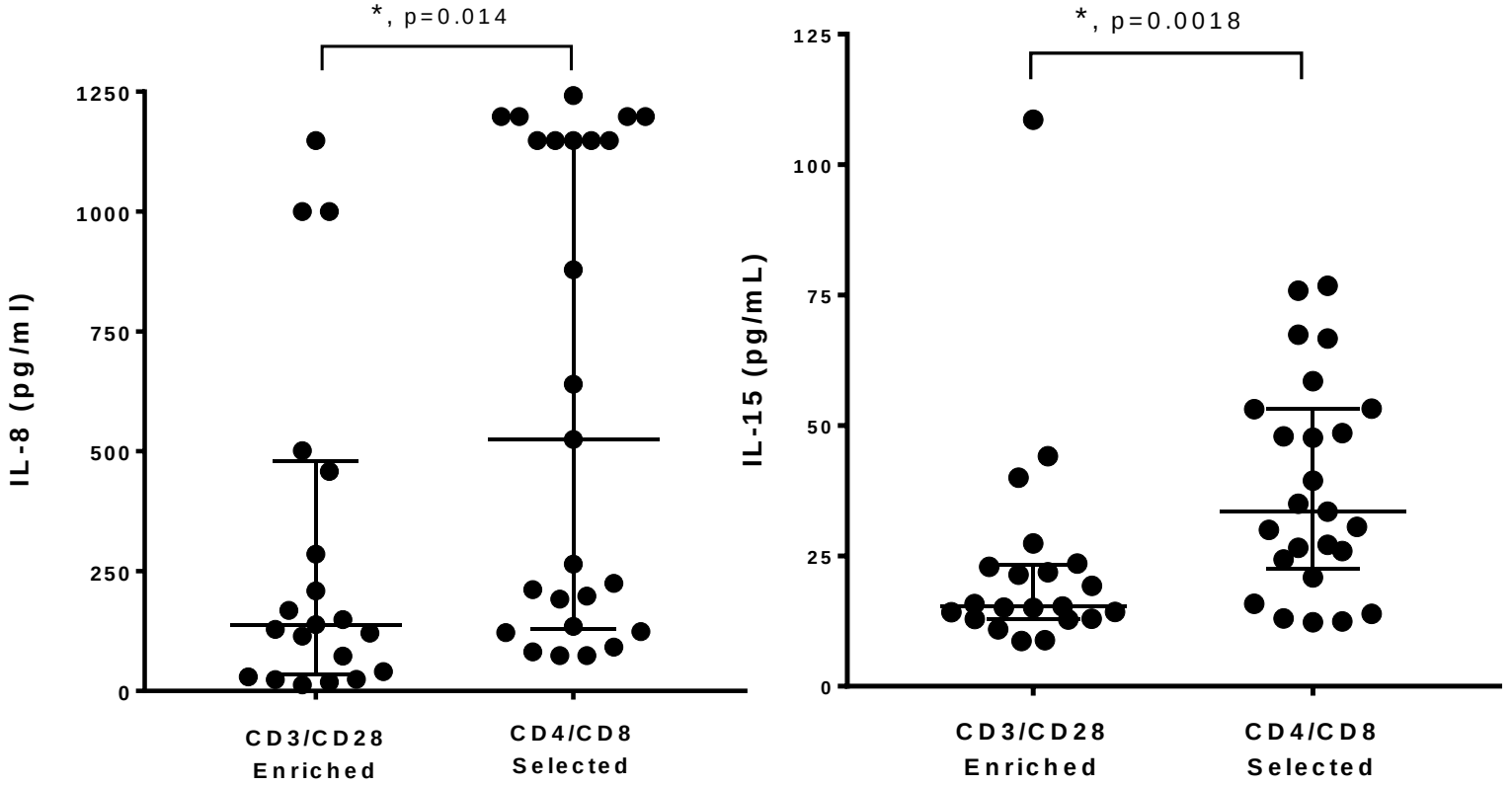


Impact of manufacturing change on in vitro expansion and post-infusion cytokine levels

In vitro



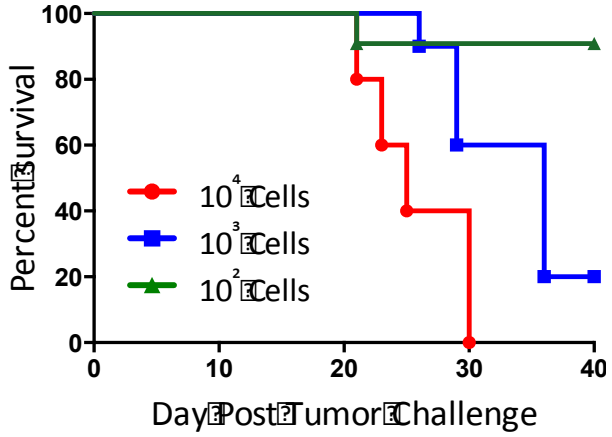
Post-Infusion

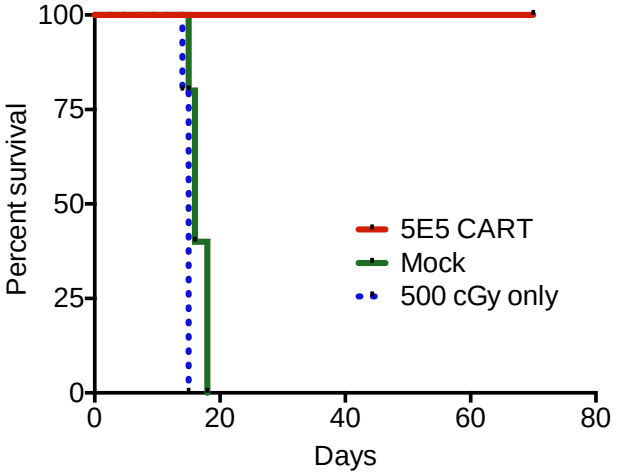


Steve Highfill

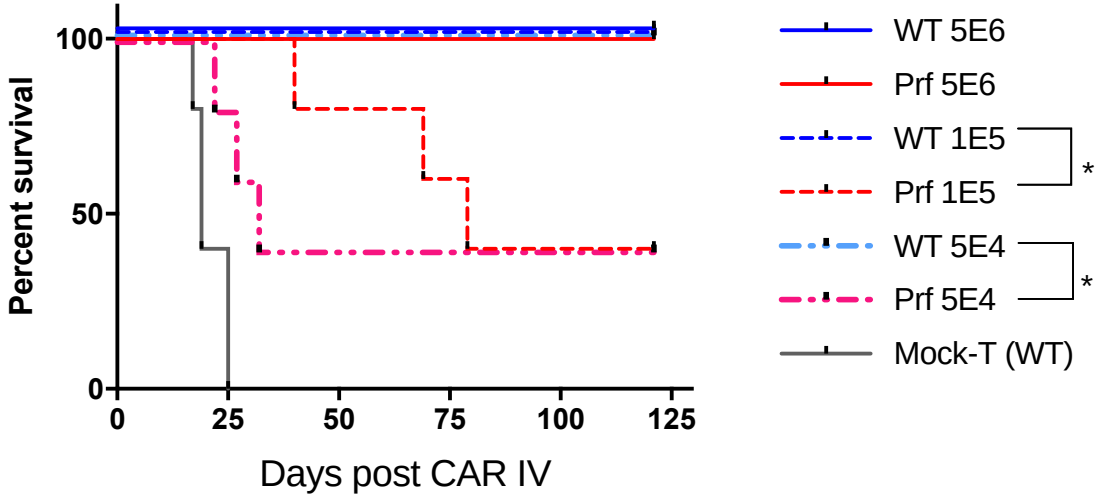
Interrogating CAR Immune Biology in an immune competent model of ALL

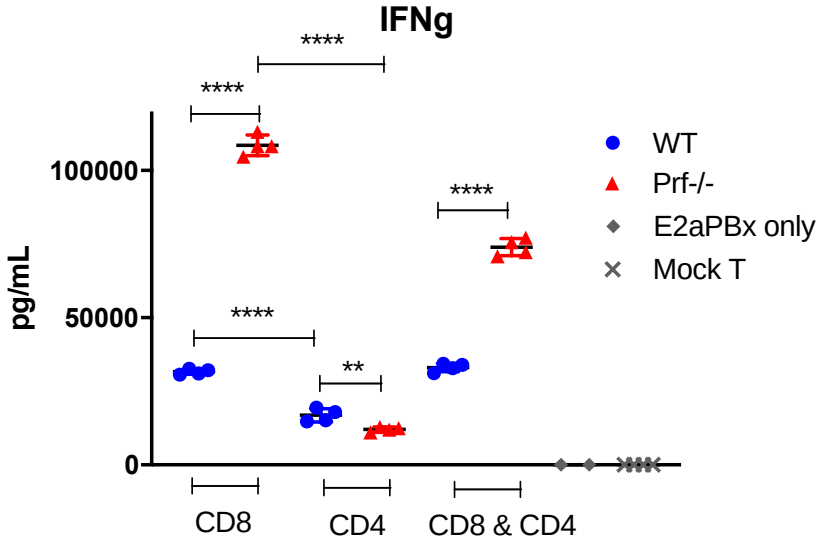
Kazusa Ishii



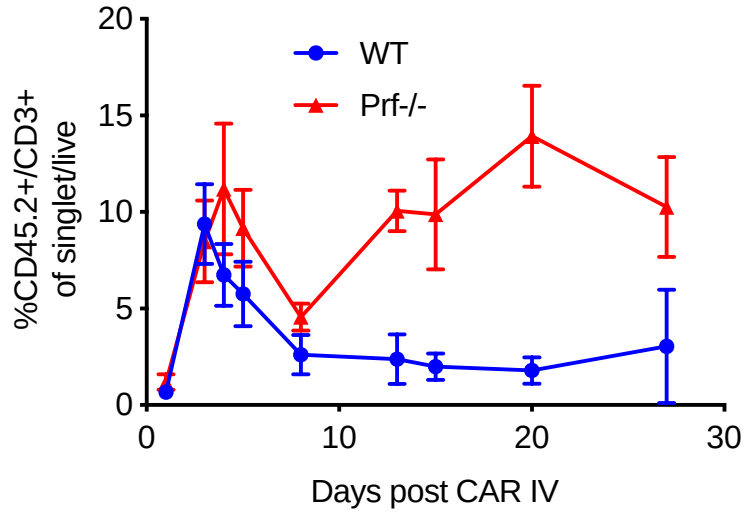


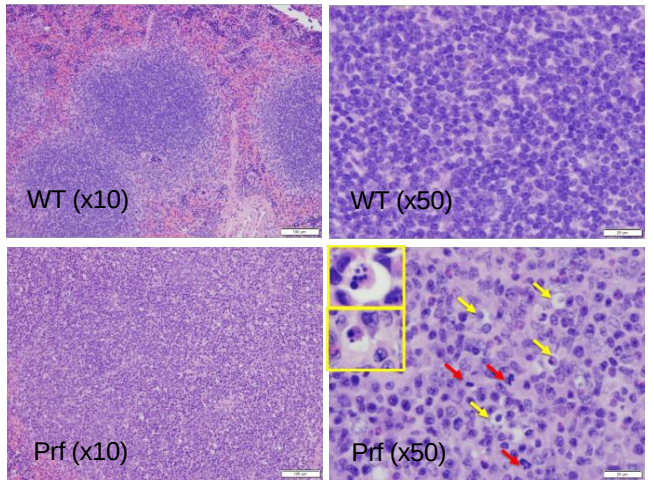
Qin et al Blood, 2017
Kochendorfer, Blood, 2011
Yang, Y, Sci Trans Med, 2017

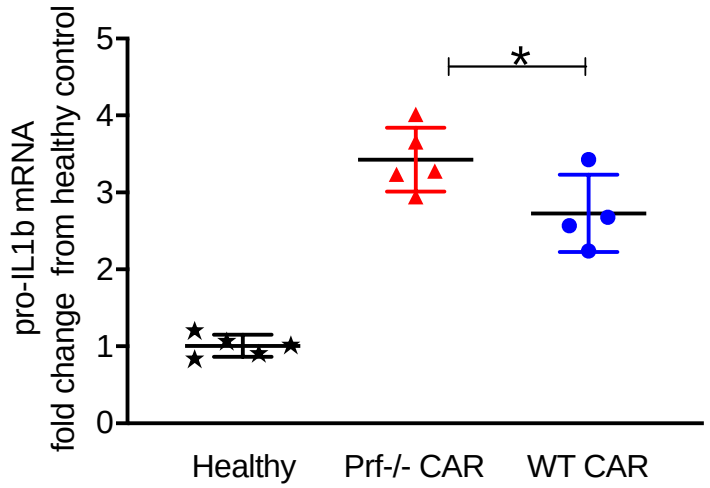


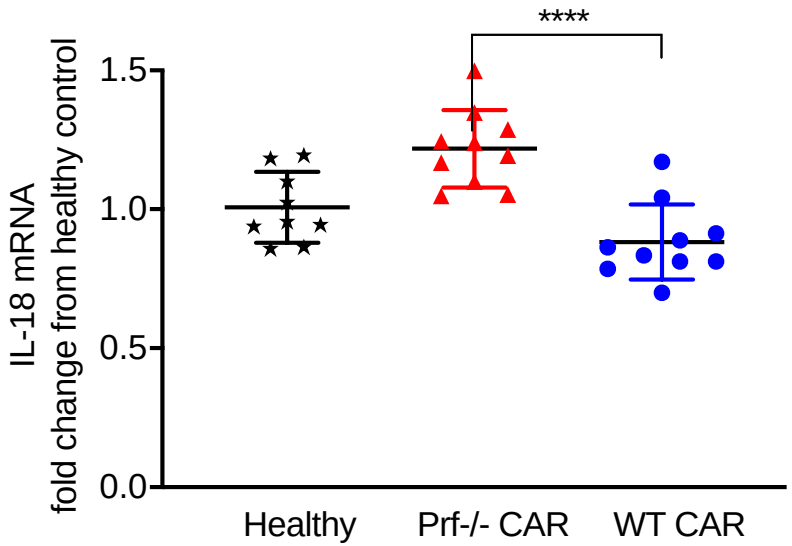


Syngeneic CAR Mouse Model Provides Insights into CAR T cell Toxicity

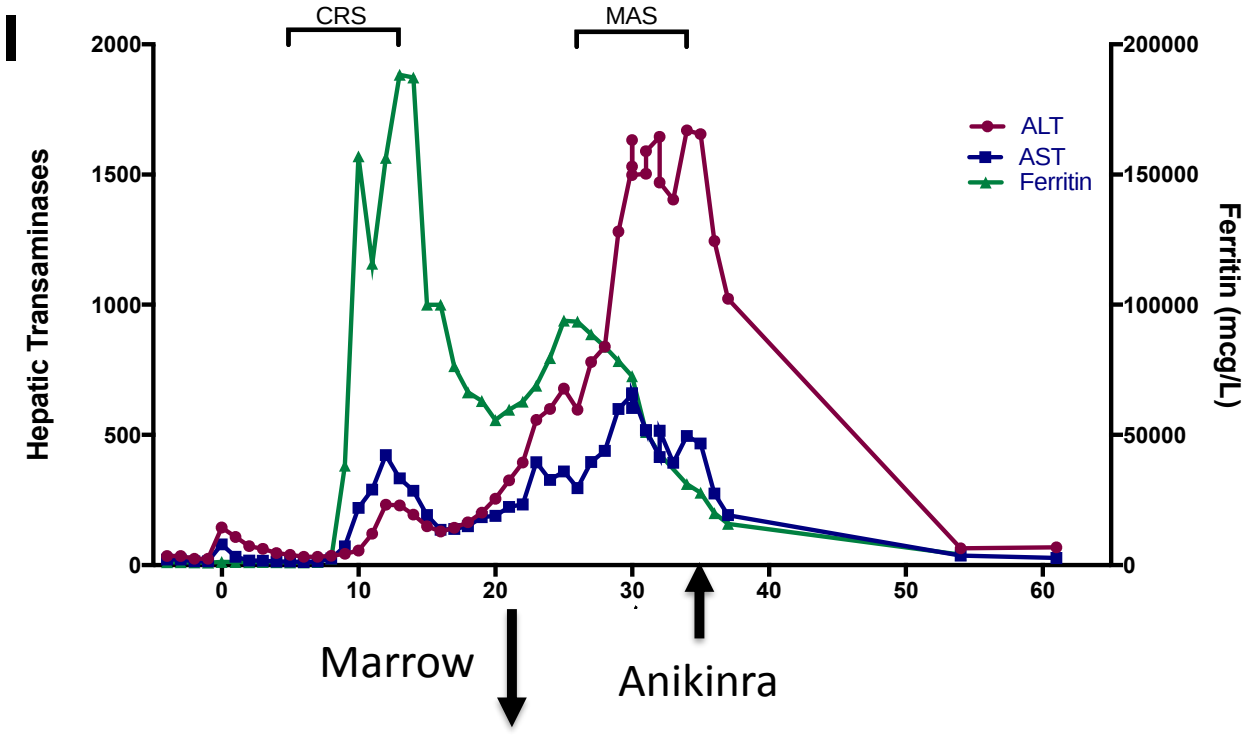


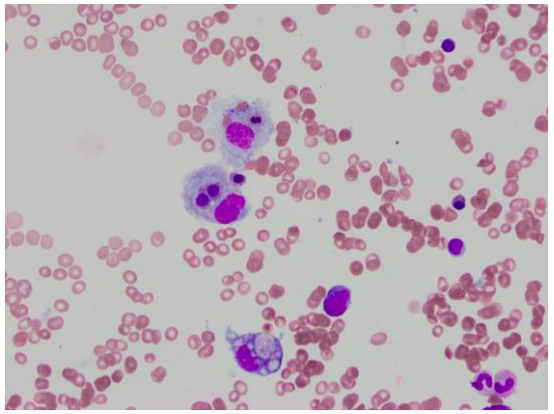


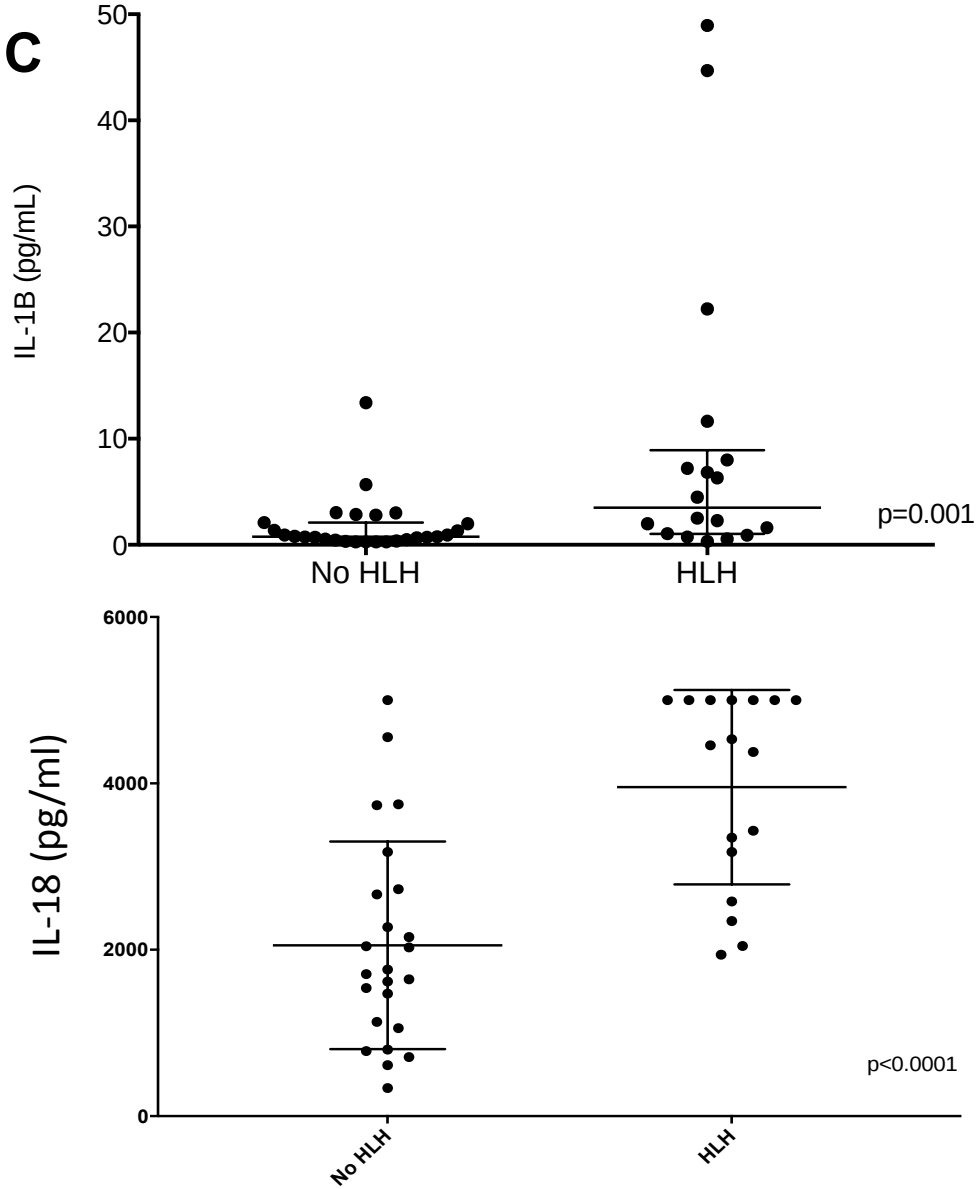




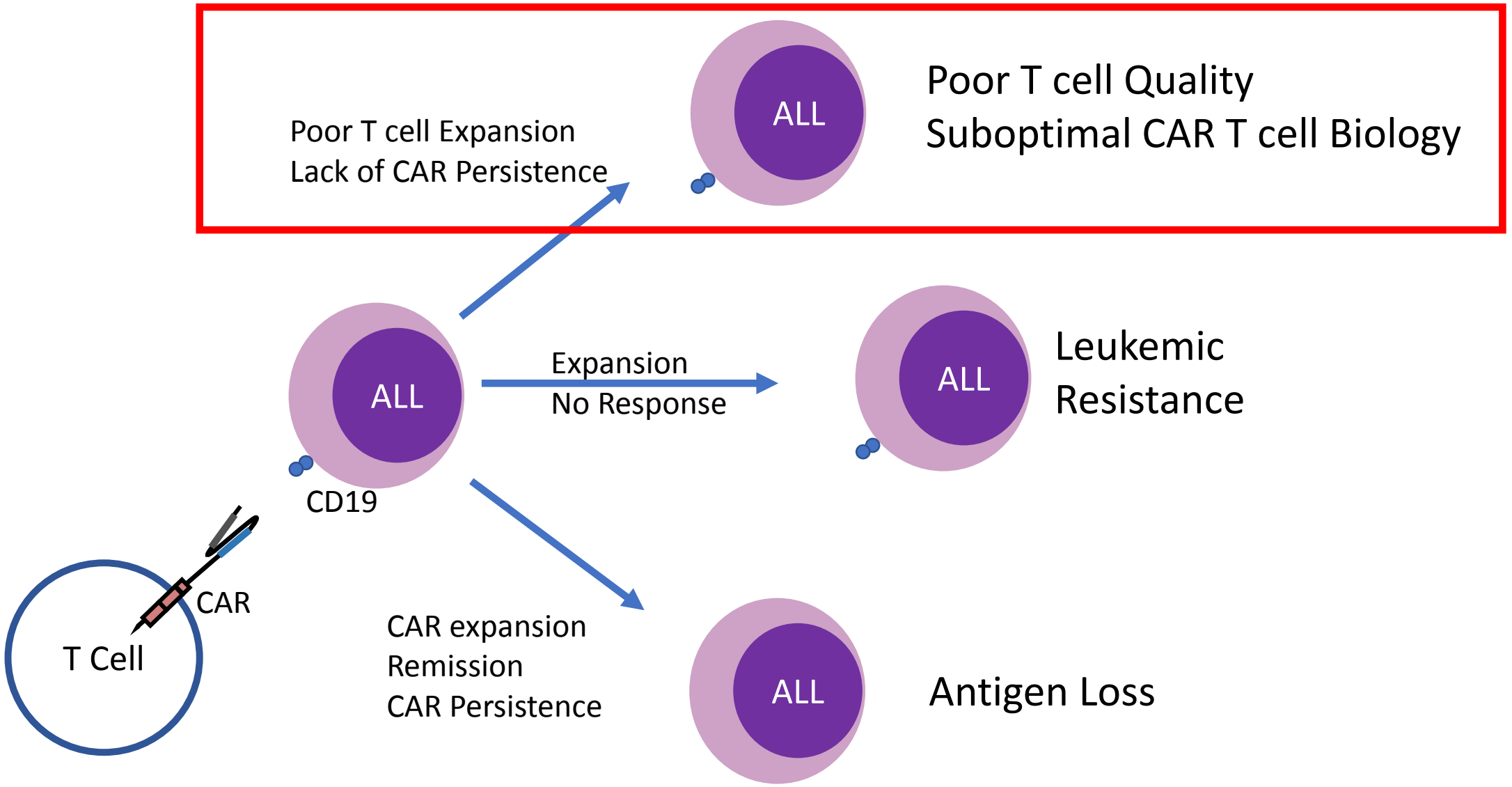
HLH/MAS in CD22 CAR Trial







Patterns of Failure Following CAR T cells for ALL

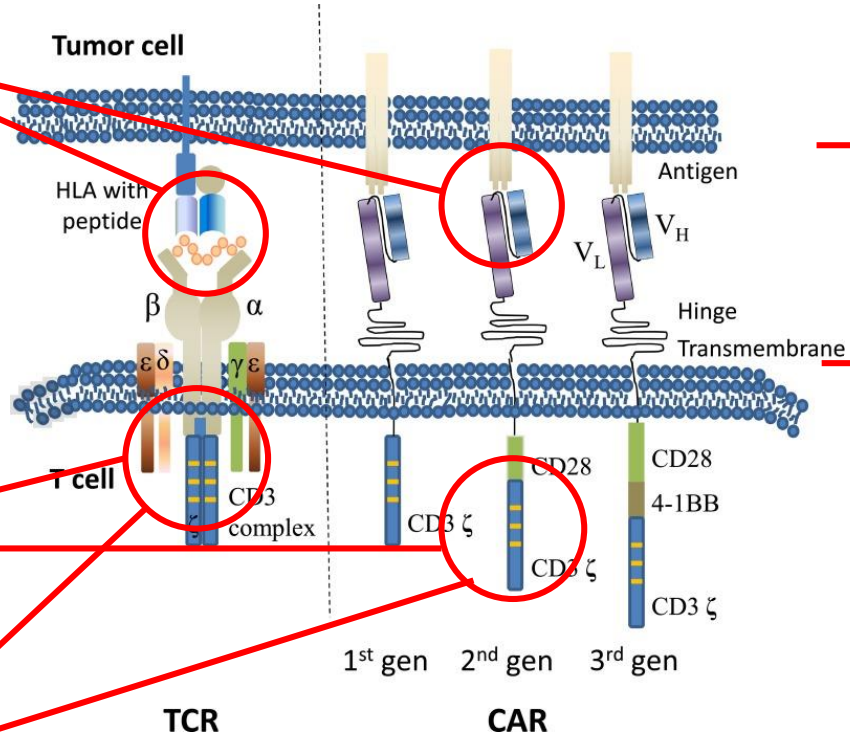


Structural and physical differences exist between CARs and endogenous TCRs

Affinity for antigen is ~1000 fold higher in CARs

10 vs 3 ITAMs per receptor

CAR contains in-line co-stimulatory signaling



Unknown if CAR activation results in organized synapse

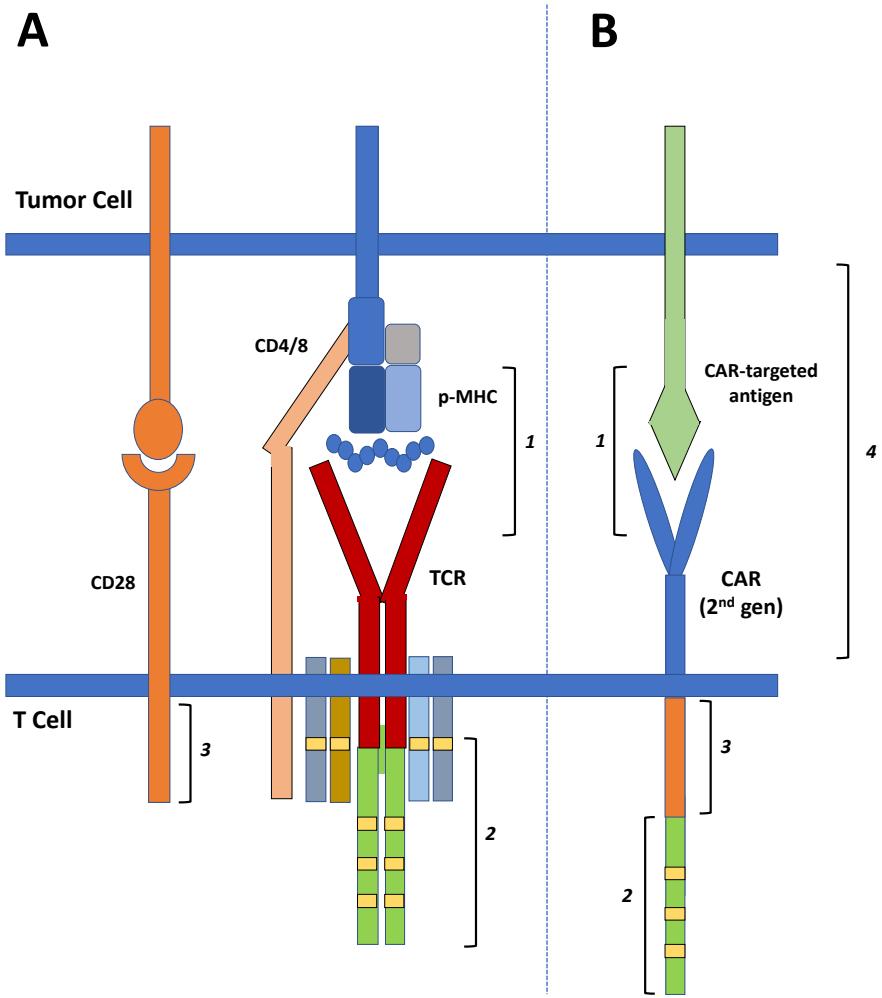
Distance between cells variable with CARs

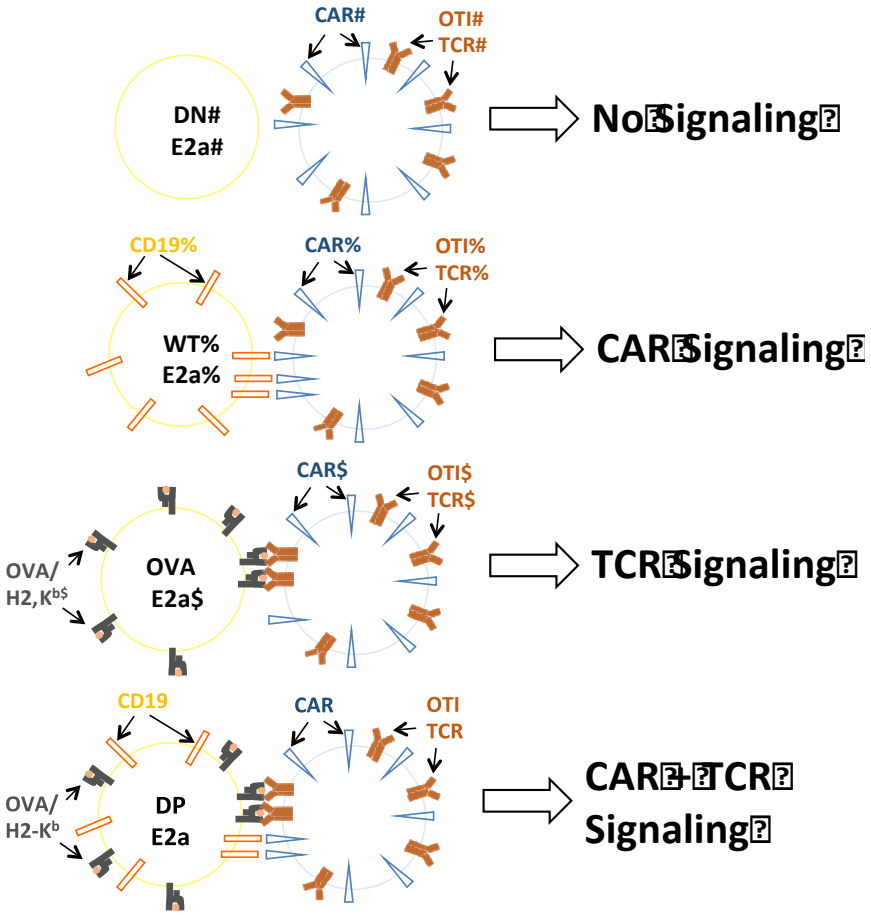
CD4/CD8 co-receptors not recruited by CARs

Modified from
Hillerdal et al. BioDrugs, 2015

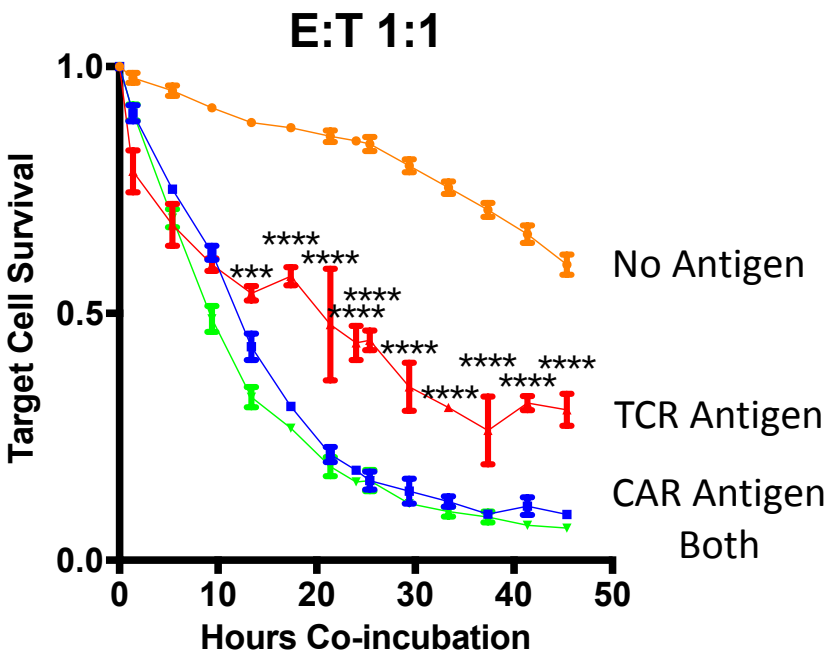
CAR Signaling: Redirection or Reprogramming?

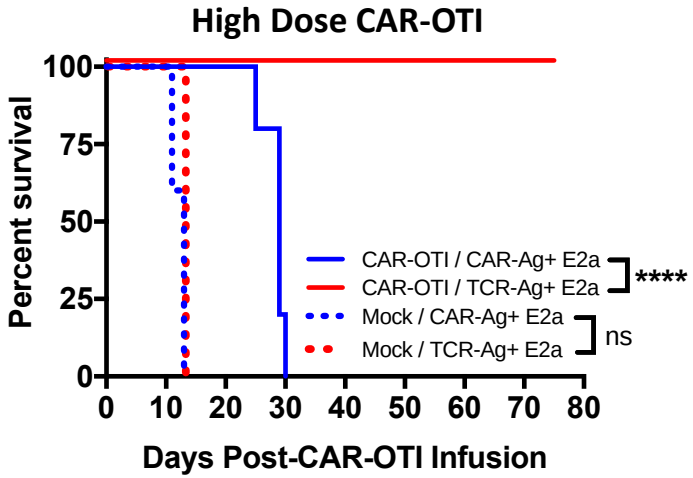
Eric Kohler

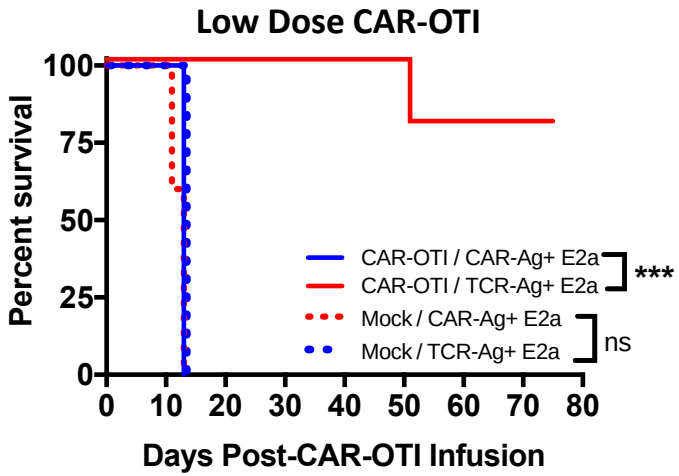


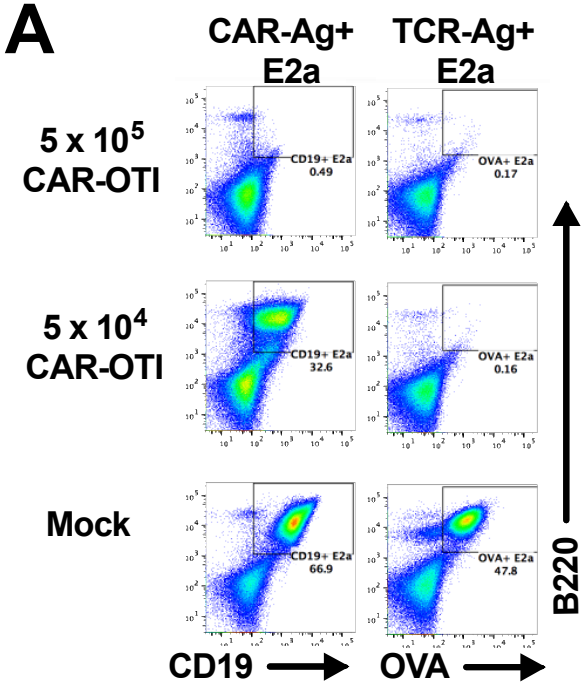


CAR-mediated activation results in more robust in vitro killing but less efficient at clearing leukemia in vivo

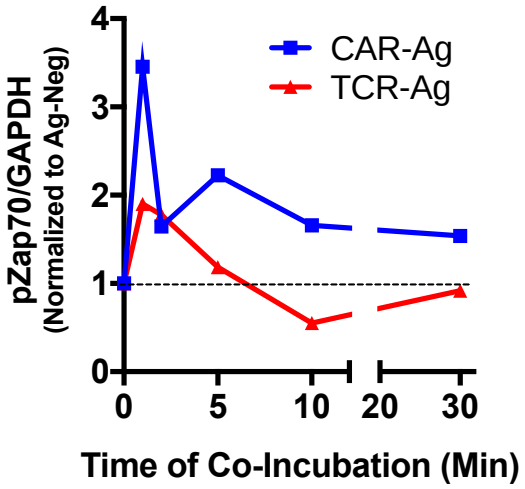


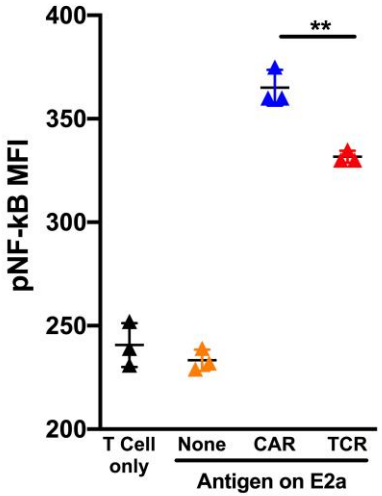


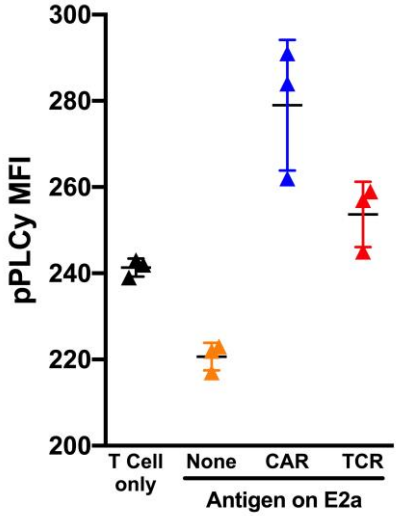


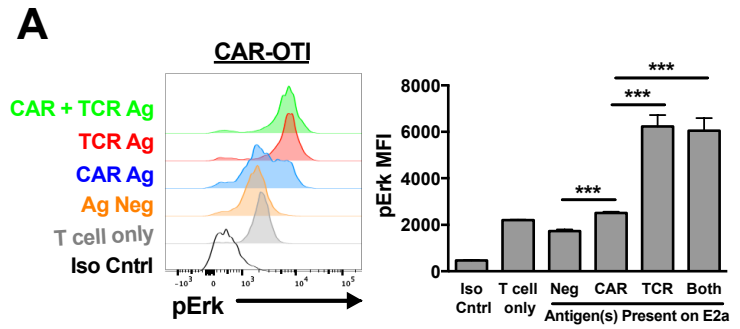


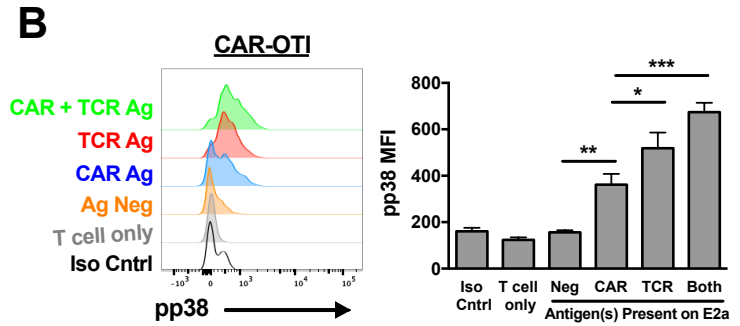
CAR-stimulation leads to sustained proximal signaling, enhanced activation of the NF-kB pathway, but less MAPK activation relative to TCR-stimulation

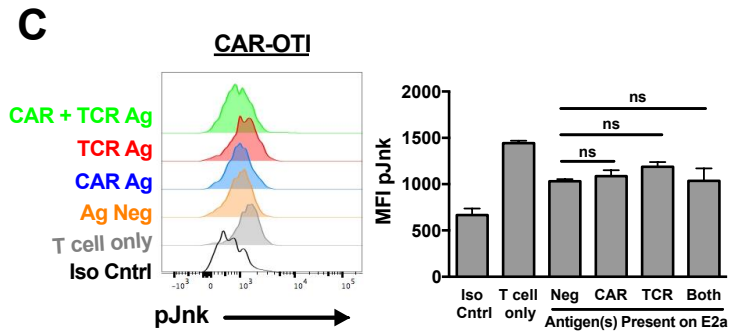




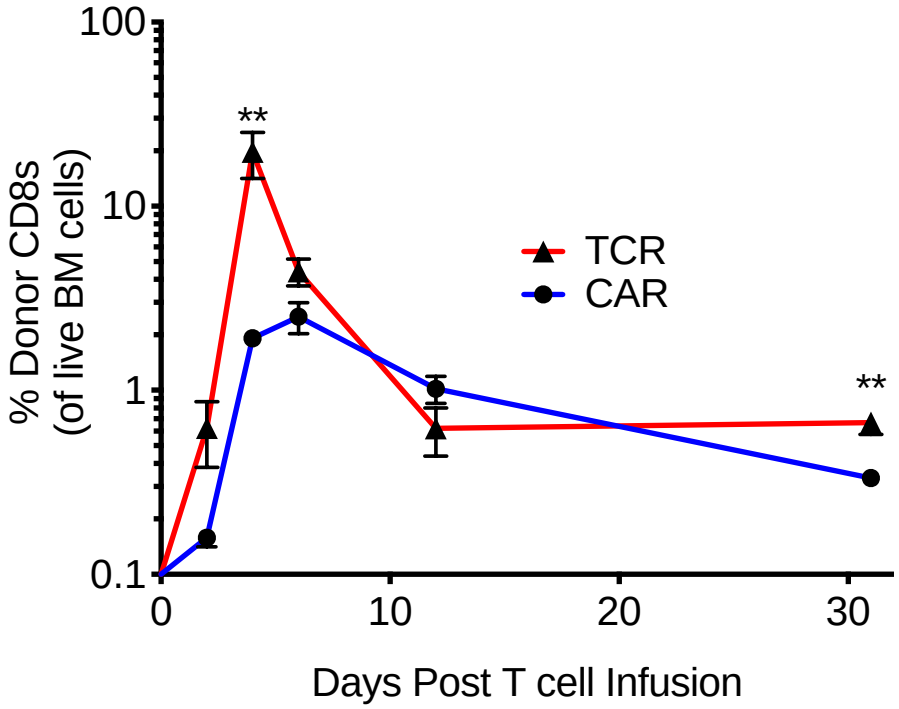


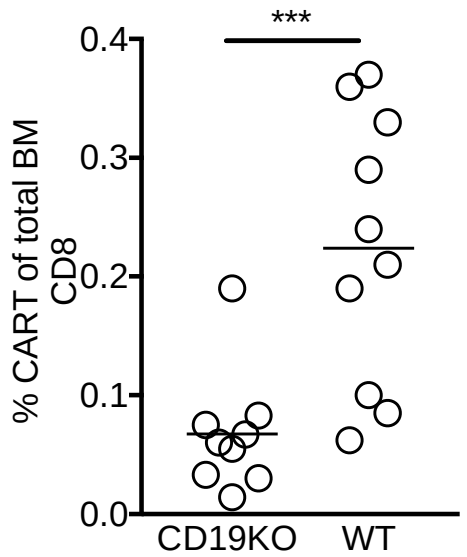




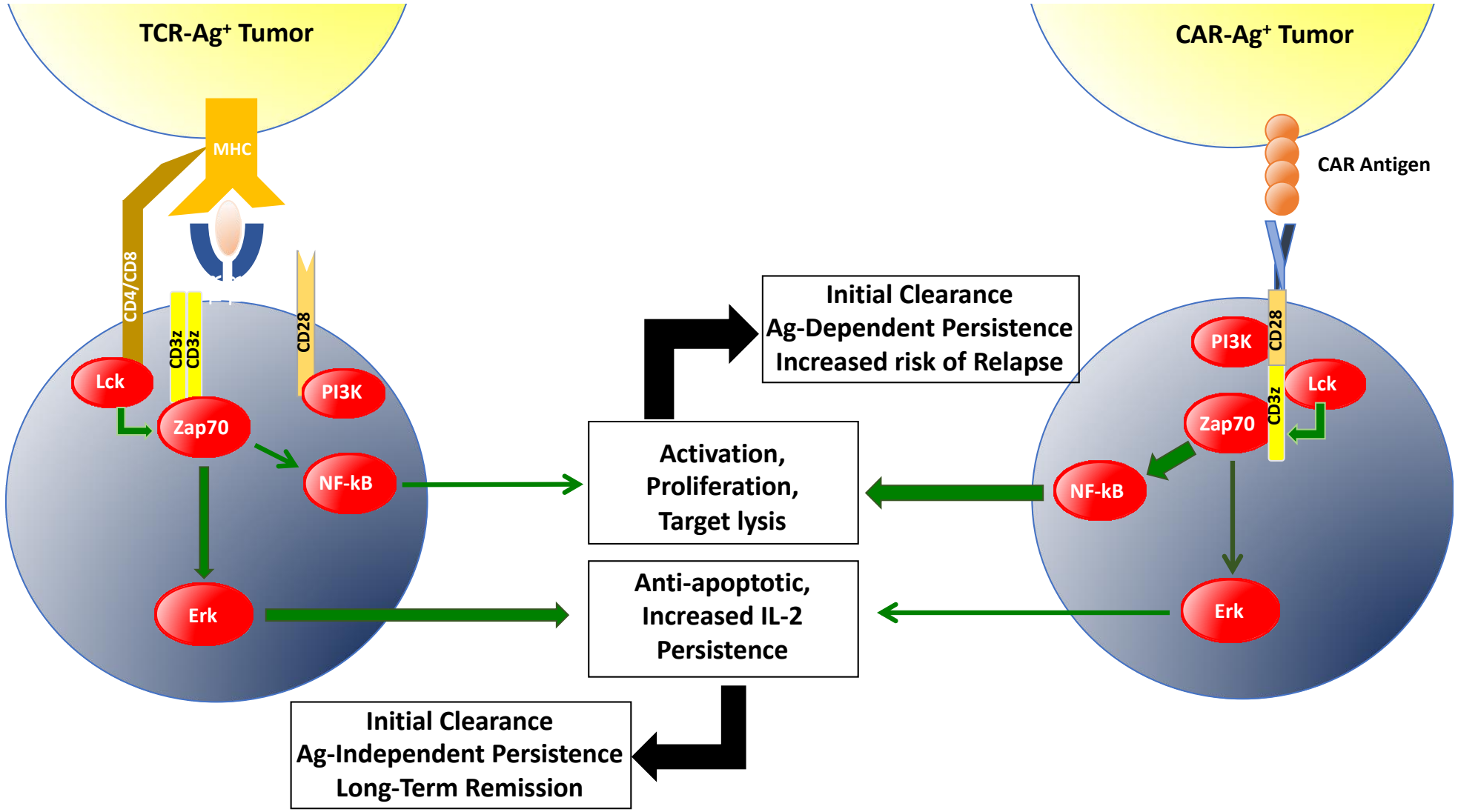


CAR activated T cells show less persistence that is more antigen dependent



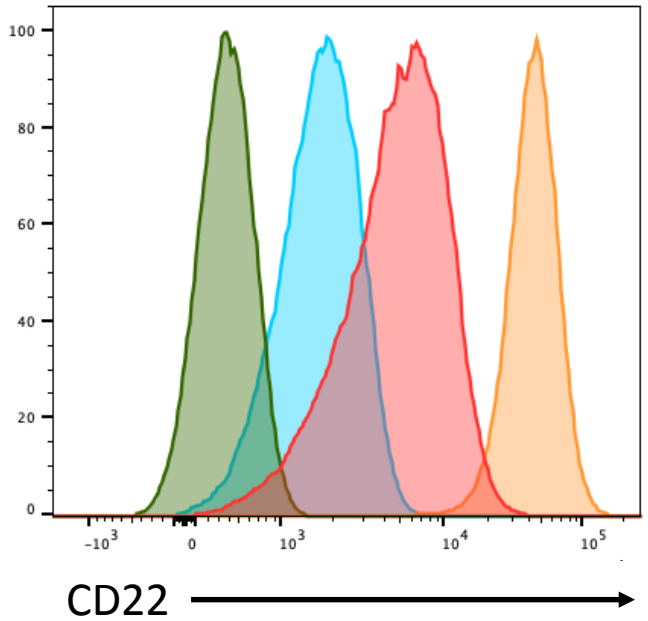


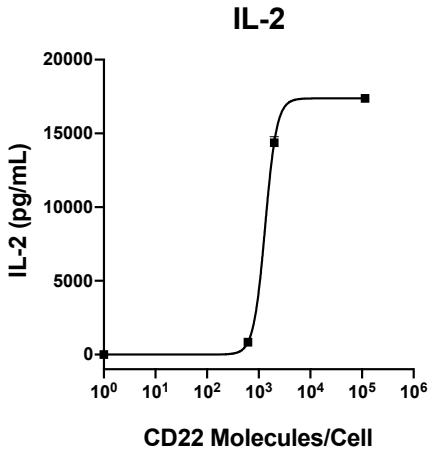
Structural and physical differences in CARs relative to TCRs results in unique signaling, that correlates with altered *in vivo* biology and potency

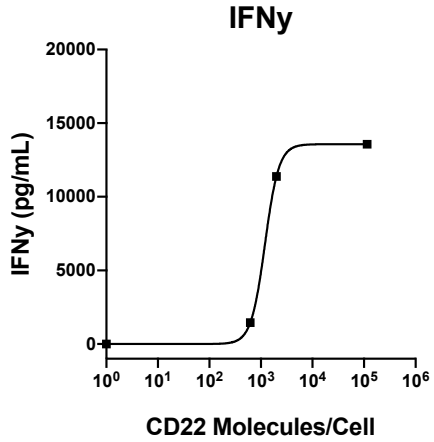


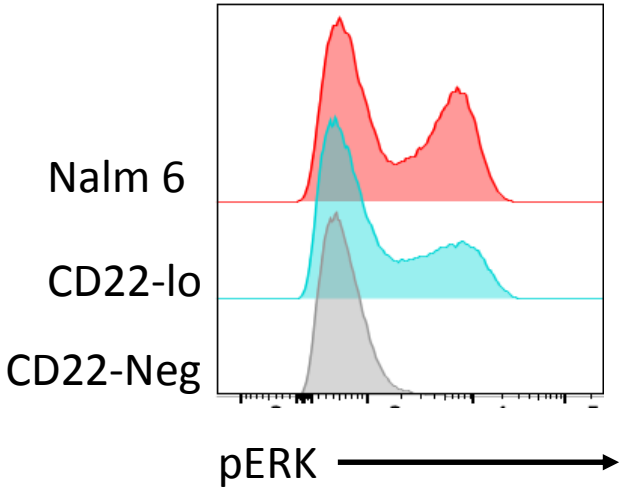
Site Density Affects CD22 CAR Function and Signaling

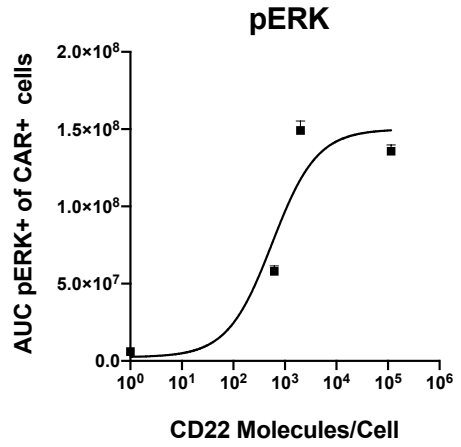
Sneha Ramakrishna





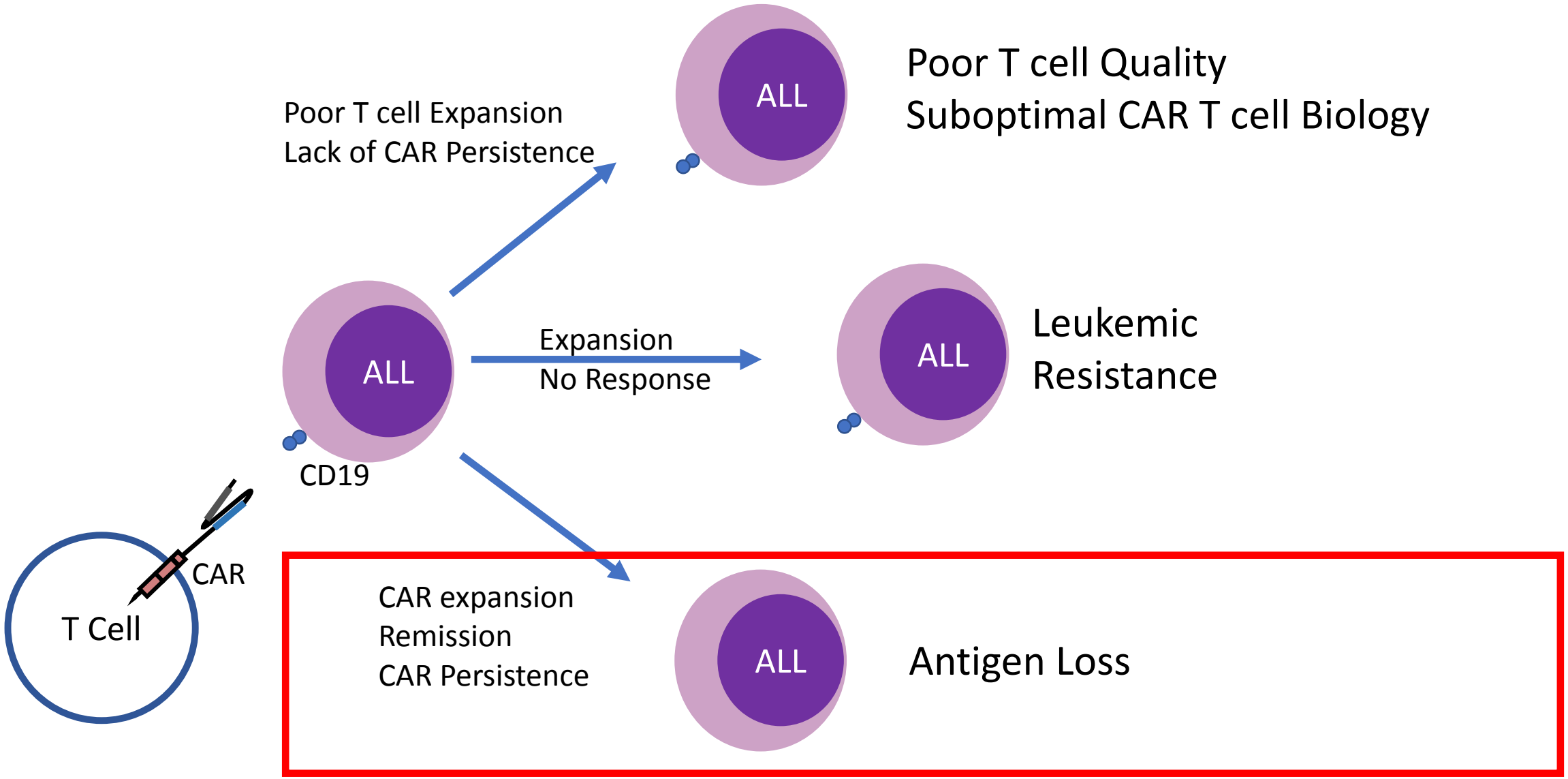




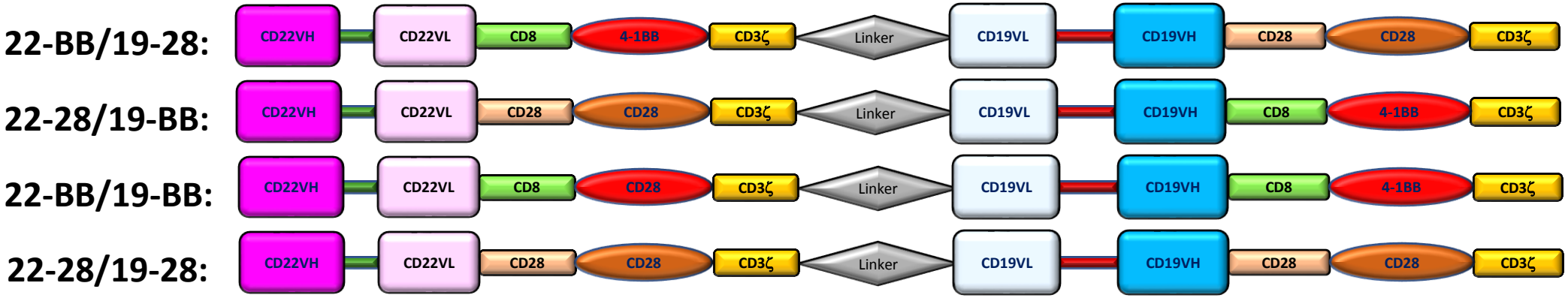


Ramakrishna, Clin Can Res, 2019

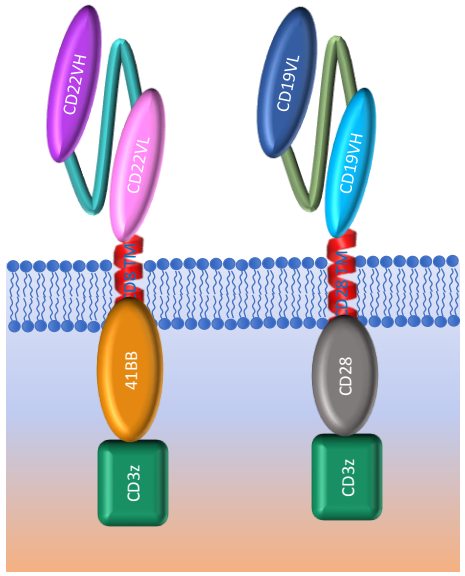
Patterns of Failure Following CAR T cells for ALL

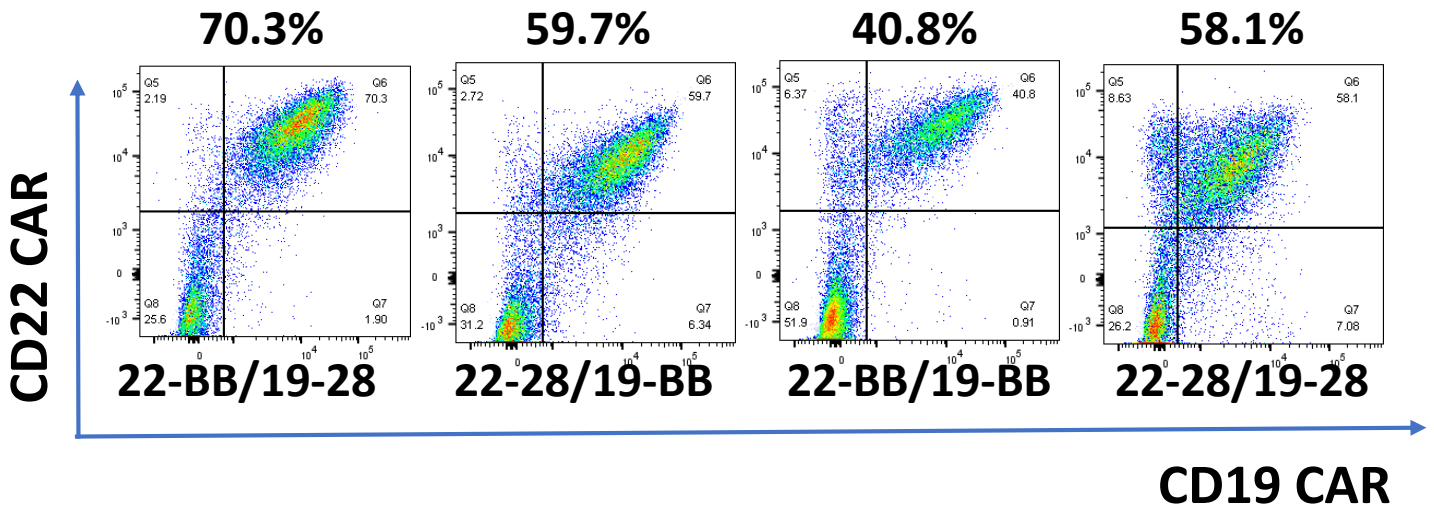


Achieving Uniform Expression of Two CARS using Bicistronic Vectors



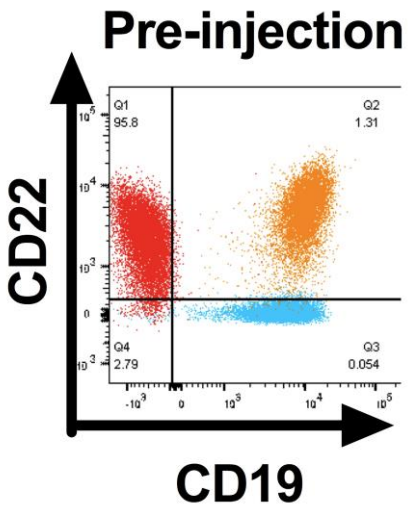
Translation



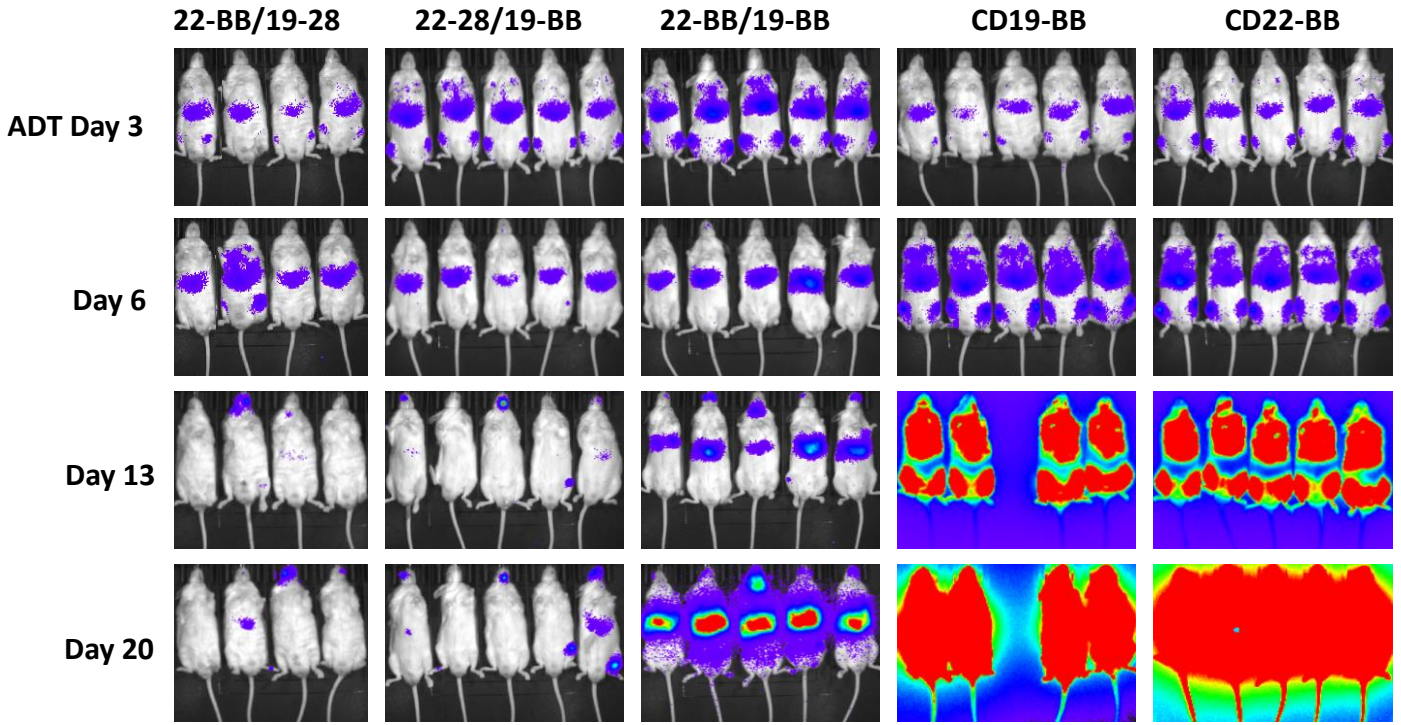


Haiying Qin

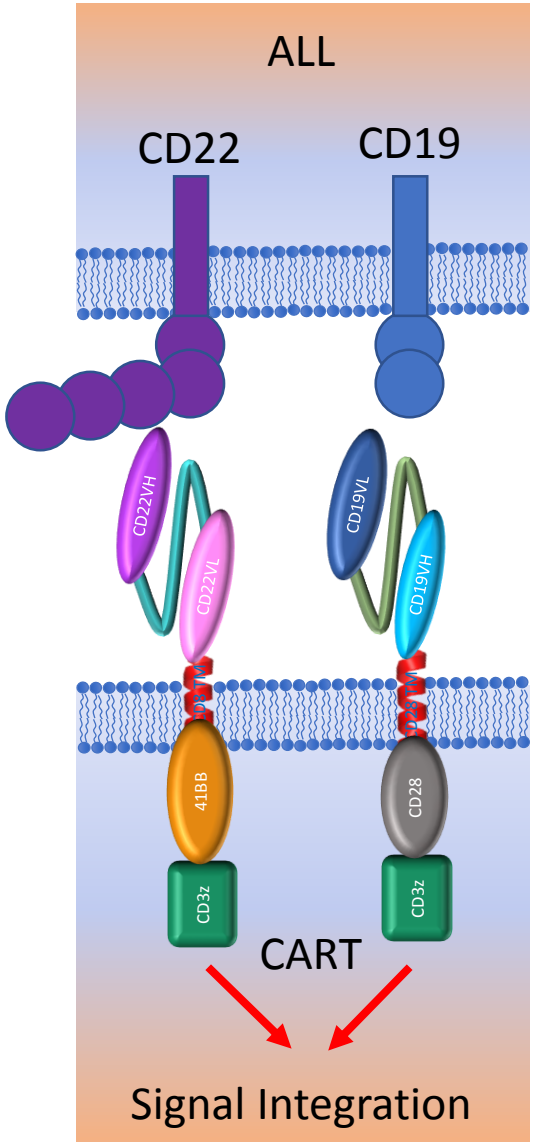
Dual CAR expressing T cells mediate potent single antigen activity

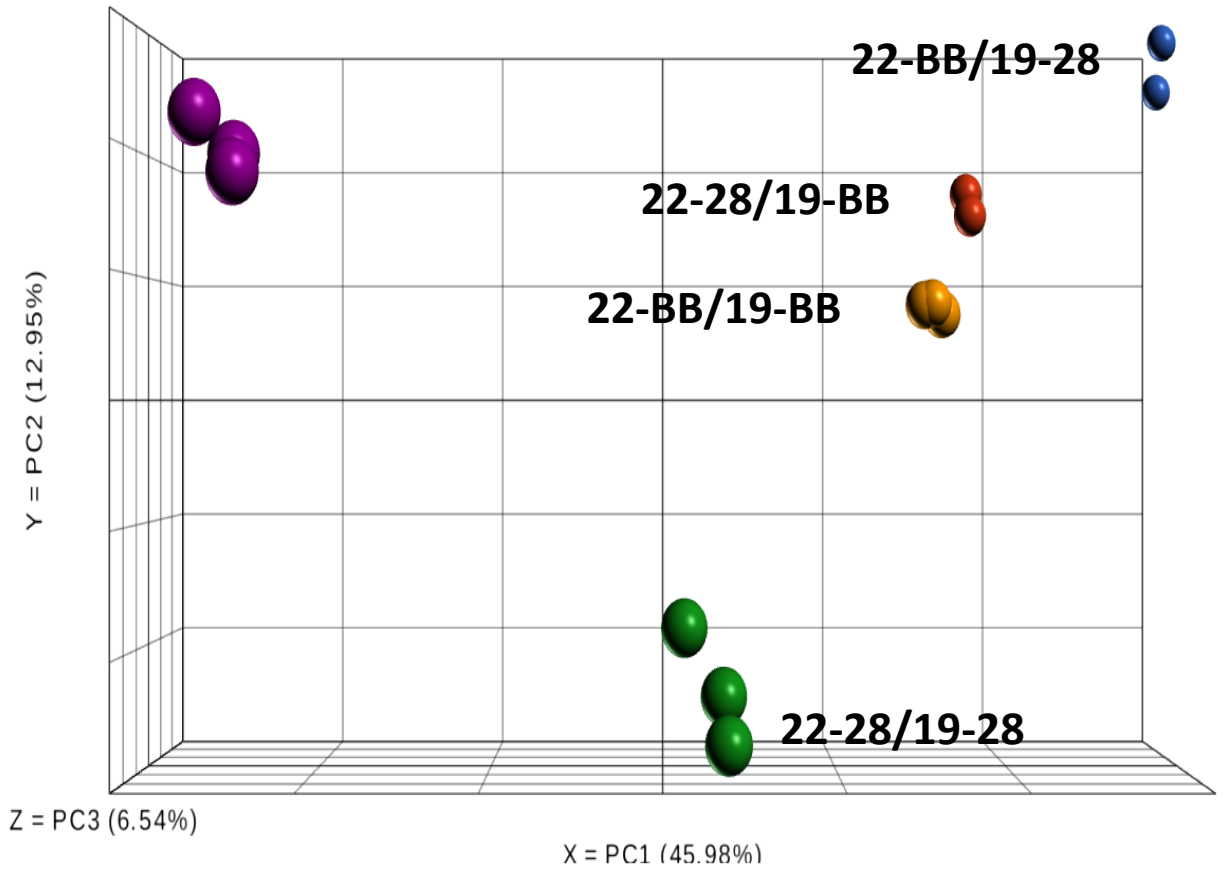


D0: 1E5 NALM6-CD19KO + 1E5 NALM6-CD22KO + 1E5 NALM6
D3: IV 3E6 CAR

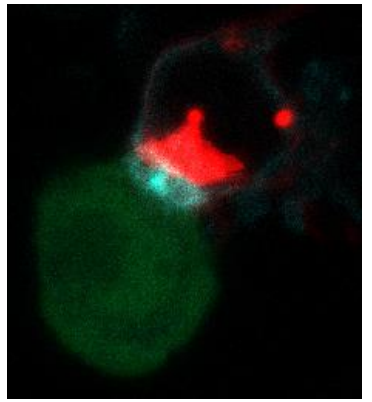


Signal integration in Dual CAR Expressing T cells results in distinct profiles depending on binder/costim combinations





22-BB/19-28



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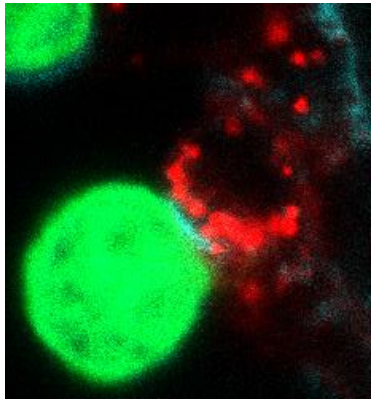
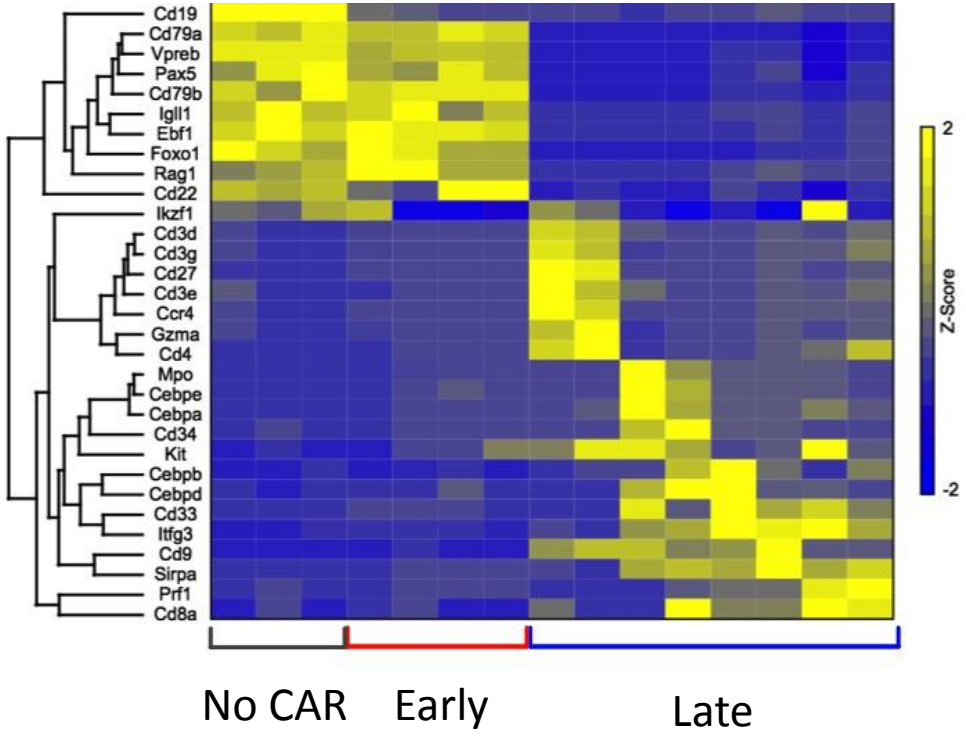
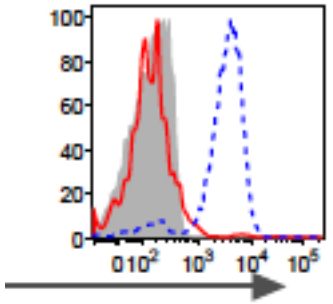


GFP: Nalm6 ALL
Red: CD22 CAR
Blue: CD19 CAR

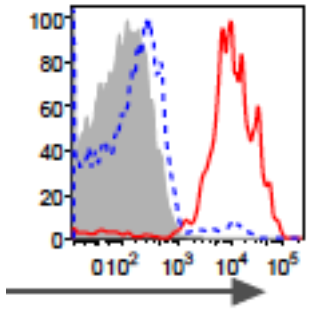
Leukemic evolution in the context of targeted Immunotherapy can be complex



Jacoby et al, Nature Communications, 2016



CD19



CD11b

KMT2A-R ALL, but also reported in other subtypes.

----- Pre-CD19 CAR

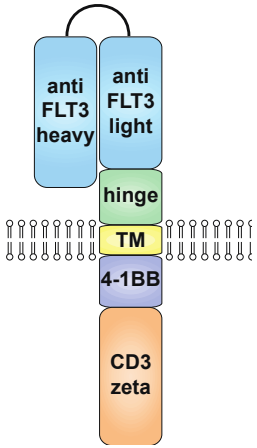
——— Post-CD19 CAR

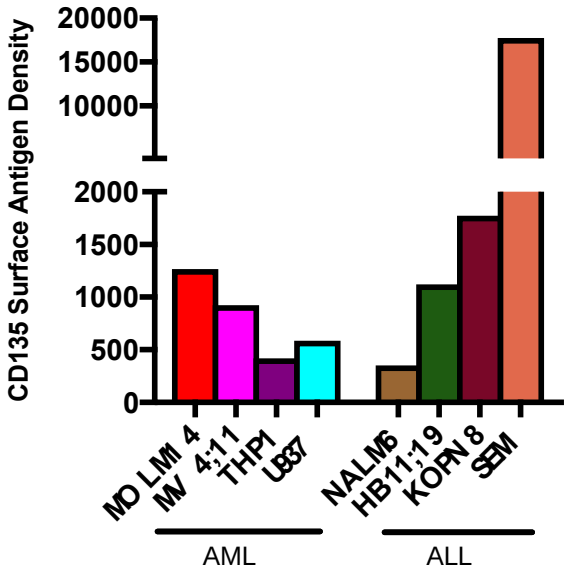
Gardner et al, Blood, 2016

Preclinical Activity of FLT3R CAR T Cells (CD135CART)

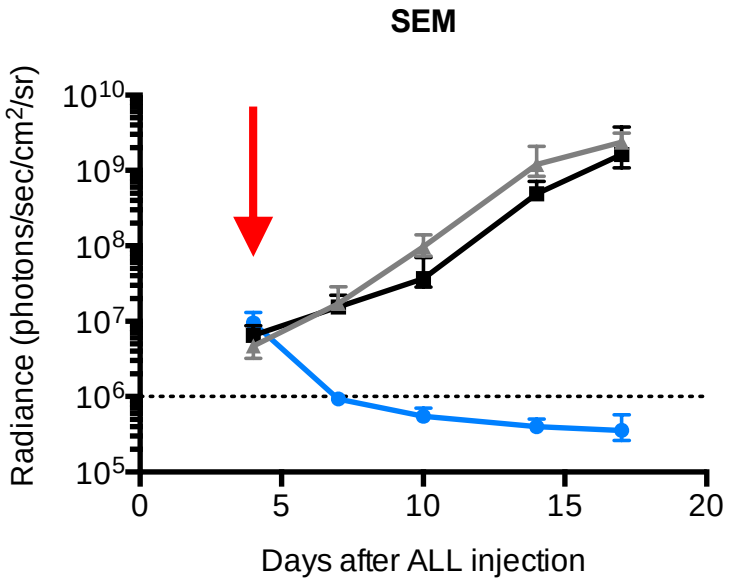
Chris Chien

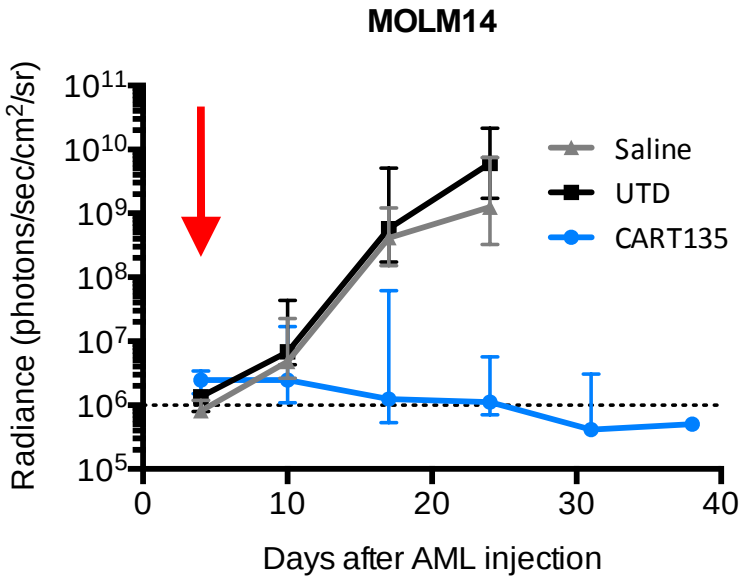
Hypothesis: Targeting cytokine receptors in high-risk leukemia subtypes will decrease likelihood of antigen loss





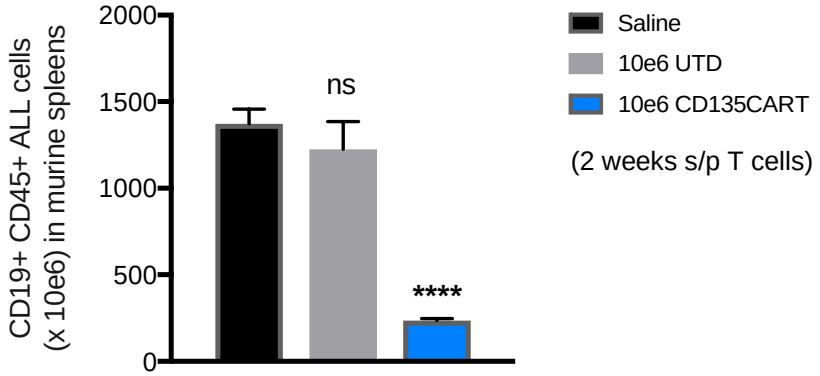
In vivo testing in luciferase+ ALL and AML cell line xenografts

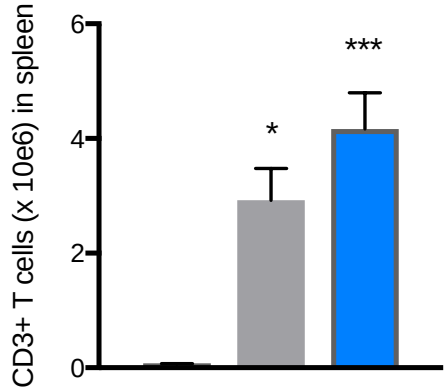




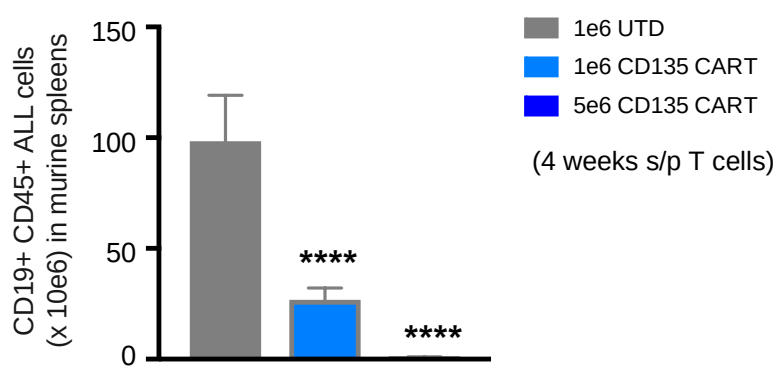
In Vivo CD135CART Activity in *KMT2A*-R ALL PDX Models

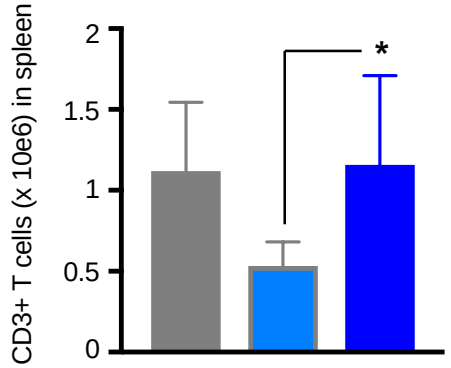
KMT2A-MLLT3 infant ALL PDX





KMT2A-AFF1 adult ALL PDX





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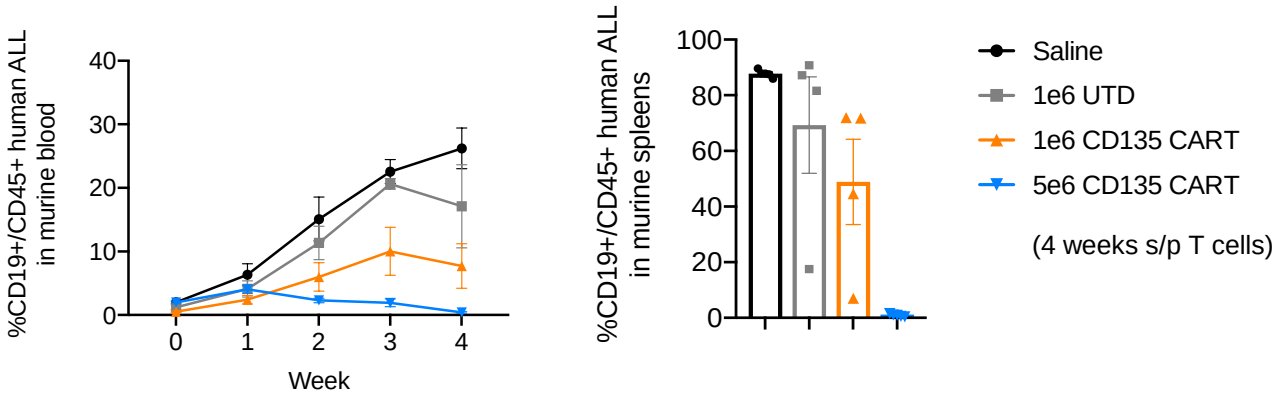
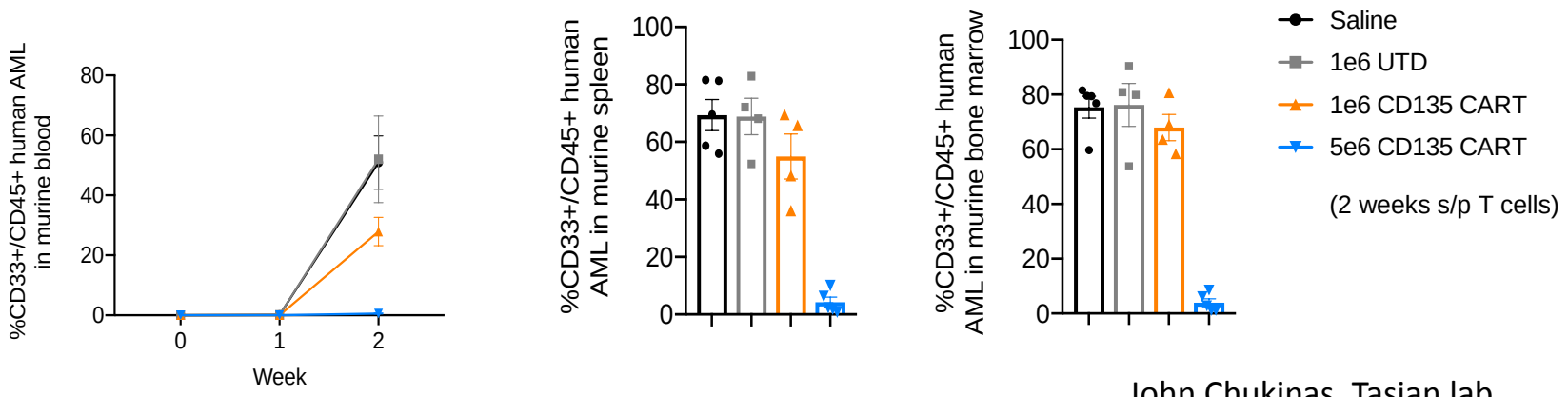
In Vivo CD135CART Activity in Lineage Switch Models

KMT2A-R ALL PDX



KMT2A-R AML PDX (lineage switch after CD19CART)



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Summary

- Single antigens comparable to CD19 will be difficult (Impossible?) to find
- Antigen modulation as well as more complex patterns of cancer resistance will frequently emerge
- Current CAR formats do not fully recapitulate T cell biology
- Details matter – construct design, manufacturing, target antigen, disease

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