Precision NK cells Engineering to advance Adoptive Therapies

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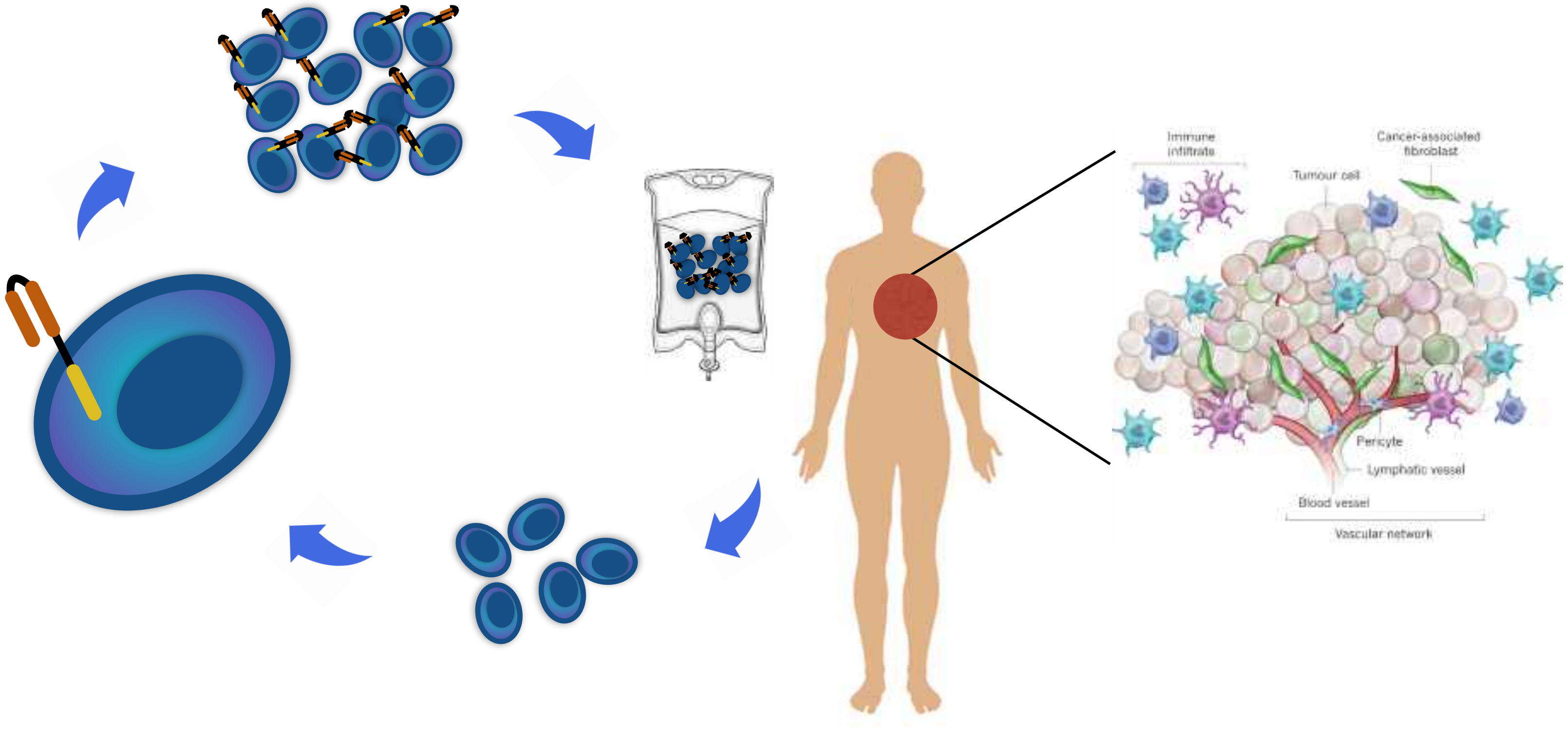
Limits in CAR T cells

Relapse
- Low / negative antigen
- CAR not sensitive to low antigen

Toxicities
- Cytokine Release Syndrome
- Cerebral Edema

Manufacturing
- Cost
- Variability in the final product



CAR NK cells advantages

Relapse

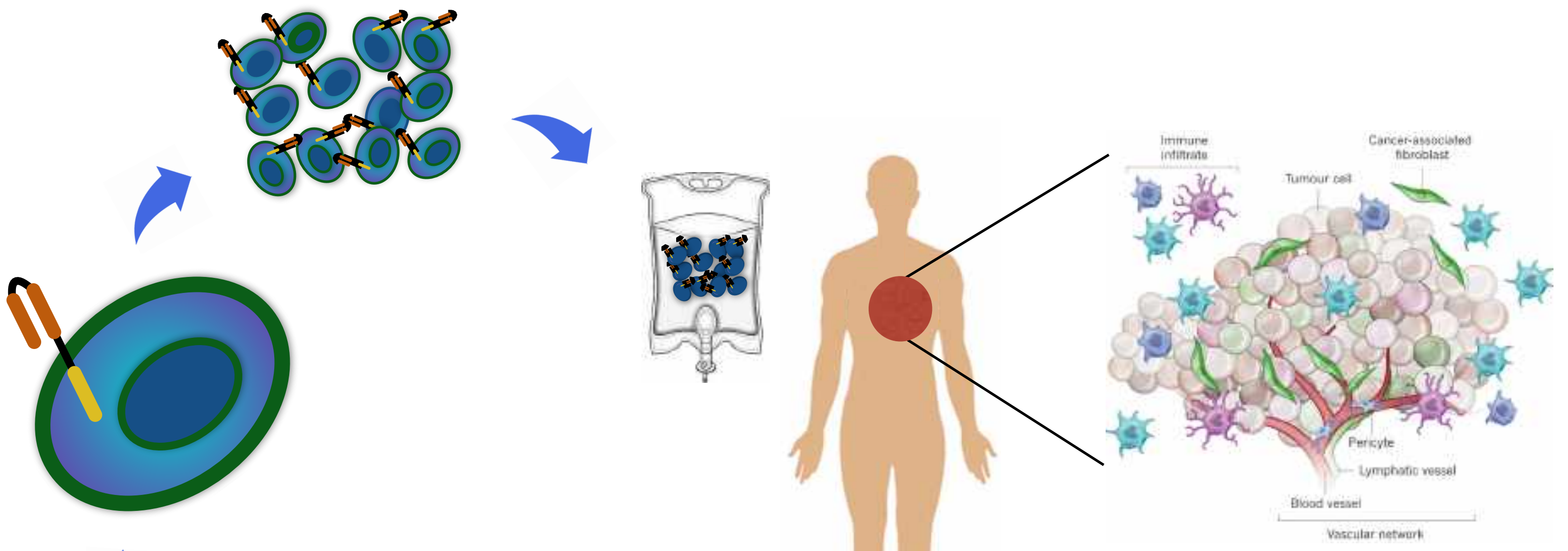
- Multiple receptors can targets heterogenous tumors

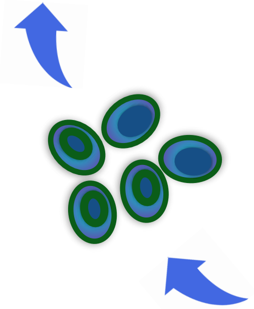
Toxicities

- No clonal expansion associated toxicity

Manufacturing

- No GVHD - allogeneic by design
- Production form HSCs/iPSC

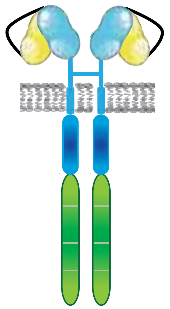




- **Healthy donor PBMC**
- **Cord blood HSCs**
- **iPSCs**

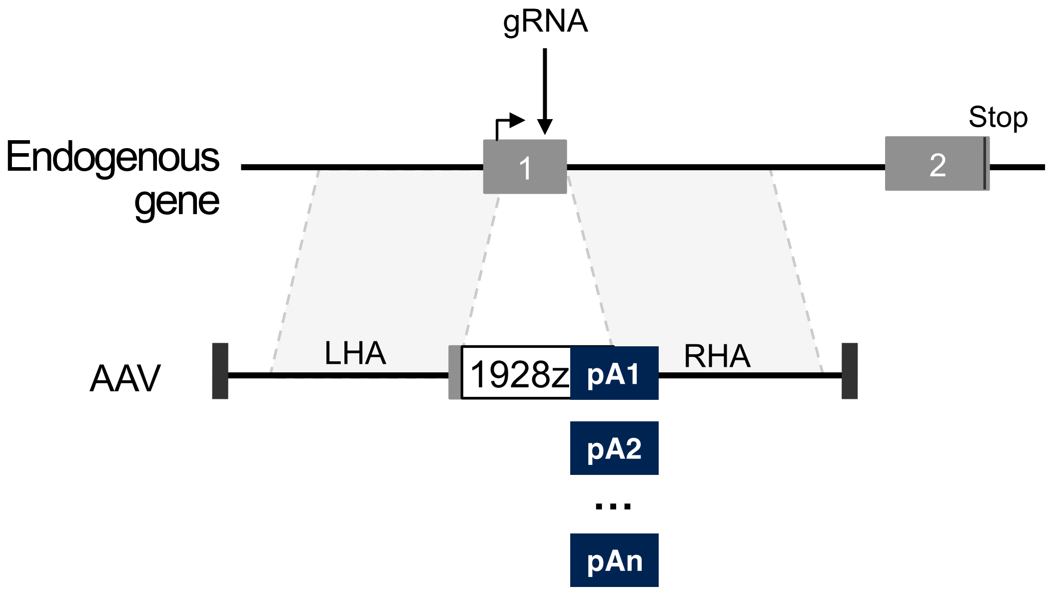
Improving Adoptive NK cell therapy

Synthetic Receptor Design

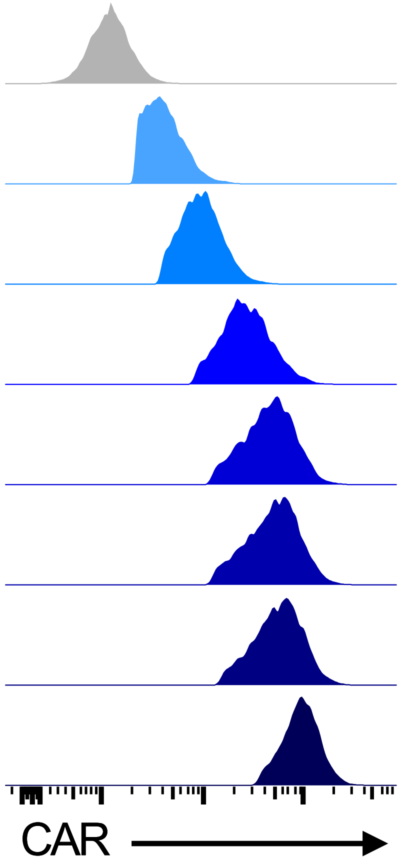


Optimizing
Costimulatory domains
for NK

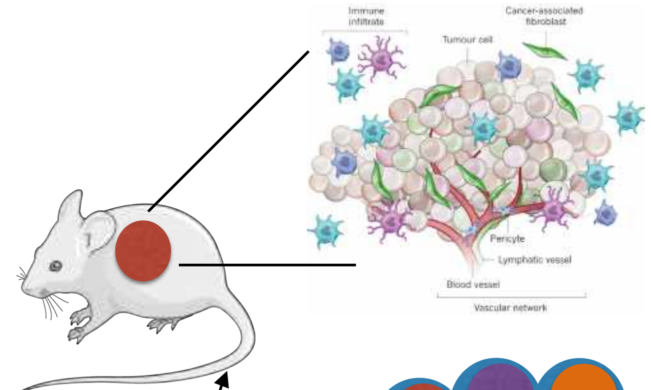
Genome editing



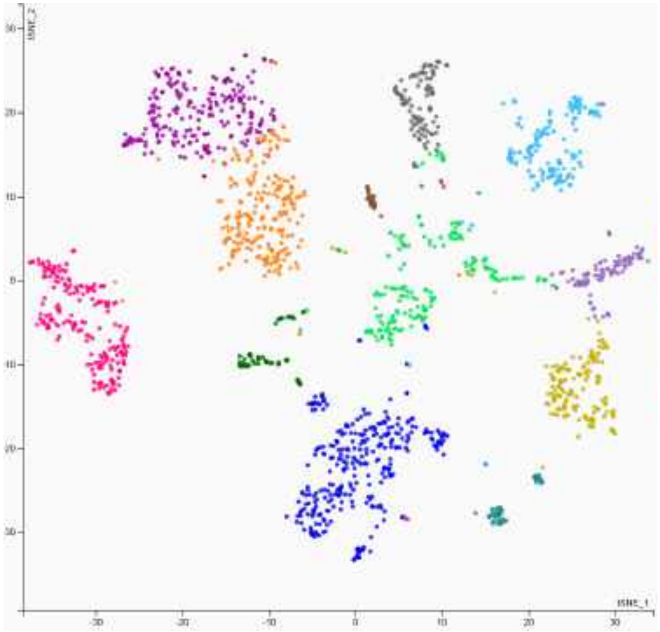
Targeting the CAR in specific
loci offering optimal
CAR expression



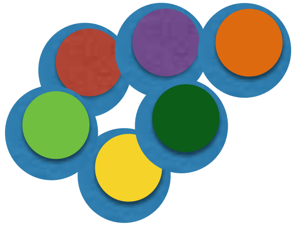
In vivo functional studies to assess engineered CAR NK cells



Harves tumor and Spleen



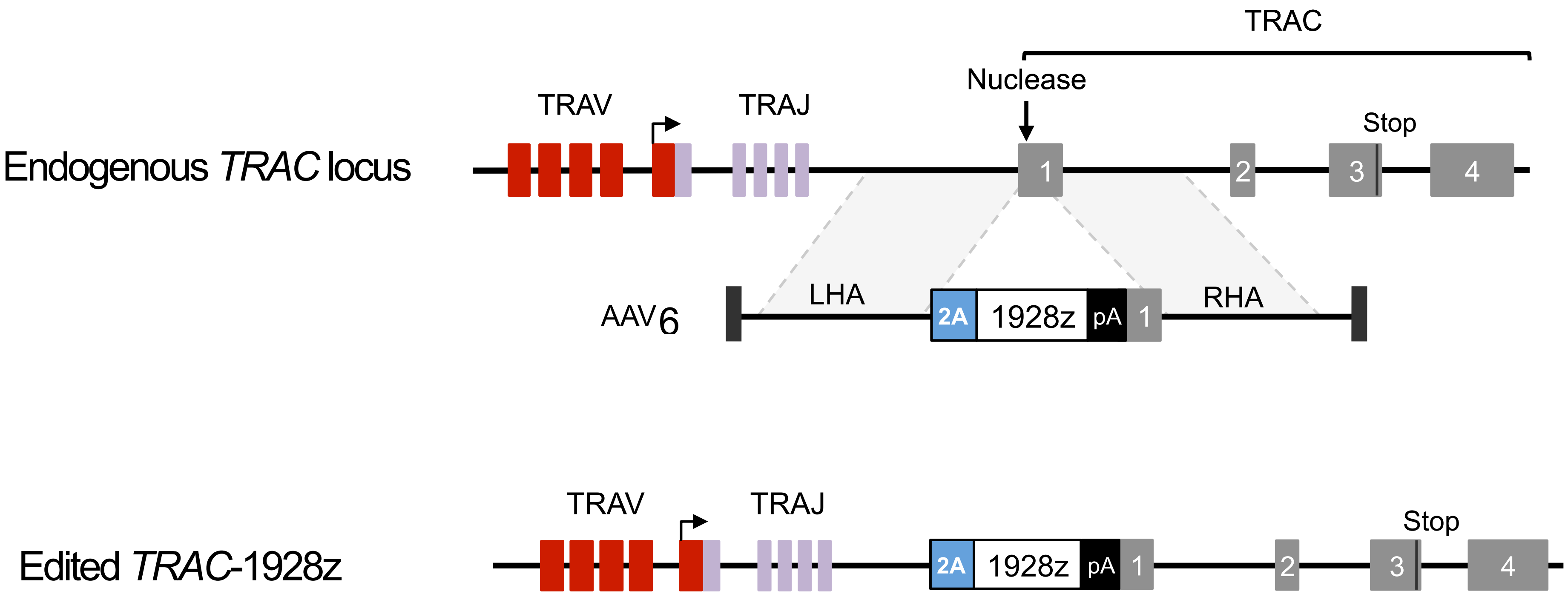
Xenograft tumor model



Edited mouse CAR NK cells

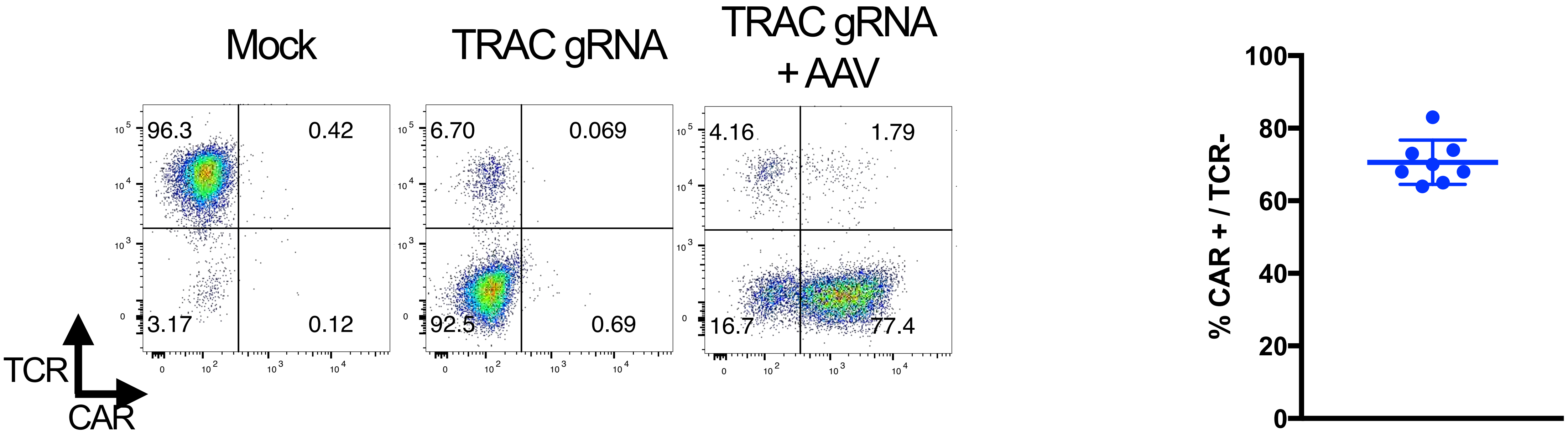
Associate CAR design and NK phenotype

Targeting the CAR transgene into the TRAC locus



Eyquem et al., *Nature 2017*

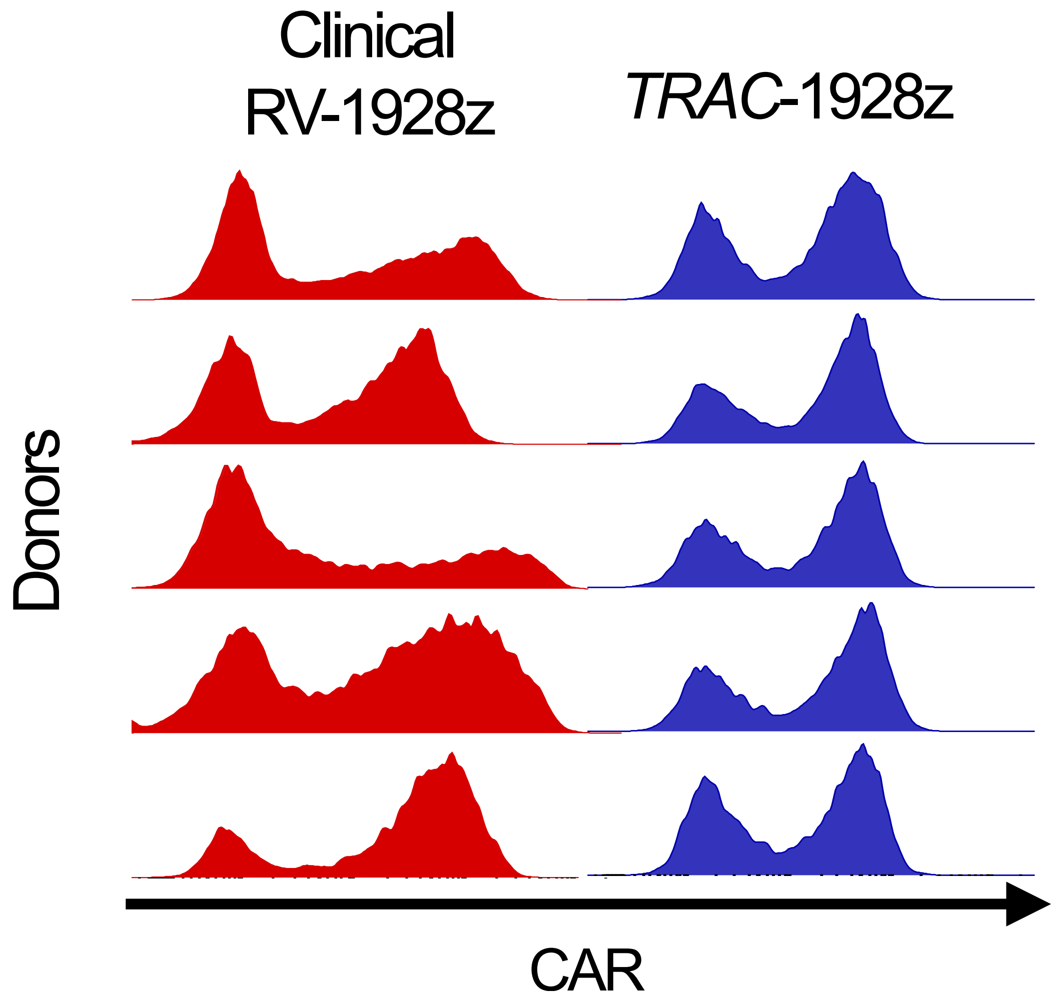
Highly Efficient CAR KI

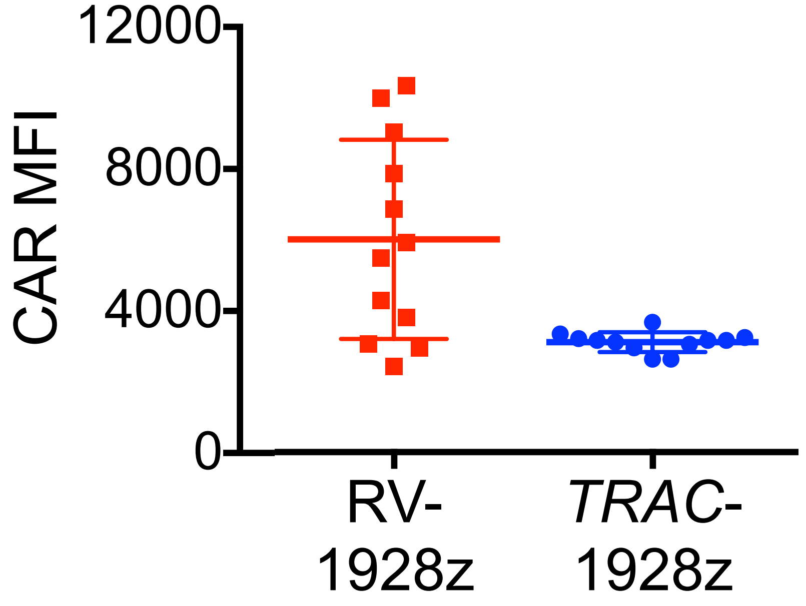


n = 8

Eyquem et al., *Nature 2017*

Homogeneous and Predictable CAR expression

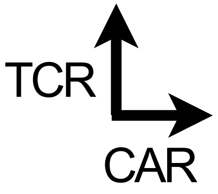




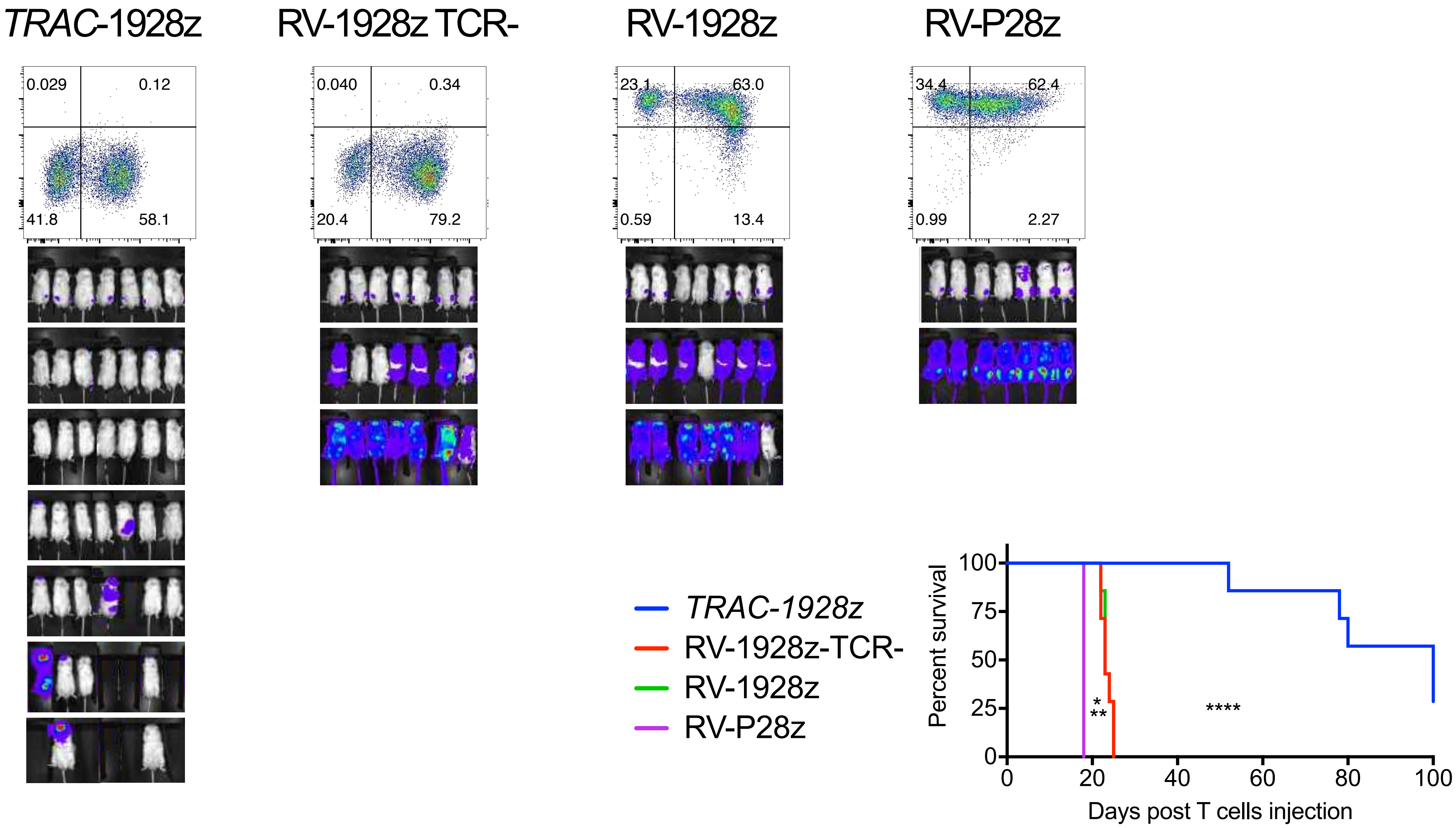
n=12

Eyquem et al., *Nature 2017*

TRAC-CAR T cells display superior *in vivo* activity

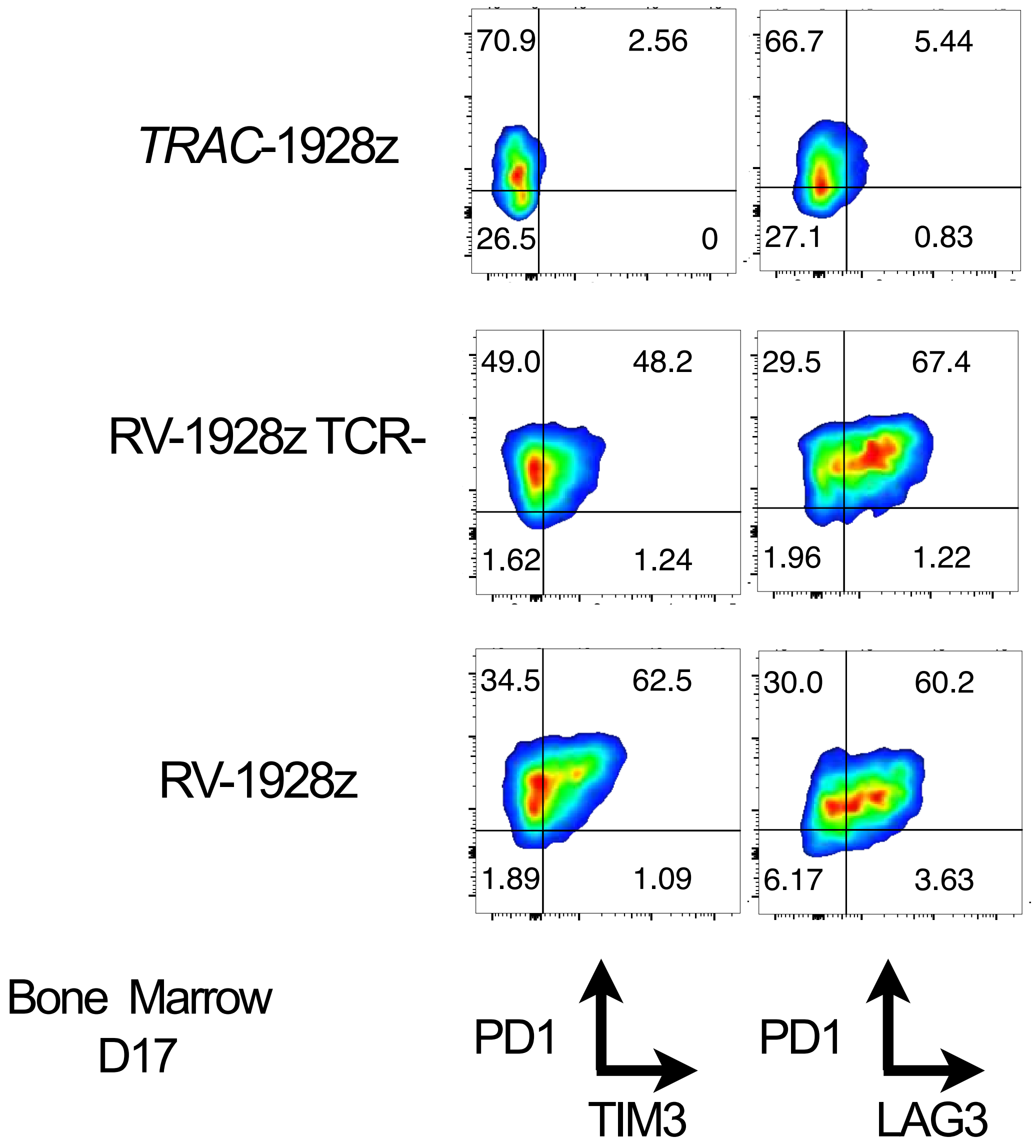


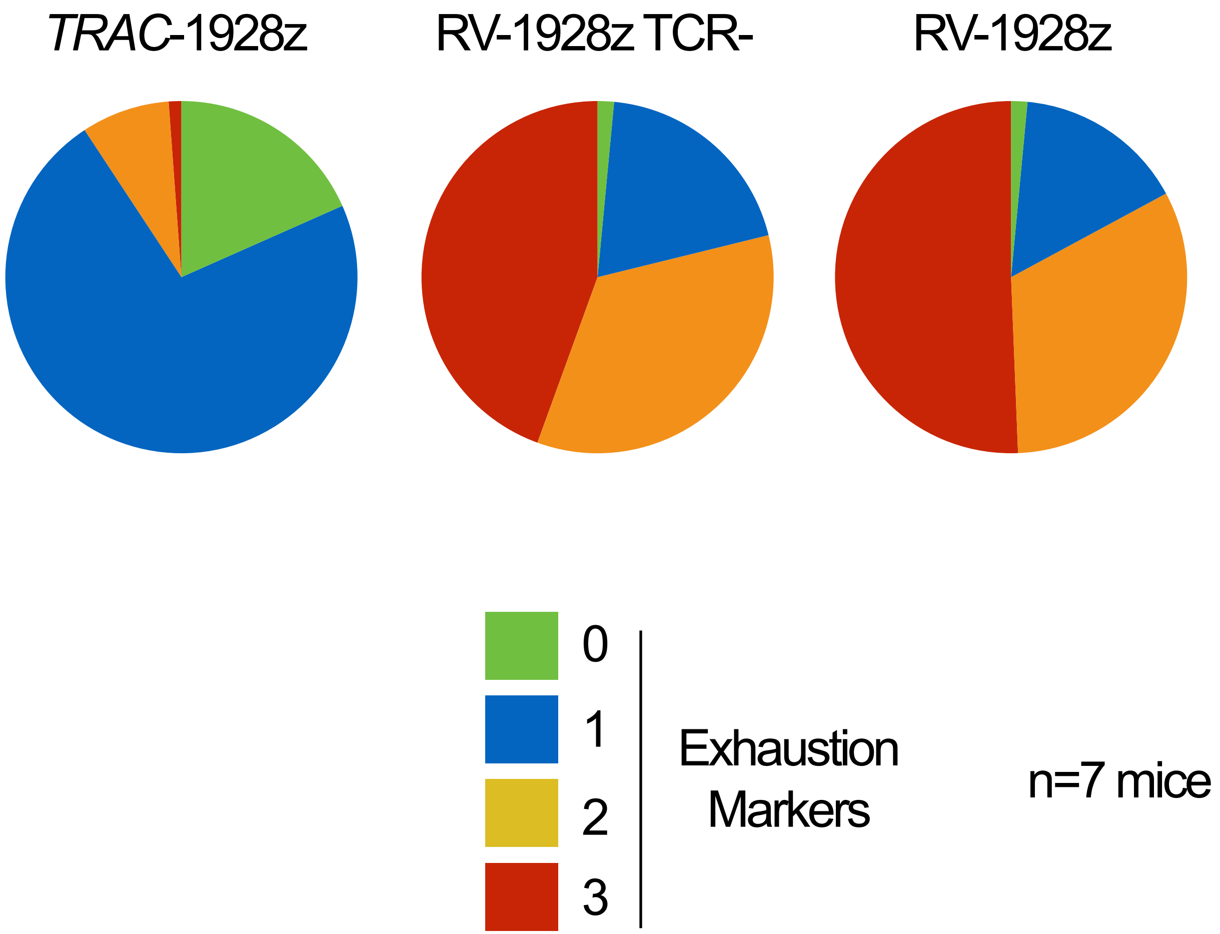
5e5 Nalm6 in NSG
-
2e5 CAR T cells



Eyquem et al., *Nature 2017*

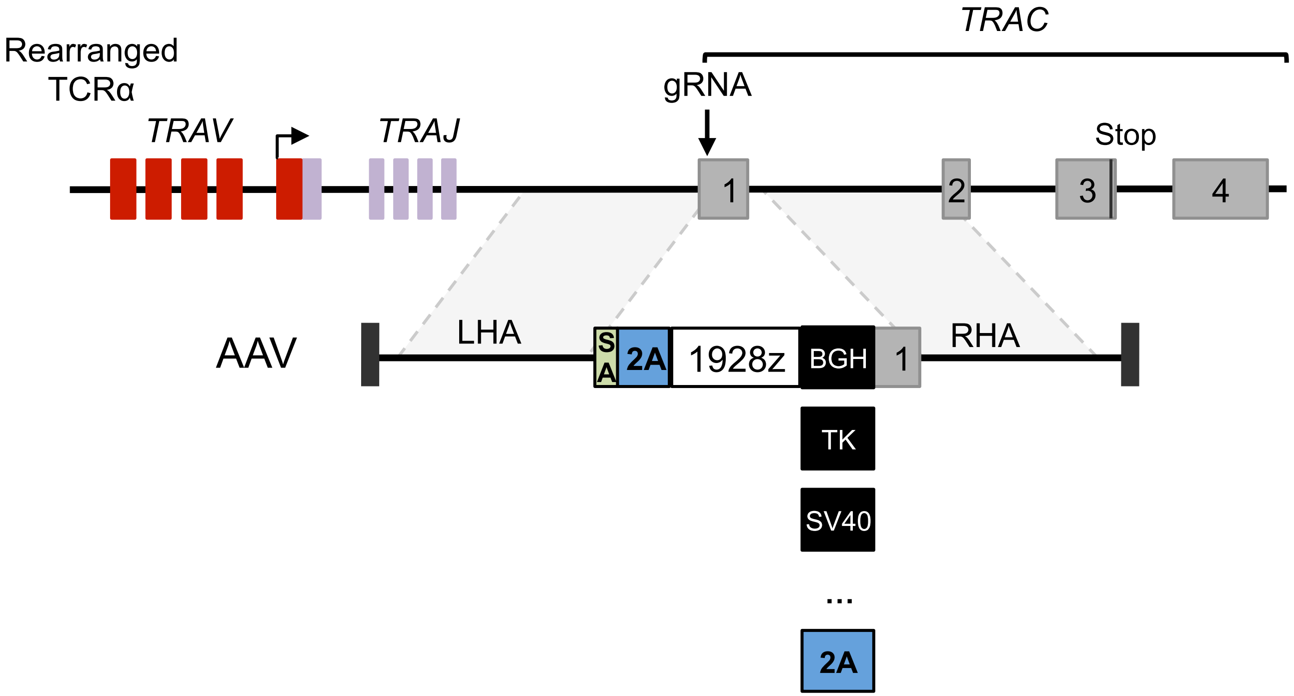
TRAC-CAR T cells are less exhausted

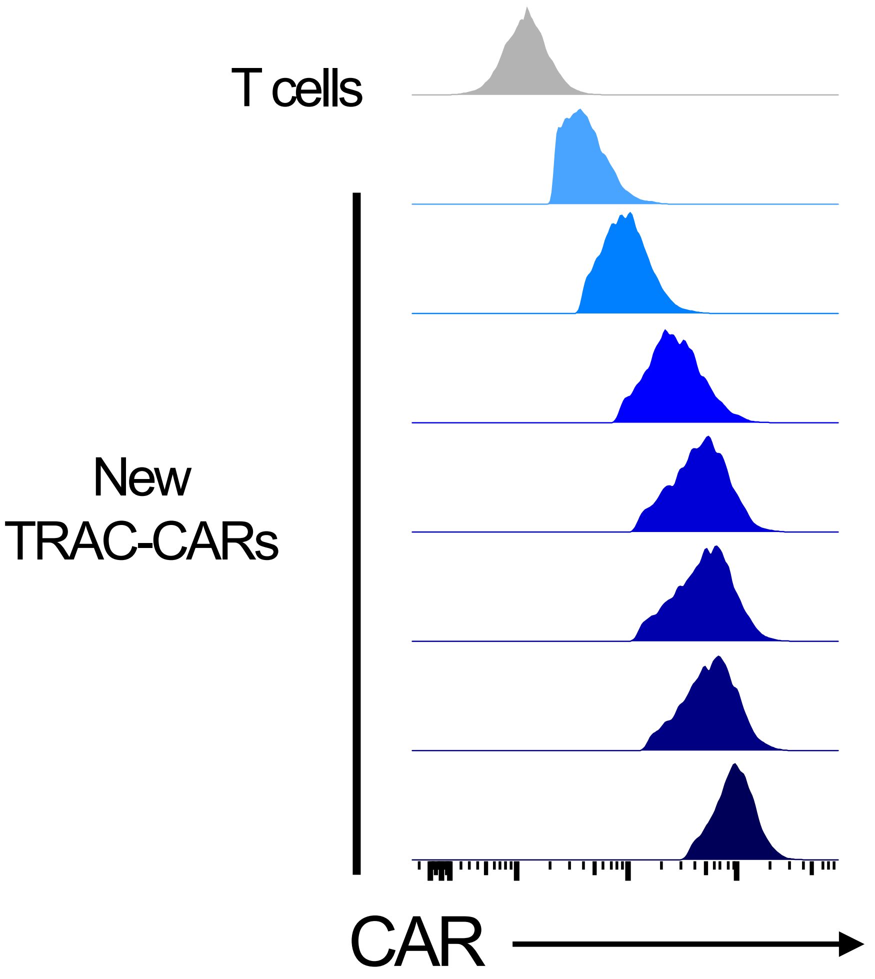




Eyquem et al., *Nature 2017*

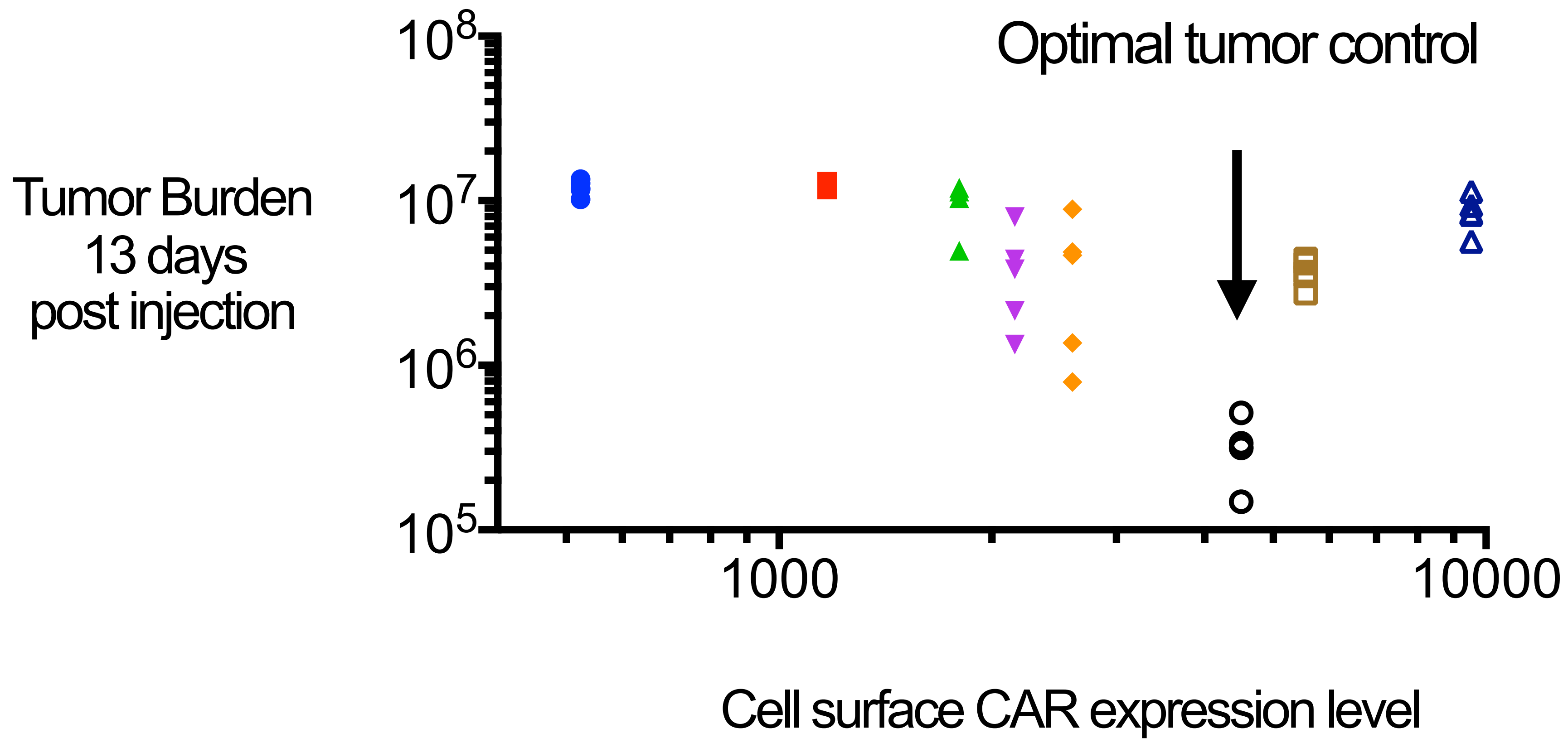
Possibility to tune TRAC-CAR expression





Eyquem et al., *Unpublished*

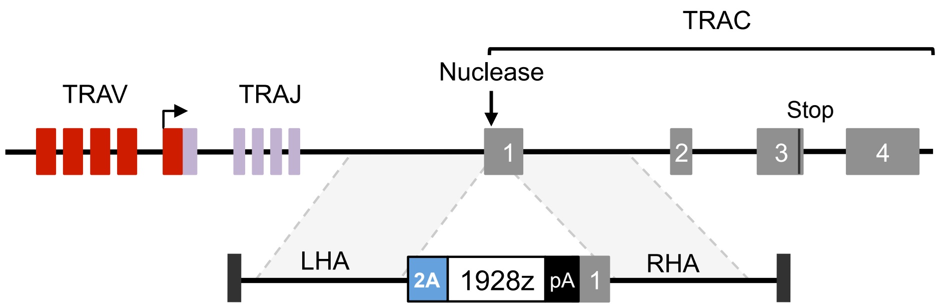
And find the optimal CAR expression level



5e5 Nalm6 in NSG
-
1e5 CAR T cells

Eyquem et al., *Unpublished*

CAR gene targeting



- **Safe:** targeted and promoter-less
- **Standardized:** Homogeneous, predictable expression
- **Controlled**: Improves therapeutic activity
- **Flexible:** cassette design, expression levels
- **Adaptable** to every gene editing platform