Creating Smarter T Cells For Immunotherapy

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Member, Fred Hutchinson Cancer Research Center
American Cancer Society Virginia Hobbs Research Professor

Disclosures

Founder and Sponsored Research

Juno Therapeutics/Celgene/BMS

Lyell Immunopharma

Consultant and Equity

Juno Therapeutics/Celgene/BMS

Lyell Immunopharma

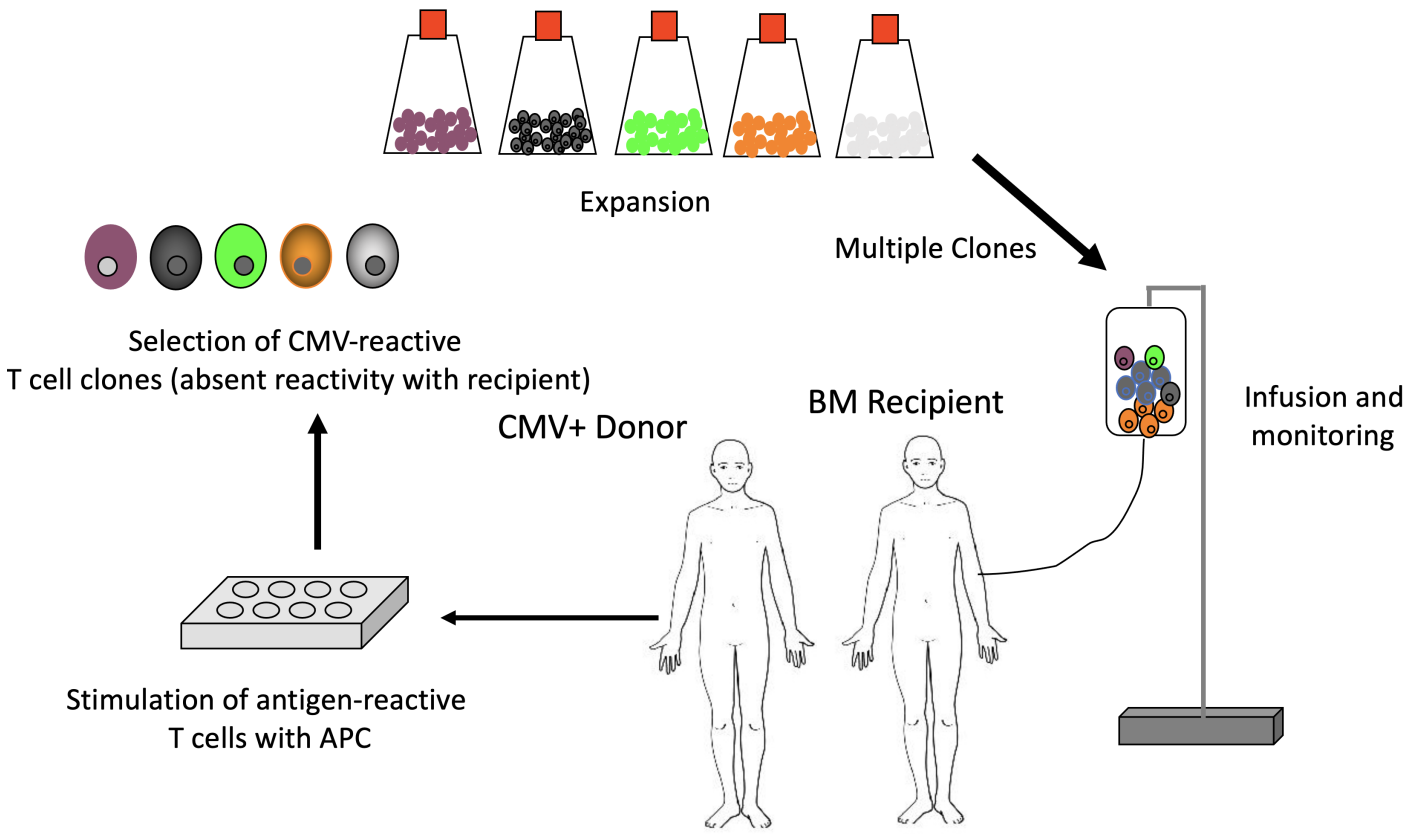
Adaptive Biotechnologies

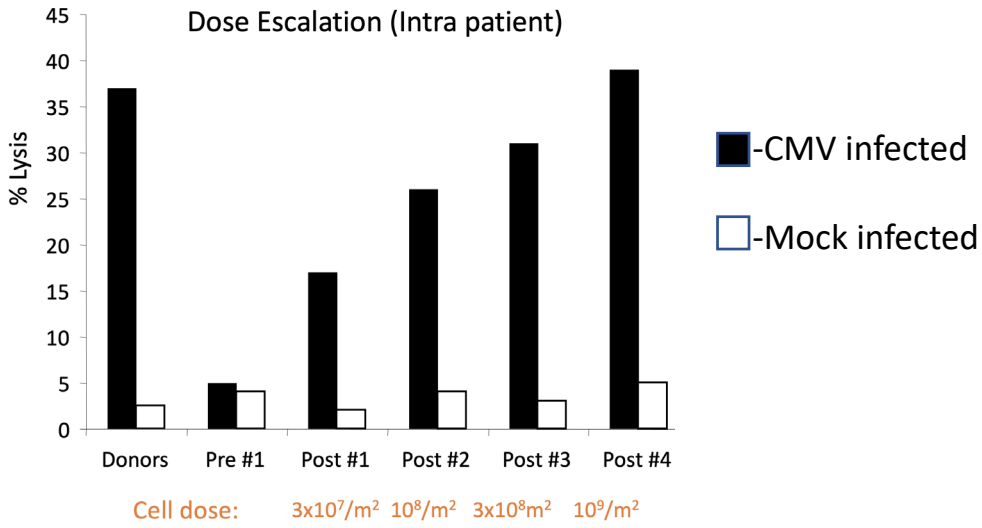
I. T cell fitness

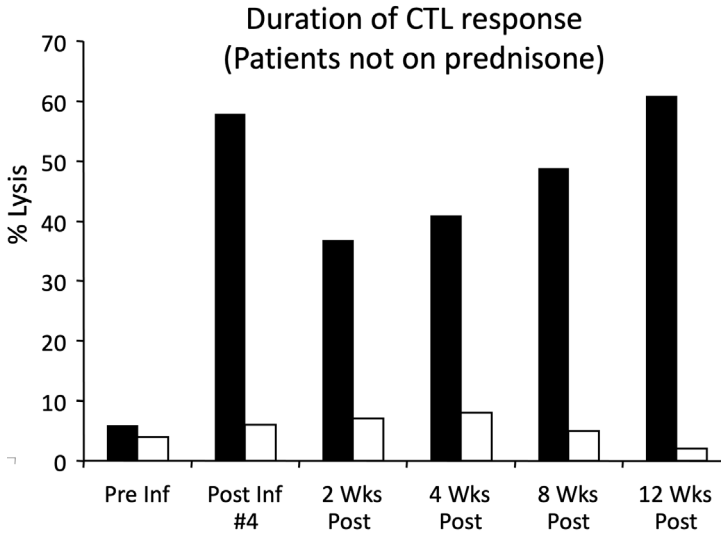
II. Infiltration and function of CAR-T cells in solid tumors

III. Enhancing the sensitivity and specificity of receptors

Reconstituting CMV-specific T cell immunity after allogeneic bone marrow transplant







- **TCRVb - not all transferred T cells were detected post infusion**
- **Ability of T cells to persist was not dose related**

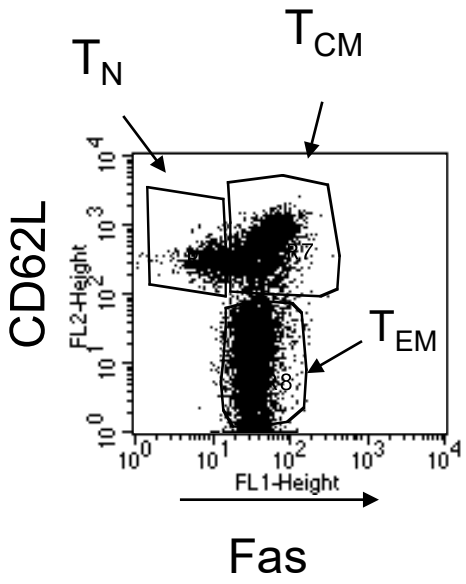
Riddell et al. Science, 1992; Walter et al New Engl J Med, 1995

T cells derived from T_{CM} and T_{EM} subsets exhibit different capacities for reconstituting durable immunity

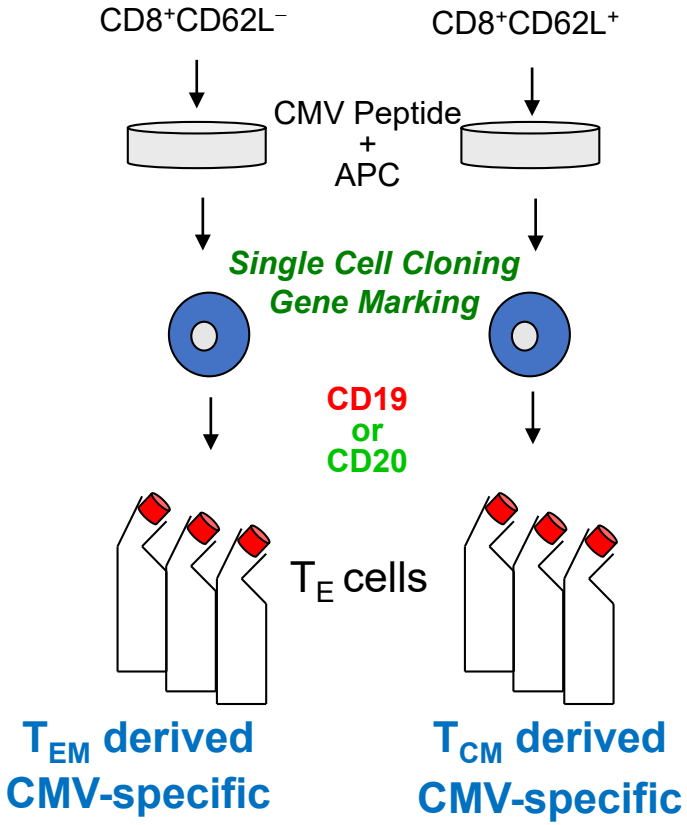
letters to nature

Two subsets of memory T lymphocytes with distinct homing potentials and effector functions

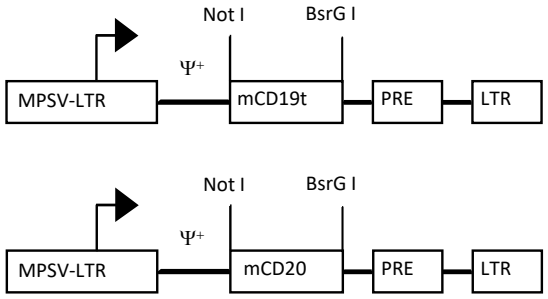
Federica Sallusto*, Danielle Lenig*, Reinhold Förster†, Martin Lipp† & Antonio Lanzavecchia*

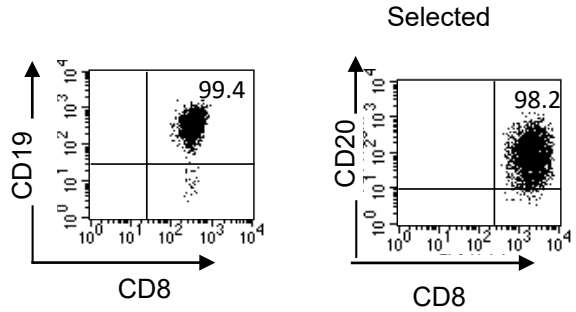


Gene marking of RhCMV-specific T cells for adoptive transfer in non-human primates



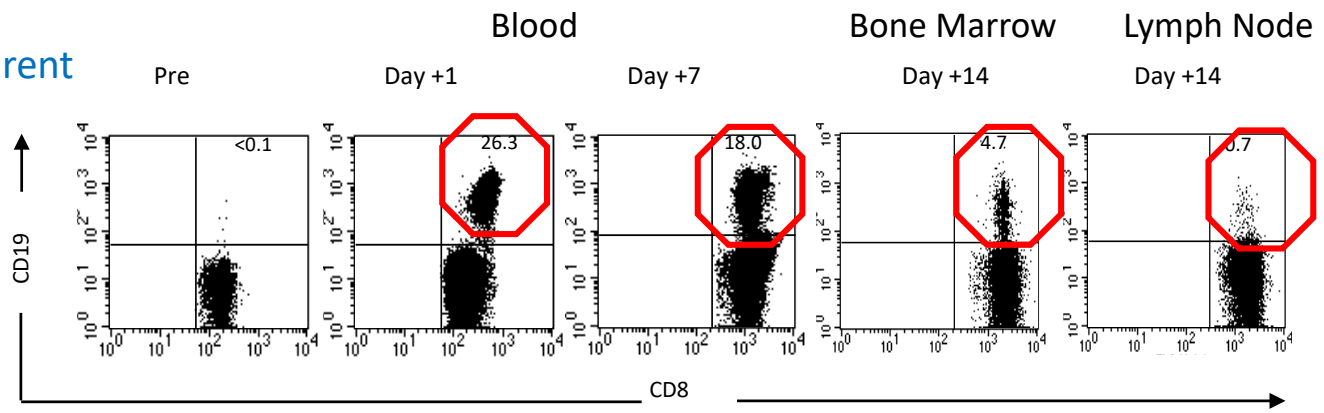
Retroviral Vectors: MP71-mCD19; mCD20

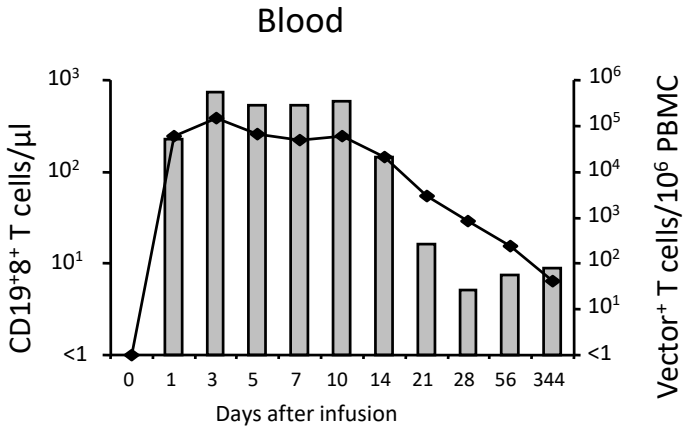




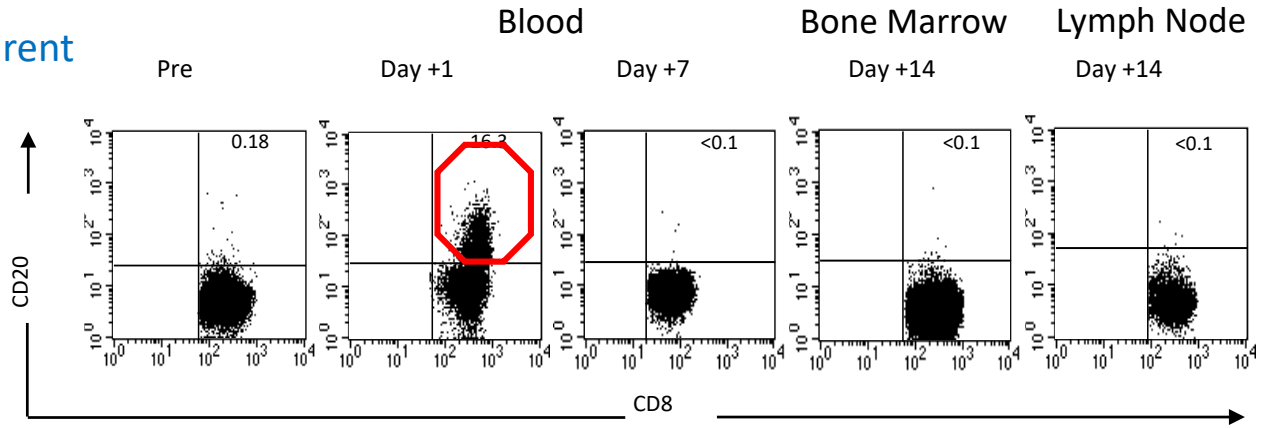
Virus-specific T_E clones derived from T_{CM} but not T_{EM} persist long term after adoptive transfer into animals without lymphodepletion

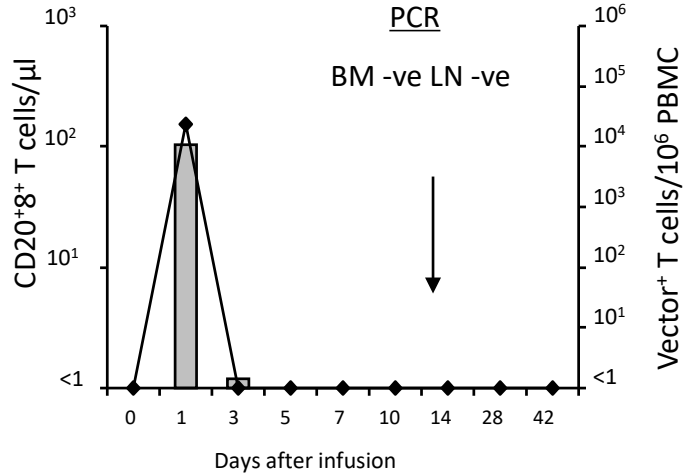
T_{CM} parent





T_{EM} parent

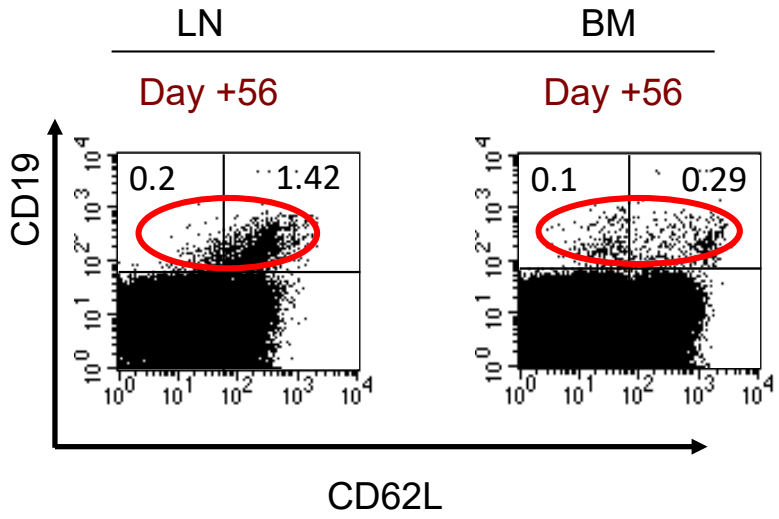


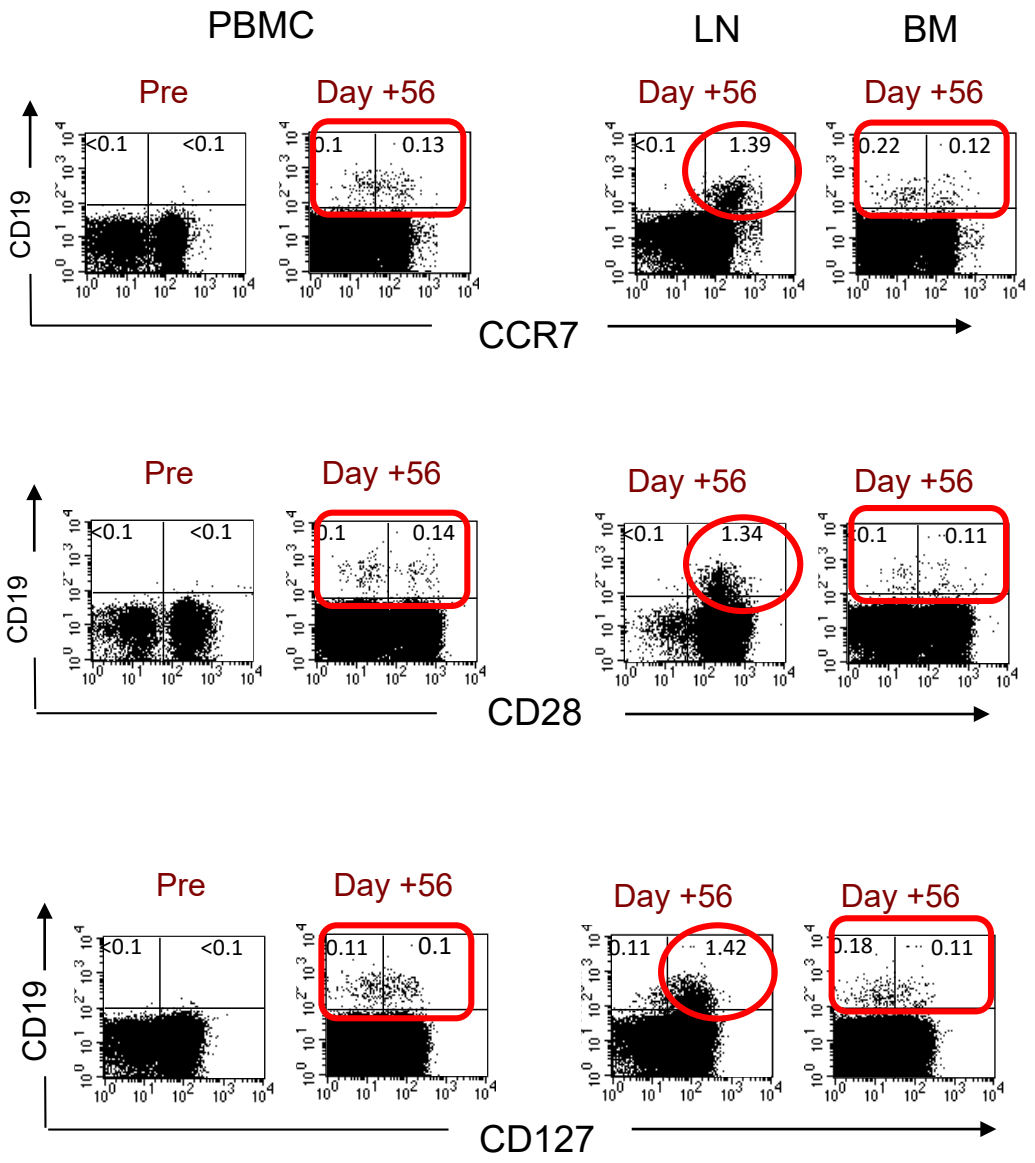


Berger C, Journal of Clinical Investigation, 2008

Transfer of T_{CM}-derived T_E cells establishes diverse memory phenotypes

Gated on CD3+
CD8+ T Cells

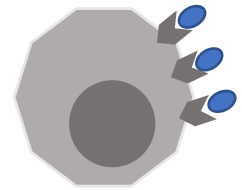




Berger et al, Journal of Clinical Investigation, 2008

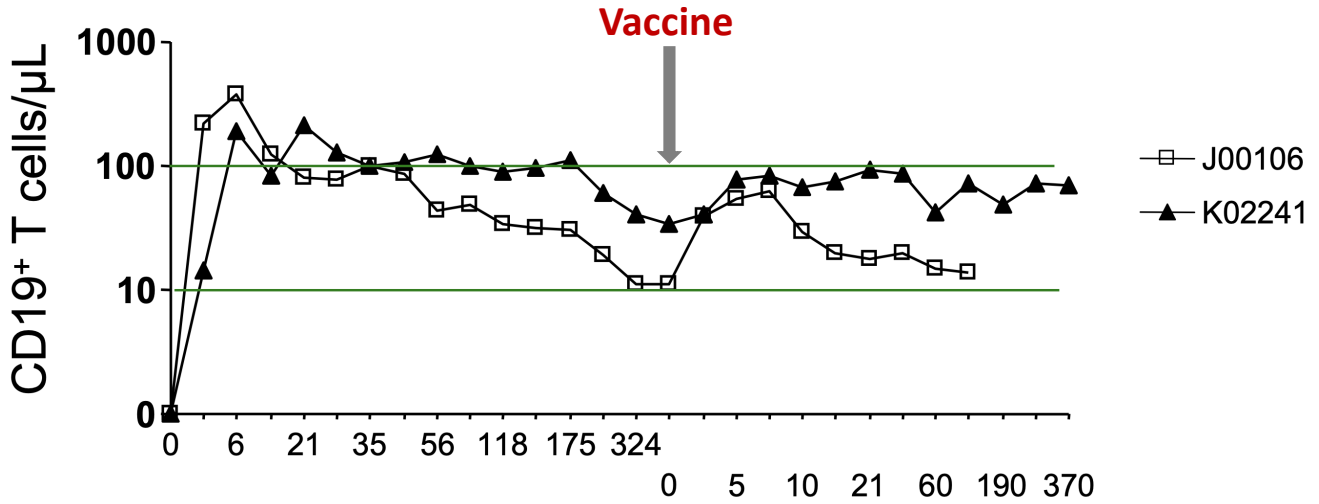
T cell memory established by transfer of T_{CM} derived cells is antigen responsive and durable

T cell vaccine (T-APC)

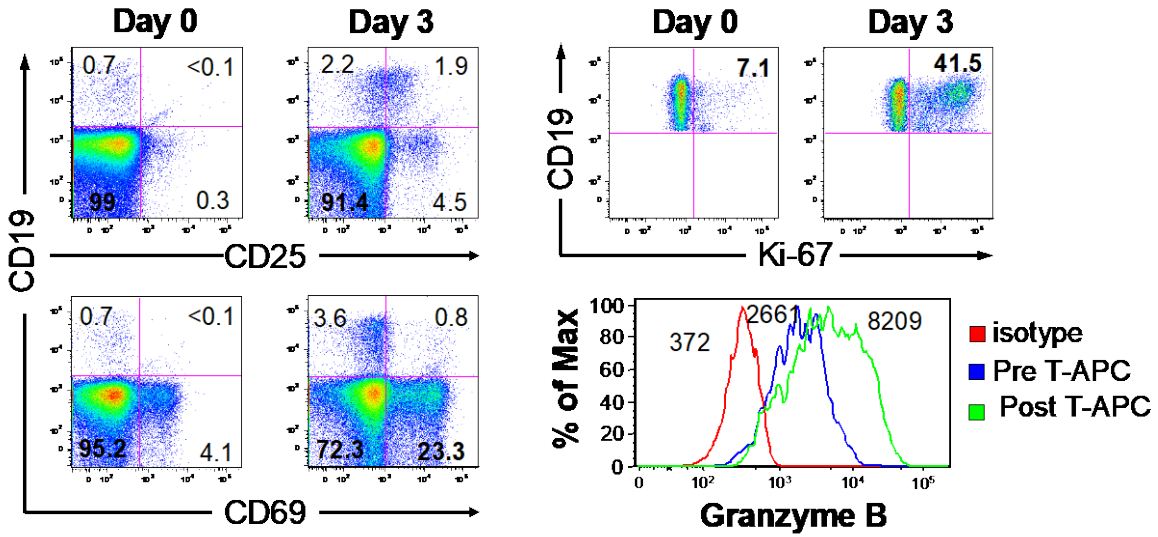


Autologous T cell
CMV peptide -

Administered T-APC
~ 1 yr post transfer

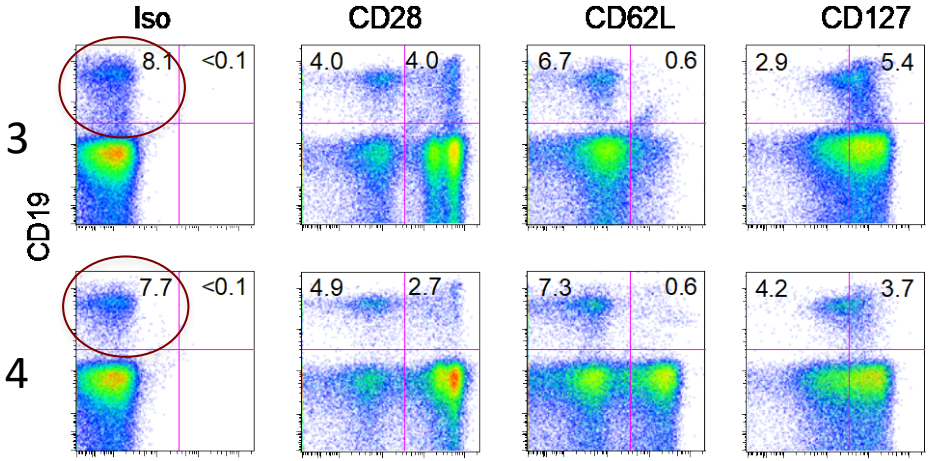


Gated on CD3+
CD8+ T Cells



Gated on CD3+
CD8+ T cells

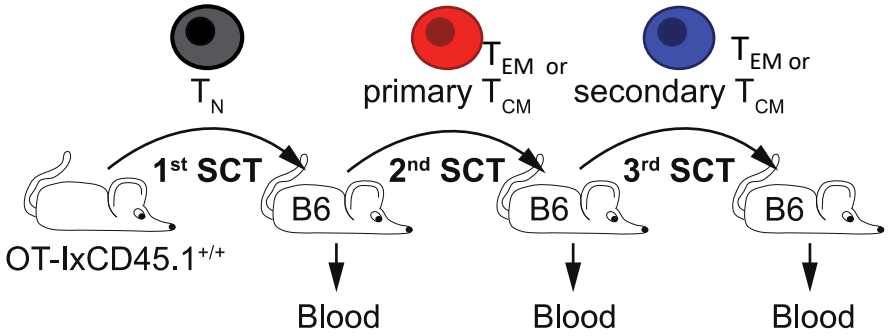
Peripheral Blood

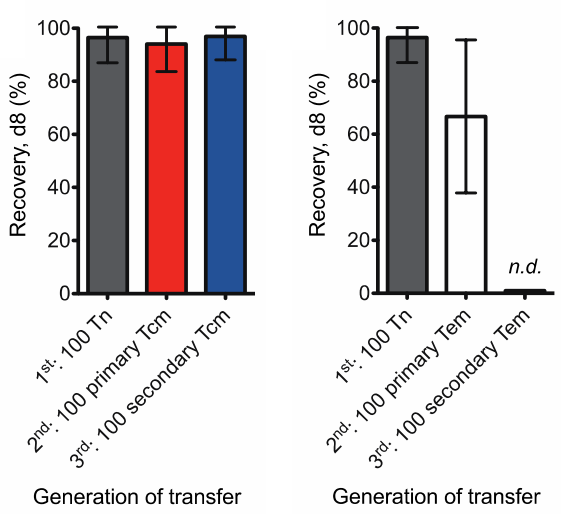


Berger et al. J Med Primatol, 2011

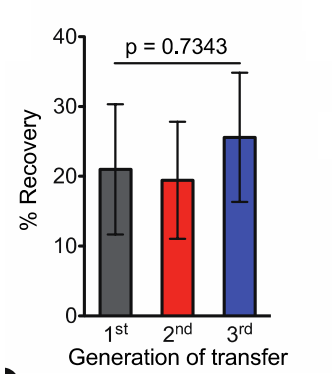
Serial transfer of T_{CM} and T_{EM} CD8$^+$ OT-1 specific T cells in mice

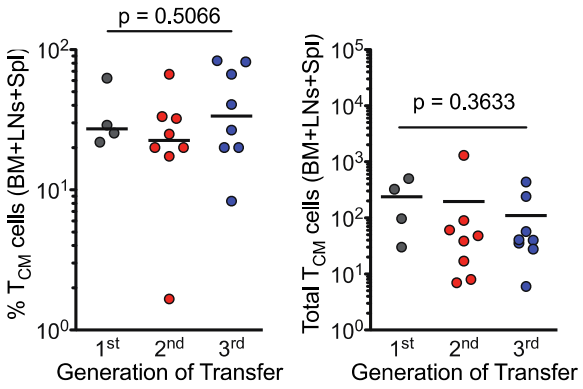
Listeria/ova challenge after each transfer

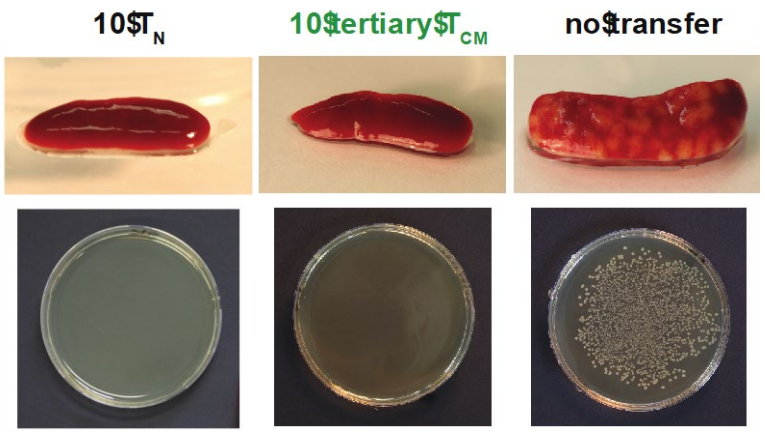




Single T_{CM} transfer and re-expansion



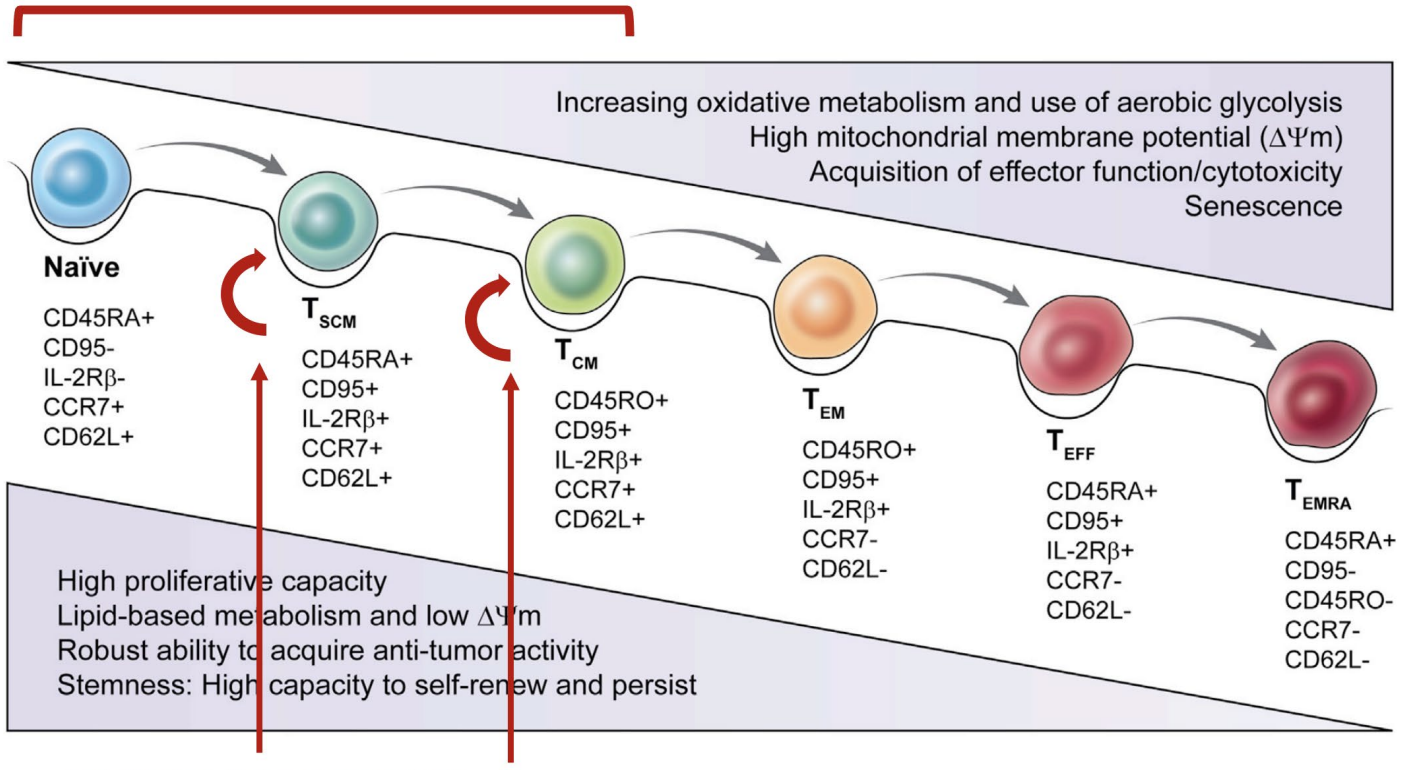




- T_{CM} exhibit stemness – self-renewal, differentiation to T_{EM} and T_E subsets

Graef et al Immunity, 2014

T Cell Differentiation State and Utility in Adoptive Therapy



Galetti et al. Nat Immunol 2020

Graef et al. Immunity, 2014

Adapted from Kishton et al. Cell Metabolism 2017

Preclinical data for CAR-T cells

- $CD8^+$ T_N, T_{SCM} or T_{CM} cells superior to T_{EM}: Gattinoni et al. Nat Med. 2011; Sommermeyer et al. Leukemia 2016
- $CD4^+$ T cells and combining CD4s and CD8s : Sommermeyer et al. Leukemia 2016; Boulch et al. Sci Immunology, 2021

→ ***Defined composition CAR-T cells targeting CD19 (Turtle et al. JCI, 2016 Science Translational Medicine, 2016)***

The “gemisch” problem in T cell therapy…..

Correlative clinical data suggests response driven by “effective” subsets

nature medicine
LETTERS
https://doi.org/10.1038/s41591-018-0010-1
There are amendments to this paper

Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia

Joseph A. Fraietta[1,2,3], Simon F. Lacey[1,2,3,9], Elena J. Orlando[4,9], Iulian Pruteanu-Malinici[4], Mercy Gohil[2], Stefan Lundh[2], Alina C. Boesteanu[2], Yan Wang[2], Roddy S. O'Connor[2], Wei-Ting Hwang[5], Edward Pequignot[2], David E. Ambrose[2], Changfeng Zhang[2], Nicholas Wilcox[2], Felipe Bedoya[2], Corin Dorfmeier[2], Fang Chen[2], Lifeng Tian[2], Harit Parakandi[2], Minnal Gupta[2], Regina M. Young[2], F. Brad Johnson[1], Irina Kulikovskaya[2], Li Liu[2], Jun Xu[2], Sadik H. Kassim[4], Megan M. Davis[1,2], Bruce L. Levine[1,2], Noelle V. Frey[2,6], Donald L. Siegel[1,2,7], Alexander C. Huang[3,8], E. John Wherry[3,8], Hans Bitter[4], Jennifer L. Brogdon[4], David L. Porter[1,6], Carl H. June[1,2,3] and J. Joseph Melenhorst[1,2,3]*

*“Sustained remission was associated with an elevated frequency of **CD27+CD45RO- CD8+ T cells** before CAR T cell generation, and these lymphocytes possessed memory-like characteristics.”*

ARTICLES
https://doi.org/10.1038/s41591-020-1061-7
nature medicine
Check for updates

Characteristics of anti-CD19 CAR T cell infusion products associated with efficacy and toxicity in patients with large B cell lymphomas

Qing Deng[1,5], Guangchun Han[2,5], Nahum Puebla-Osorio[1], Man Chun John Ma[1], Paolo Strati[1], Beth Chasen[3], Enyu Dai[2], Minghao Dang[2], Neeraj Jain[1], Haopeng Yang[1], Yuanxin Wang[2], Shaojun Zhang[2], Ruiping Wang[2], Runzhe Chen[2], Jordan Showell[1], Sreejoyee Ghosh[1], Sridevi Patchva[1], Qi Zhang[1], Ryan Sun[4], Frederick Hagemeister[1], Luis Fayad[1], Felipe Samaniego[1], Hans C. Lee[1], Loretta J. Nastoupil[1], Nathan Fowler[1], R. Eric Davis[1], Jason Westin[1], Sattva S. Neelapu[1]✉, Linghua Wang[2]✉ and Michael R. Green[1,2]✉

“ CR had 3-fold higher frequencies of CD8 T cells expressing memory signatures….”

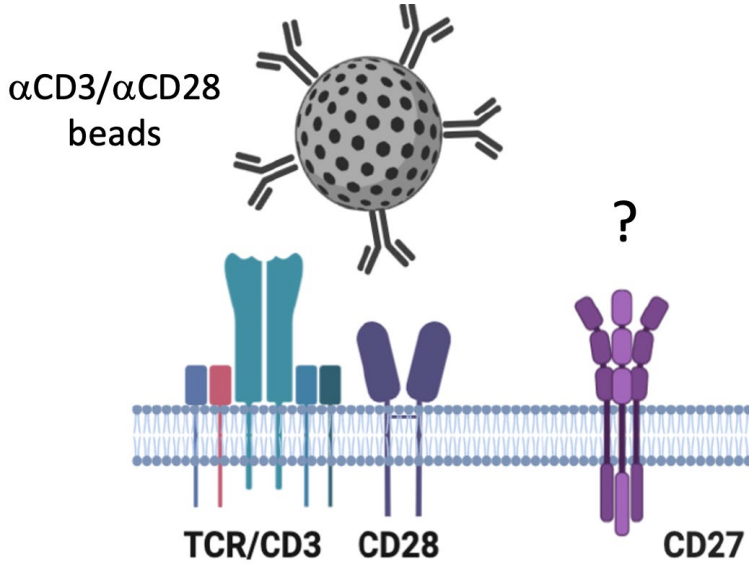
CANCER DISCOVERY 10

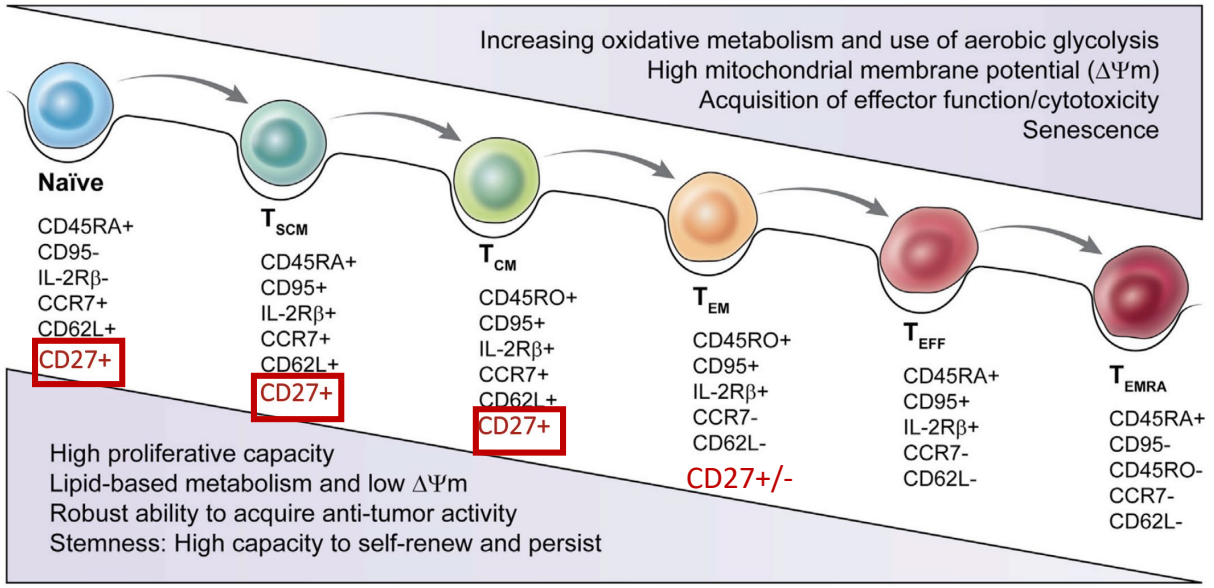
Integrative bulk and single-cell profiling of pre-manufacture T-cell populations reveals factors mediating long-term persistence of CAR T-cell therapy

Gregory M Chen, Changya Chen, Rajat K Das, Peng Gao, Chia-Hui Chen, Shovik Bandyopadhyay, Yang-Yang Ding, Yasin Uzun, Wenbao Yu, Qin Zhu, Regina M Myers, Stephan A. Grupp, David M. Barrett, and Kai Tan

“ …the TCF7 regulon not only associates with the favorable naive T-cell state, but is maintained in effector T-cells among patients with long term CAR T-cell persistence.”

Role of CD27 costimulation in T cell differentiation and function





nature immunology

CD27 is required for generation and long-term maintenance of T cell immunity

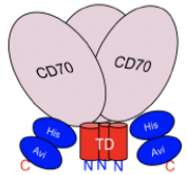
Jenny Hendriks, Loes A. Gravestein, Kiki Tesselaar, René A. W. van Lier, Ton N. M. Schumacher & Jannie Borst ✉

nature COMMUNICATIONS

TNIK signaling imprints CD8+ T cell memory formation early after priming

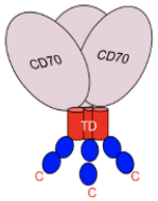
Carla A. Jaeger-Ruckstuhl [1,2,3,4,7], Magdalena Hinterbrandner[1,2,3,7], Sabine Höpner[1,2], Colin E. Correnti[5], Ursina Lüthi[1,2], Olivier Friedli[3,6], Stefan Freigang [6], Mohamad F. Al Sayed[1,2,3], Elias D. Bührer[1,2,3], Michael A. Amrein [1,2,3], Christian M. Schürch [1,2,6], Ramin Radpour [1,2], Carsten Riether [1,2] & Adrian F. Ochsenbein[1,2]✉

Design of functional CD70 trimers for costimulation



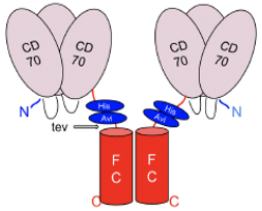
Mono-Trimer Tetranectin^{TD}

- Site-specific biotinylation of AviTag
- Binding to Streptavidin Magnetic Beads



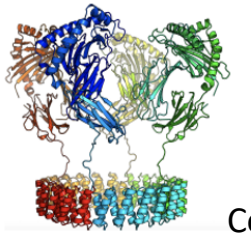
Mono-Trimer Collagen^{TD}

- Site-specific biotinylation of AviTag
- Binding to Streptavidin Magnetic Beads



Dimer-Trimer CD70^{DT}

- Plate—coated activation system

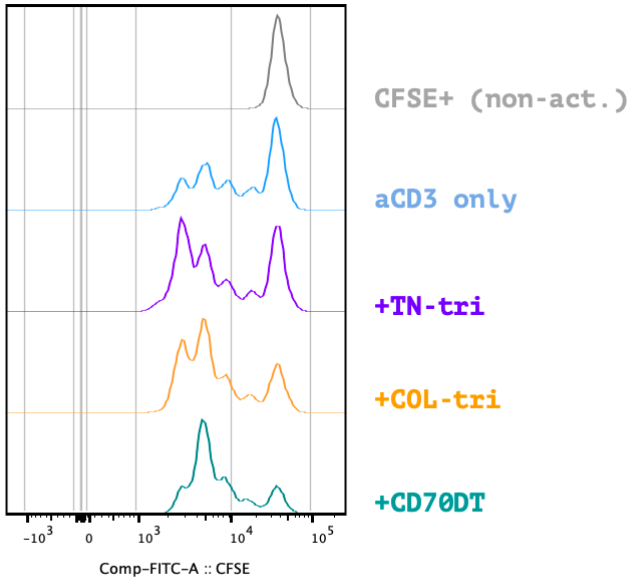


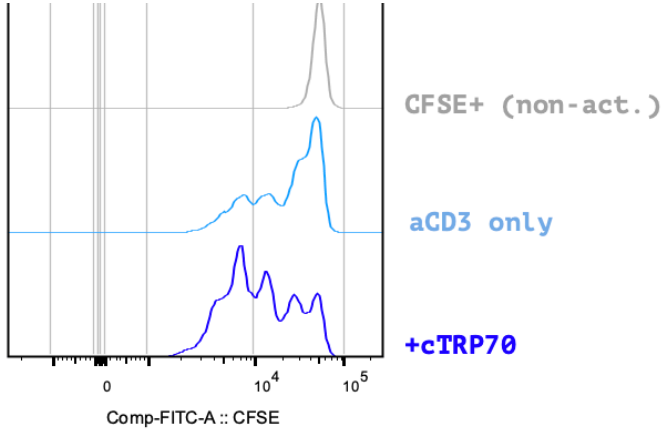
Tetra-Trimer cTRP70

- Soluble superagonist

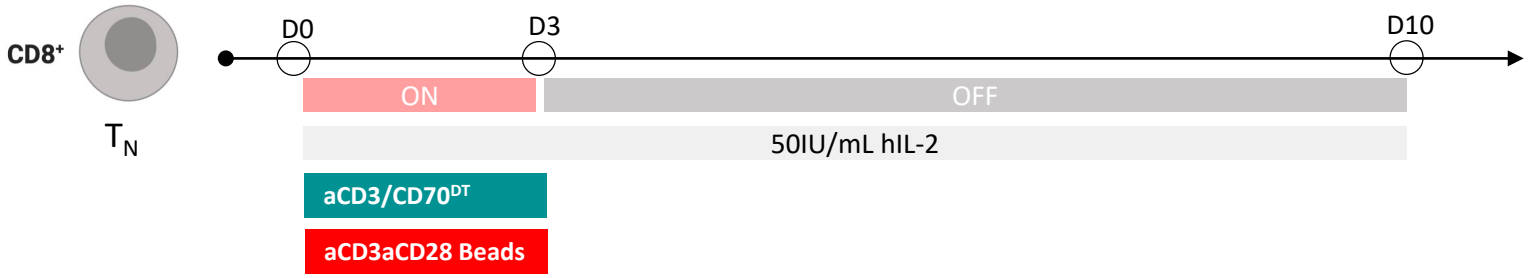
Correnti et al Nature Struct Mol Biol, 2020

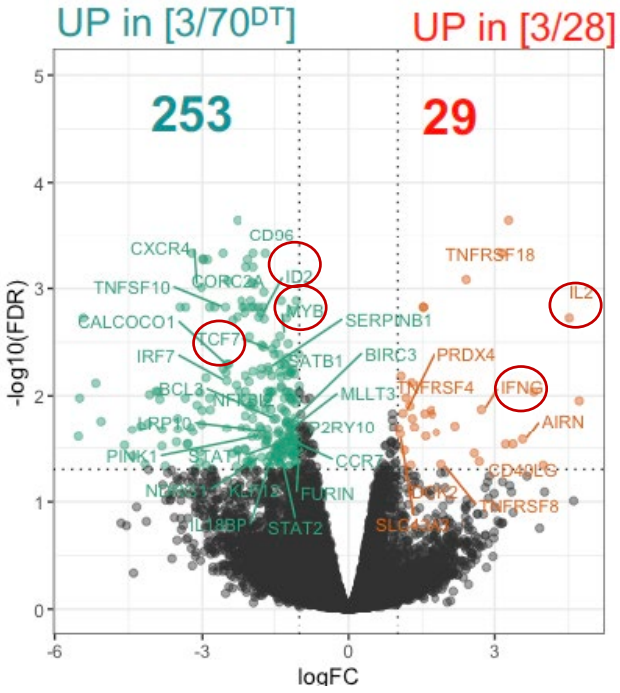
Bulk CD8^{+} T cells : CFSE dye dilution (day 3)

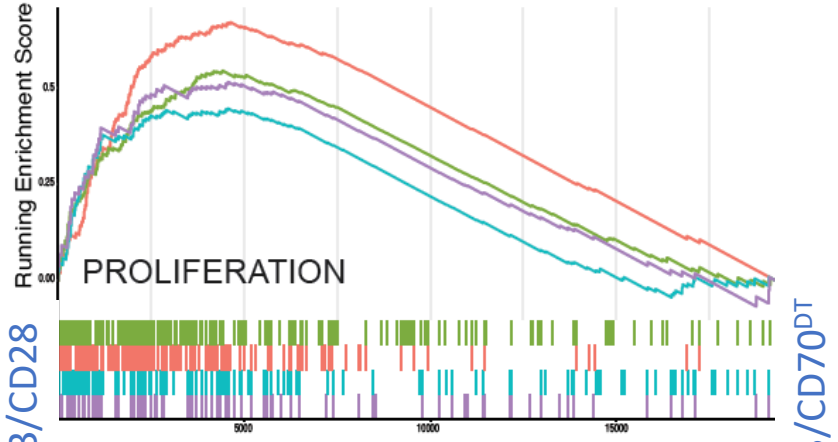




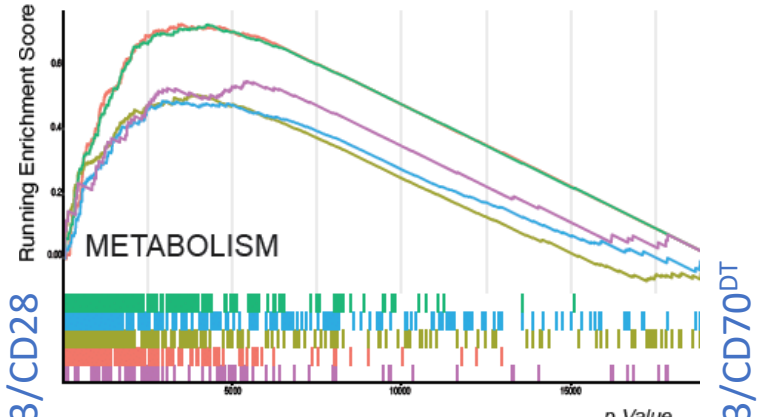
RNAseq shows early divergence in genes associated with cell proliferation and metabolism in CD3/CD28 vs CD3/CD70^{DT} activated CD8^{+} T_N cells







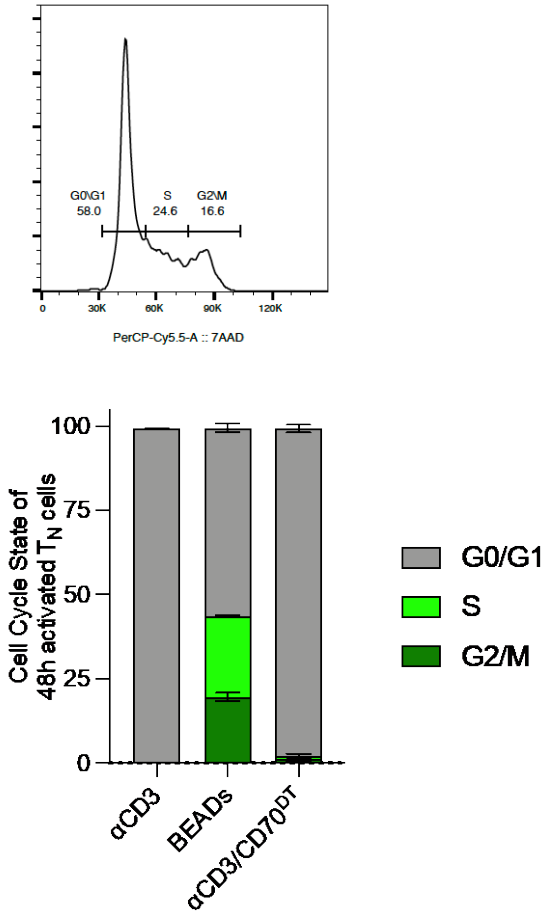
	p-Value	FDR
CELL CYCLE (I) (M4.1)	5.99E-15	1.85E-12
HALLMARK_G2M_CHECKPOINT	4.56E-09	3.80E-08
KEGG_PURINE_METABOLISM	4.03E-05	0.001249752
KEGG_PYRIMIDINE_METABOLISM	1.15E-06	4.29E-05



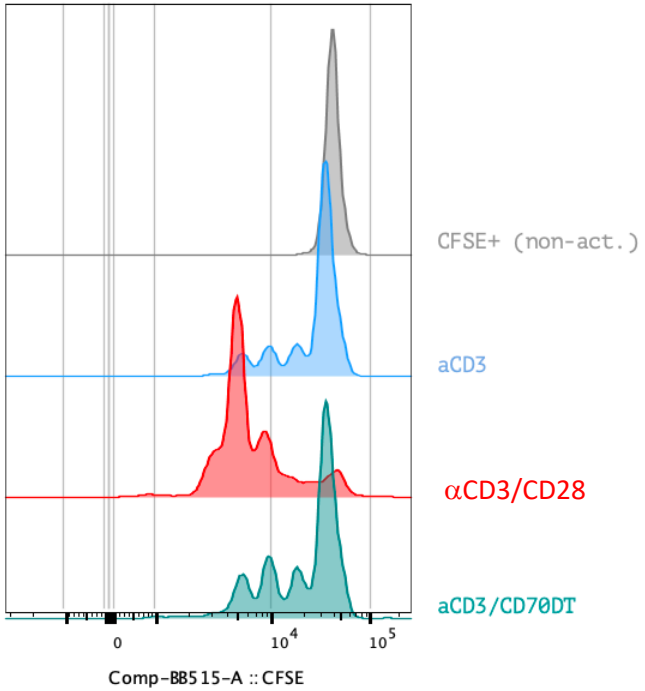
	p-Value	FDR
GO_MITOCHONDRIAL_TRANSLATION	3.30E-21	3.80E-19
HALLMARK_MTORC1_SIGNALING	2.15E-08	4.94E-07
HALLMARK_MYC_TARGETS_V1	3.34E-23	1.67E-21
HALLMARK_OXIDATIVE_PHOSPHORYLATION	9.90E-07	5.50E-06
REACTOME_GLUCOSE_METABOLISM	2.60E-07	4.98E-06

CD3/CD70^{DT} activated CD8^{+} T_N cells exhibit delayed entry into cell cycle compared to αCD3/CD28 but similar proliferation over 9 days

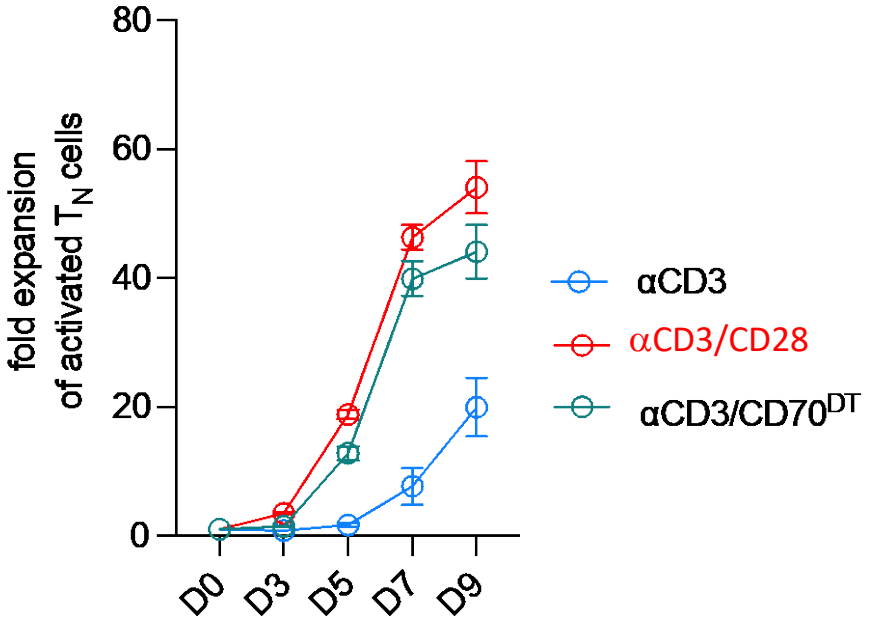
48h post act.: Cell cycle entry



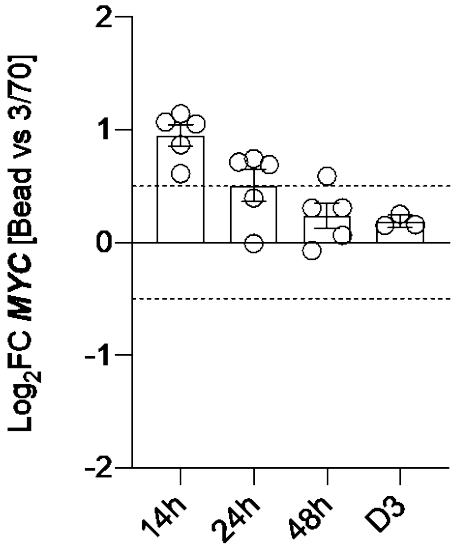
72h post act.: CFSE

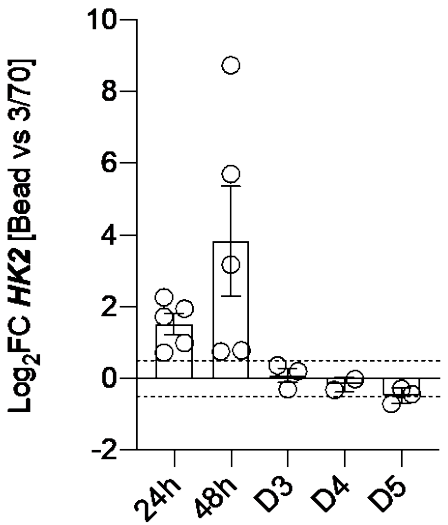


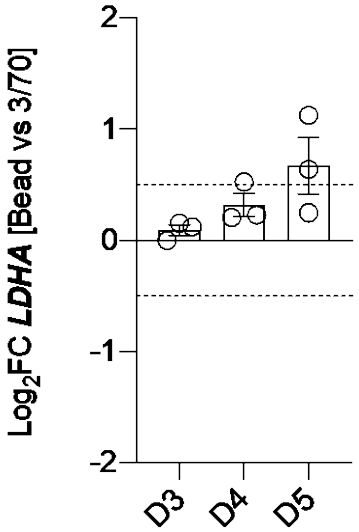
Day 9 expansion

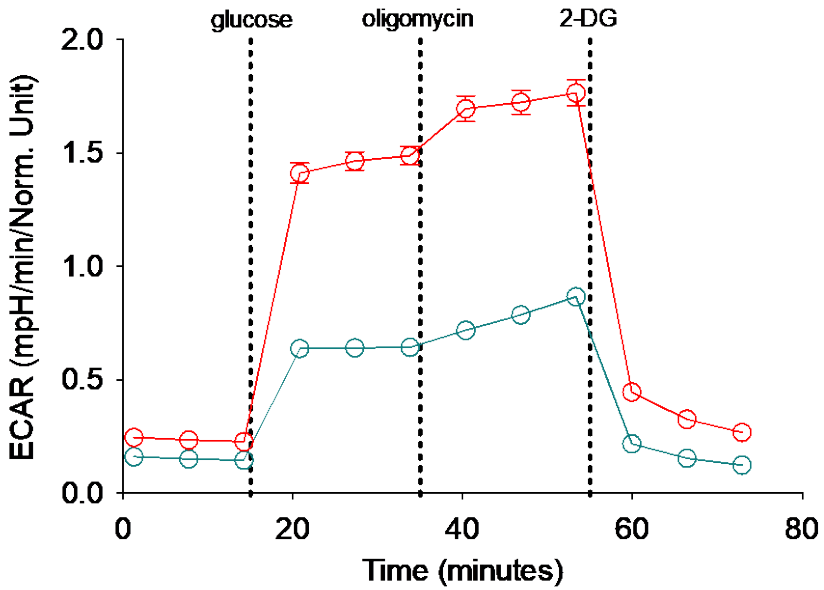


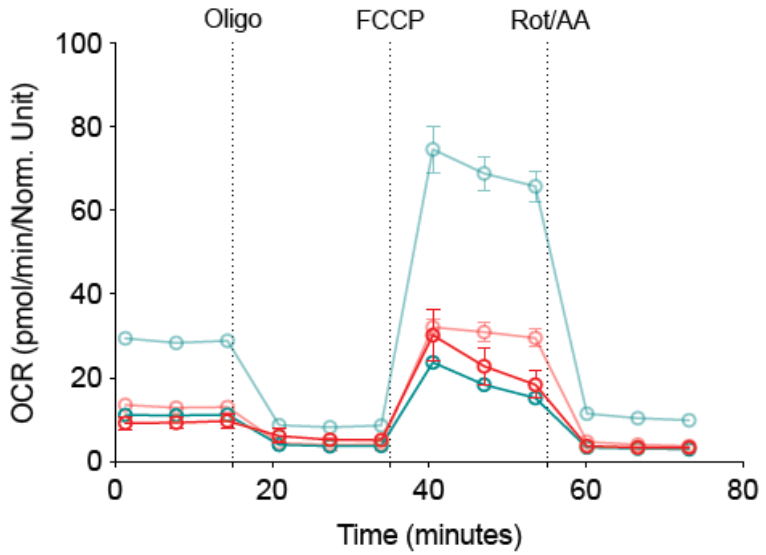
αCD3/CD28 drives early effector metabolism, lactate production and reduction in mitochondrial spare respiratory capacity





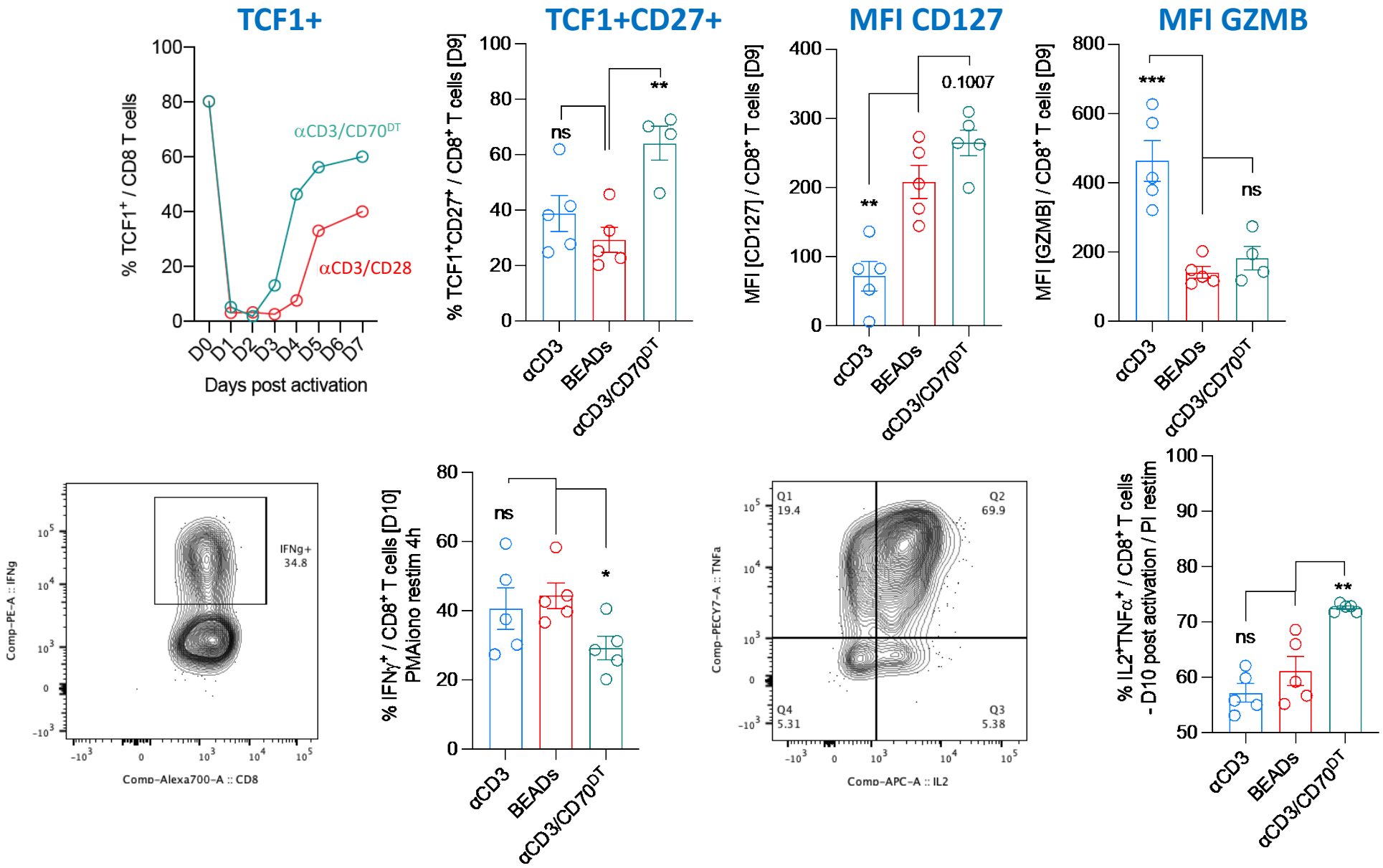




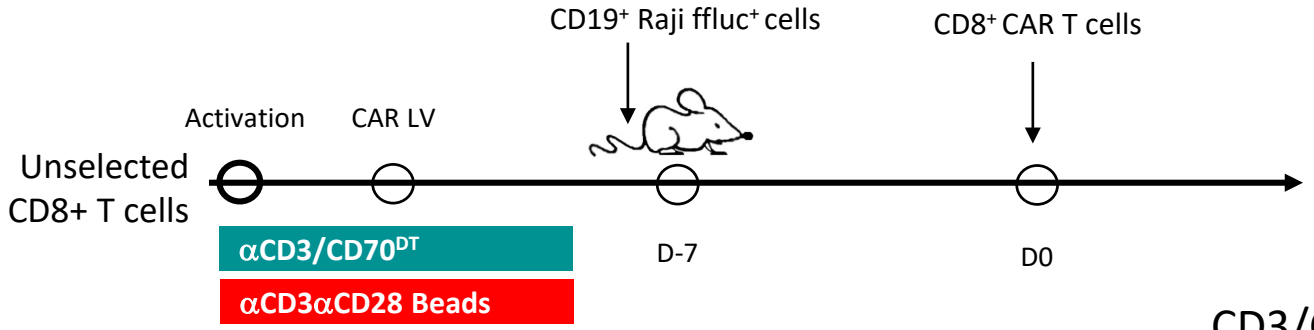


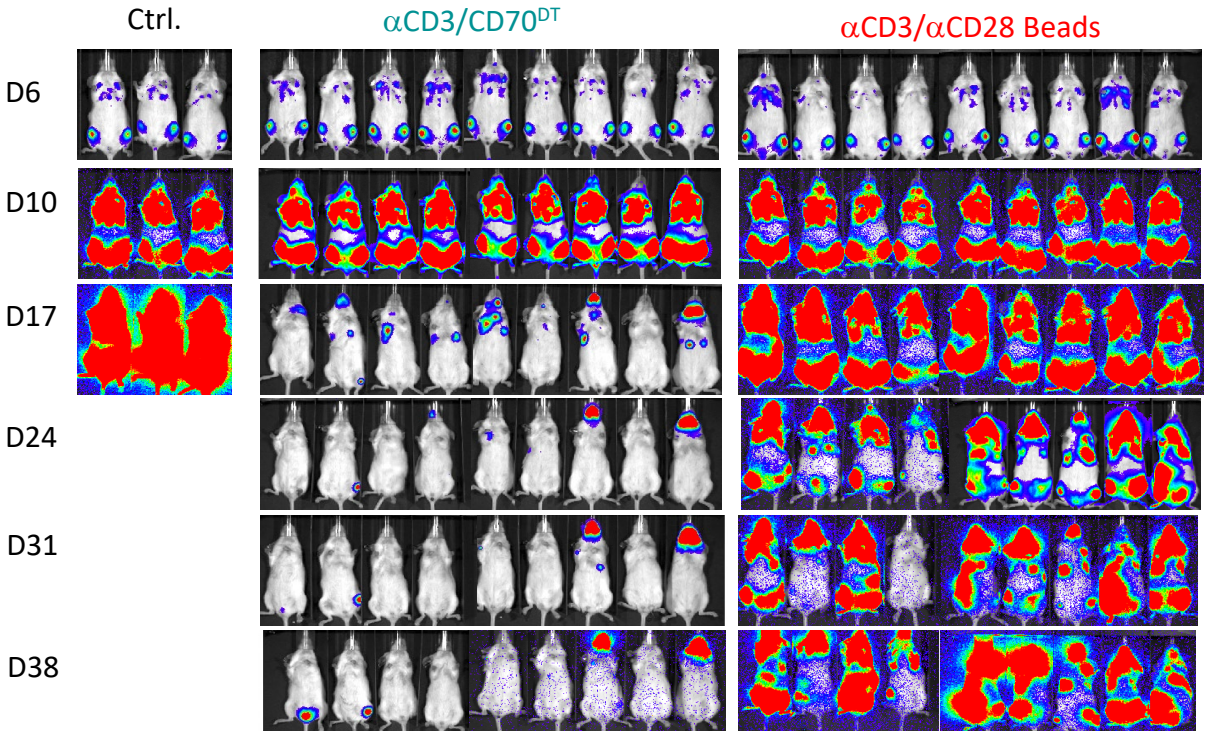
- D5 αCD3/CD28
- D5 αCD3/CD70^{DT}
- D10 αCD3/CD28
- D10 αCD3/CD70^{DT}

CD27 primed CD8⁺ T cells recover TCF7 more rapidly and maintain a less differentiated phenotype and polyfunctionality after *in vitro* expansion

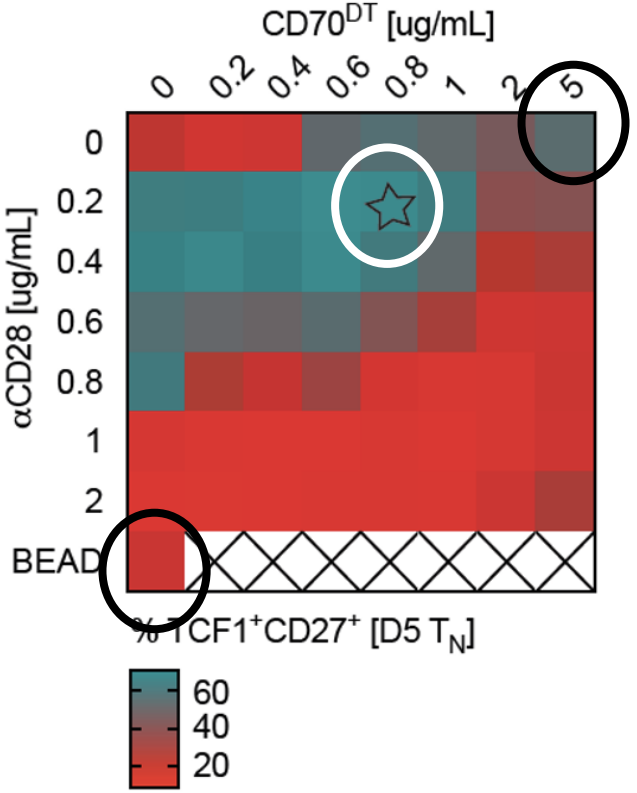


CD27 activated CD19/BB/ζ CAR T cells are effective in treating Raji lymphoma





CD3/CD28/CD27 stimulation



- Improved CAR-T proliferation
- Superior tumor control

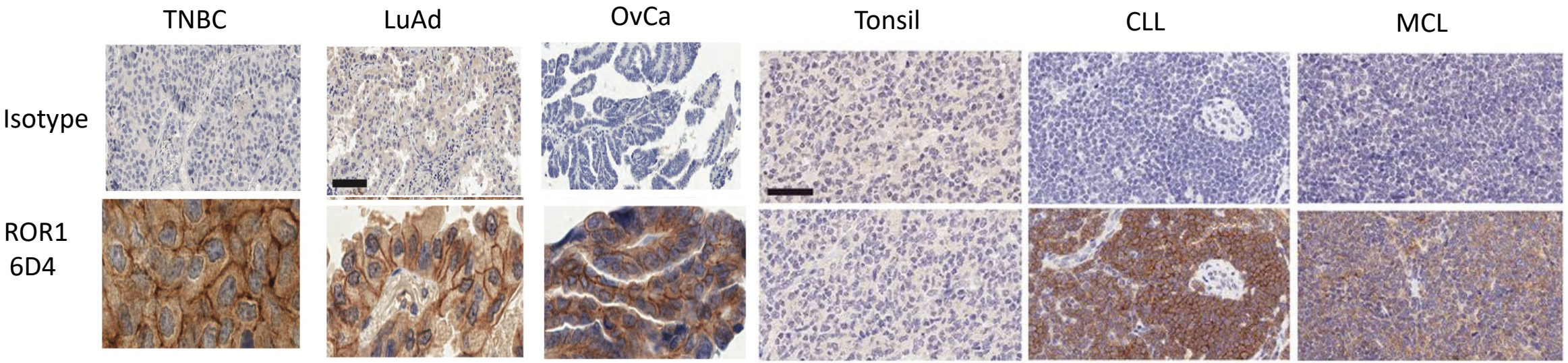
I. T Cell Fitness

II. Infiltration and Function In Solid Tumors

III. Enhancing sensitivity and specificity of receptors

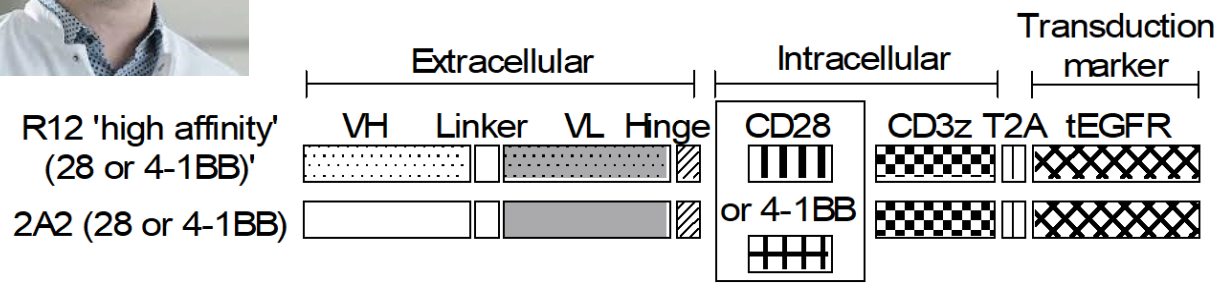
Targeting ROR1 on hematologic malignancies and solid tumors with CAR T cells

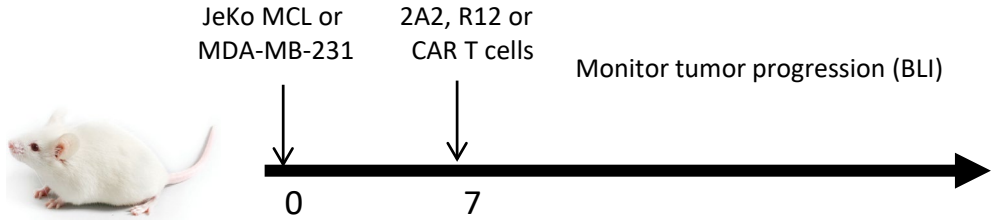
- ROR1 -- Receptor tyrosine kinase-like orphan receptor 1
- Expressed during embryonic development; **overexpressed** in many common, incurable solid tumors and in B cell malignancies (CLL, Mantle cell lymphoma, ALL)
- May regulate **tumor growth and metastasis;** Expression associated with **poor prognosis**
- Some **expression in normal tissues** *(parathyroid, esophagus, pancreatic islets)*
- ADC linked to monomethyl auristatin exhibits antitumor activity in MCL, DLBCL without serious toxicity (ASH 2020)



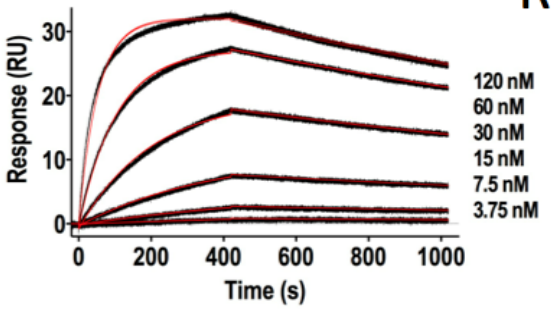
Balakrishnan et al, Clin Can Res 2016

Design of ROR 1 chimeric antigen receptors



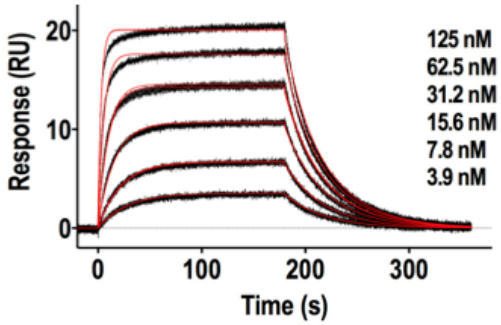


R12



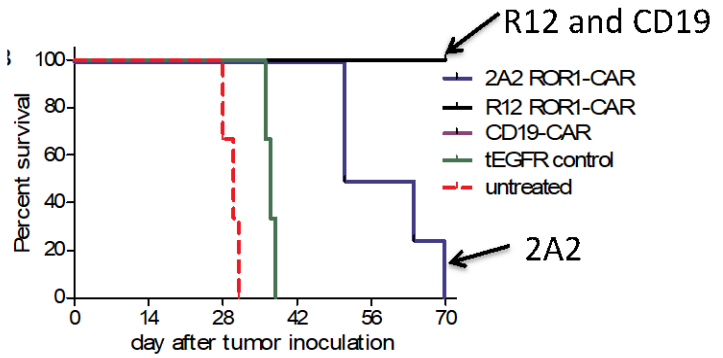
$k_a = 1.547(1) \times 10^5\ M^{-1}s^{-1}$
$k_d = 4.101(4) \times 10^{-4}\ s^{-1}$
$K_D = 2.651(3)$ nM

2A2

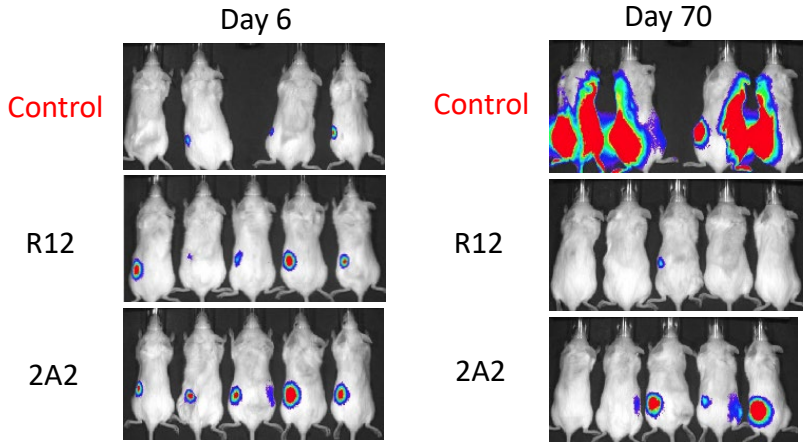


$k_a = 2.65(1) \times 10^6\ M^{-1}s^{-1}$
$k_d = 3.02(1) \times 10^{-2}\ s^{-1}$
$K_D = 11.39(7)$ nM

JeKo MCL



MDA-MB-231



Hudecek et al. Clin Cancer Research 2013

Phase 1 Clinical Trial of ROR1 CAR-T Cells In Refractory Lung Cancer, TNBC, and CLL (David Maloney, Jennifer Specht, Sylvia Lee)

Primary Objective

- Safety of targeting ROR1 with autologous $CD8^+$ and $CD4^+$ CAR-T cells (4-1BB/CD3ζ)

Two patient groups

- Lung/Breast cancer
- CLL/Mantle cell lymphoma

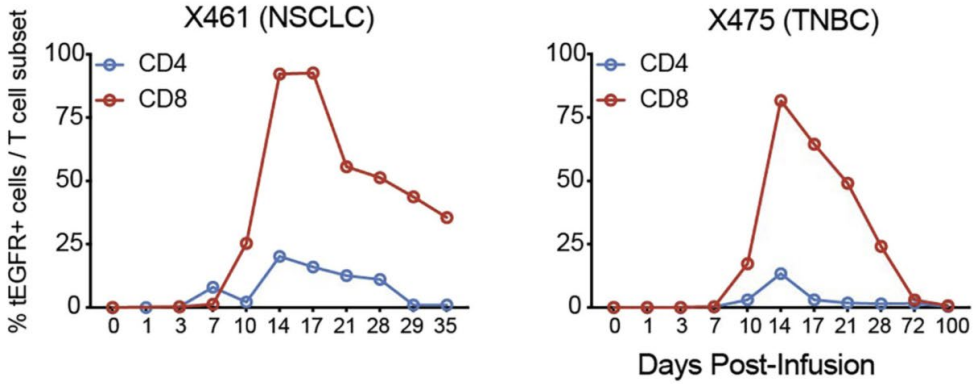
Lymphodepletion: Cy/Flu; Ox/Cy

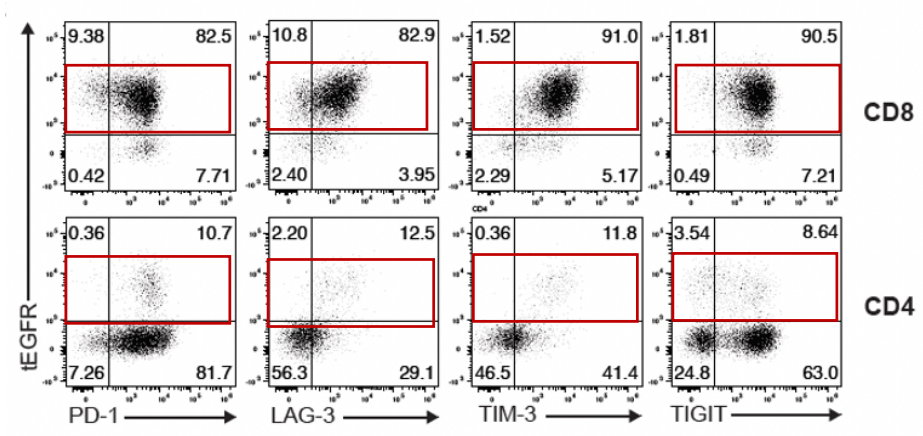
CAR-T cell Dosing - CD4/CD8 1:1 Formulation)

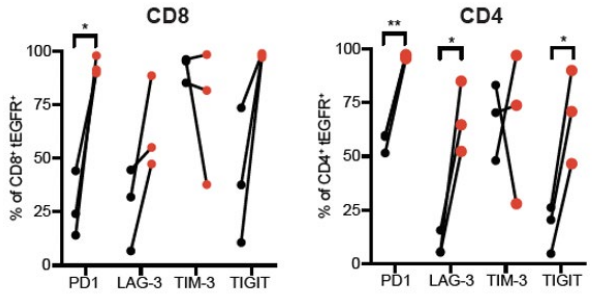
- Dose Escalation/De-escalation (Continuous Reassessment Method)

Dose level 0:	up to $1x10^5$ EGFR+ cells/kg
Dose level 1:	up to $3.3x10^5$ EGFR+ cells/kg (Starting dose level)
Dose level 2:	up to $1x10^6$ EGFR+ cells/kg
Dose level 3:	up to $3.3x10^6$ $EGFR^+$ cells/kg
Dose level 4:	up to $1.0x10^7$ $EGFR^+$ cells/kg

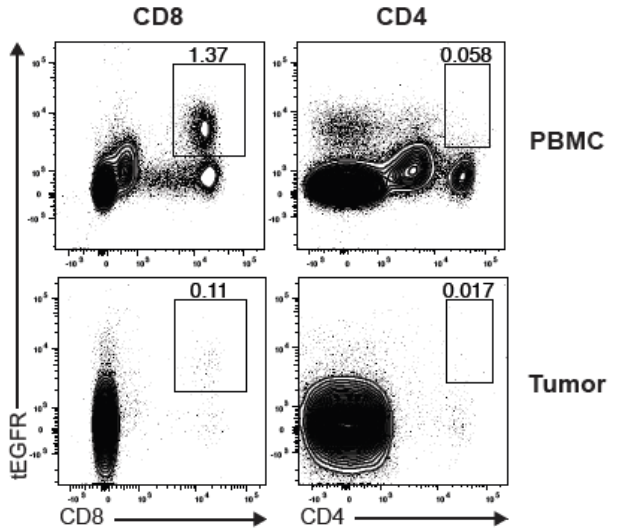
Solid Tumors: ROR 1 CAR-T cells proliferate in vivo in a subset of patients, upregulate inhibitor receptors, and lack sustained tumor infiltration







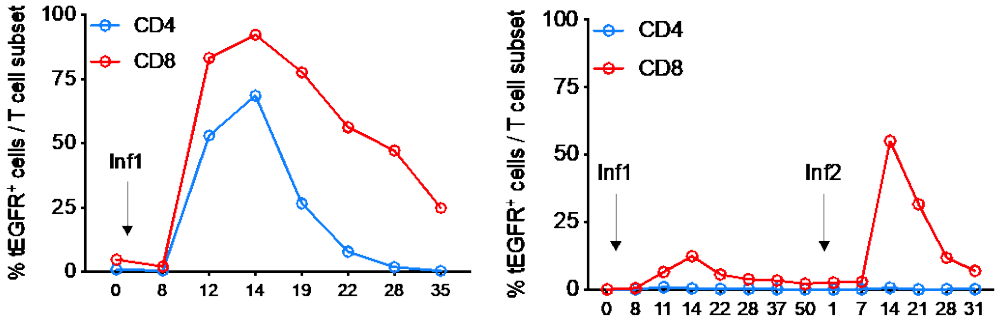
- Infusion Product
- Day 14 post-infusion



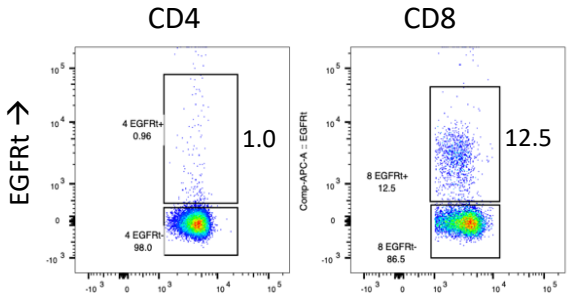
Tumor Biopsy (Day 28)

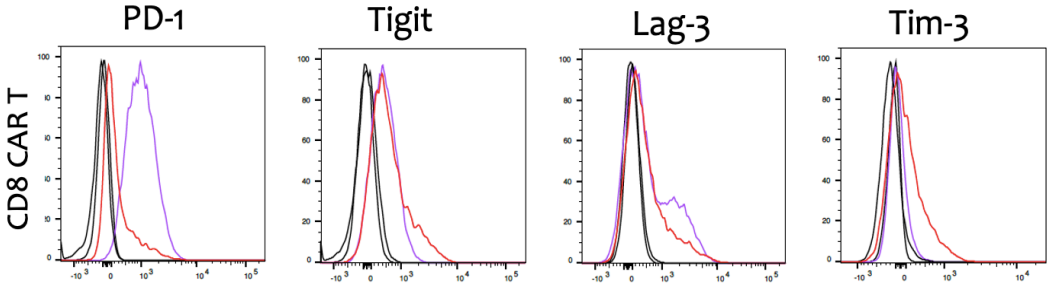
Response Rate (RECIST): 1 of 14 patients (PR)

CLL: CAR-T cells proliferate and infiltrate tumor sites and eliminate ROR1+ CLL cells without upregulating all inhibitory receptors

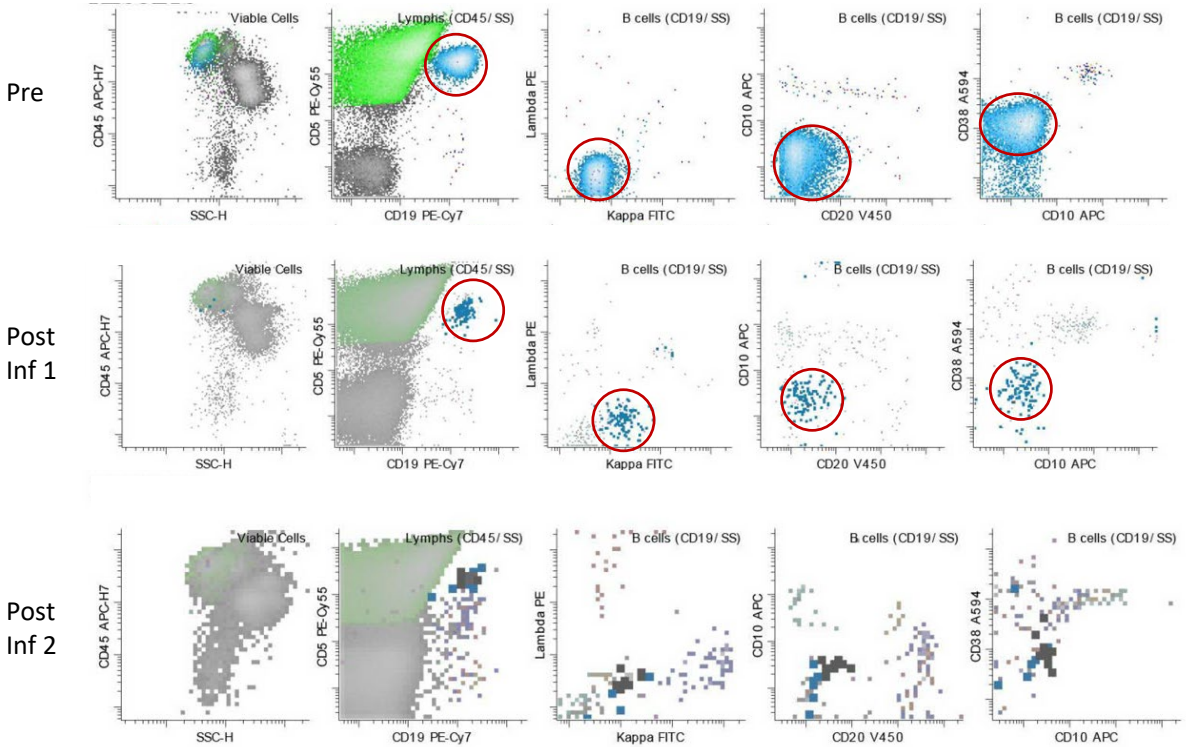


Bone Marrow





Bone Marrow Analysis



Abnormal:
CD5
CD20
CD23
99.5% ROR1+
10% of total WBC

Abnormal:
CD5,
CD20,
CD23
ROR1+
0.02% of total WBC

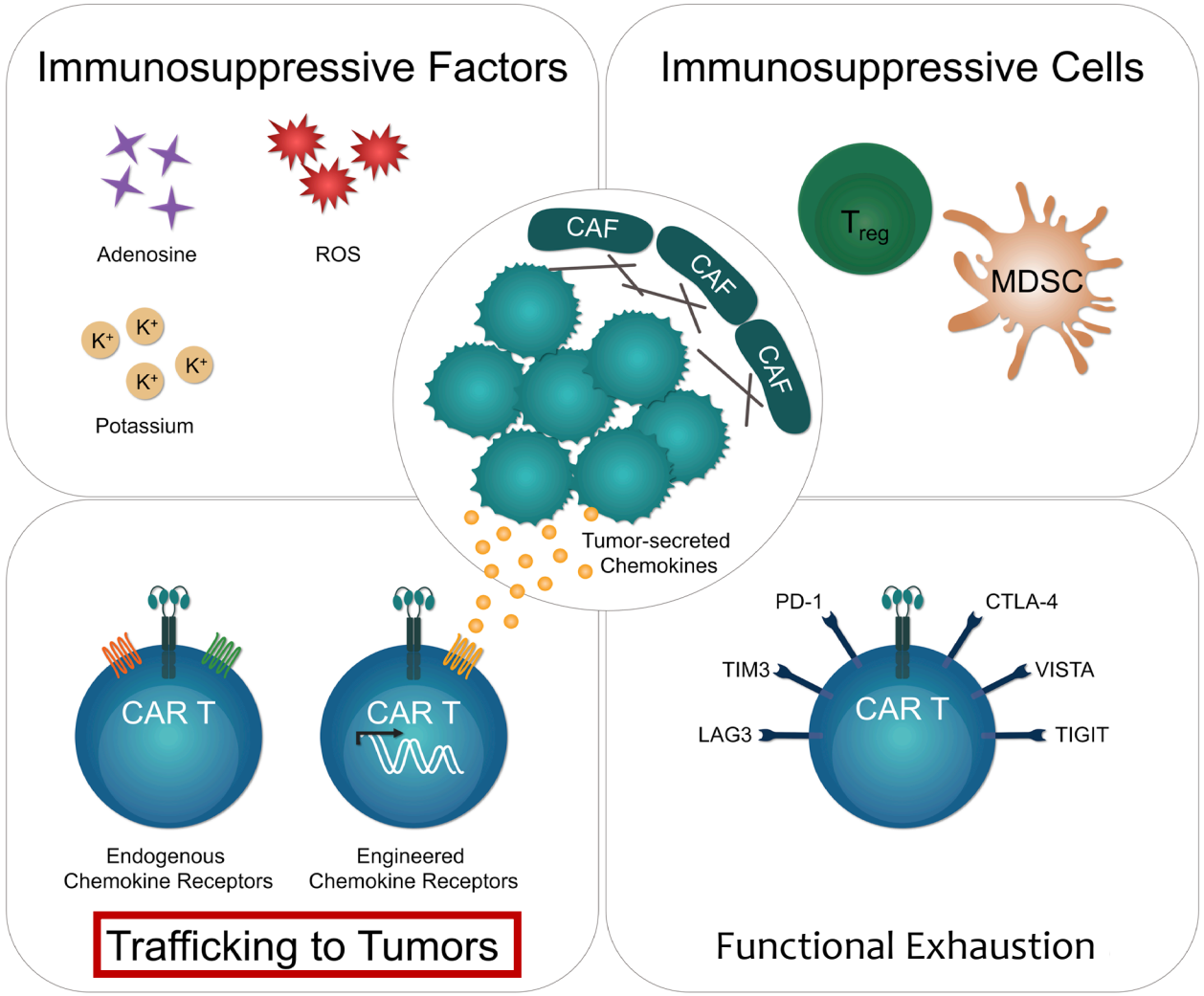
Small number **(.004%)** of questionable events

Repeat BM →CR

IP CAR

Peak CAR

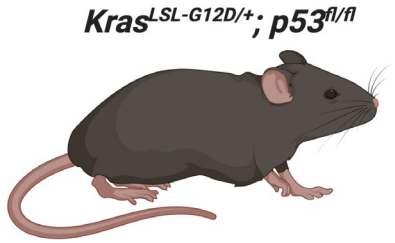
Overcoming obstacles for T cell therapy of solid tumors

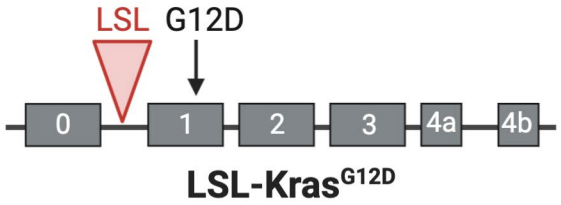


Most current models for CAR T cells are not representative of human tumors

Srivastava S, Riddell SR J Immunology 2018

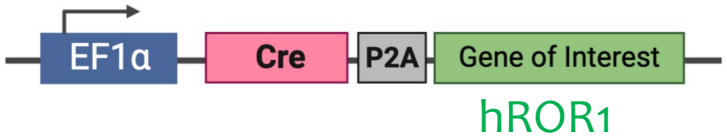
KP conditional immunocompetent syngeneic mouse model of ROR1+ non-small cell lung cancer (NSCLC)





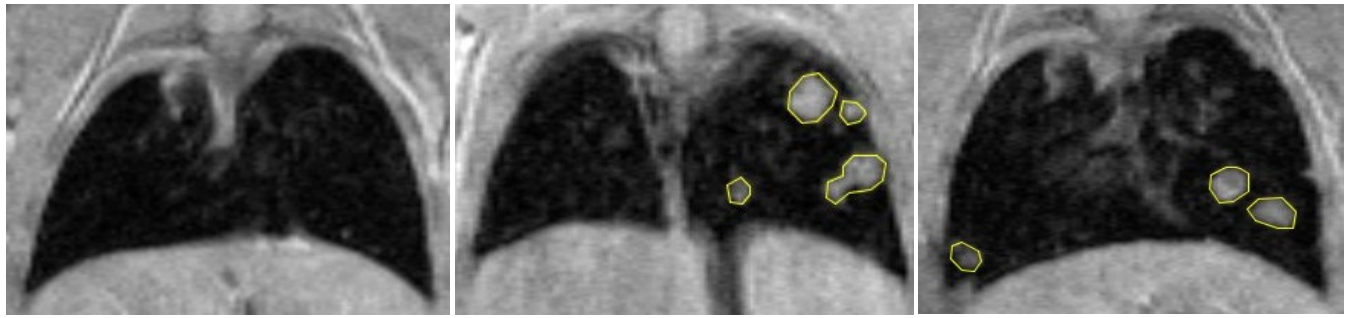
DuPage M, Dooley AL, Jacks T Nat Protoc. 2009

- Use cre-recombinase to induce the two most common mutations in NSCLC:
  - LoxStopLox K-ras allele - activating K-ras G12D mutation
  - LoxP p53 alleles -- biallelic loss of function
  - Deliver Cre through intra-tracheal lentiviral infection
- Tumors arise naturally in their site of origin vs. transplantable models
- Tumors co-evolve a relevant TME over 3-4 months with host immune system
- Introduction of CAR target antigen accomplished via cre-lentivirus



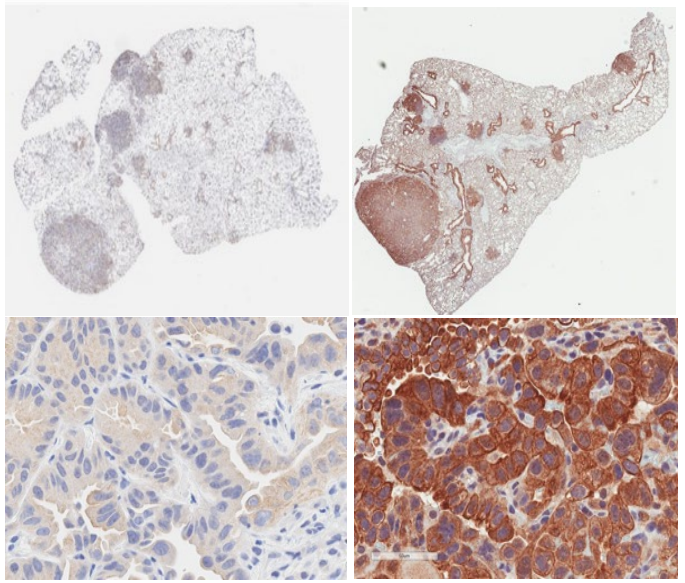
Characteristics of ROR1^{+} (KP ^{ROR1}) non-small cell lung cancer (NSCLC)

MRI



Cre-ffluc

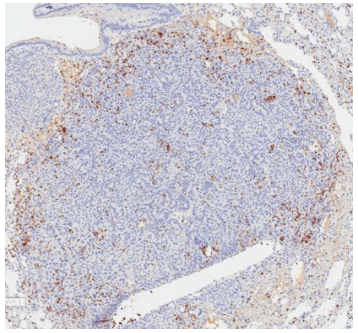
Cre-ffluc-hROR1



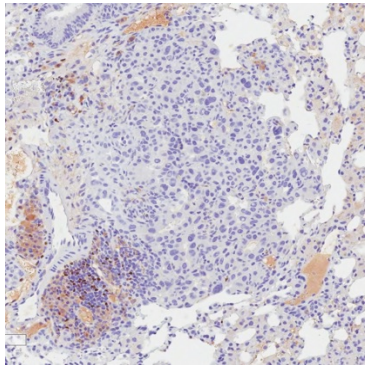
1X ROR1

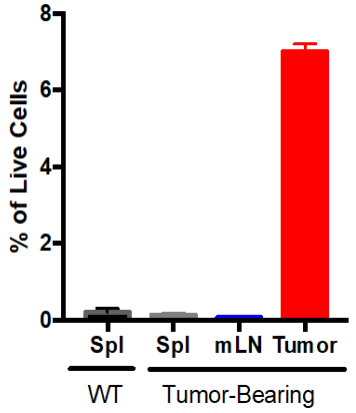
40X ROR1

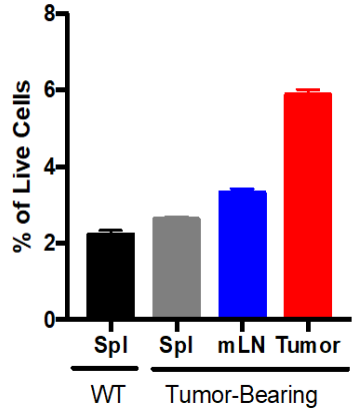
Ly6G

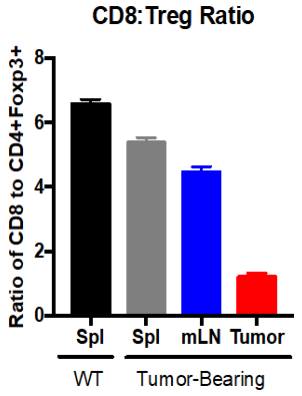


Foxp3

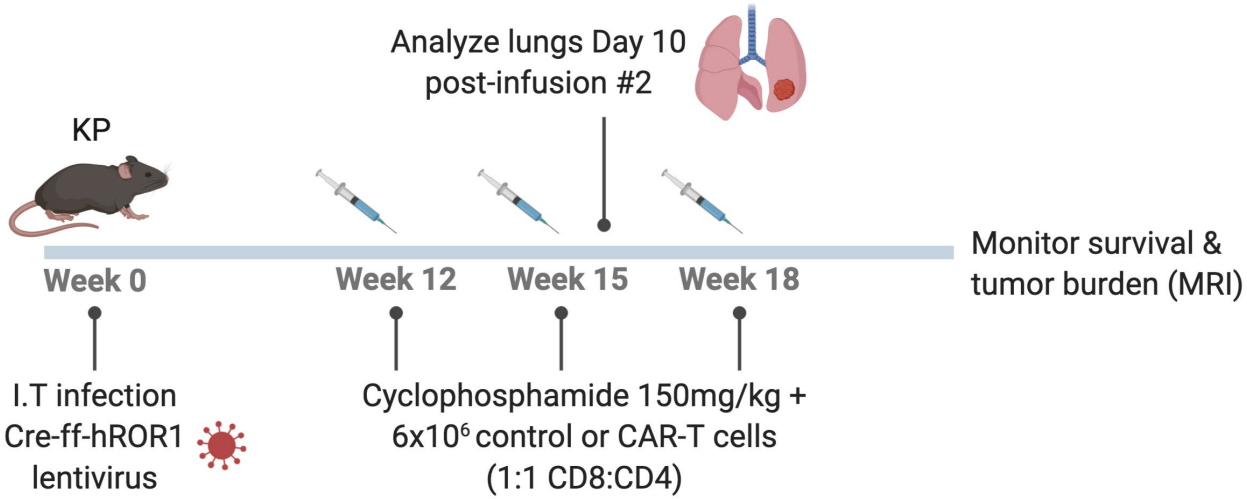


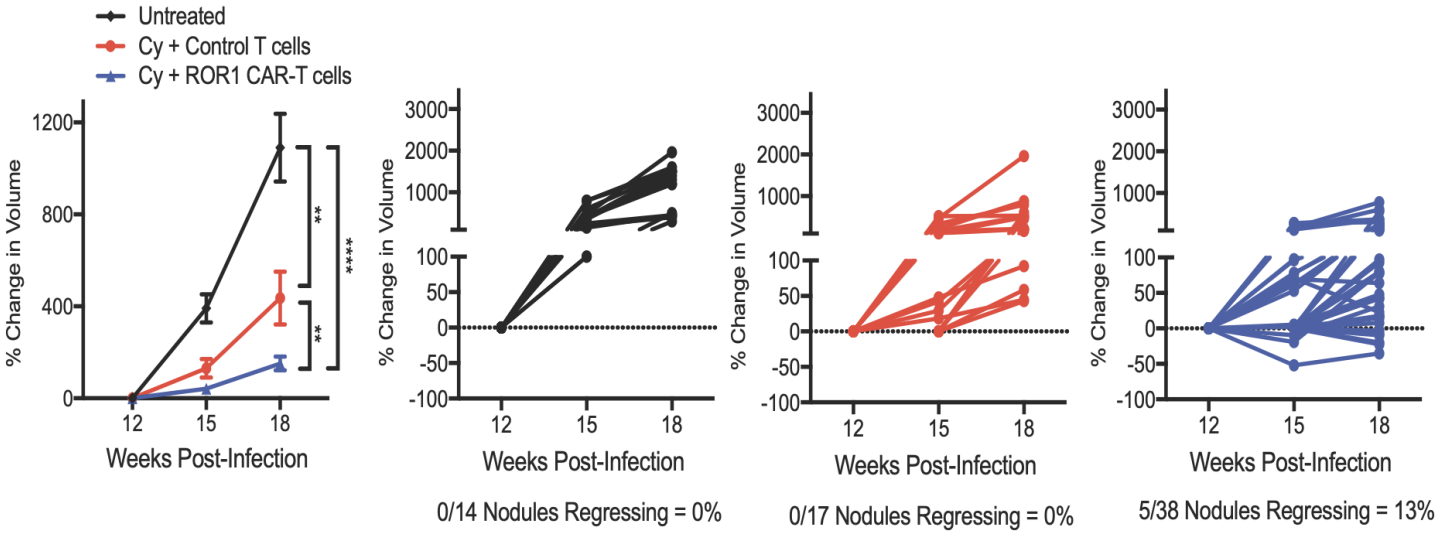




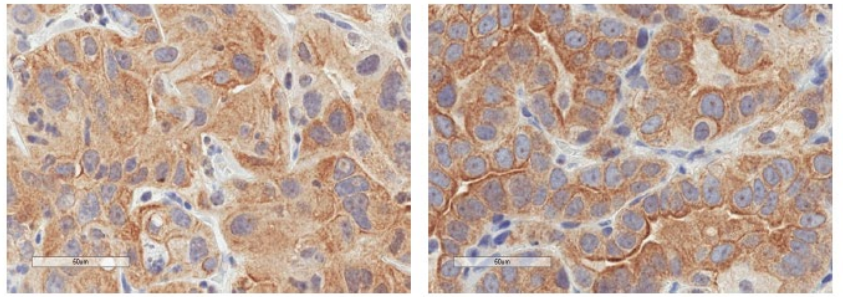


ROR1 CAR-T cells given after Cy lymphodepletion have limited activity in KP^{ROR1} mice



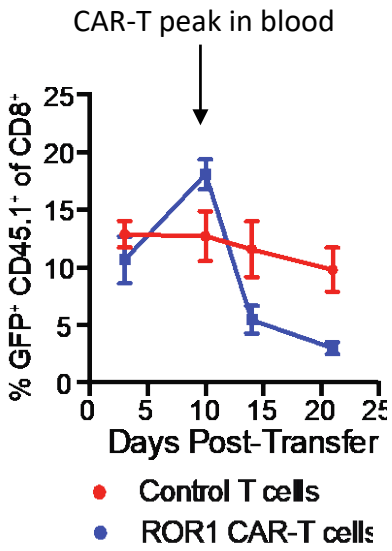


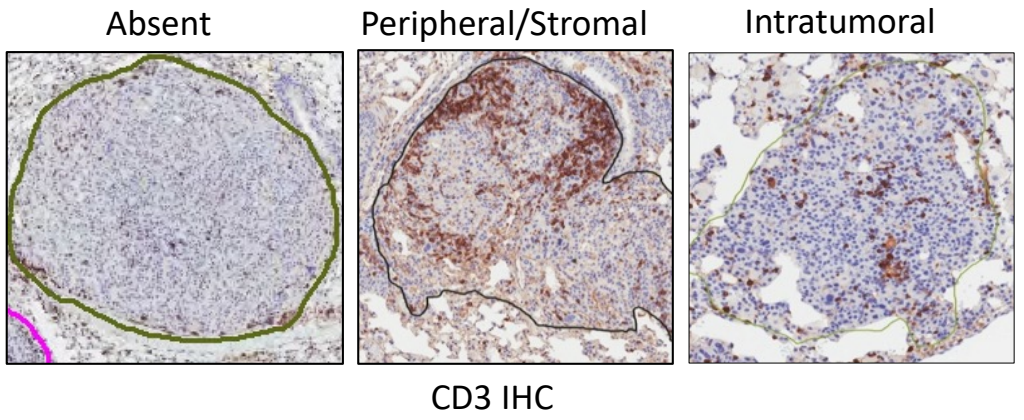
Mixed Response After ROR1 CAR-T

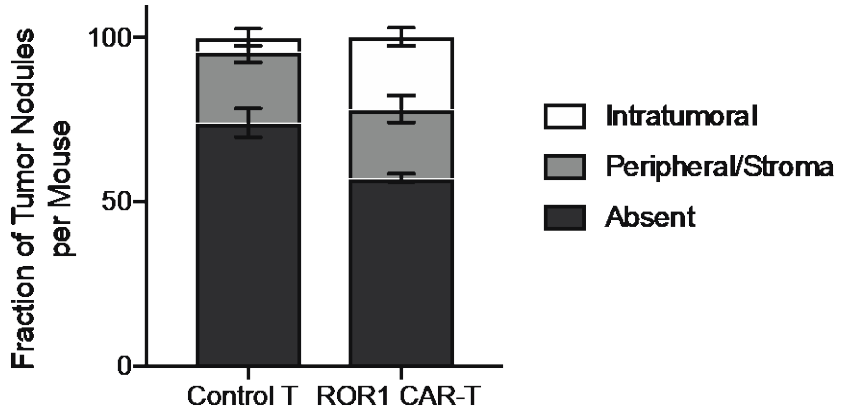


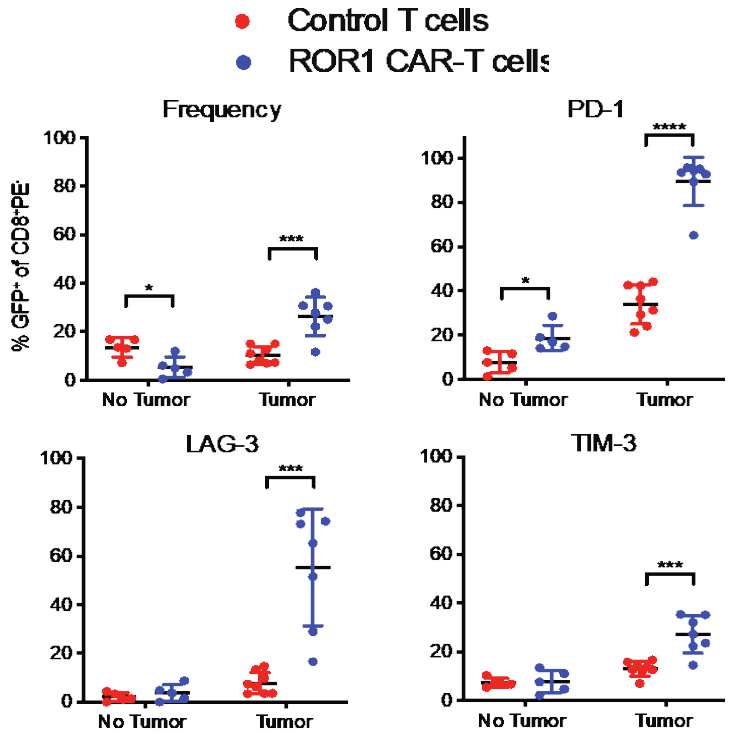
Control T cell-treated ROR1 CAR-T cell-treated

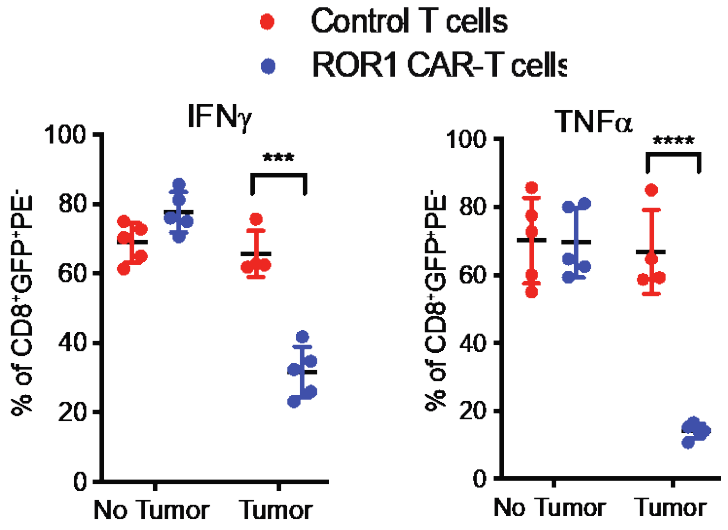
ROR1 CAR-T cells expand in blood but infiltrate lung tumors poorly and become dysfunctional









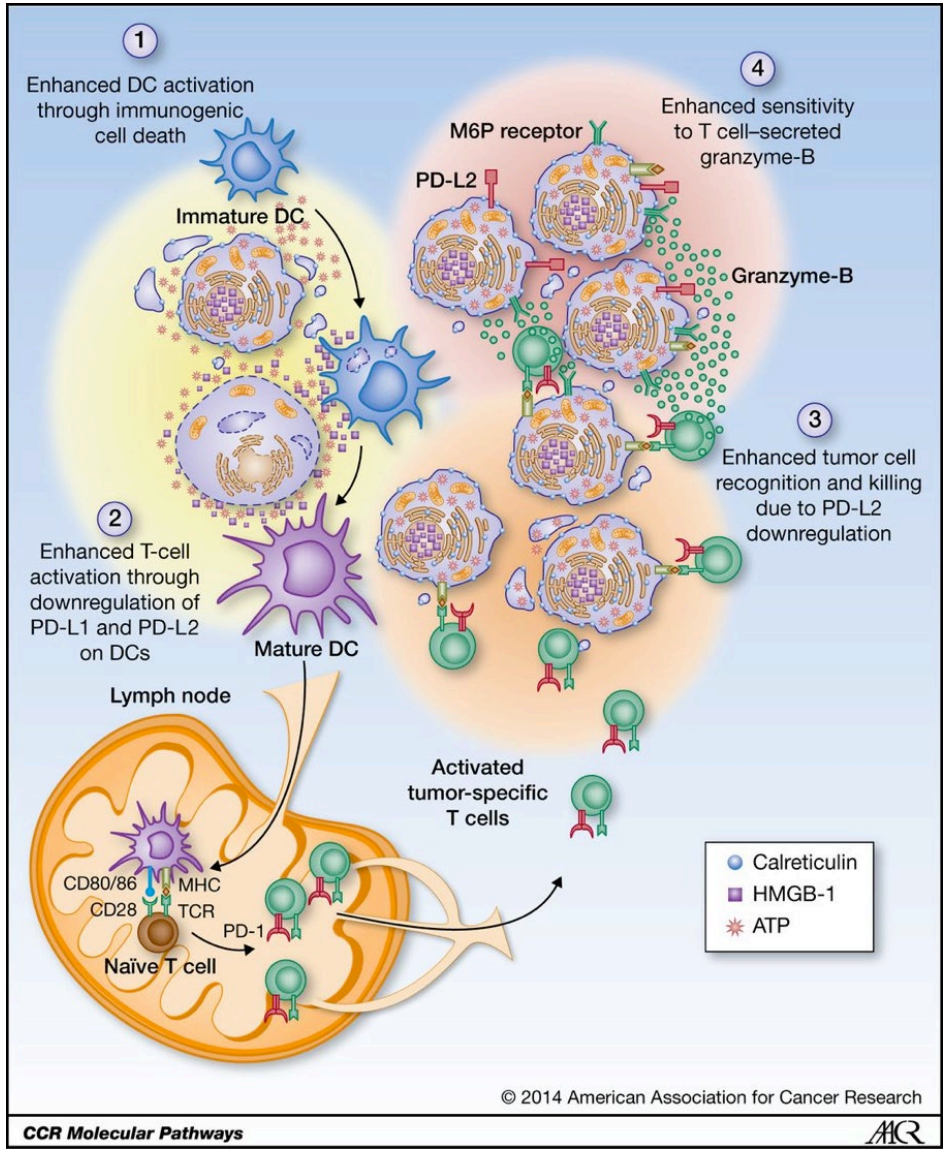


10 days post 2nd T cell infusion

“Immunogenic” chemotherapy can increase infiltration of endogenous T cells into tumors

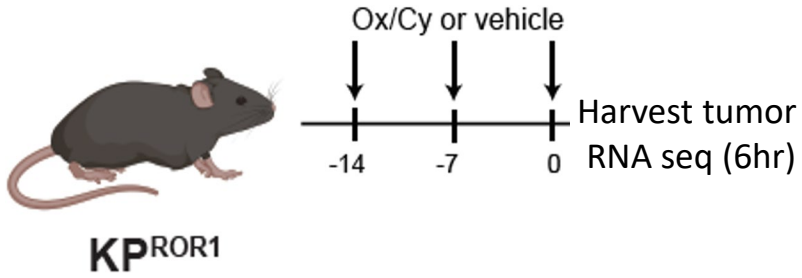
Immunogenic cell death

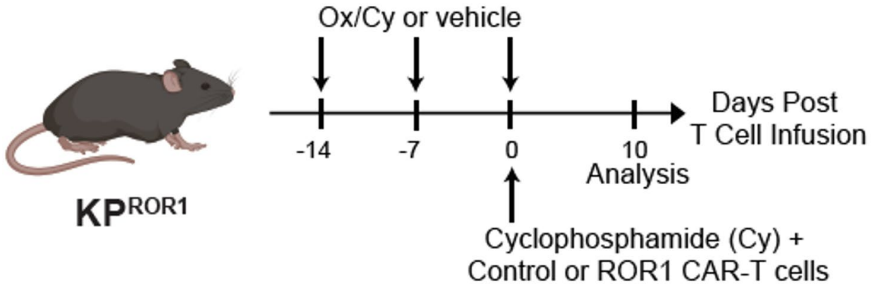
- Anthracyclines, platinum-based agents plus cytoxan, radiotherapy
- Release of DAMPs including calreticulin, ATP, and HMGB1
- Activation of DCs/macrophages, induction of chemokines, pro-inflammatory cytokines, antigen presentation
- Oxaliplatin + cyclophosphamide (Ox/Cy) induced ICD in KP-Ova tumors and response to ICB (Pfirschke et al, Immunity 2016)

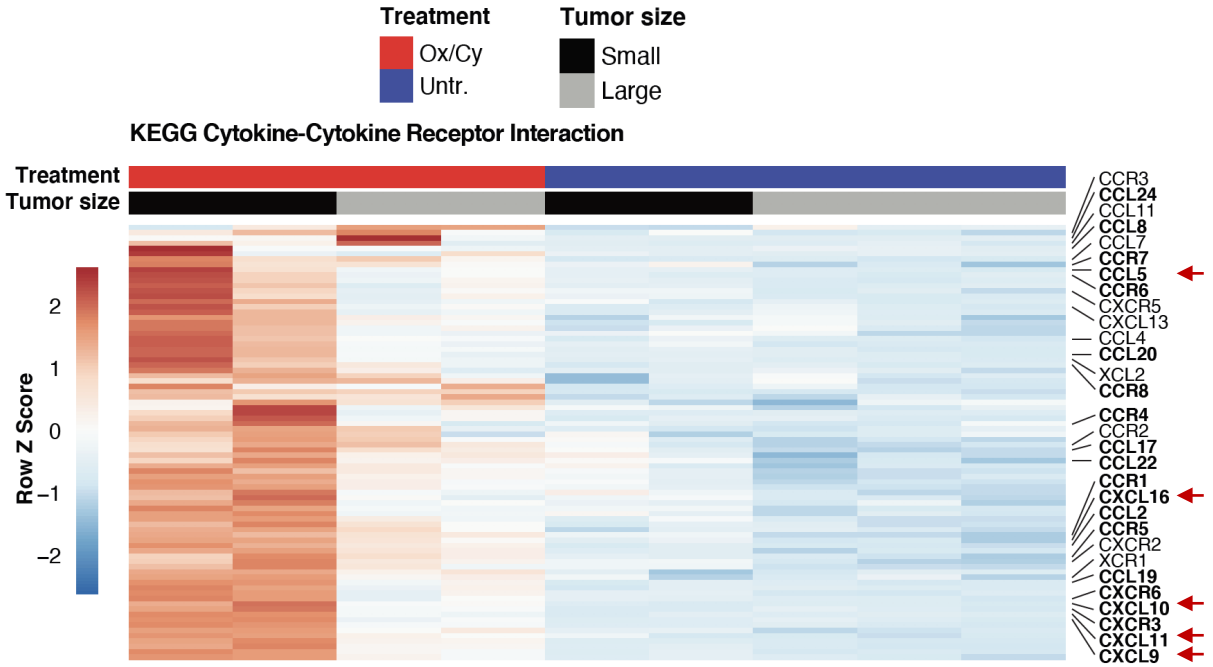


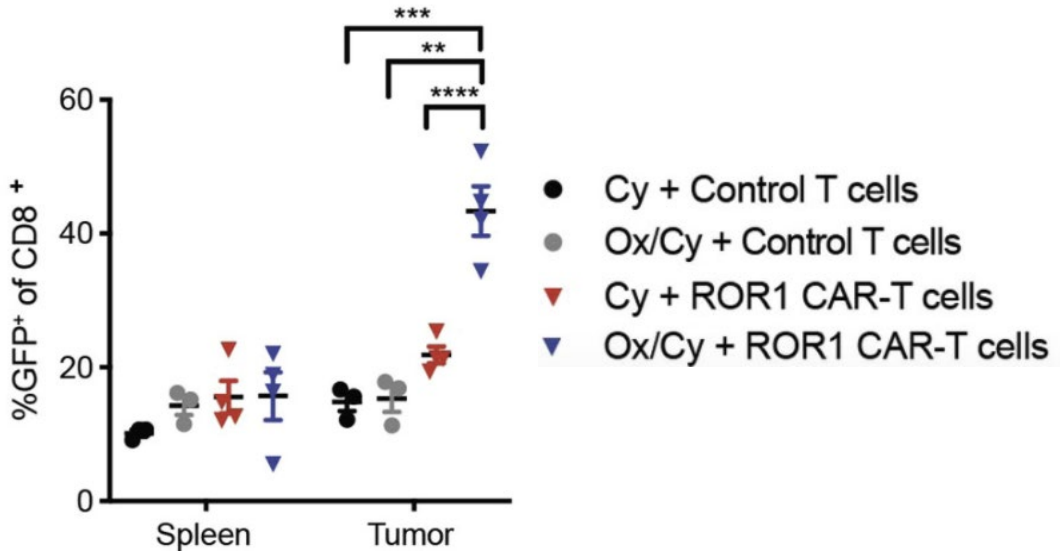
Hato et al, Clin Cancer Res 2014

Ox/Cy induces expression of T cell-recruiting chemokines in KP^{ROR1} tumors and markedly improves infiltration of CAR-T cells



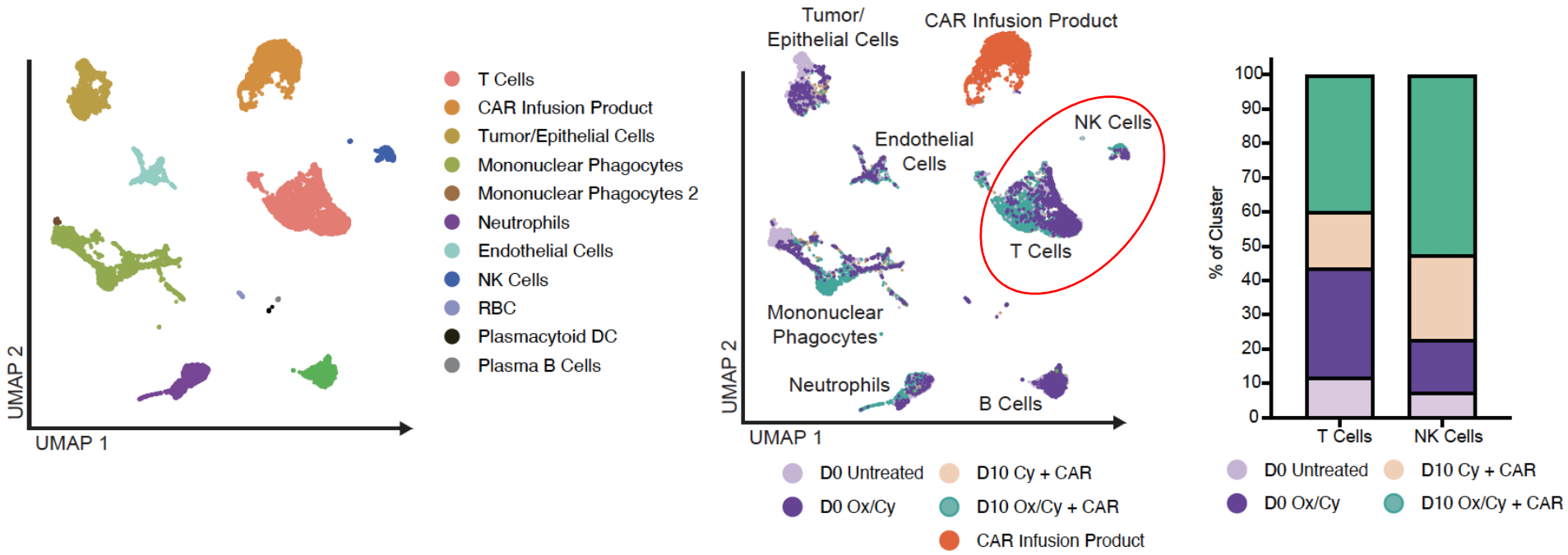






Srivastava et al Cancer Cell 2021

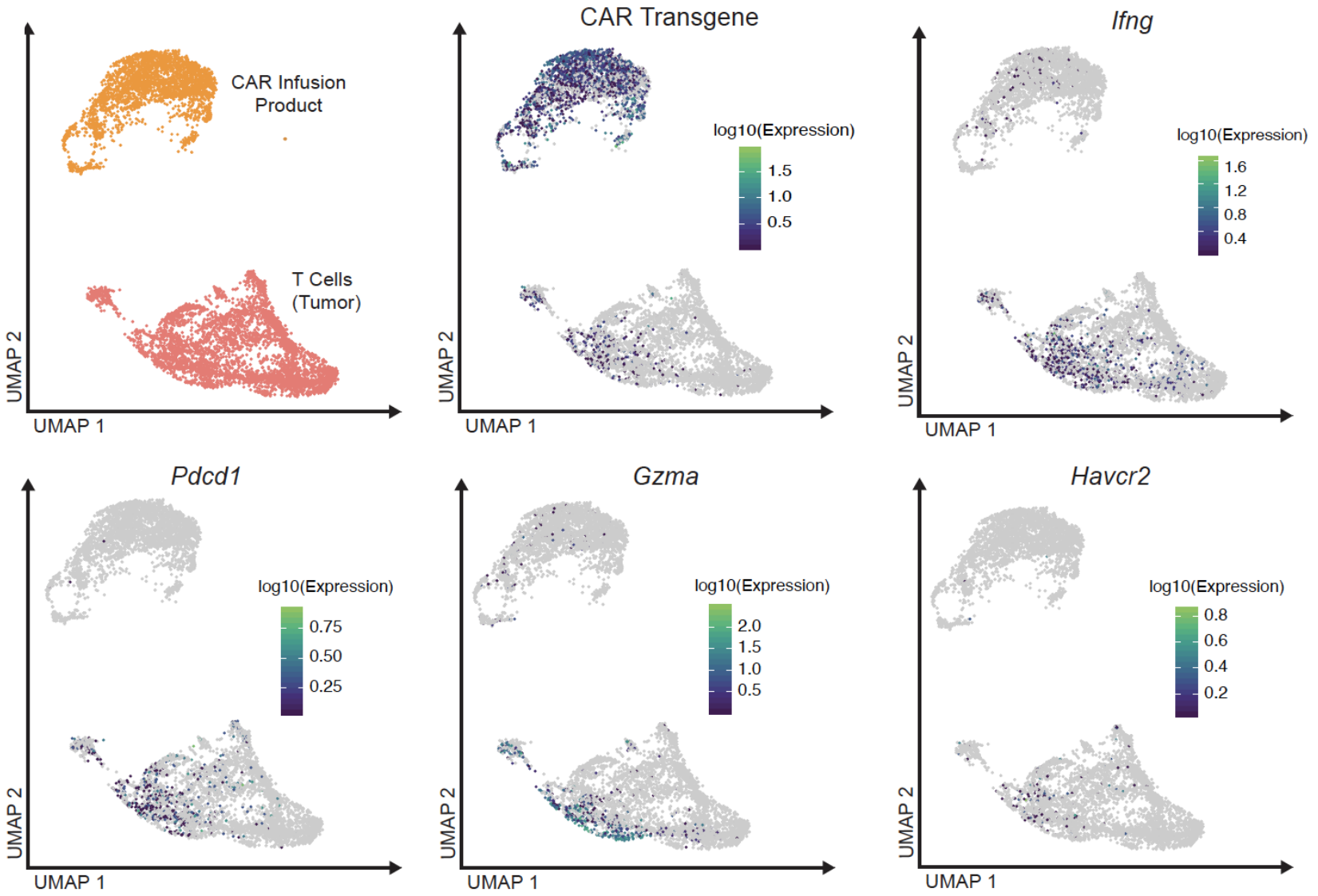
How does Ox/Cy alter cell composition and phenotype in the TME?



- CAR infusion product clusters separately from tumor-infiltrating CARs
- T cell, NK cell clusters: mostly comprised of D0 and D10 Ox/Cy samples
- Most sample-dependent changes occur in macrophage/DC cluster

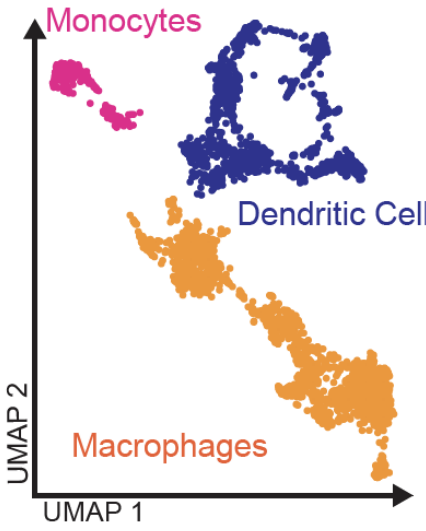
Srivastava et al Cancer Cell 2021

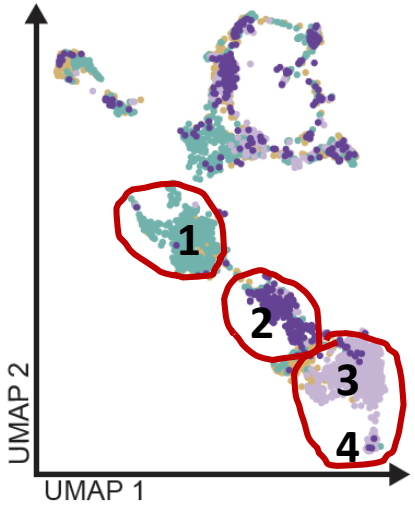
Tumor-infiltrating CAR-T cells have an effector phenotype

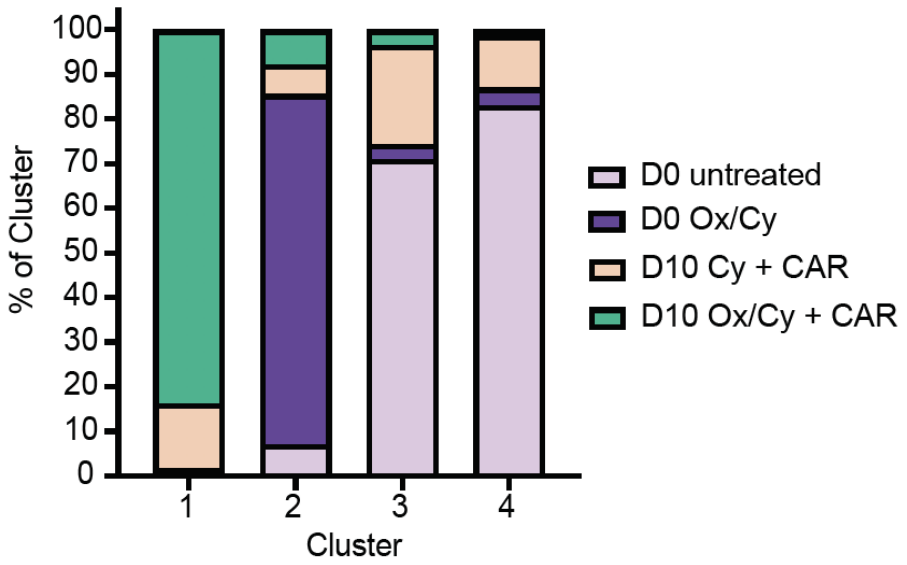


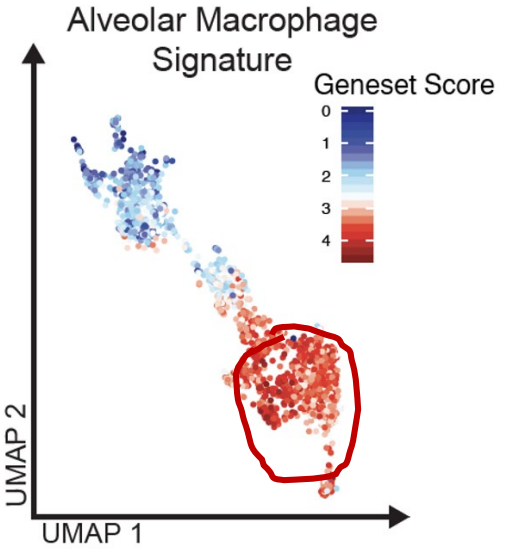
Srivastava et al Cancer Cell 2021

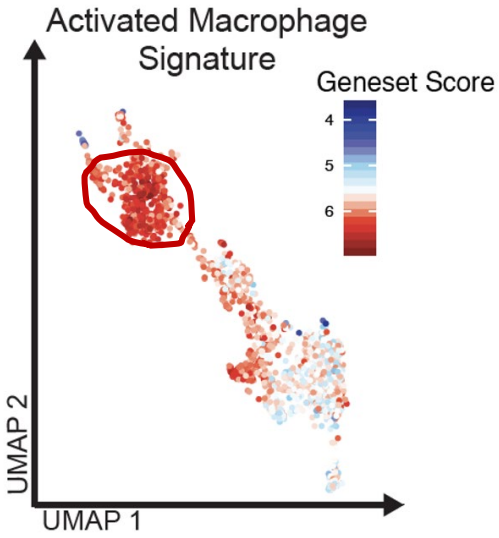
Ox/Cy and CAR T cells remodel macrophages in the TME









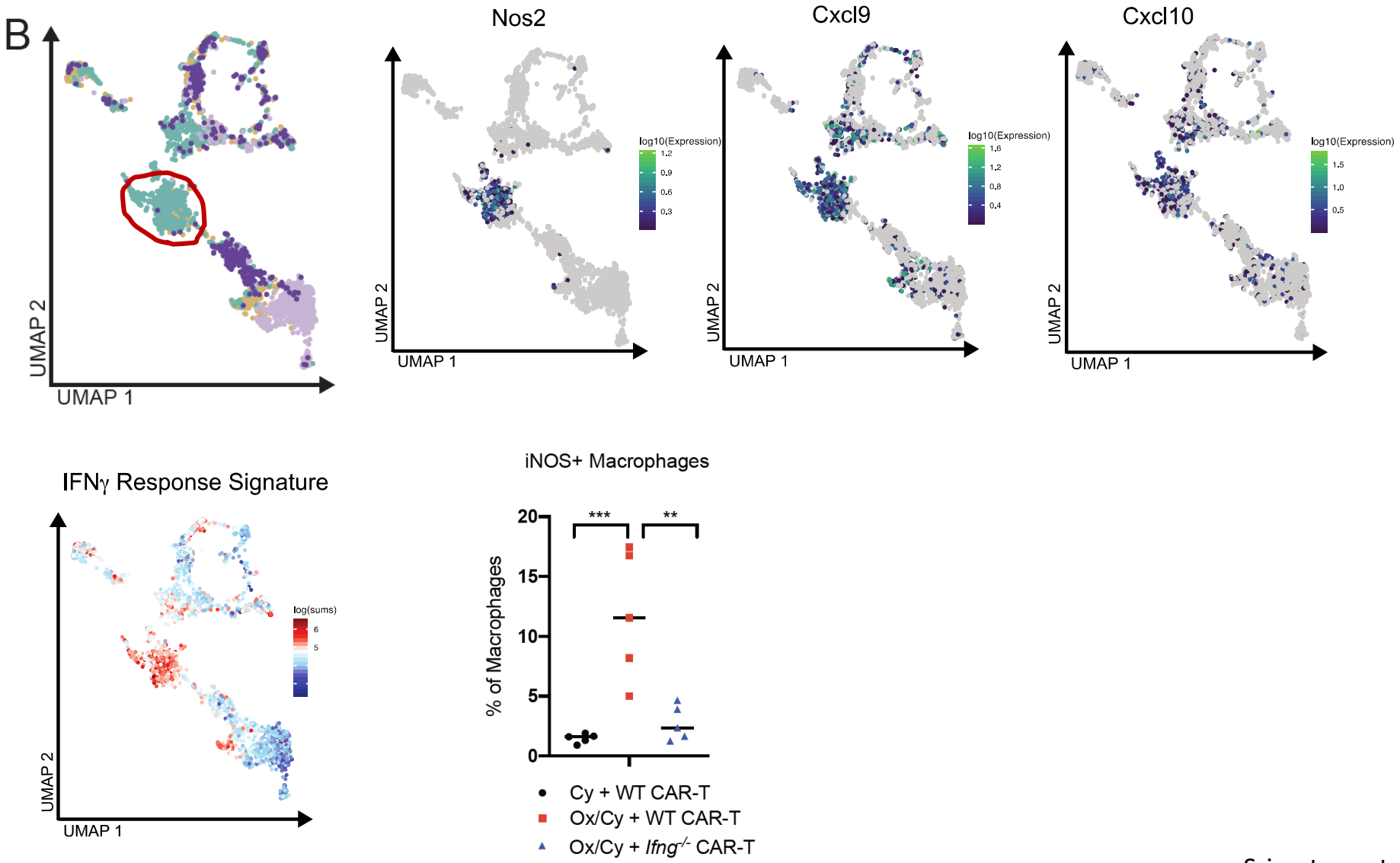


<u>Pathways upregulated in C2 > C3:</u>

- Phagocytosis
- Antigen presentation
- IFNγ and IFNα signaling
- Toll-like receptor signaling
- Chemokines
  - ↑ T cell recruiting (Ccl4, Cxcl16)
  - ↑ monocyte recruiting (Ccl2, Ccl7)
  - ↓ neutrophil recruiting (Cxcl3, Cxcl15)

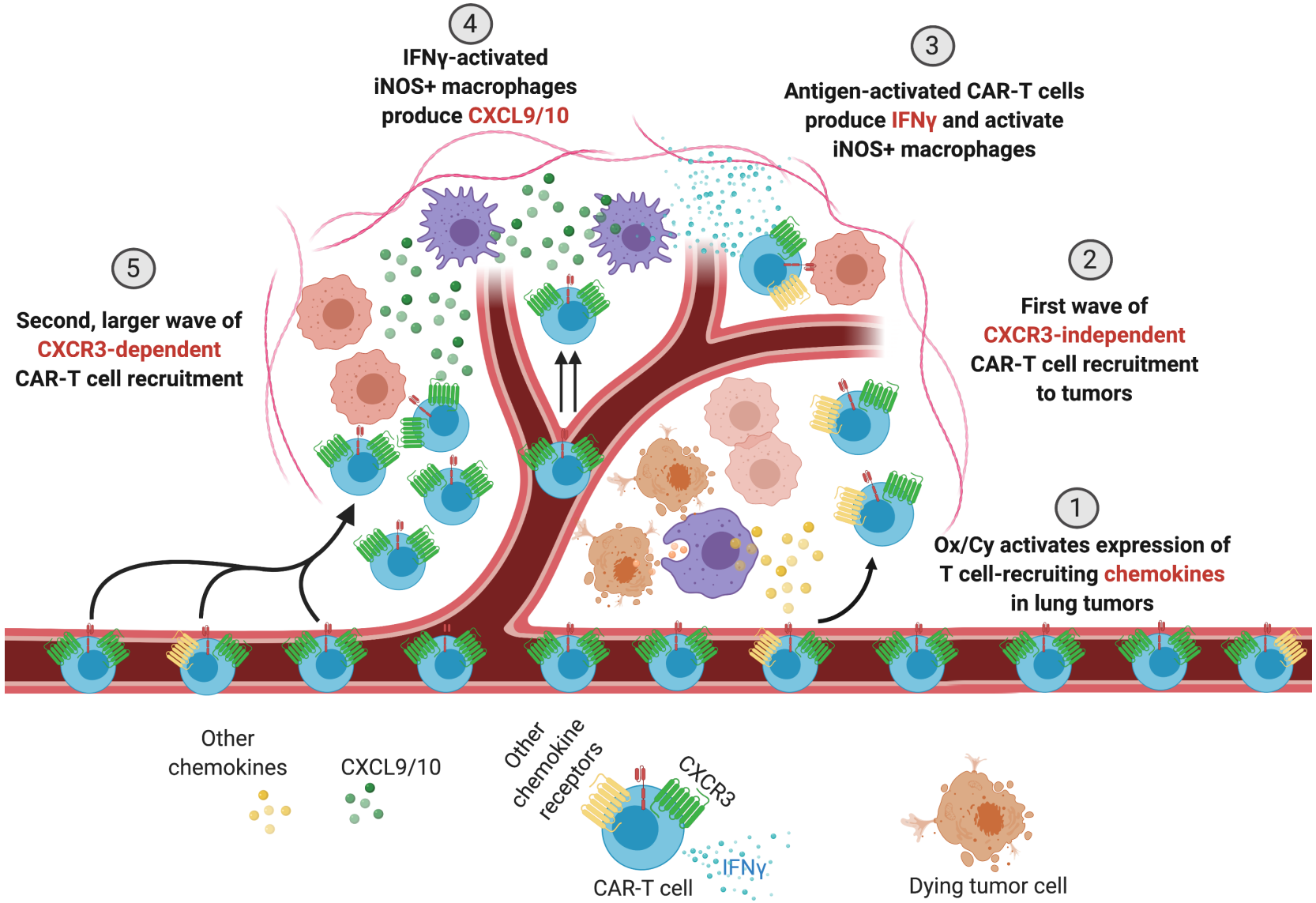
Srivastava et al Cancer Cell 2021

CAR-T cells in Ox/Cy-treated tumors promote accumulation of pro-inflammatory macrophages that express CXCR3 ligands

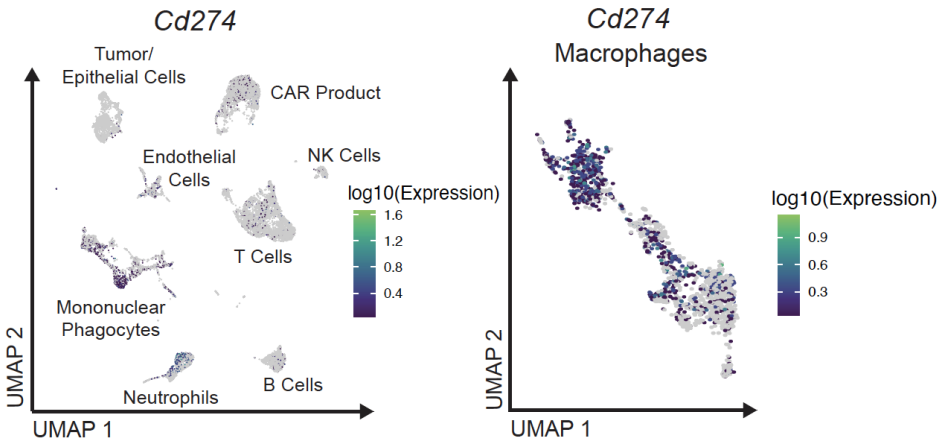


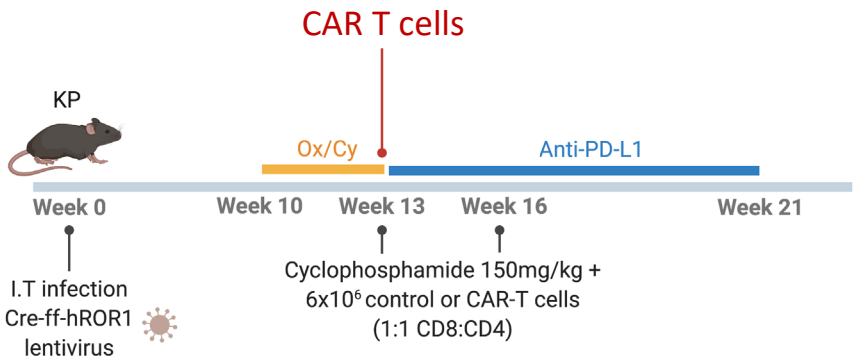
Srivastava et al Cancer Cell 2021

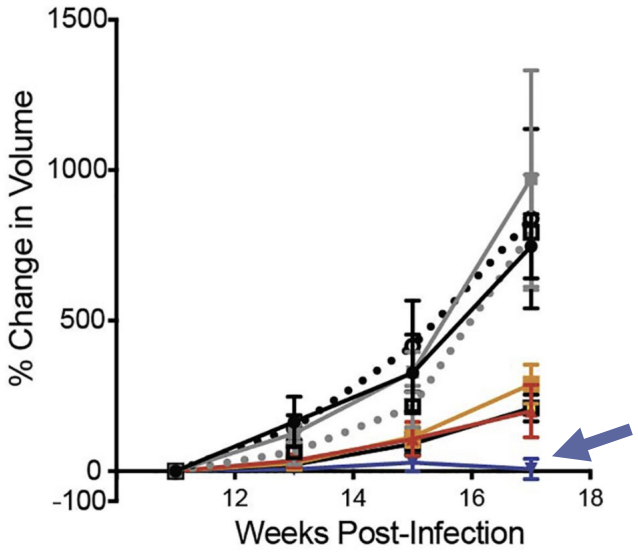
In this model immunogenic chemotherapy breaks the barrier to CAR T cell entry, which then remodels the TME to promote further T cell infiltration

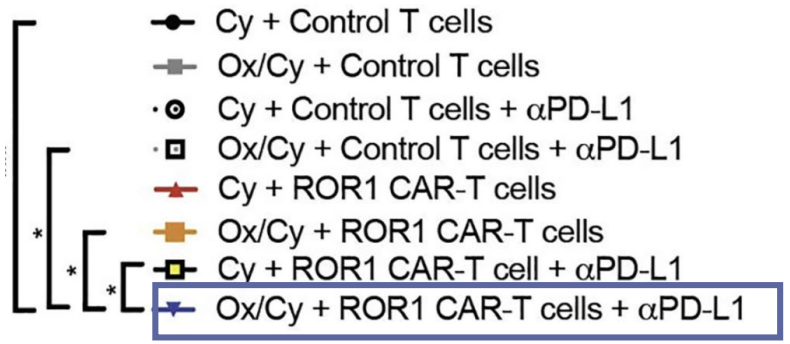


Does this improve antitumor efficacy?



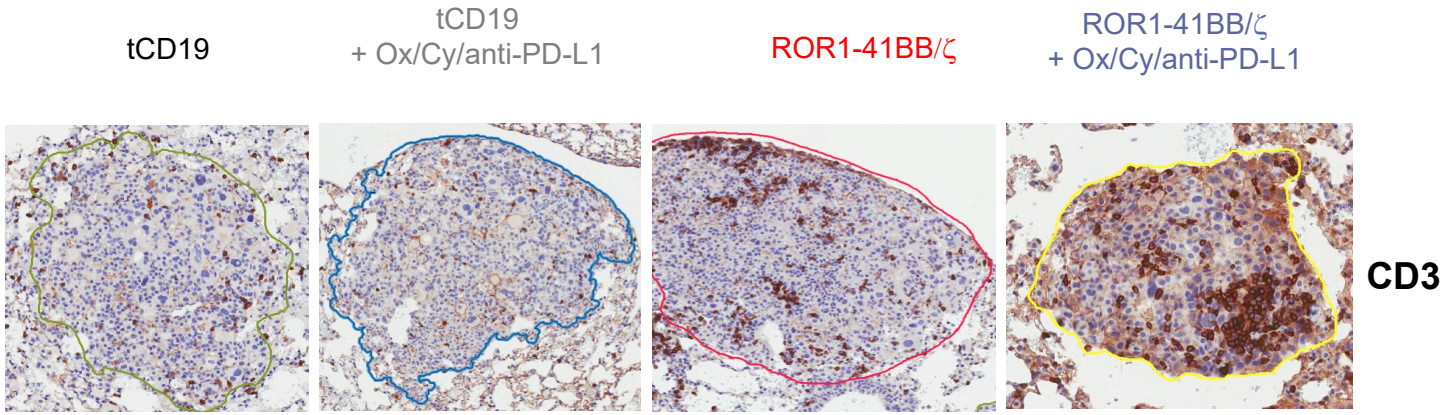


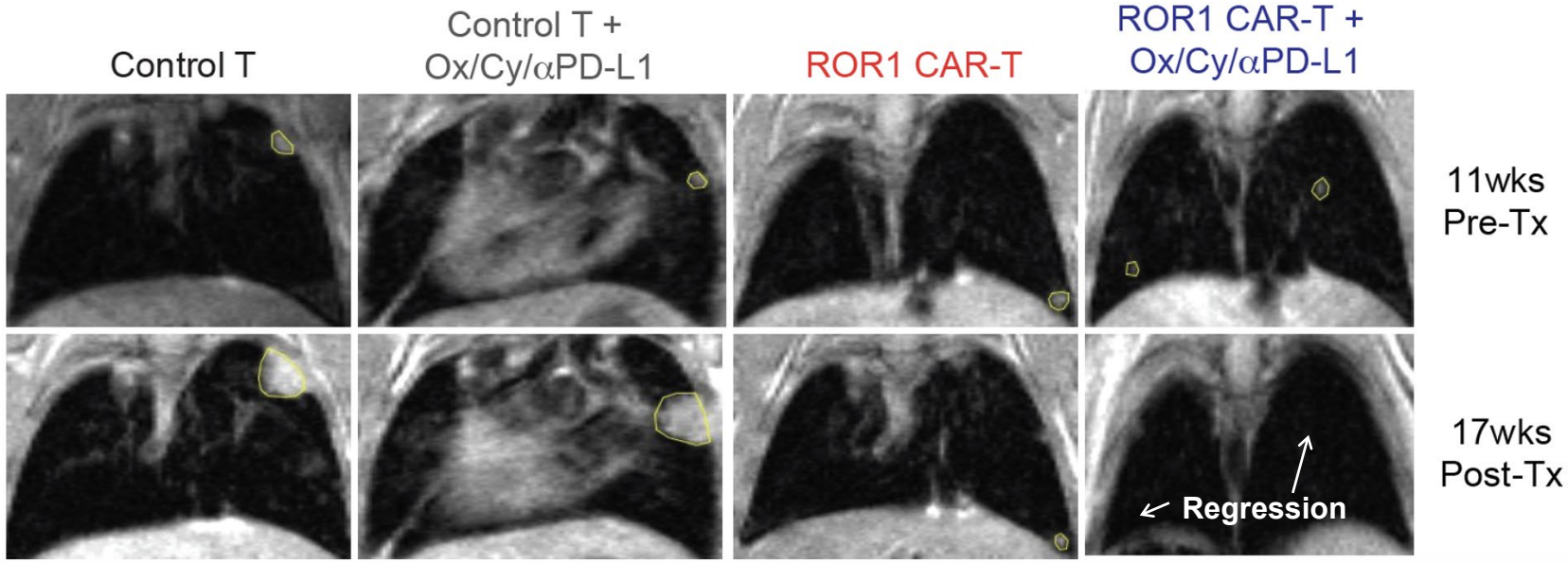




Srivastava et al Cancer Cell 2021

CAR-T infiltration into tumor nodules is markedly improved in Ox/Cy anti PD-L1 treated mice and associated with tumor regression



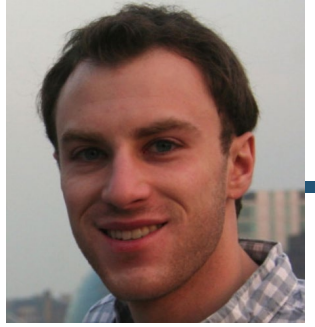


Srivastava et al Cancer Cell 2021

I. T Cell Fitness

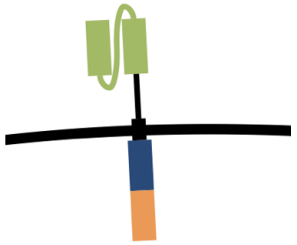
II. Infiltration and Function In Solid Tumors

III. Enhancing sensitivity and specificity of receptors



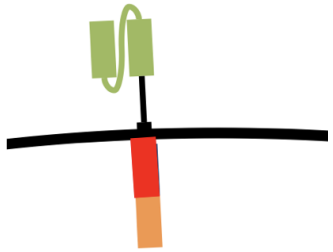
CAR signaling in primary T cells

4-1BB/CD3ζ CAR

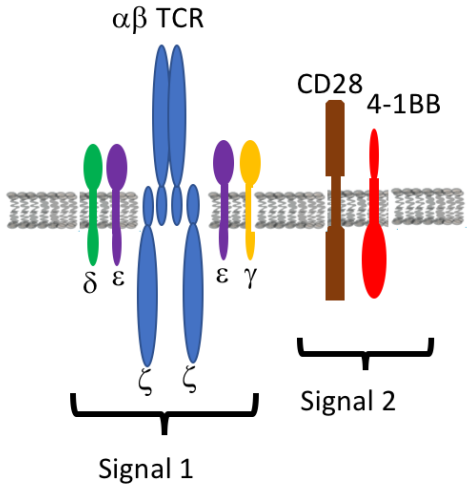


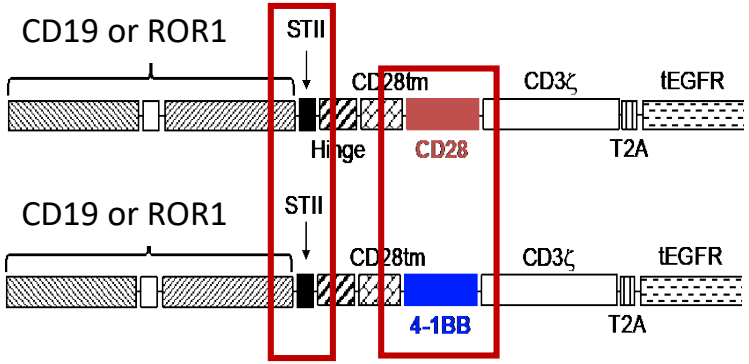
- Expand more slowly in vivo post transfer
- Persist longer (months) in some patients

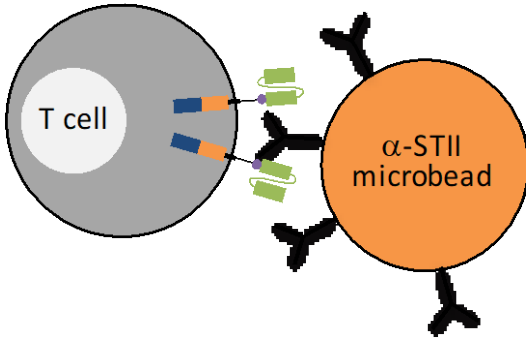
CD28/CD3ζ CAR



- Expand rapidly in vivo post transfer
- Rarely persist past 60 days





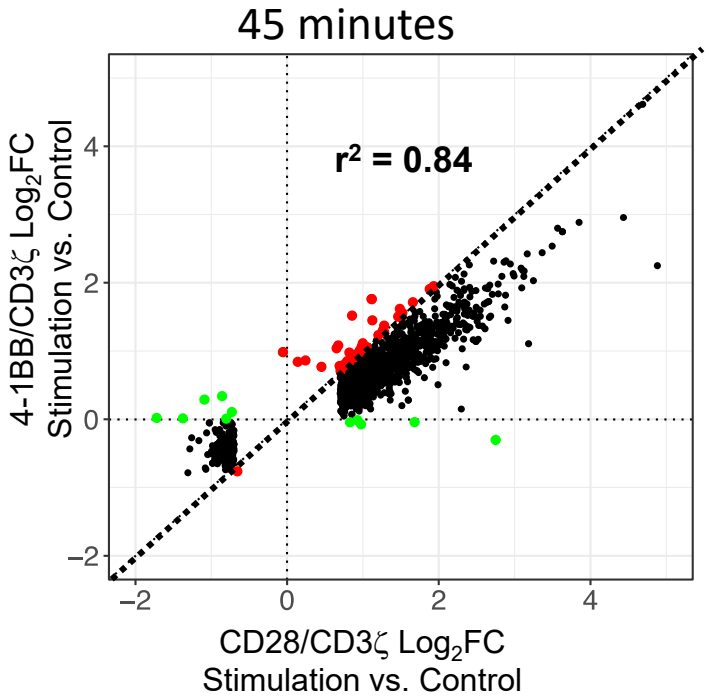


Cell lysates
LC/MS

Liu et al Nature Biotech, 2016

Salter et al Science Signaling, 2018

Downstream protein phosphorylation differs in intensity between CD28/CD3ζ and 4-1BB/CD3ζ CARs

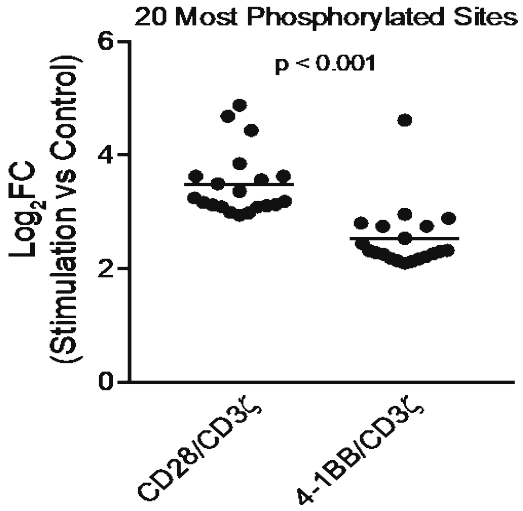


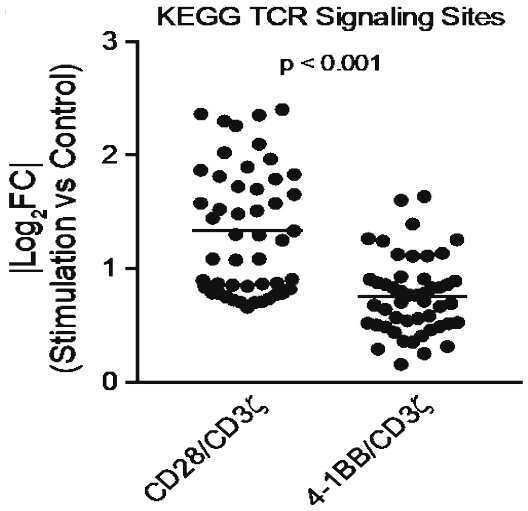
The vast majority of sites lie to the right of the diagonal – **are more intensely modulated by CD28/CD3ζ CARs;** 43 sites (red) more intensely modulated by 4-BB/CD3ζ CAR

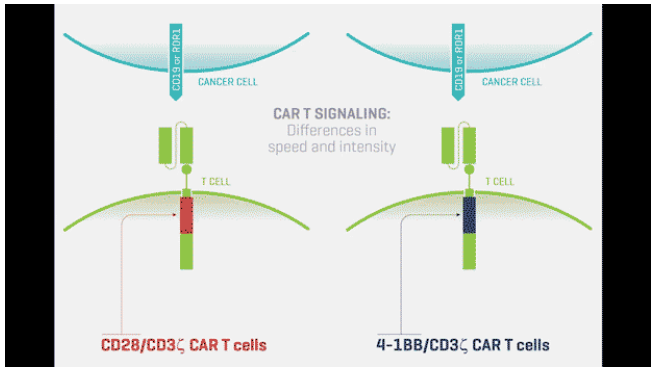
12 of >1200 sites (0.9%; green) were differentially modulated by CD28/CD3ζ and 4-1BB/CD3ζ CARs

Sites that were differentially modulated did not relate to canonical CD28 or 4-1BB signaling pathways

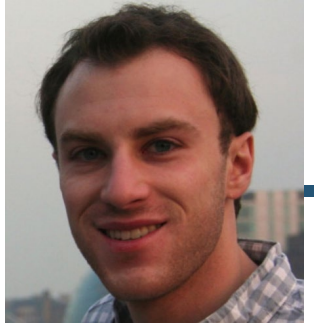
Both CARs activated CD28 and 4-1BB signaling pathway intermediates



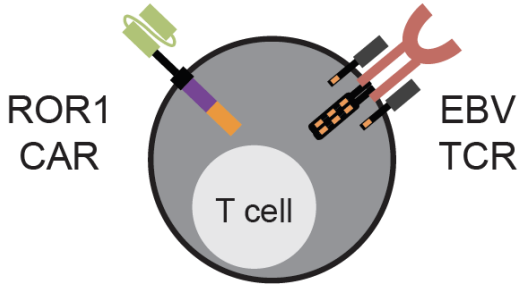


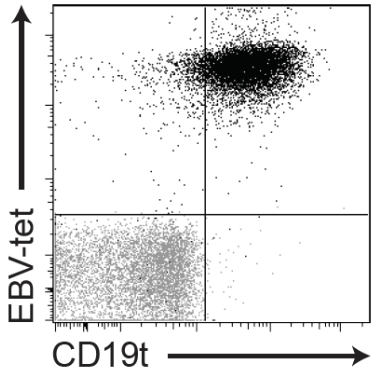


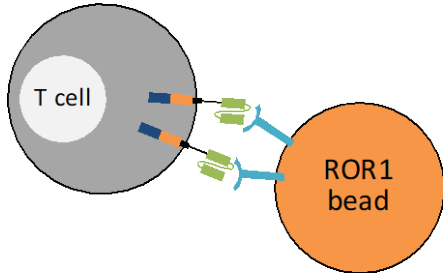
Salter et al Science Signaling, 2018



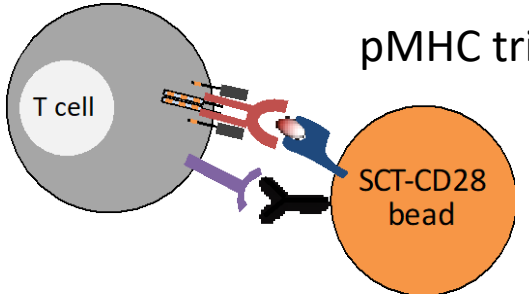
What can we learn by comparing CAR and TCR signaling?

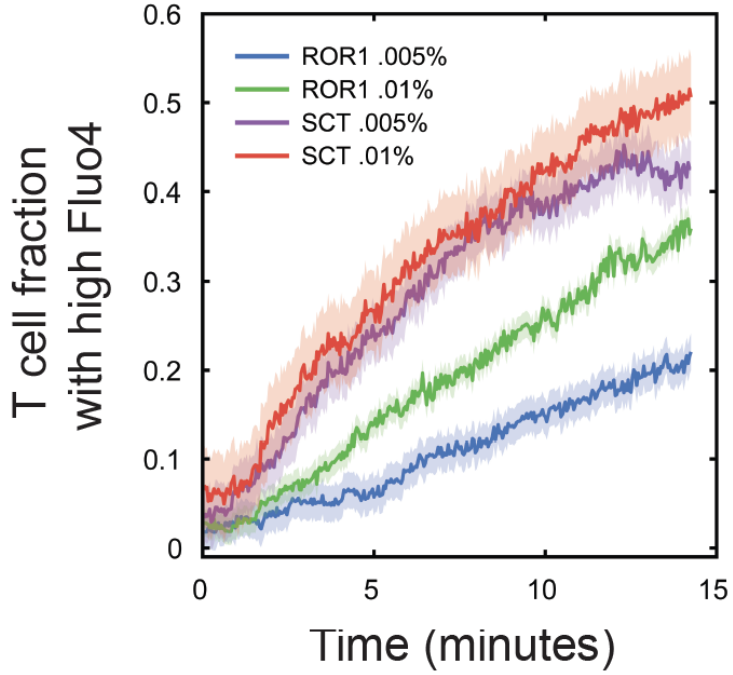






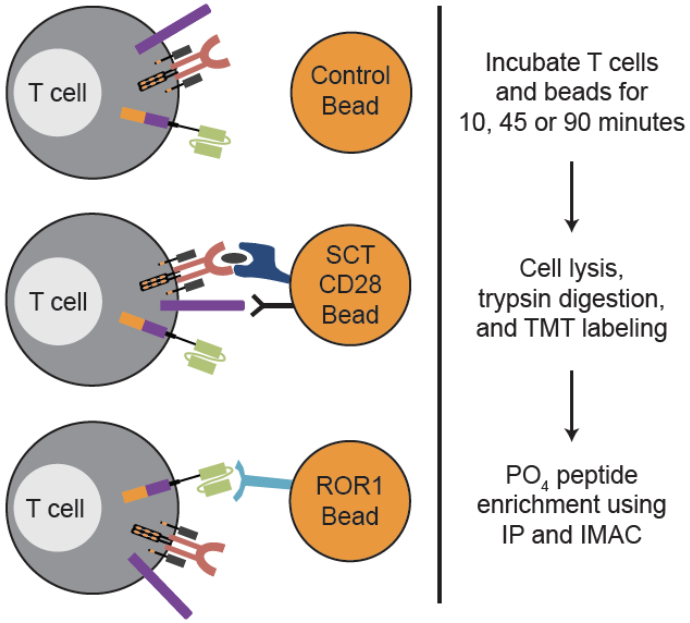
pMHC trimer

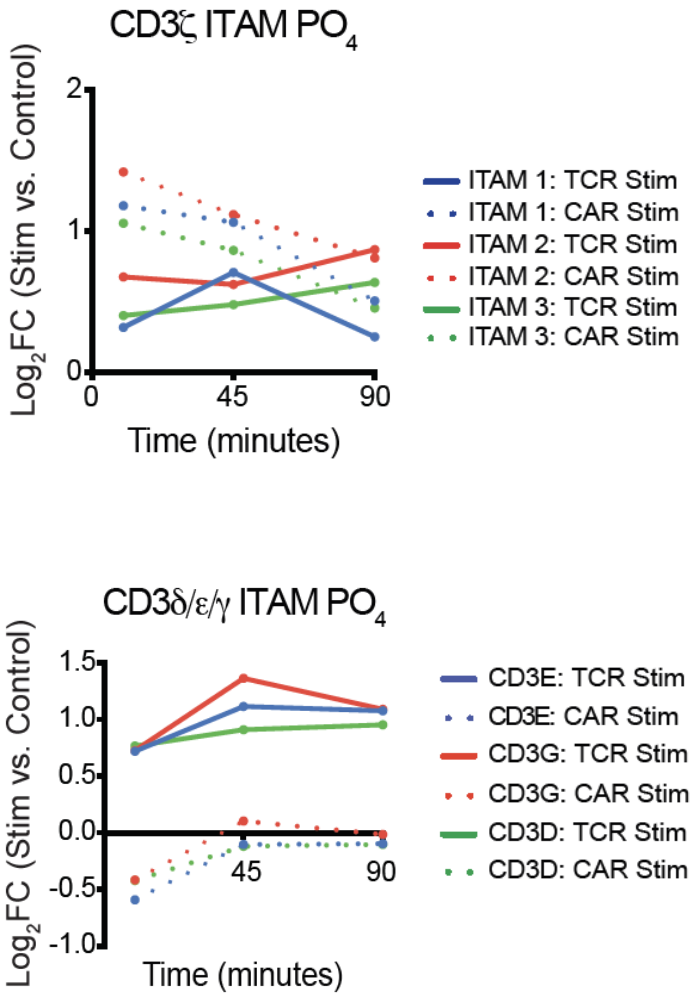


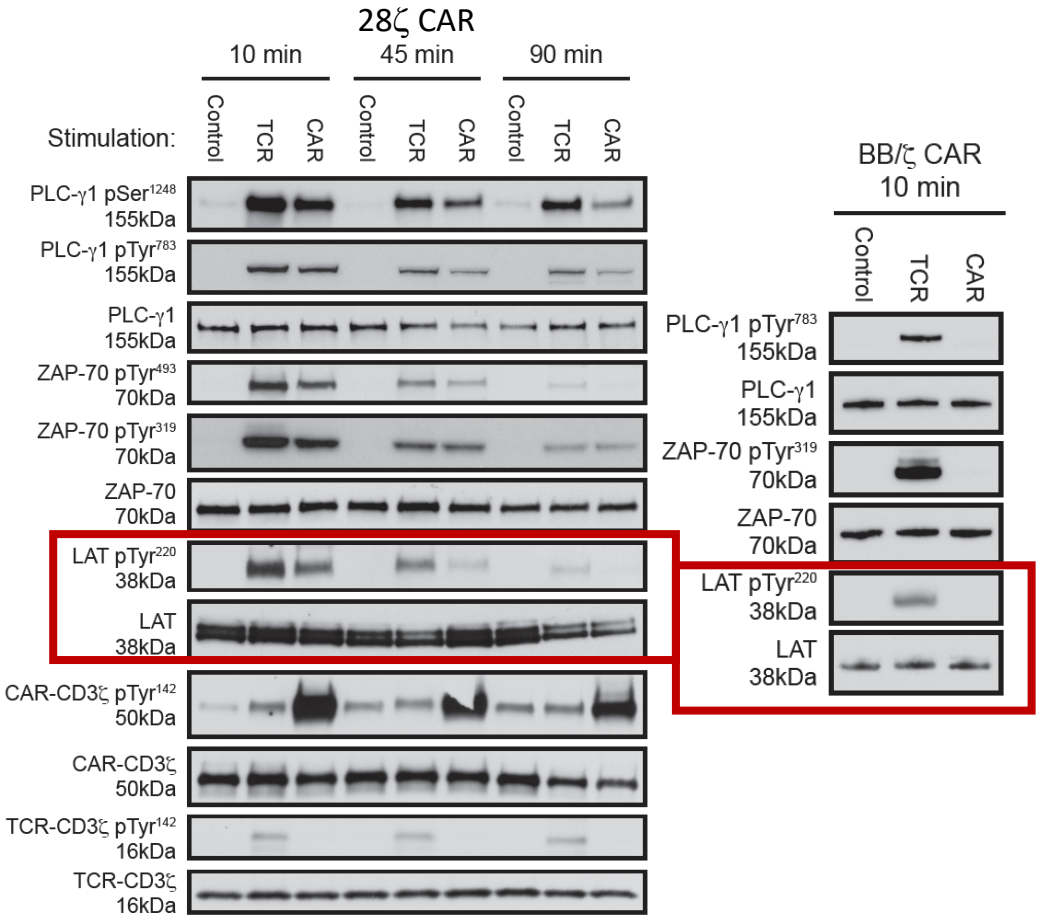


Salter et al Science Signaling, in revision

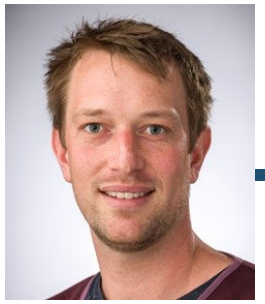
Comparison of CAR and endogenous TCR signaling in the same primary T cell reveals absence of CD3δ,ε,γ PO_4 and lower LAT PO_4 – a key hub for downstream signaling



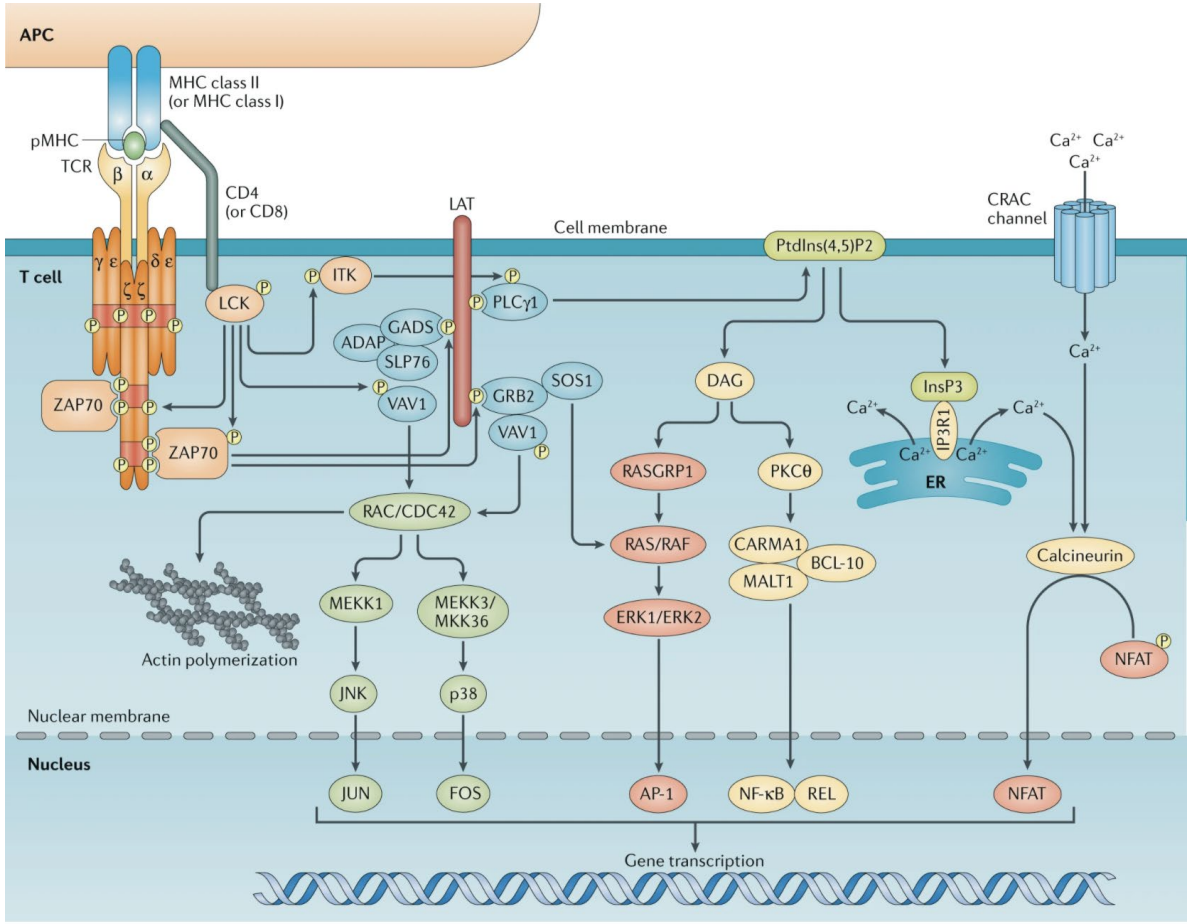




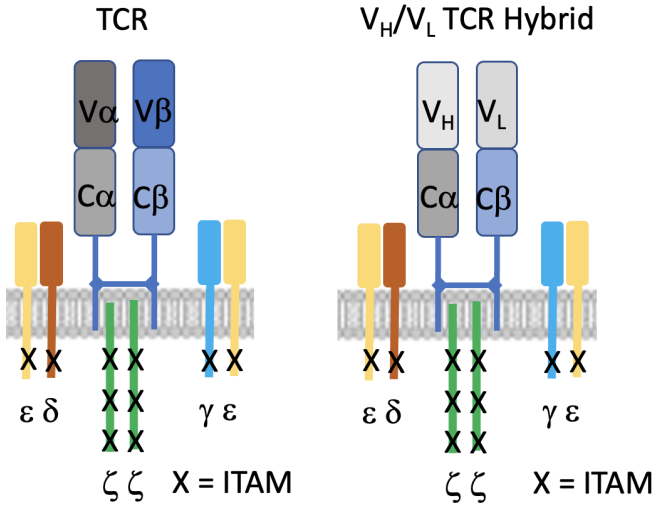
Salter et al Science Signaling, in revision



Engaging the TCR signaling apparatus with CAR/TCR hybrid receptors

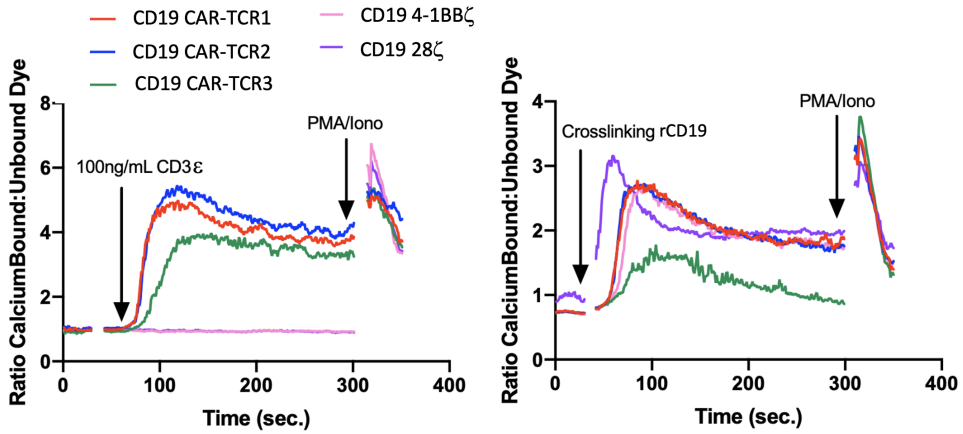


Gaud et al Nature Reviews Immunology, 2018

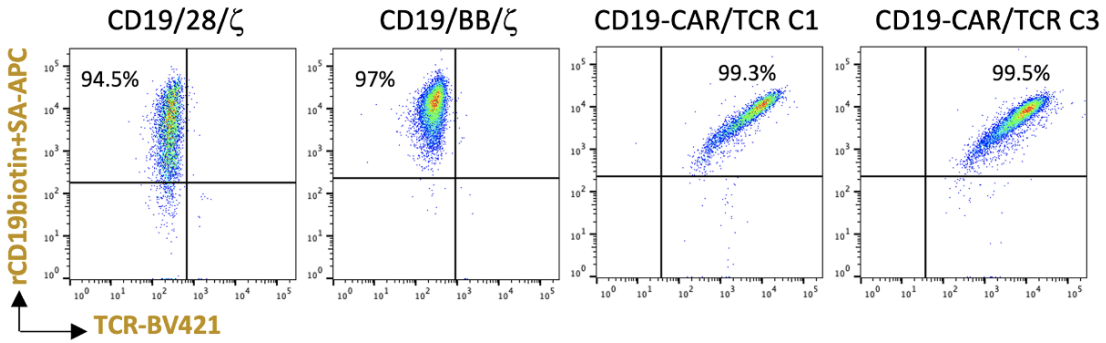


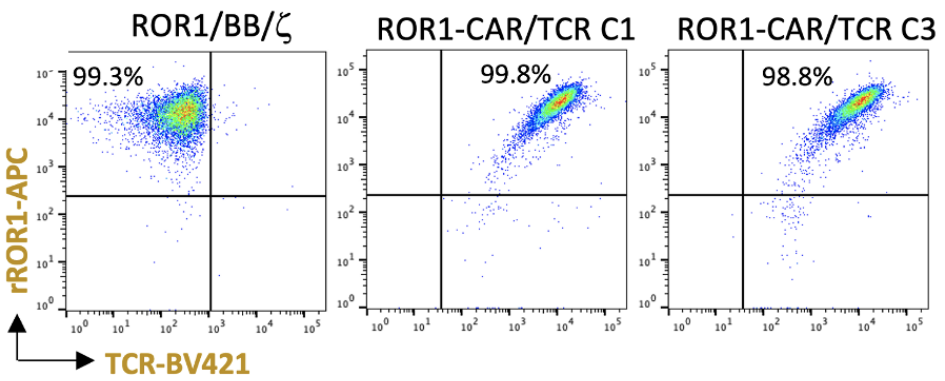
Requires KO of endogenous TCRα and TCRβ to optimize expression and prevent mispairing

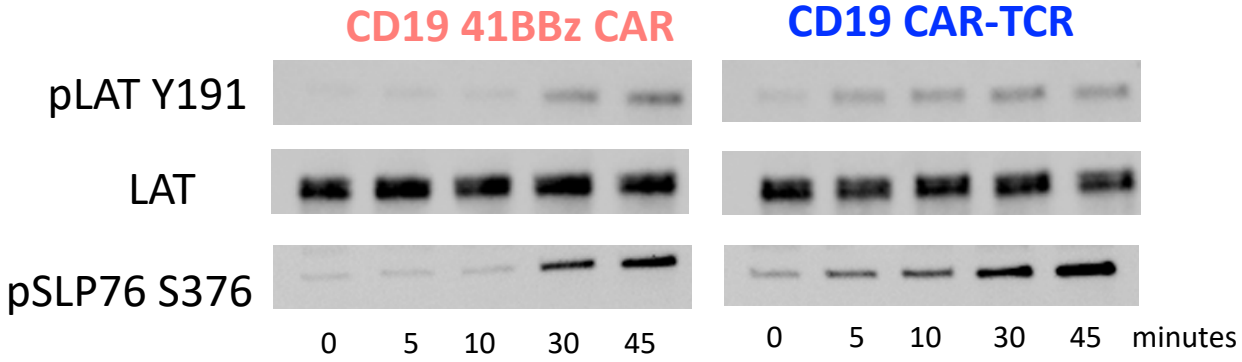
Liu Y et al Science Transl Med, 2021 (Chimeric STAR receptors)

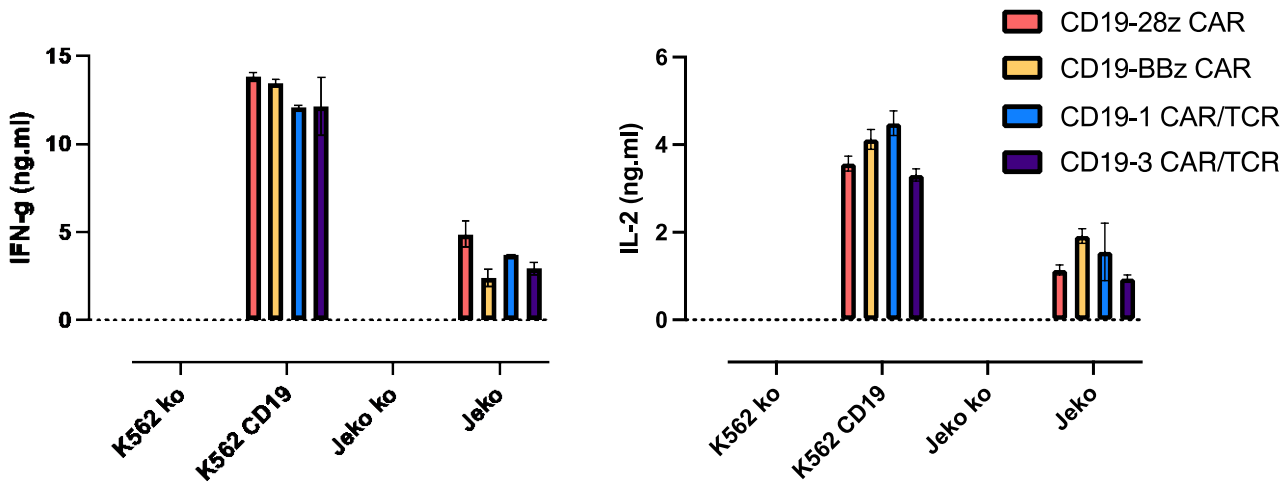


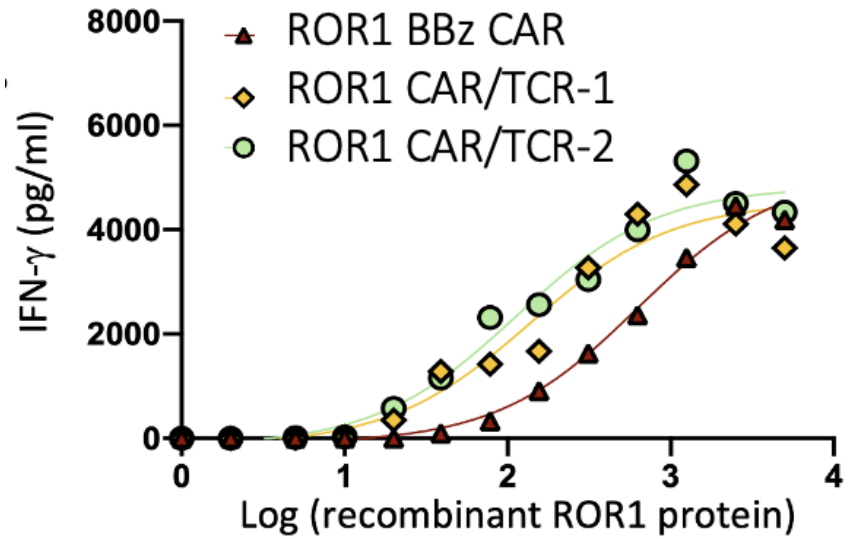
CAR/TCR hybrid receptors are expressed in primary T cells, efficiently activate LAT induce similar levels of cytokines, and exhibit superior antigen sensitivity



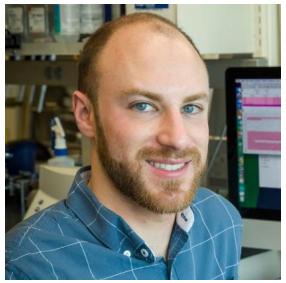


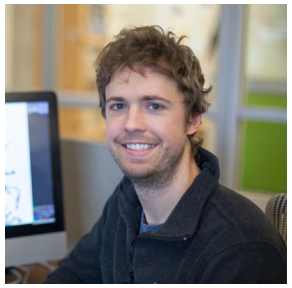


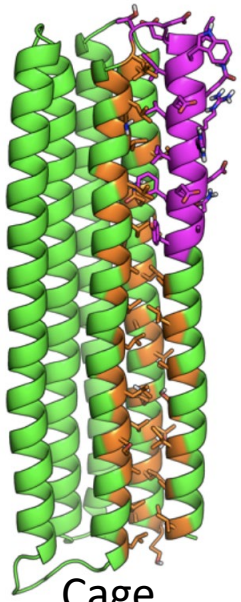




Logic Gating With Co-Localized Orthogonal Latch Key Proteins (Co-LOCKR)

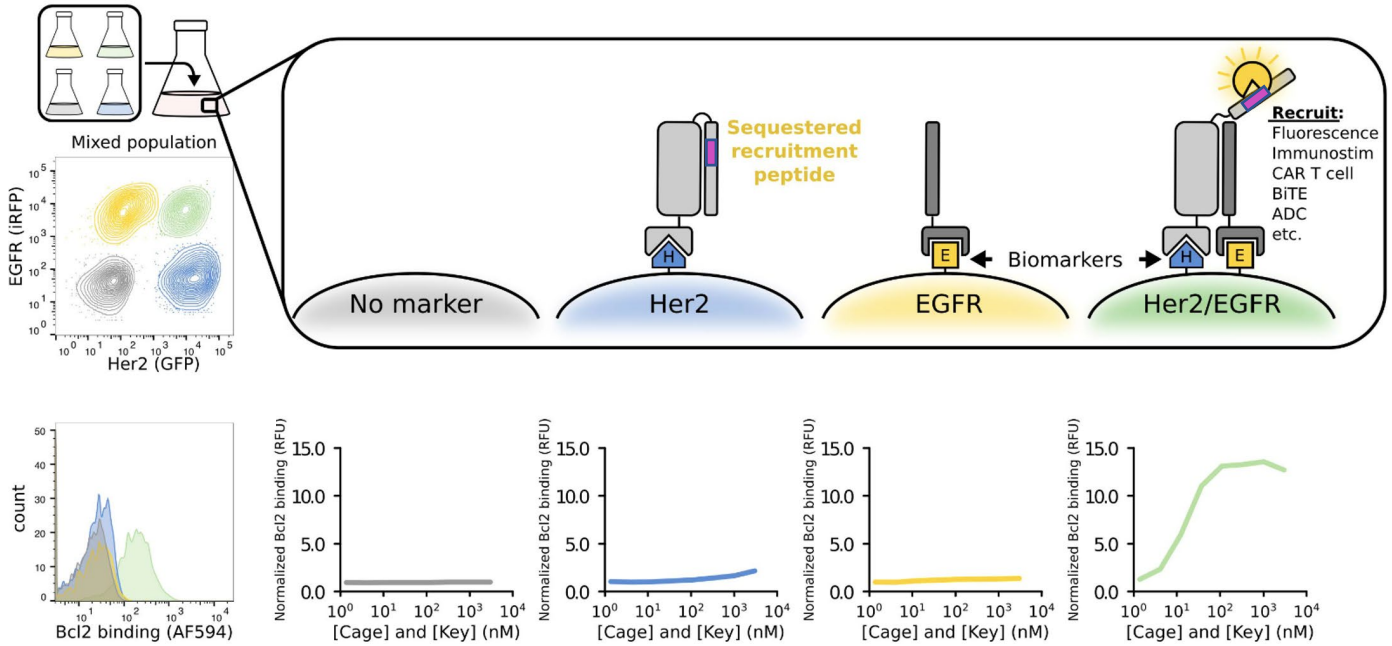






Cage
(bim – Magenta)

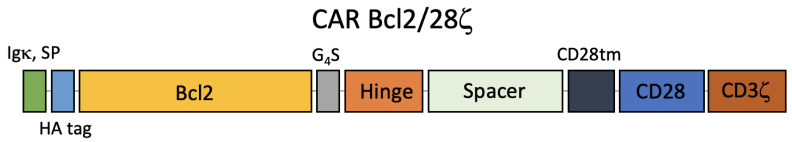

Key

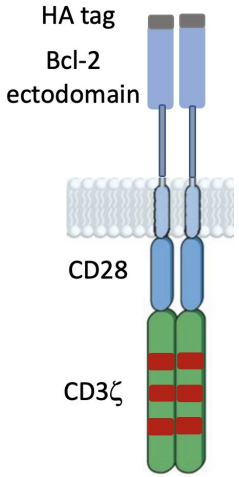
Cage and Key proteins do not associate in solution
Cage and Key can be colocalized by linking to Darpin or ScFv binding domains
Colocalization results in the Key displacing the latch and exposing the bim peptide

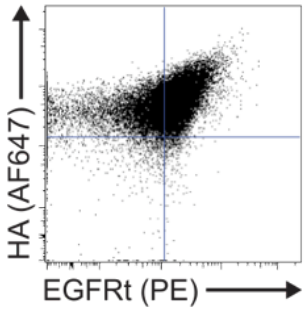


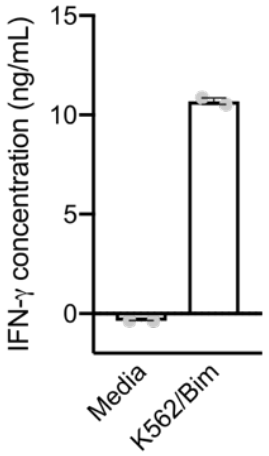
Lajoie et al Science, 2020

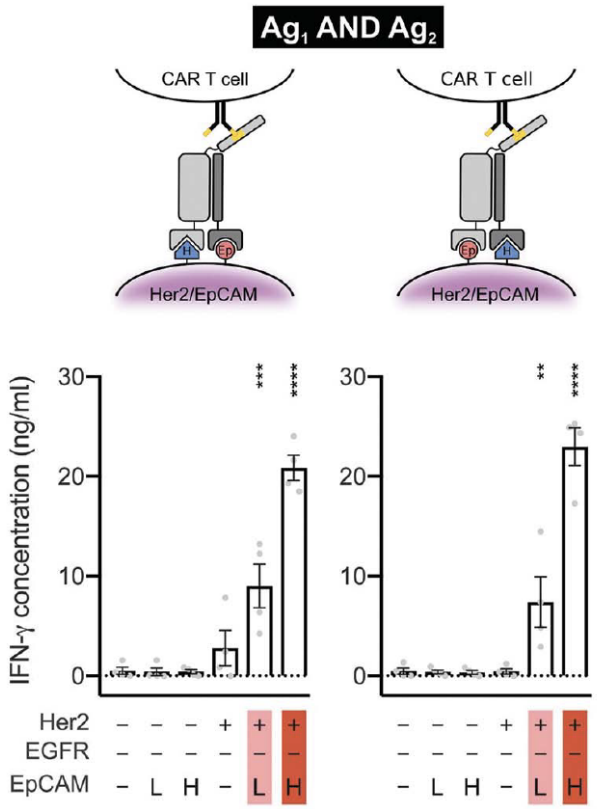
Co-LOCKR can instruct CAR-T cells in AND, OR and NOT logic

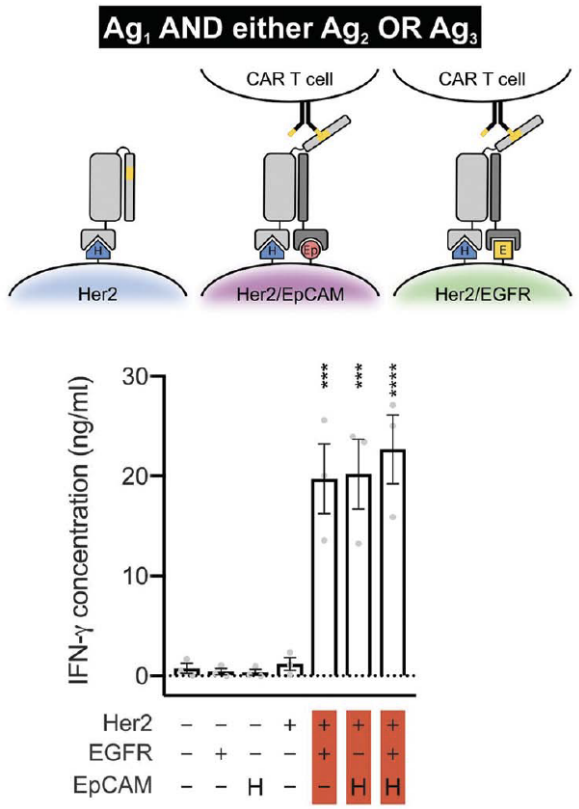


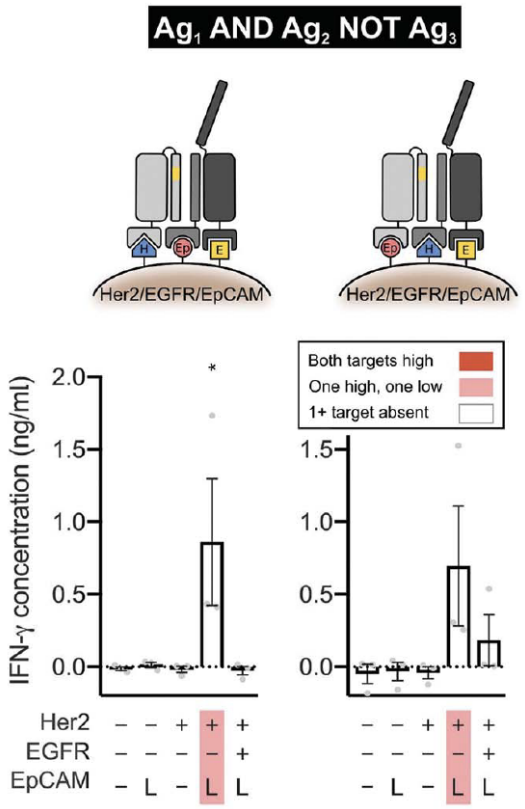






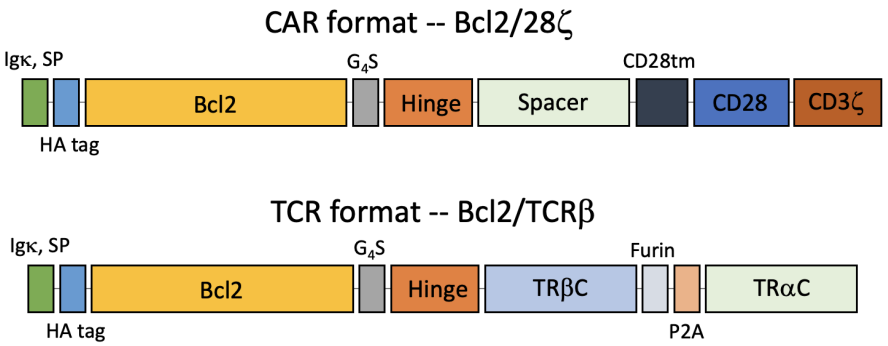


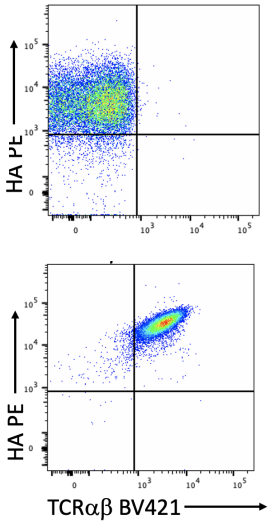


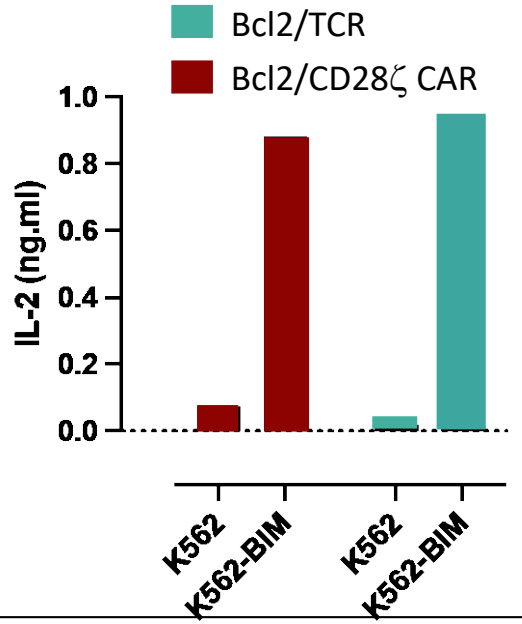


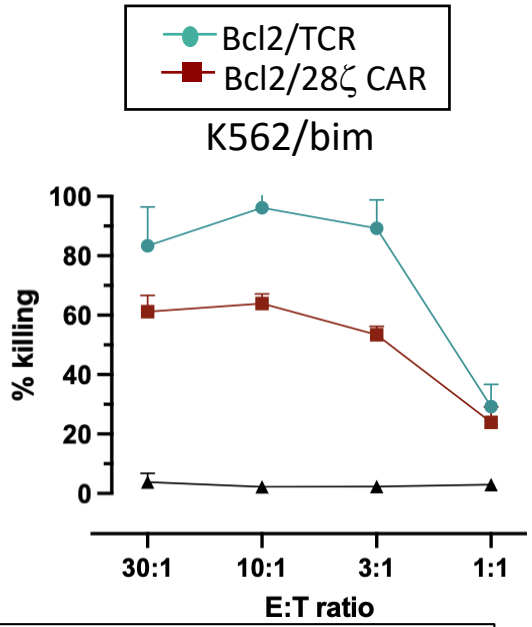
Lajoie et al Science, 2020

Bcl-2 TCR receptor format is highly functional and may provide greater sensitivity and specificity than bcl-2 CARs

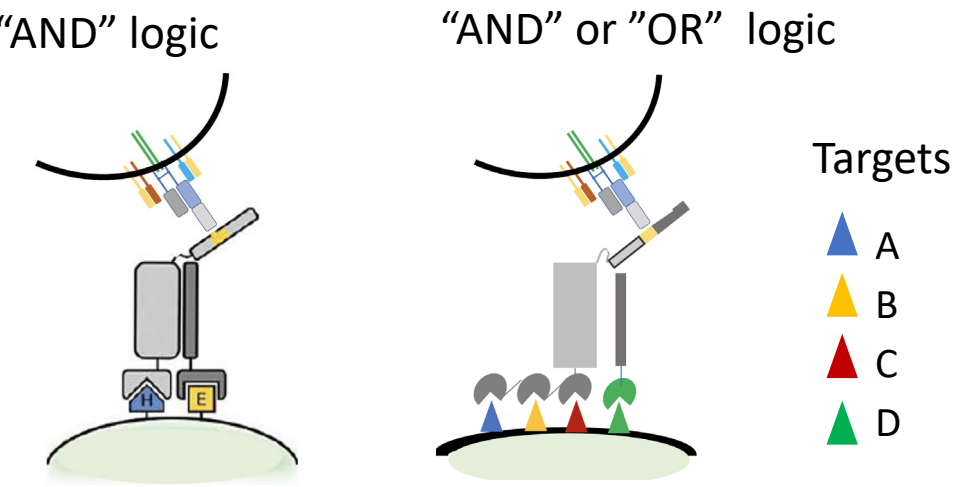








Instructing a single T cell product in complex logic to overcome normal tissue expression and tumor heterogeneity



Summary

The pillars of successful cellular therapies for cancer:

- Understanding the biology of the cell products that are administered
- Elucidating and overcoming the barriers at sites of tumor
- Providing precise and comprehensive recognition of tumor cells with natural, synthetic or enhanced receptors or cellular products

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Patients and their families