Genetic manipulation of antitumor T cells to elicit durable clinical response in adoptive immunotherapy

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Disclosure Information

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Yuki Kagoya

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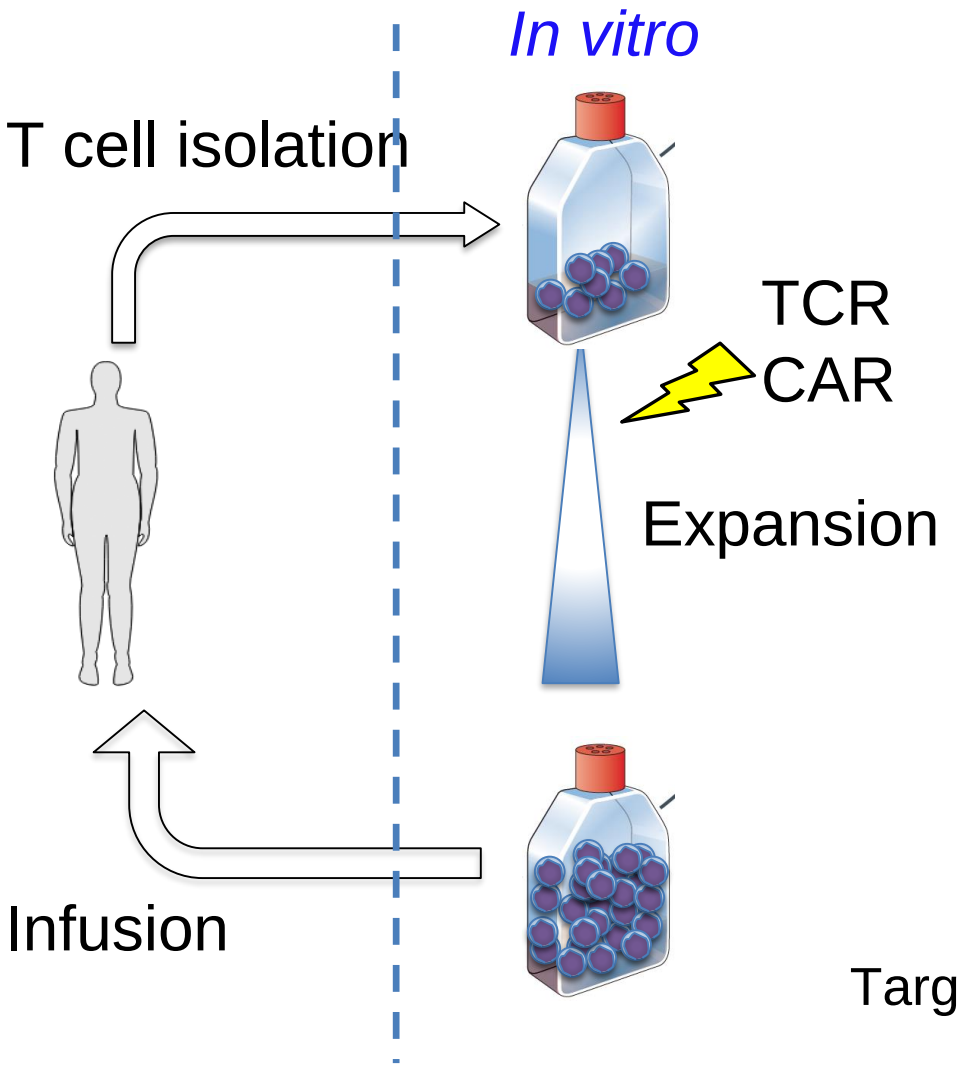
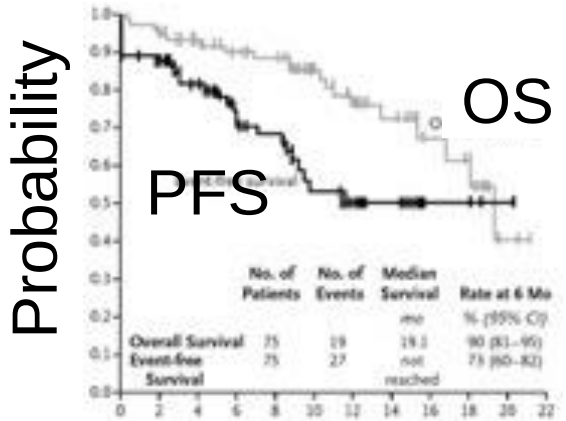
- and -

I will not discuss off label use and/or investigational use in my presentation.

Adoptive cancer immunotherapy



CD19 CAR-T cell for B-ALL

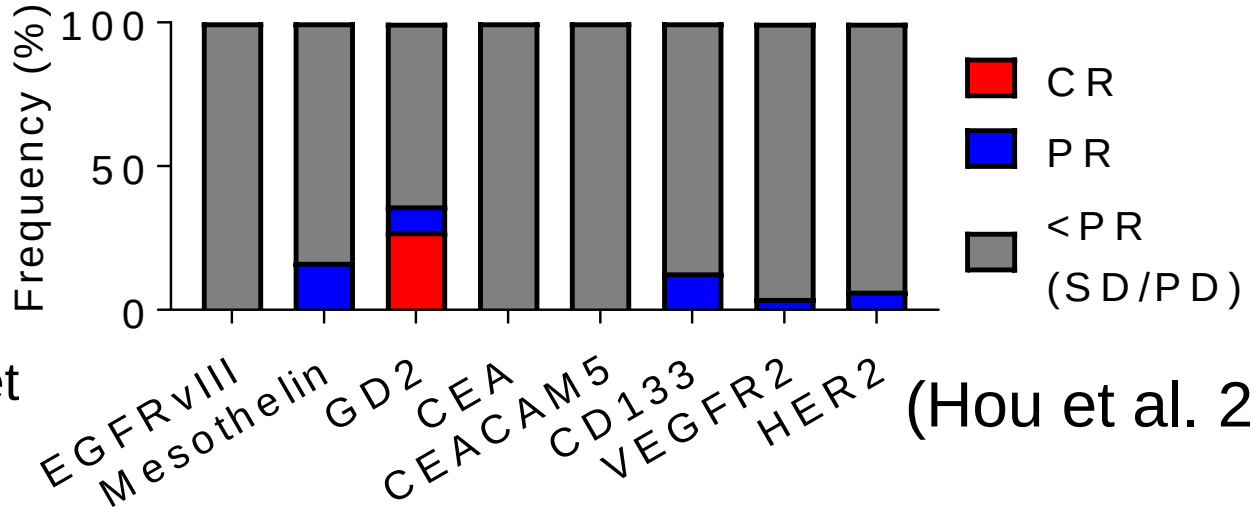


CR: 81%

OS: 90% (6 months)

(Maude et al. 2018)

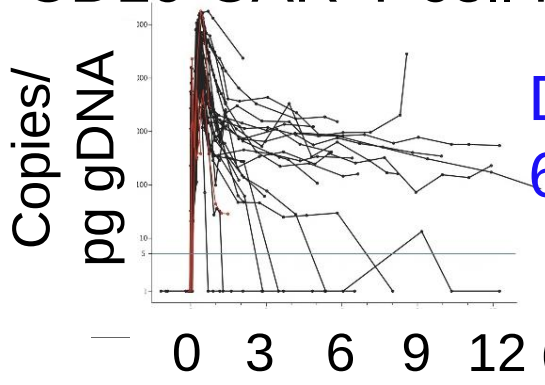
CAR-T cell for solid tumor



(Hou et al. 2019)

Poor persistence of infused antitumor T cells for solid tumor

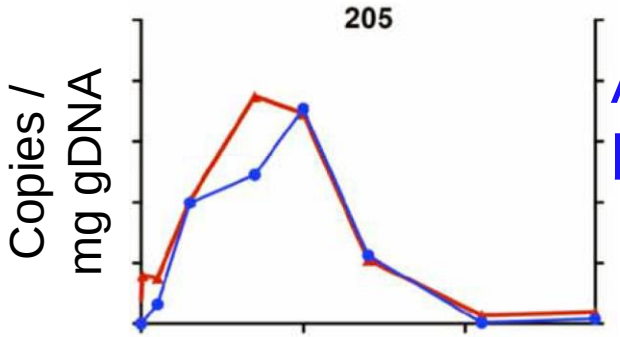
CD19 CAR-T cell for B-ALL



Detectable in
68% of Pts at 6m

(Maude et al. 2014)

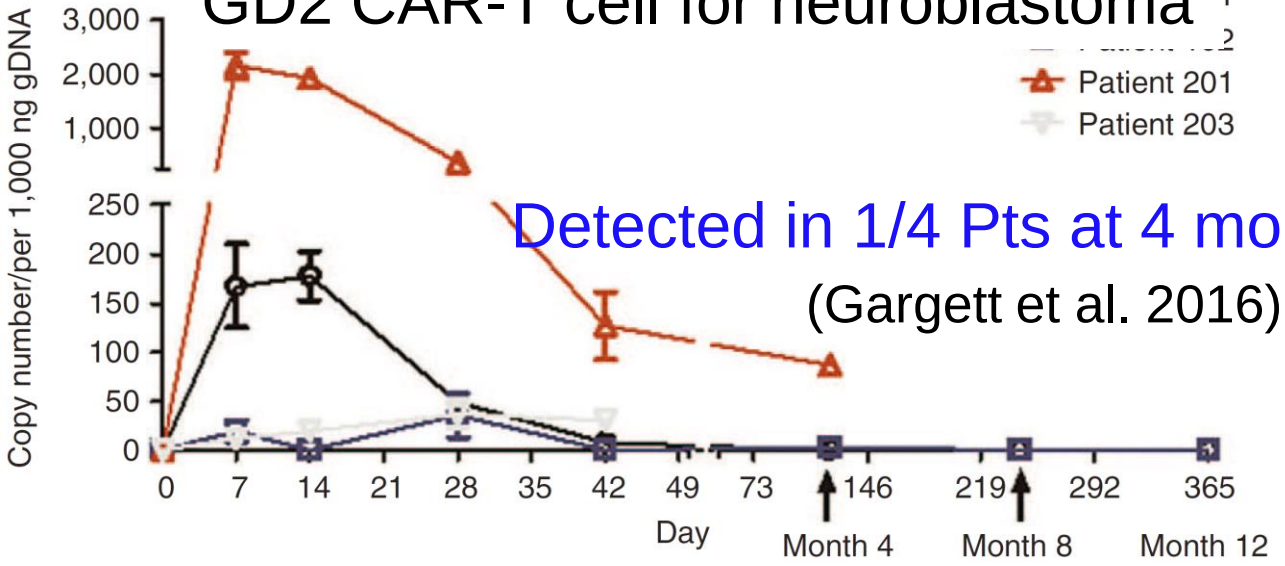
EGFRvIII CAR-T cell for glioblastoma



All disappeared
by 28 days

(O'Rourke et al. 2017)

GD2 CAR-T cell for neuroblastoma



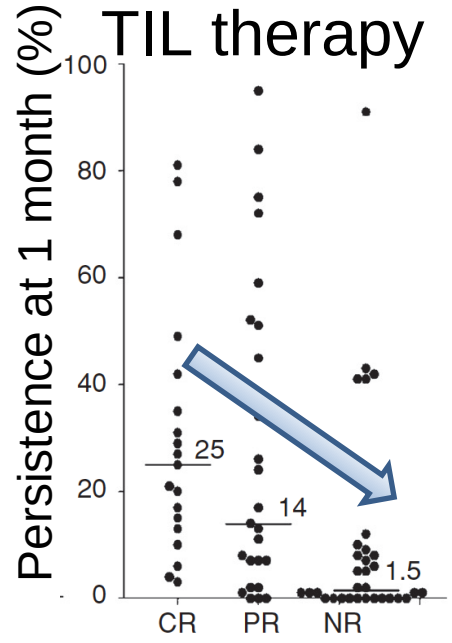
Detected in 1/4 Pts at 4 mo.

(Gargett et al. 2016)

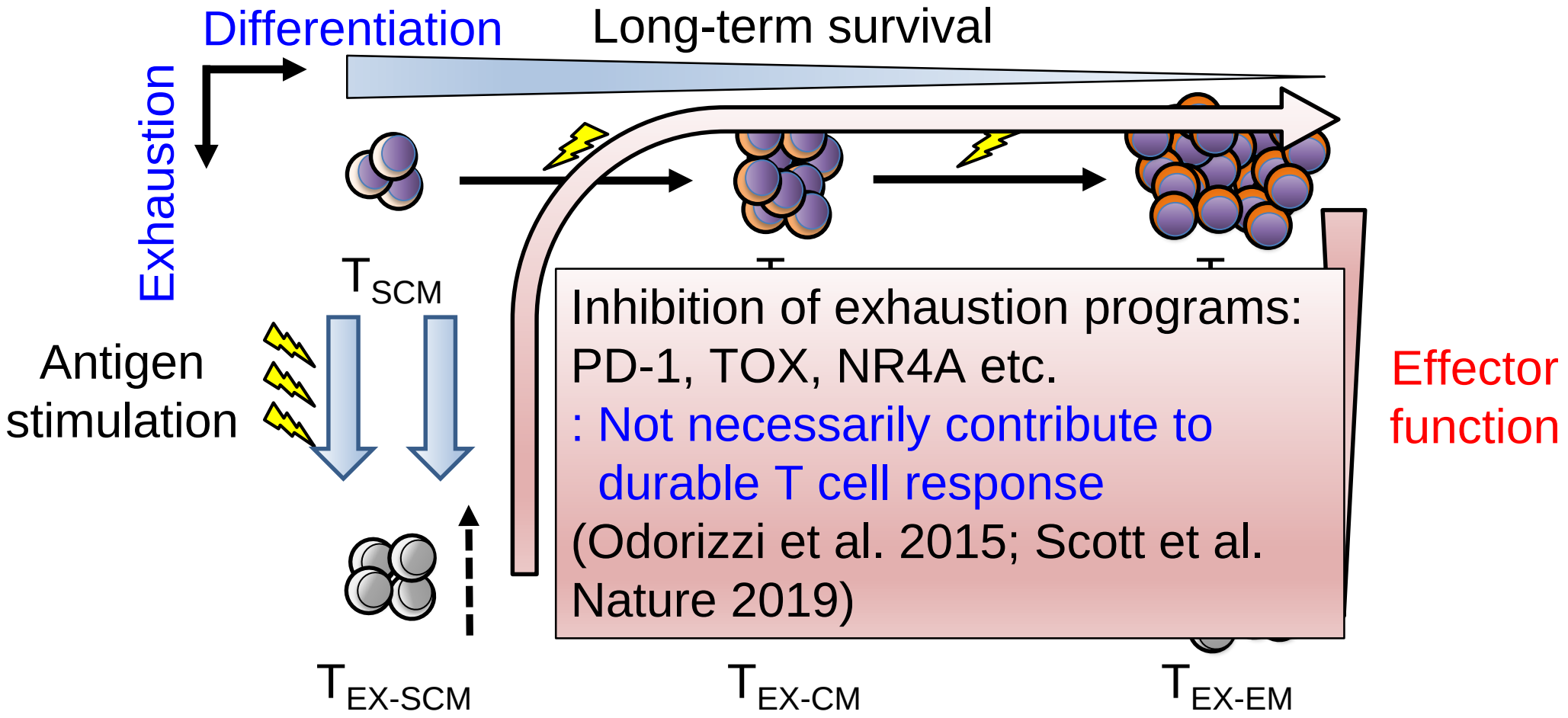
Persistence was
correlated with
treatment response

(Rosenberg et al.
Clin Cancer Res 2011)

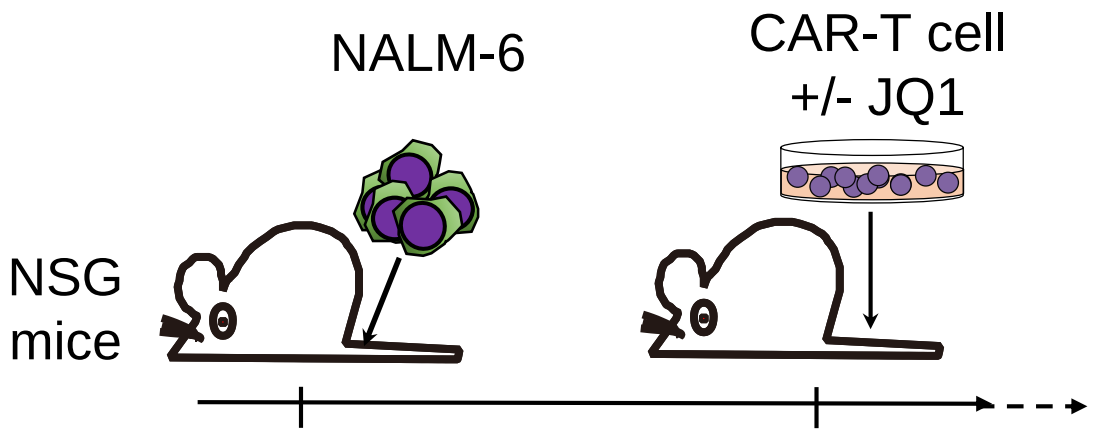
TIL therapy

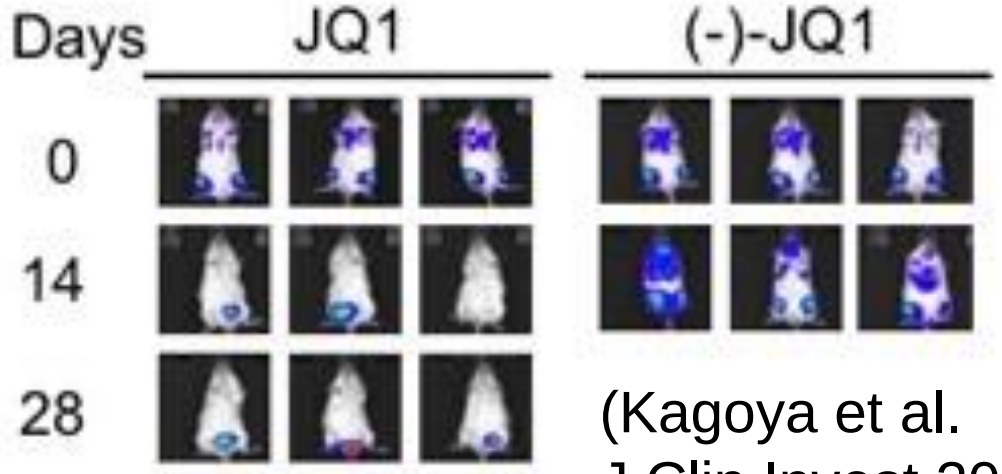


Factors to determine durable antitumor response: T cell differentiation and exhaustion

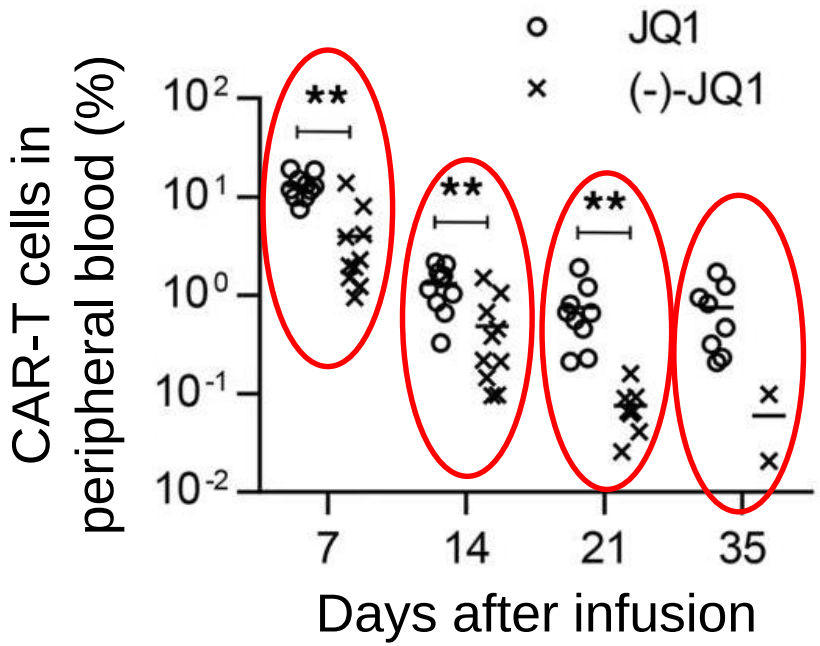


Suppression of effector programs *in vitro* enhances T cell persistence *in vivo*





(Kagoya et al.
J Clin Invest 2016)



JQ1 treatment increased CAR-T cell persistence early after infusion

→Is it possible to enhance *in vivo* T cell persistence more sustainably?

TET2 ablation promotes T cell survival

LETTER

One of the most frequently mutated genes in T cell lymphoma

https://doi.org/10.1038/s41586-018-0178-z

Disruption of *TET2* promotes the therapeutic efficacy of CD19–targeted T cells

Joseph A. Fraietta[1,2,3,4], Christopher L. Nobles[5], Morgan A. Sammons[6,10], Stefan Lundh[1,2], Shannon A. Carty[2,11], Tyler J. Reich[1,2], Alexandria P. Cogdill[1,2], Jennifer J. D. Morrissette[3], Jamie E. DeNizio[7,8], Shantan Reddy[5], Young Hwang[5], Mercy Gohil[1,2], Irina Kulikovskaya[1,2], Farzana Nazimuddin[1,2], Minnal Gupta[1,2], Fang Chen[1,2], John K. Everett[5], Katherine A. Alexander[6], Enrique Lin-Shiao[6], Marvin H. Gee[9], Xiaojun Liu[1,2], Regina M. Young[1,2], David Ambrose[1,2], Yan Wang[1,2], Jun Xu[1,2], Martha S. Jordan[2,3], Katherine T. Marcucci[1,2], Bruce L. Levine[1,2,3], K. Christopher Garcia[9], Yangbing Zhao[1,2], Michael Kalos[1,2,3], David L. Porter[1,2,7], Rahul M. Kohli[5,7,8], Simon F. Lacey[1,2,3], Shelley L. Berger[6], Frederic D. Bushman[5], Carl H. June[1,2,3,4]* & J. Joseph Melenhorst[1,2,3,4]*

Fraietta et al. Nature 2018

Hypothesis: Genetic programs underlying T cell lymphoma development may enhance peripheral T cell survival

Recurrent genetic aberrations in T cell malignancies

PTCL-NOS

Genes	Freq (%)	Function
TET2	46-49	LoF
DNMT3A	27-36	LoF
RHOA	8-18	Complex
FYN	3	GoF
VAV1	11	Active (fusion)
CDKN2A/2B	9	Deletion

ALK-negative ALCL

Genes	Freq (%)	Function
JAK1	15	Active
STAT3	10	Active
TET2	33	LoF
DNMT3A	16	LoF
DUSP22	30	Downregulated
PRDM1	56	Deletion

Extranodal NK/T cell lymphoma

Genes	Freq (%)	Function
TP53	18-24	LoF
JAK3	35	Active
DDX3X	20	LoF
STAT3	6	Active
STAT5B	6	Active

AITL

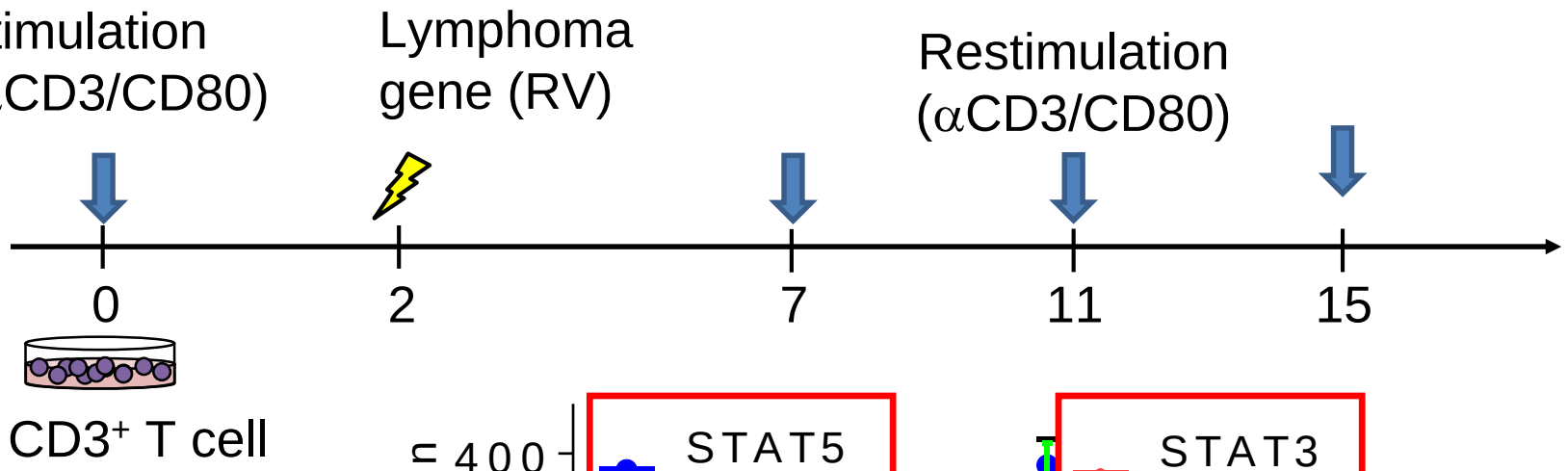
Genes	Freq (%)	Function
TET2	76-83	LoF
DNMT3A	26-38	LoF
RHOA	50-71	LoF
IDH2	20-45	LoF/GoF

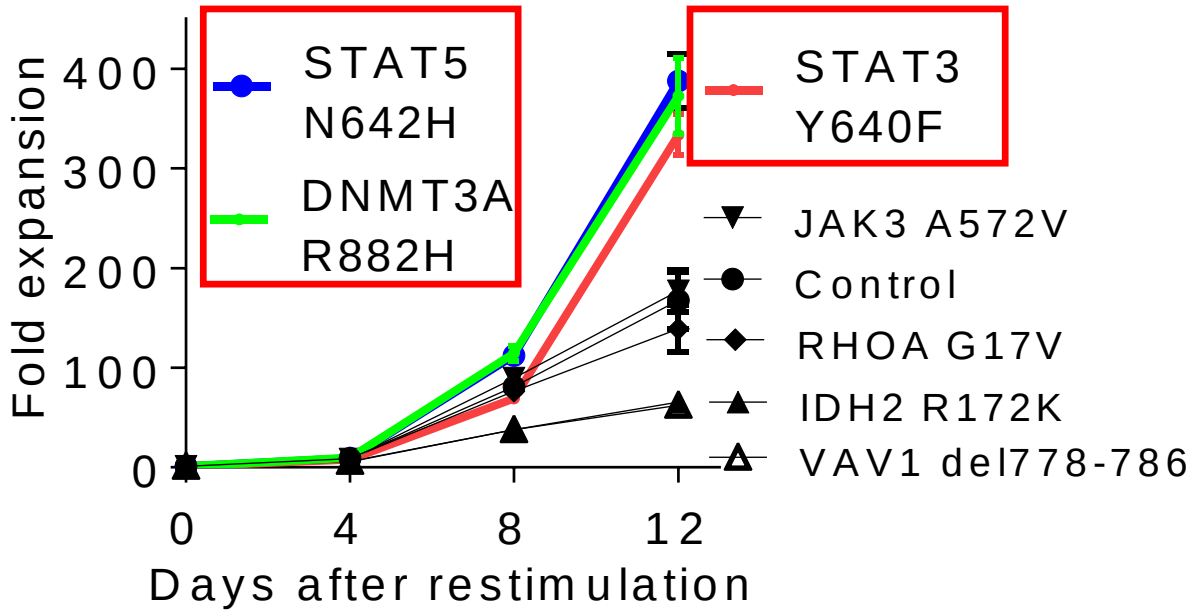
(Sandell et al. 2017)
(Keersmaecker et al. 2013)

Exploration of lymphoma genes to improve CAR-T cell function

Lymphoma genes	P2A	ΔNGFR

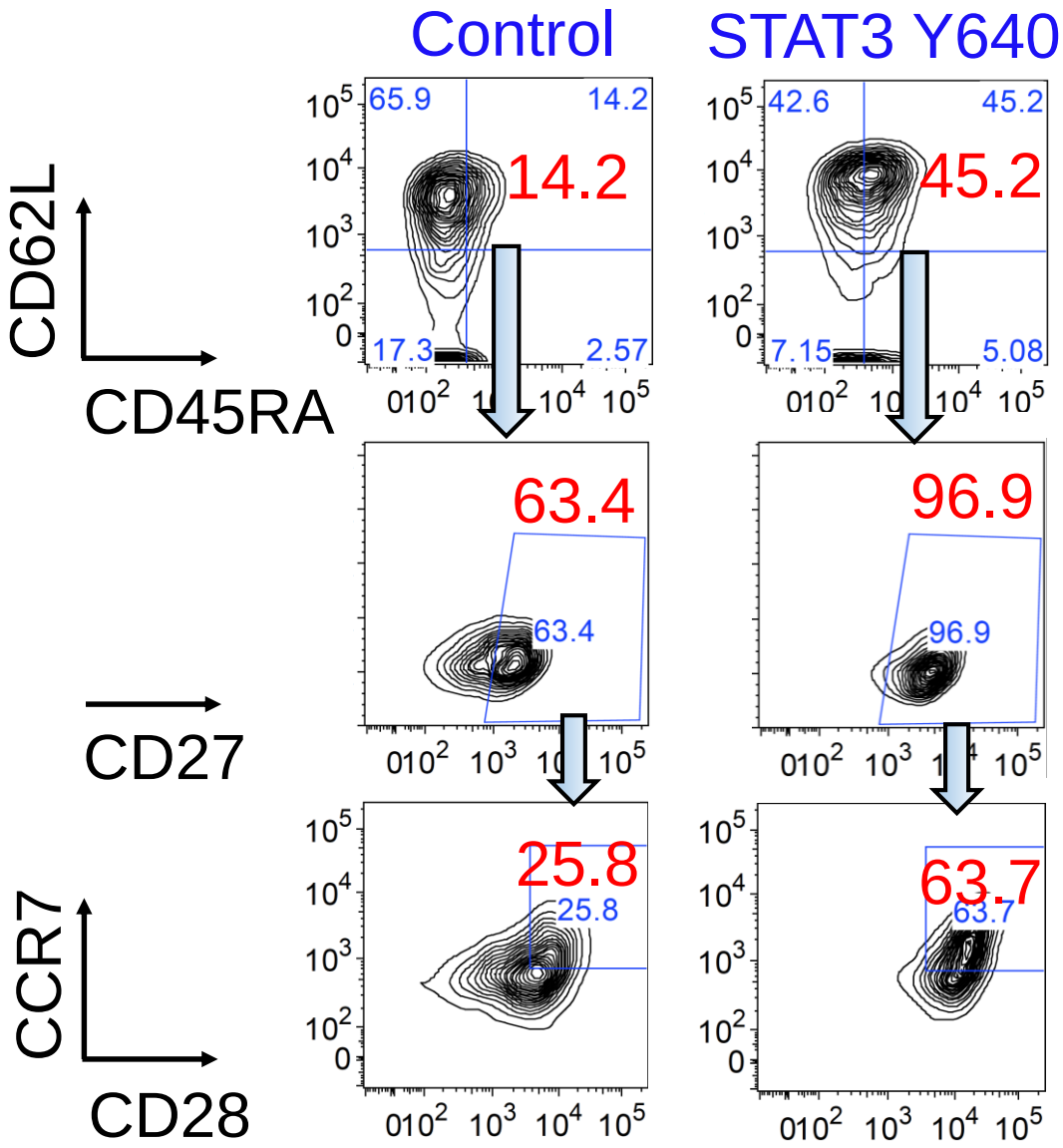
- *DNMT3A* R882H
- *IDH2* R172K
- *JAK3* A572V
- *RHOA* G17V
- *STAT3* Y640F
- *STAT5* N642H
- *VAV1* Δaa778-786

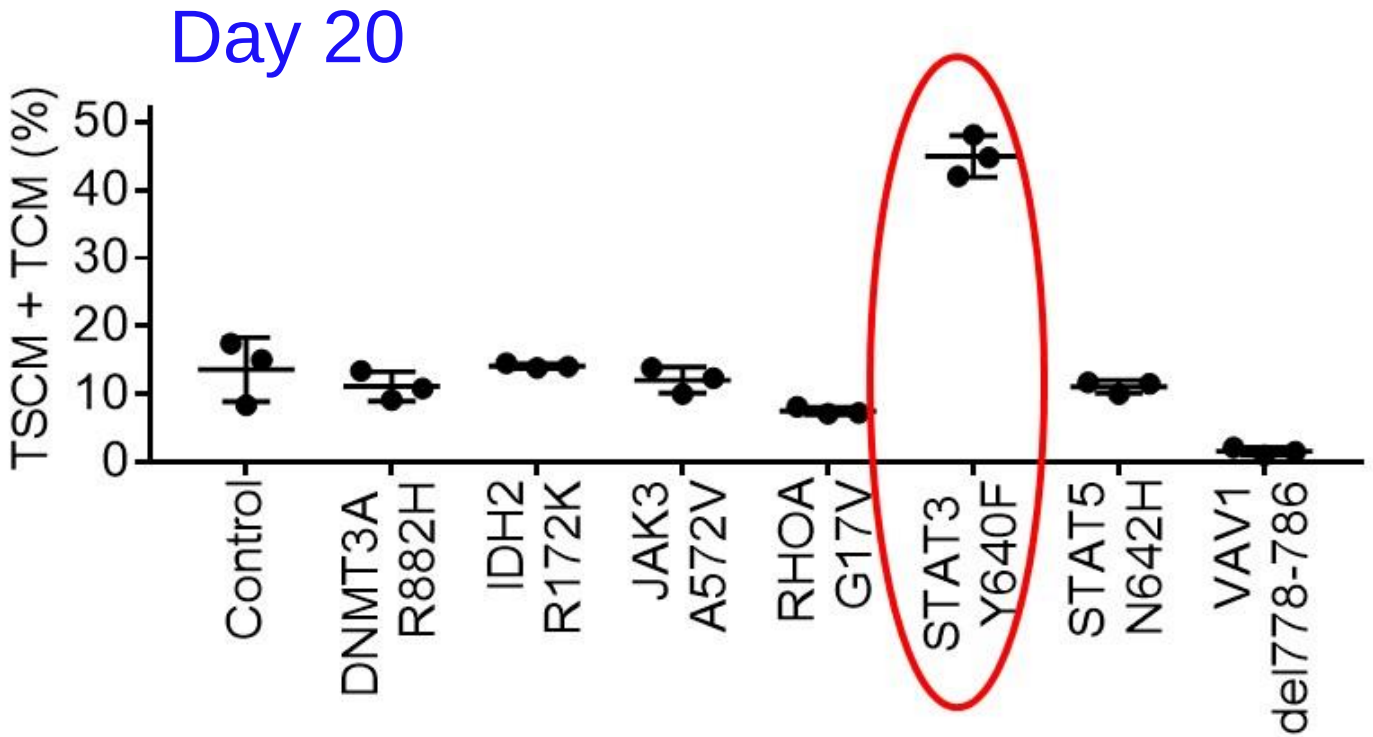




DNMT3A, STAT3, STAT5 mutations enhanced T cell proliferation

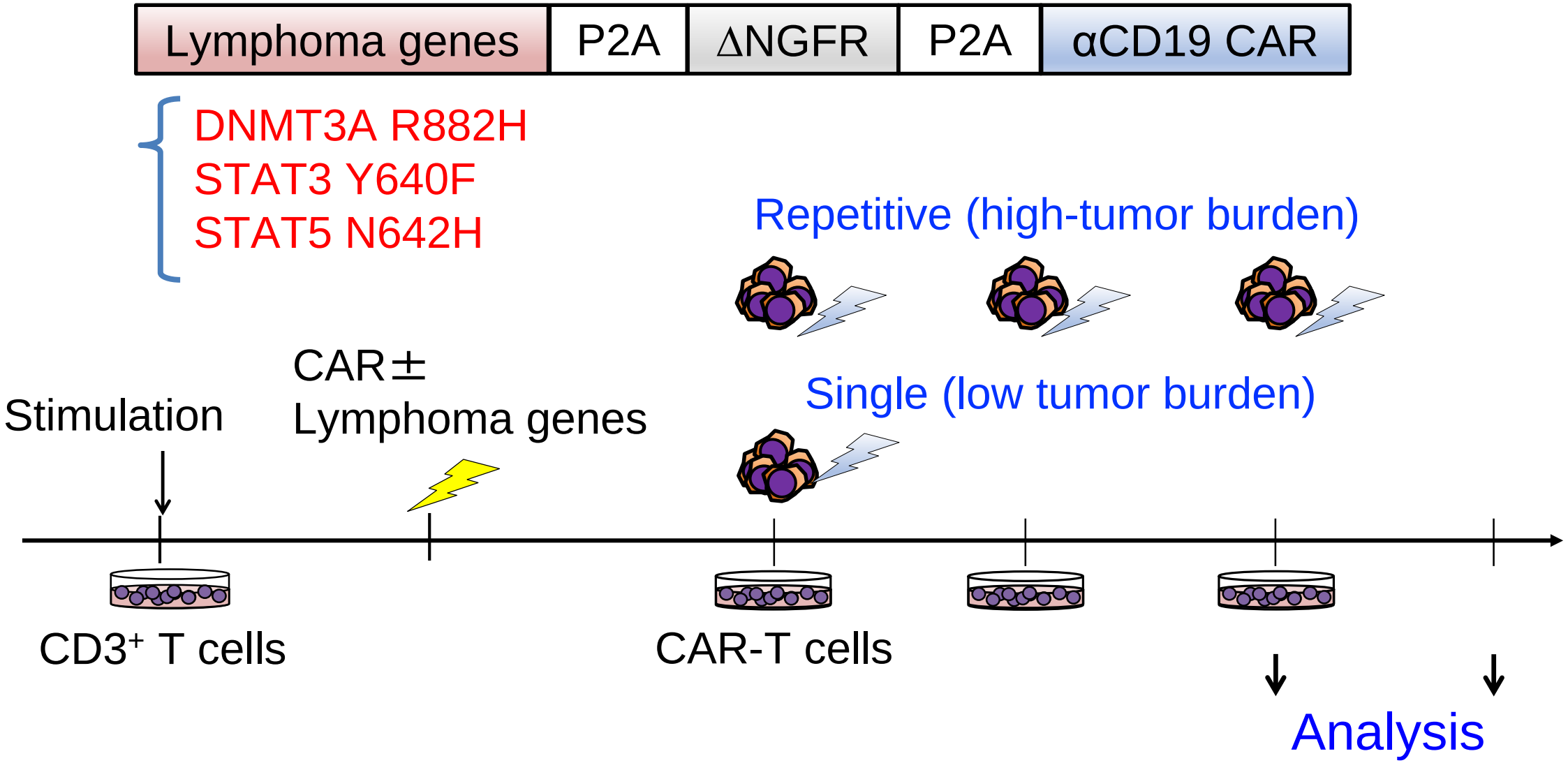
STAT3 activation helps maintain an early memory phenotype





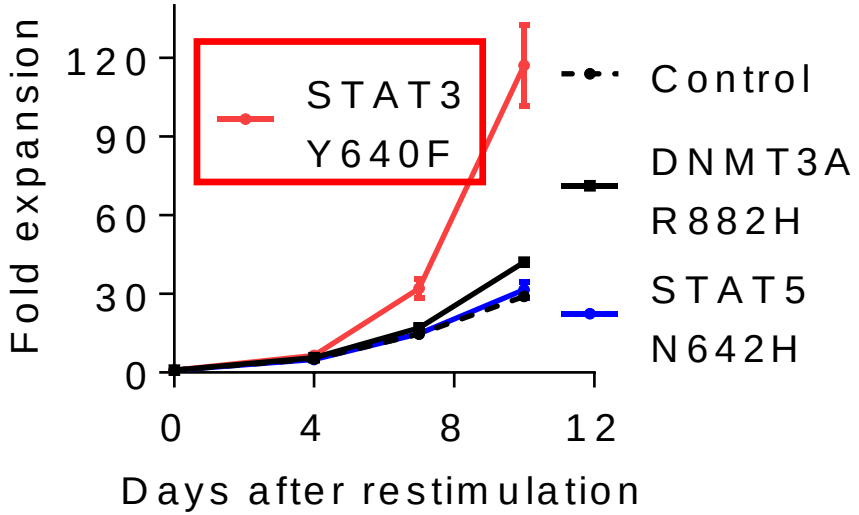
→STAT3-activated memory T cells acquire enhanced self-renewal

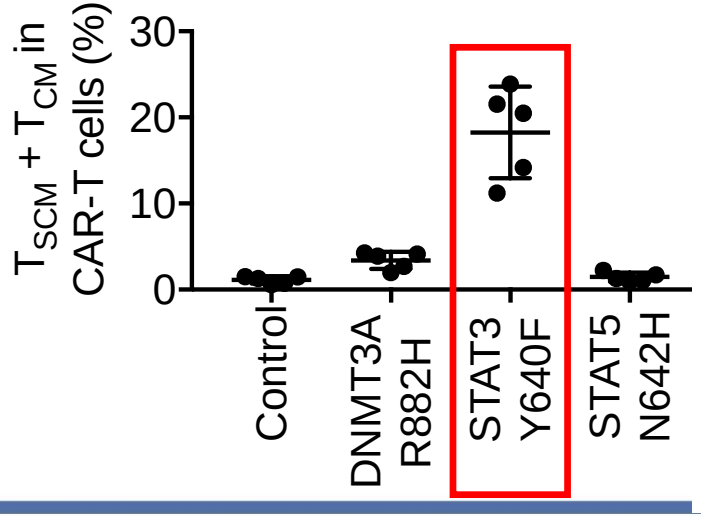
Generation of CAR-T cells expressing oncogenes

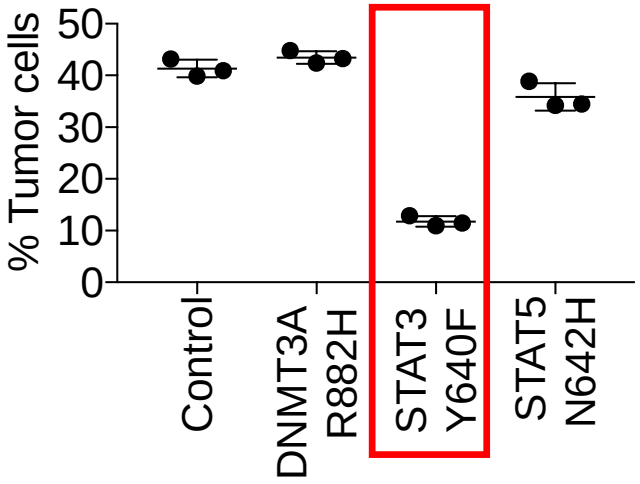


STAT3 and STAT5 differentially regulate T cell function

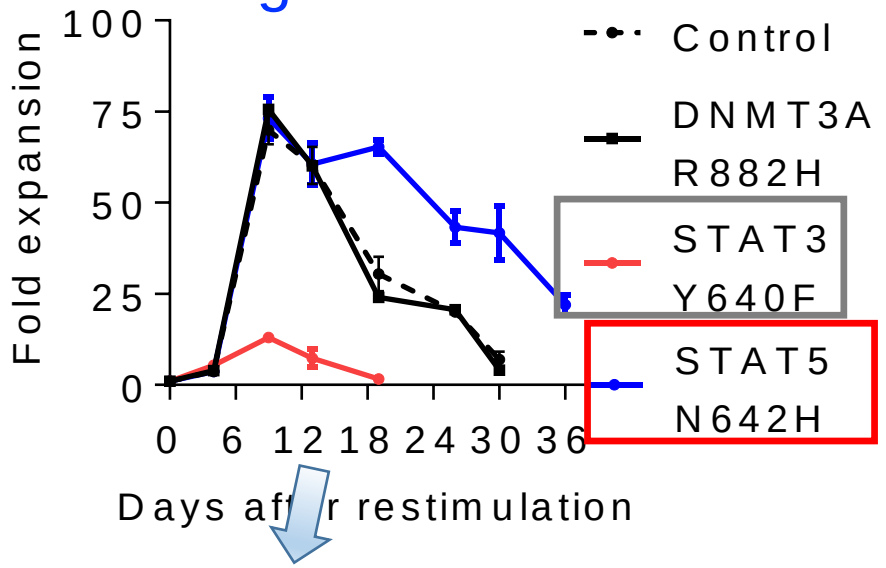
Repetitive stimulation

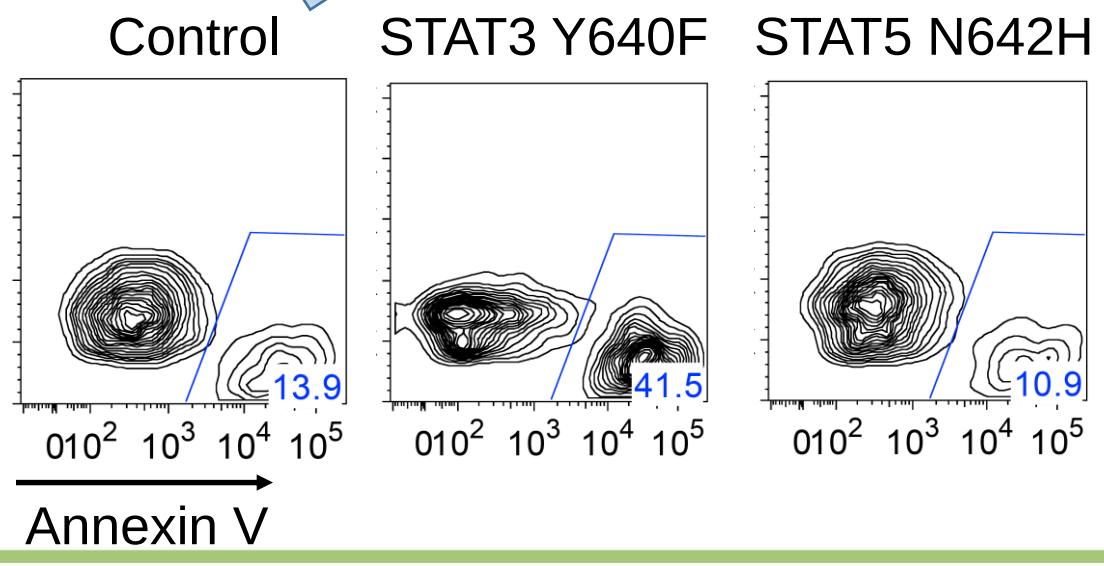




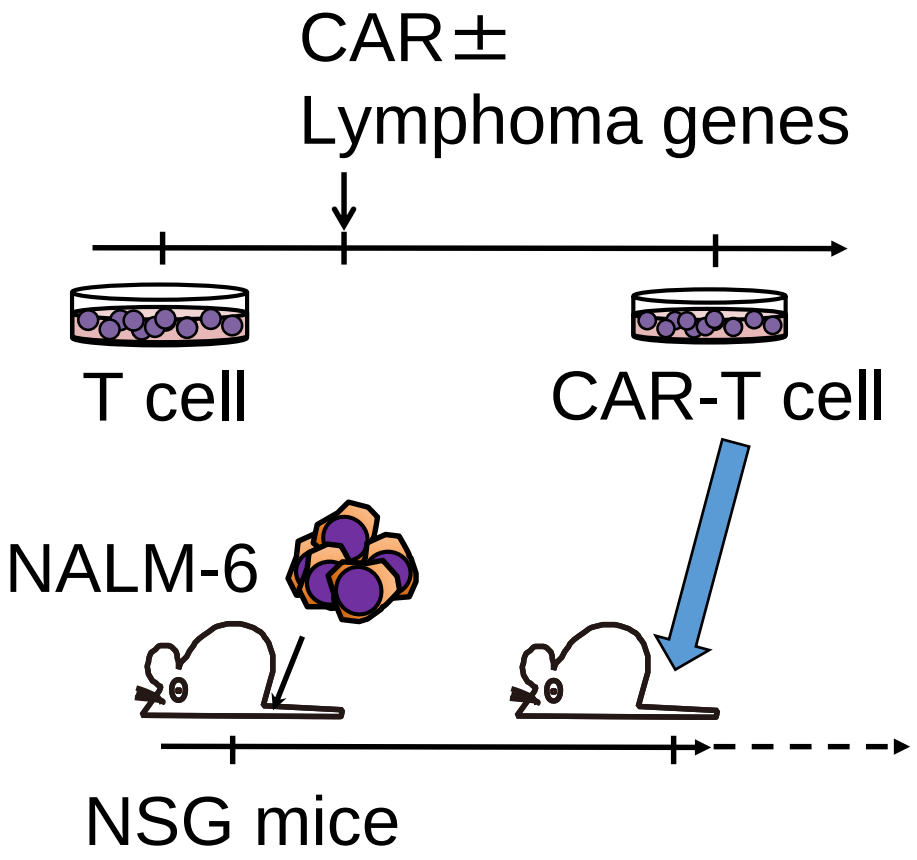


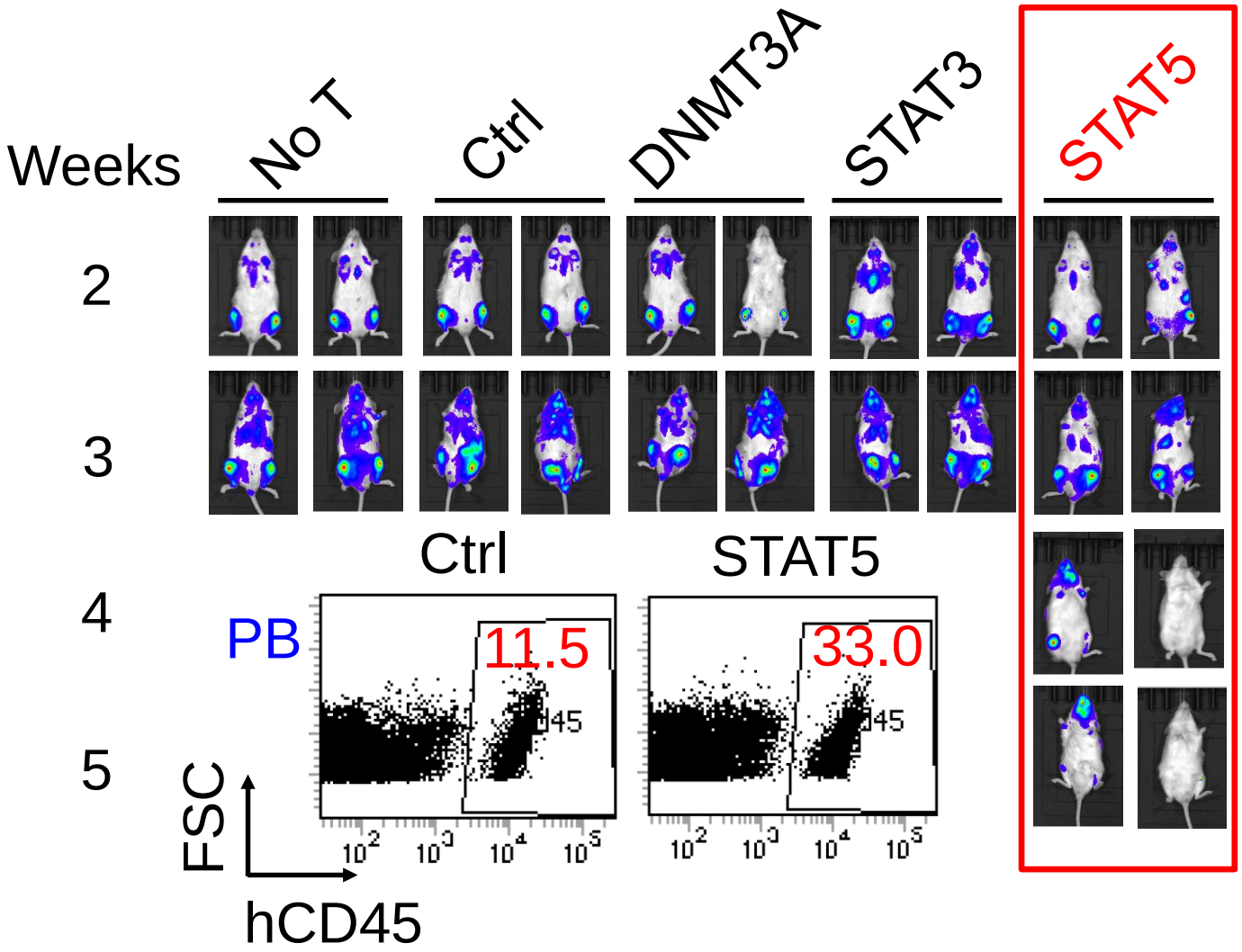
Single stimulation



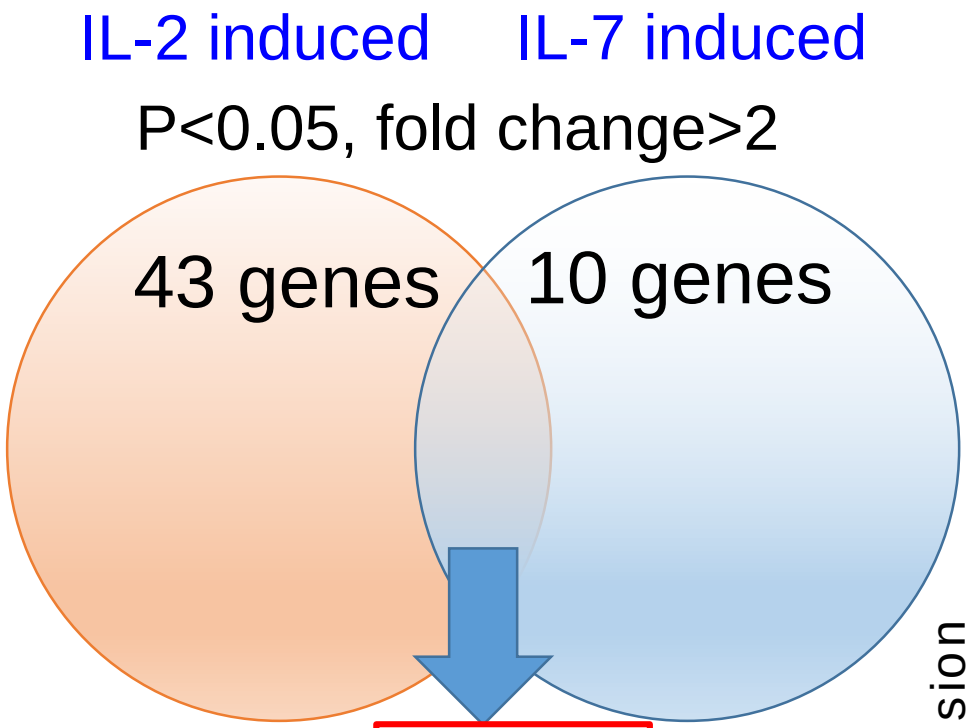


STAT5 activation elicits superior *in vivo* antitumor response



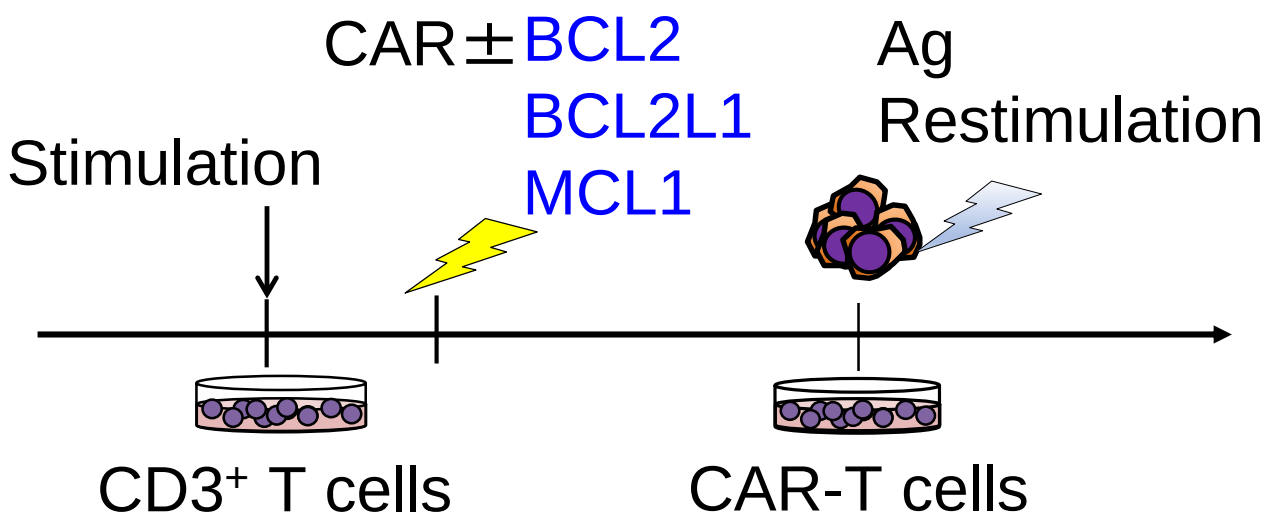


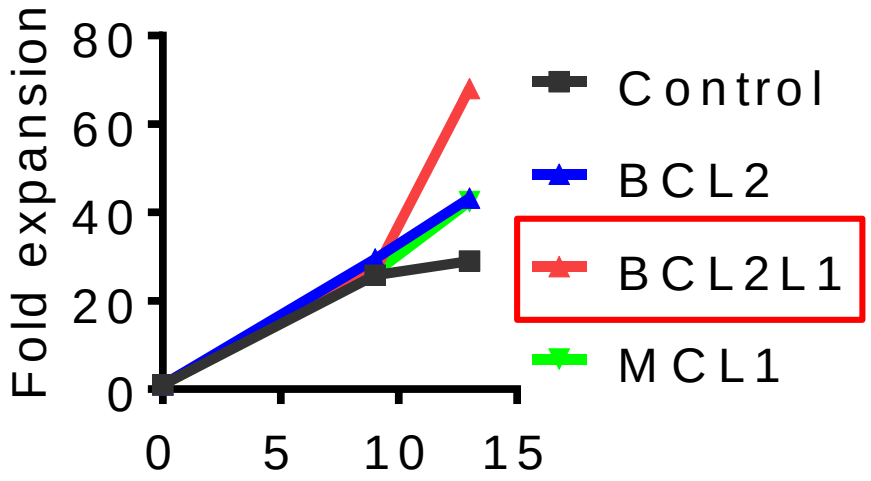
Downstream targets of STAT5



GSE58262

Nfil3
Prdm1
Bcl2
Bcl2l1





BCL2L1 was most effective to promote T cell proliferation

Summary and ongoing directions

- Genetic programs in T cell lymphoma enhance long-term CAR-T cell proliferation
  - STAT5 and its downstream genes (BCL2 family genes) are promising targets so far

- STAT3 activation confers unique properties to antitumor T cells
  - What are the responsible target genes?
  - Helpful in the context of high tumor-burden?

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Shuta Shibata

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