

Focus sur les CAR-T cells

Les Ateliers de la Recherche Clinique - RRC OncoPaca-Corse

Mougins- 31/01/19

Pr Thomas Cluzeau

Université cote d'Azur

Service d'hématologie clinique, CHU de Nice

INSERM U1065, Centre méditerranéen de médecine moléculaire



CAR-T cells 1^{ère} génération

Specific activation and targeting of cytotoxic lymphocytes through chimeric single chains consisting of antibody-binding domains and the γ or ζ subunits of the immunoglobulin and T-cell receptors

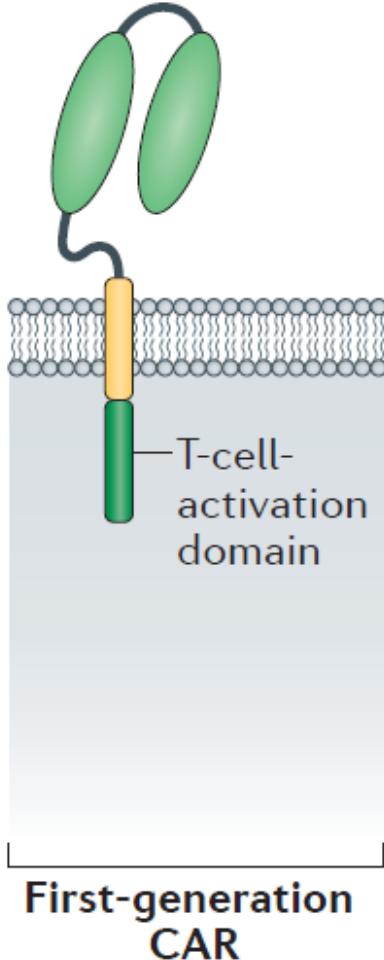
(single-chain Fv domain/chimeric receptors/immunotargeting/T cell)

ZELIG ESHHAR*, **TOVA WAKS**, **GIDEON GROSS†**, AND **DANIEL G. SCHINDLER**

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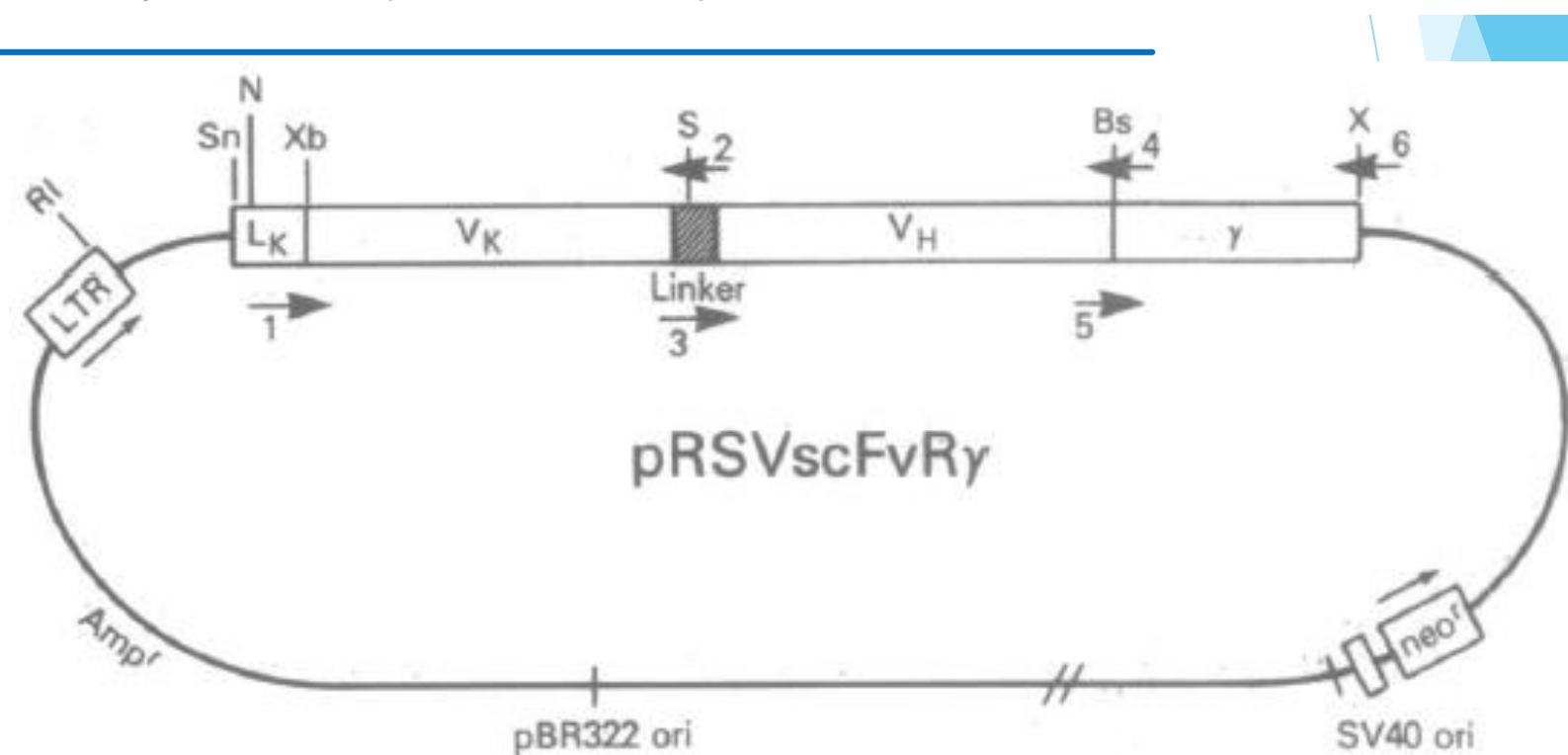
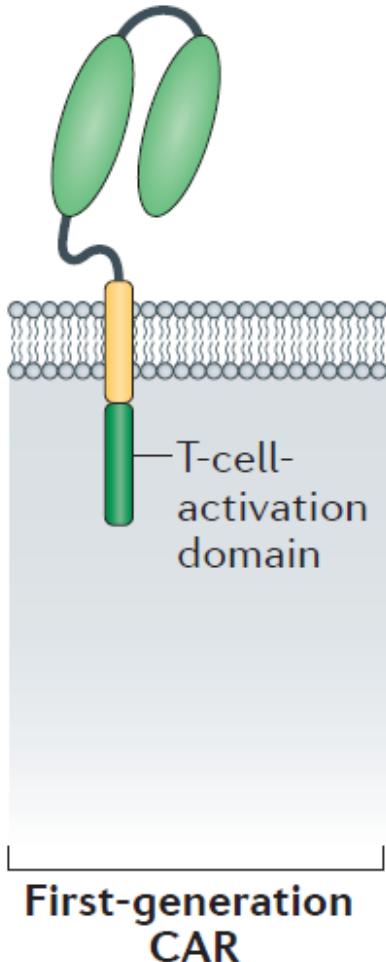
ZELIG ESHHAR*, **TOVA WAKS**, **GIDEON GROSS[†]**, AND **DANIEL G. SCHINDLER**

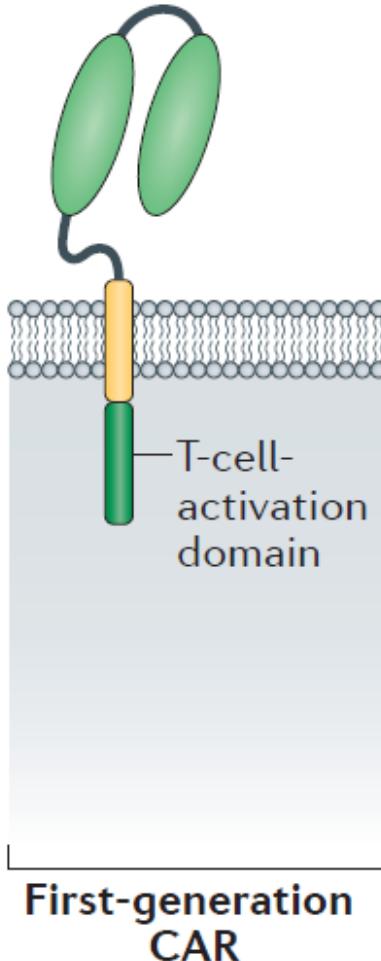


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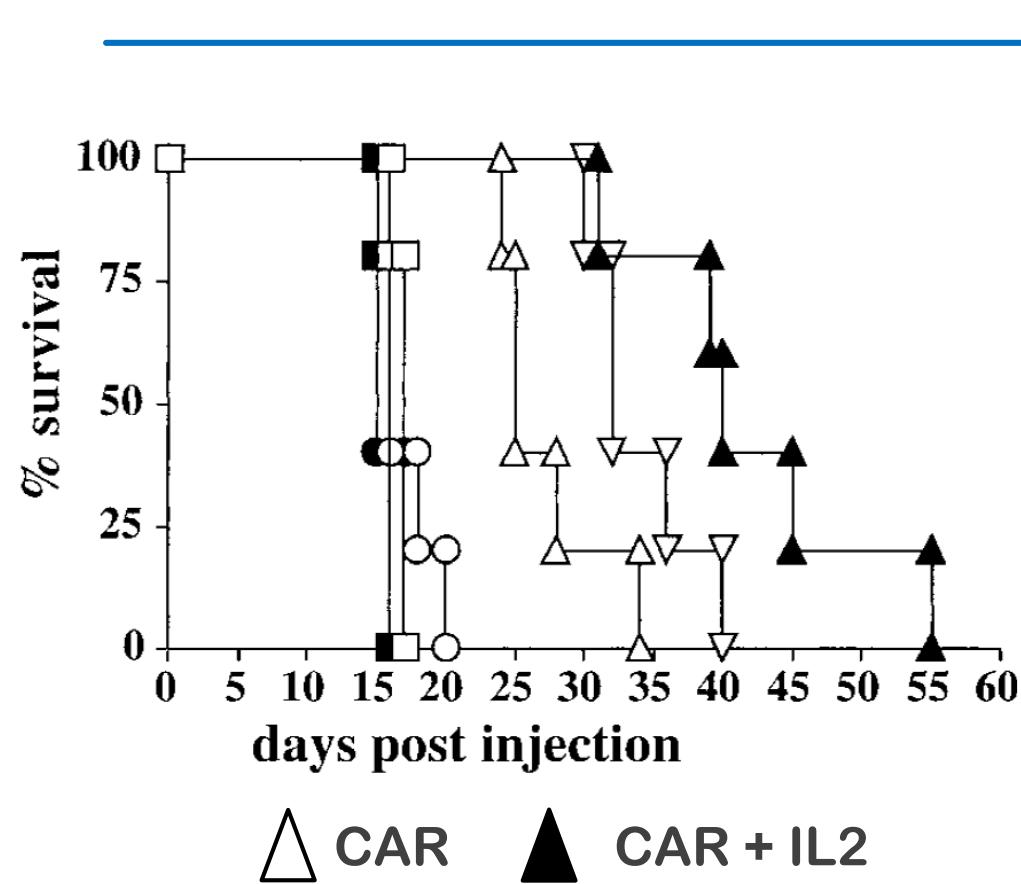
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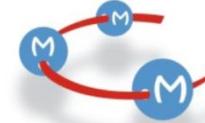




Chimeric Fv- ζ or Fv- ϵ receptors are not sufficient to induce activation or cytokine production in peripheral T cells

Thomas Brocker

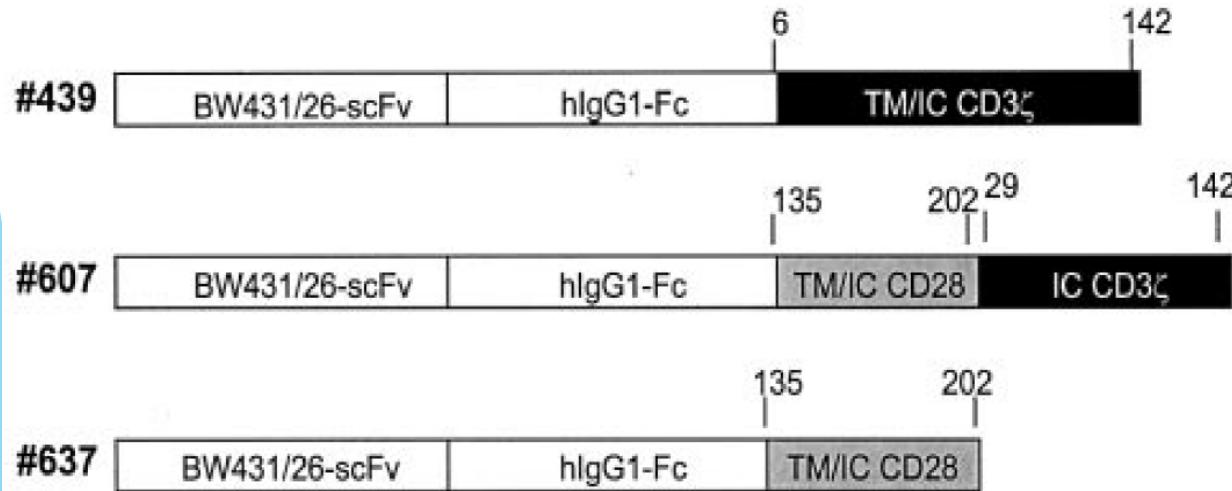




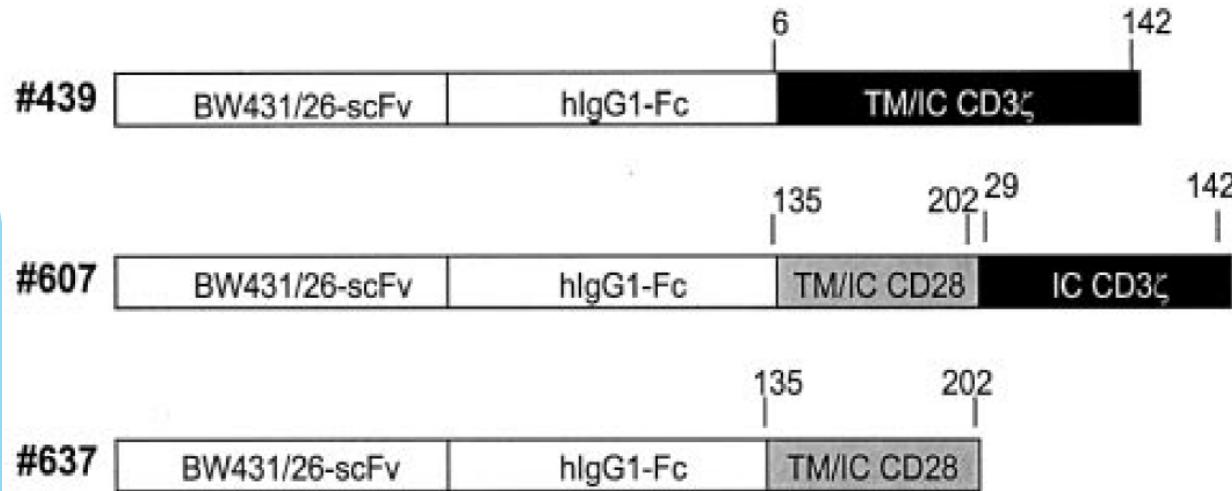
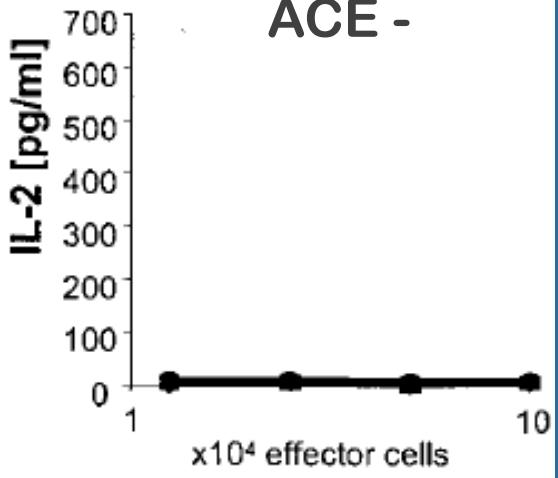
CAR-T cells 2^{ème} génération

Tumor-Specific T Cell Activation by Recombinant Immunoreceptors: CD3 ζ Signaling and CD28 Costimulation Are Simultaneously Required for Efficient IL-2 Secretion and Can Be Integrated Into One Combined CD28/CD3 ζ Signaling Receptor Molecule¹

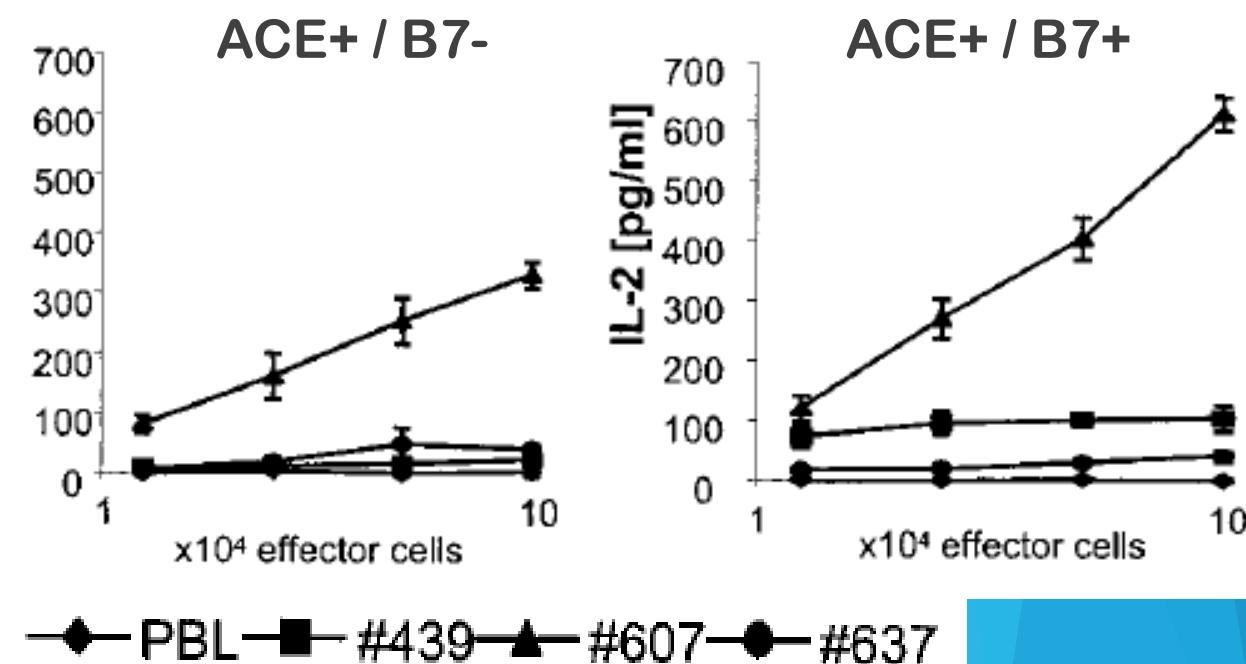
Tumor-Specific T Cell Activation by Recombinant Immunoreceptors: CD3 ζ Signaling and CD28 Costimulation Are Simultaneously Required for Efficient IL-2 Secretion and Can Be Integrated Into One Combined CD28/CD3 ζ Signaling Receptor Molecule¹



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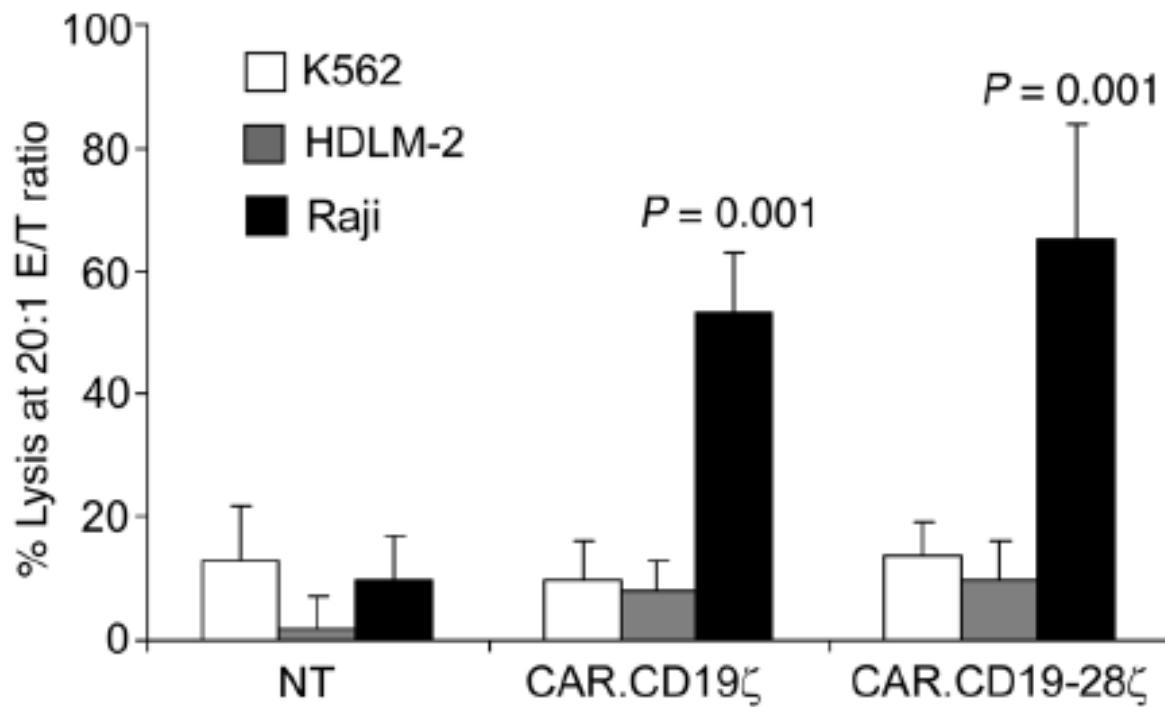


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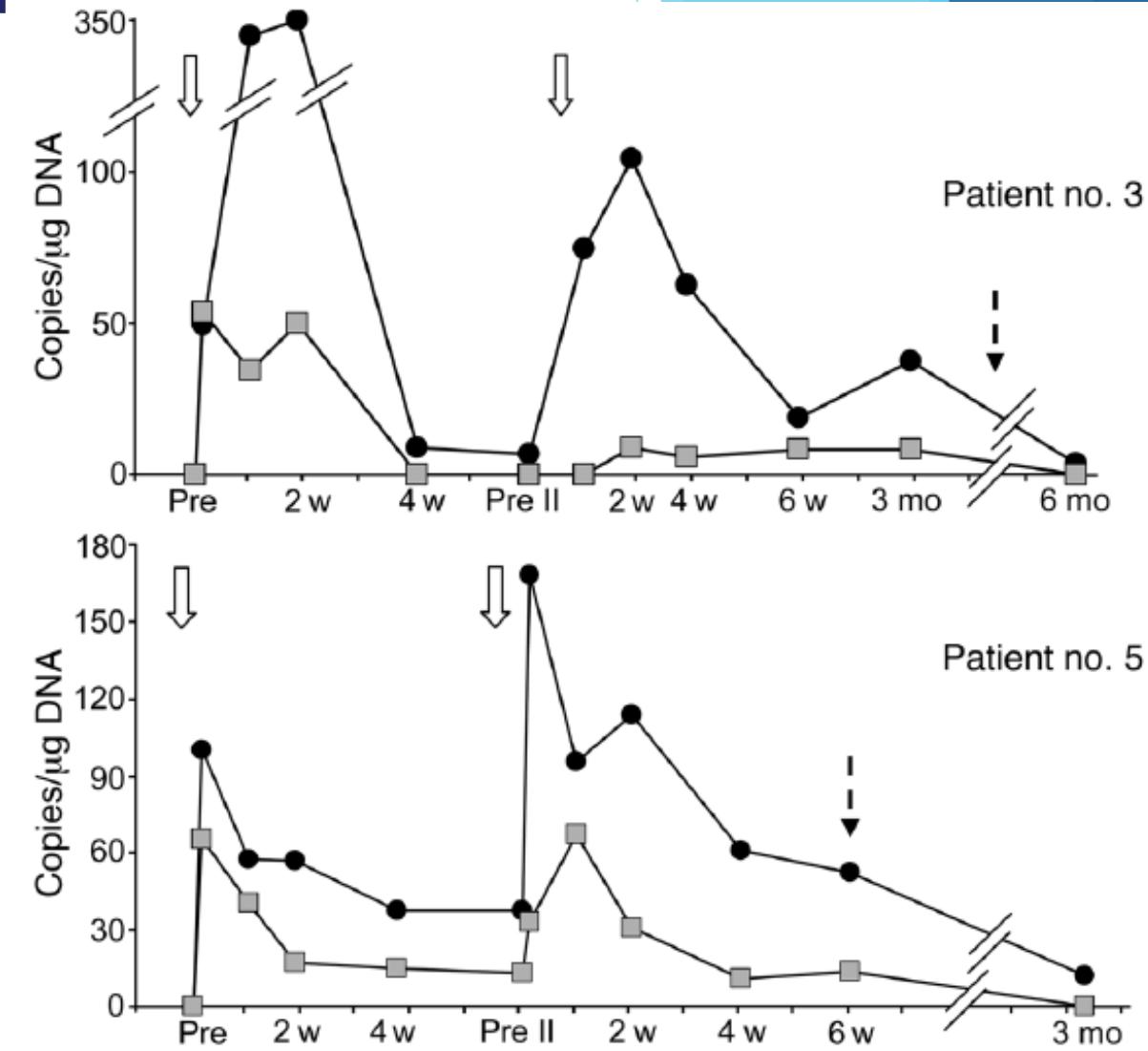


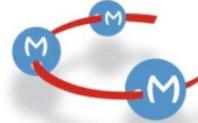
CD28 costimulation improves expansion and persistence of chimeric antigen receptor-modified T cells in lymphoma patients

Barbara Savoldo, ... , Malcolm K. Brenner, Gianpietro Dotti



Savoldo, JCI 2011

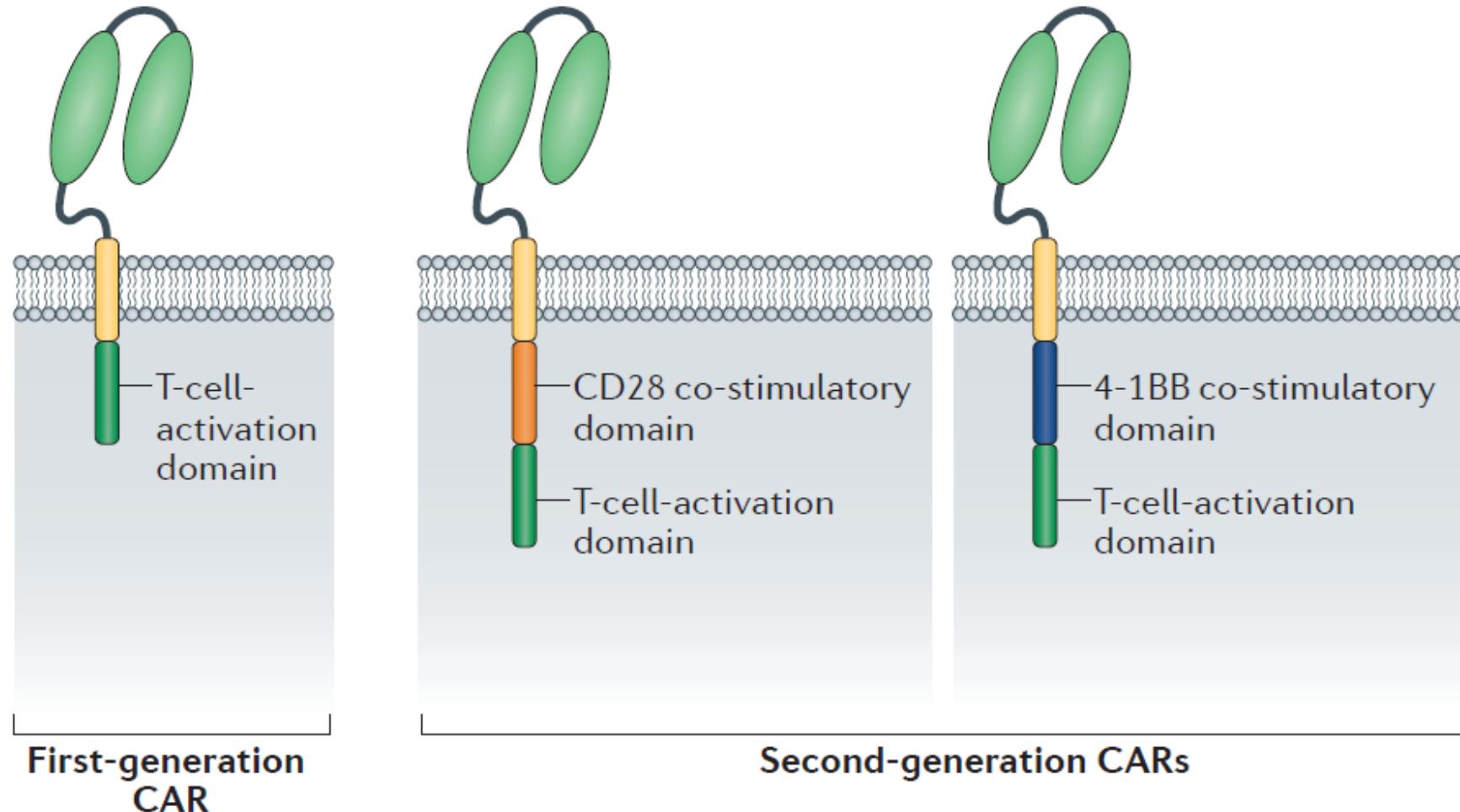




CAR-T cells 3^{ème} génération

Therapeutic T cell engineering

Michel Sadelain¹, Isabelle Rivière¹ & Stanley Riddell²



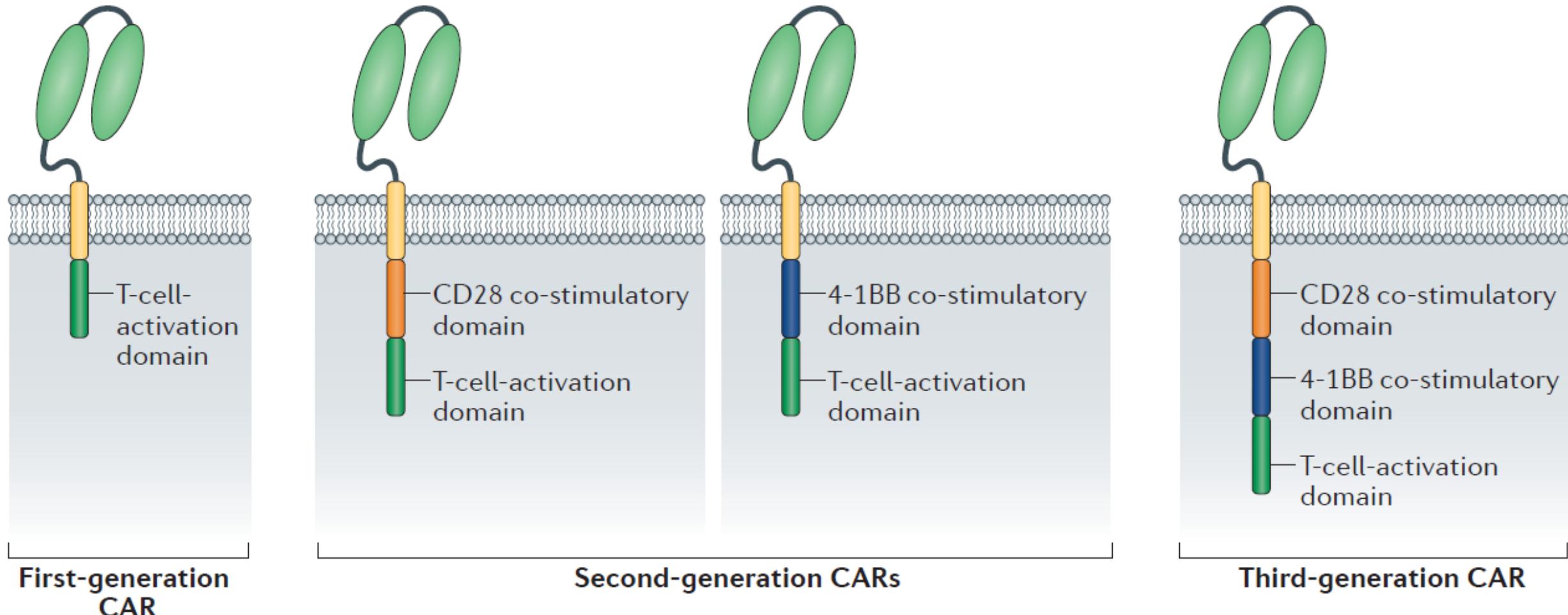
First-generation
CAR

Second-generation CARs

Sadelain, Nat 2017

Therapeutic T cell engineering

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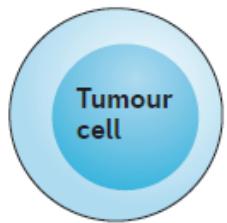
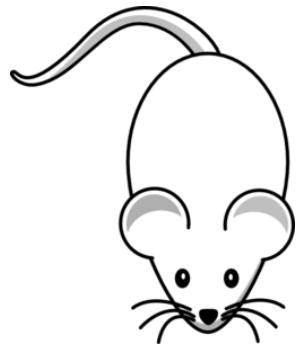


First-generation CAR

Second-generation CARs

Third-generation CAR

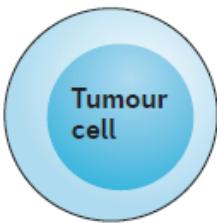
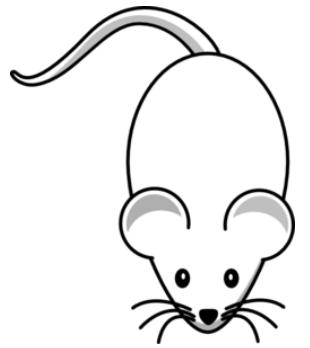
Structural Design of Engineered Costimulation Determines Tumor Rejection Kinetics and Persistence of CAR T Cells



NALM6

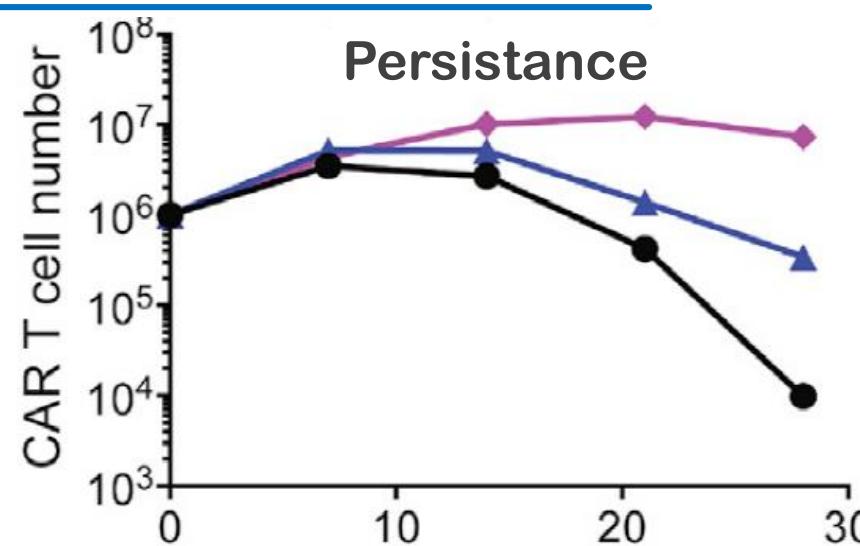
- 19z1
- ▲ 1928z
- ◆ 19BBz

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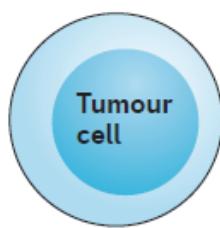
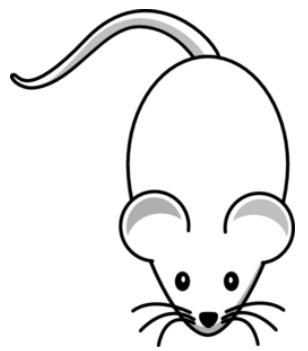


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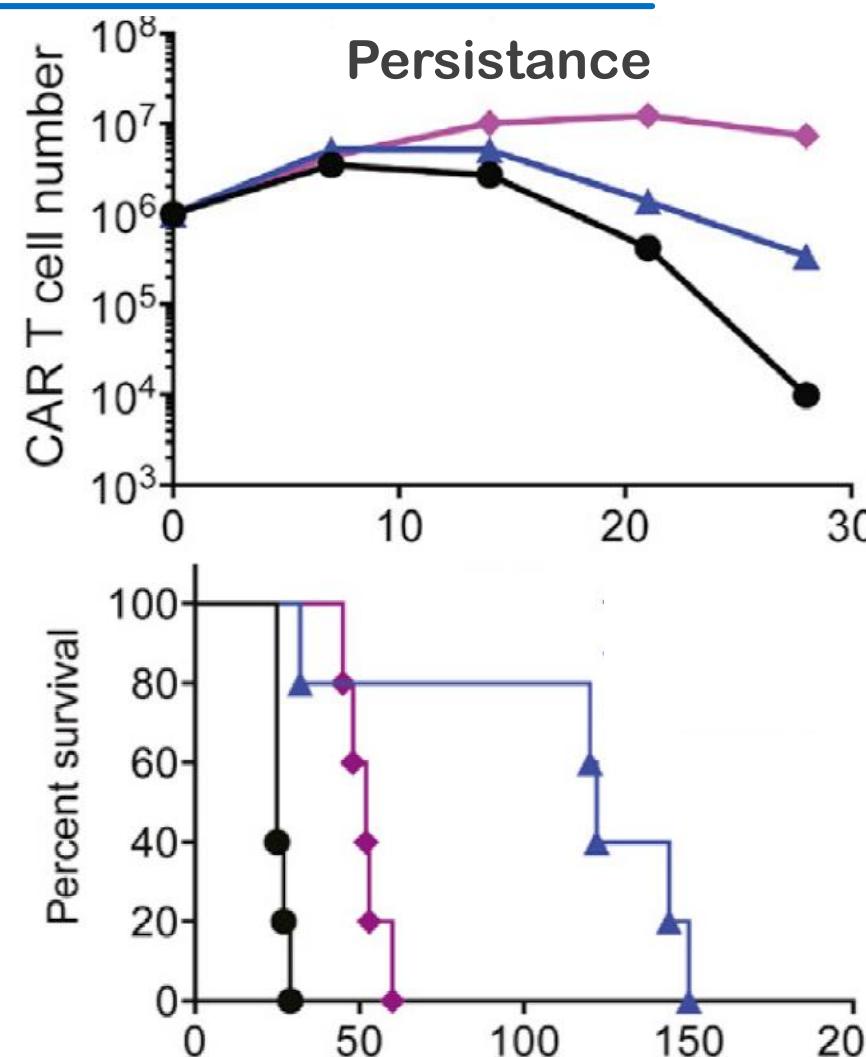


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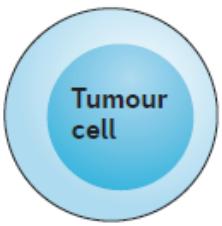
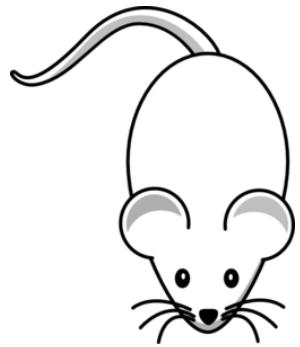


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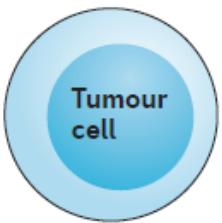
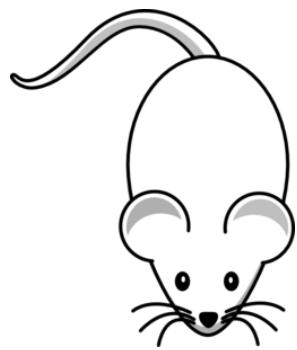
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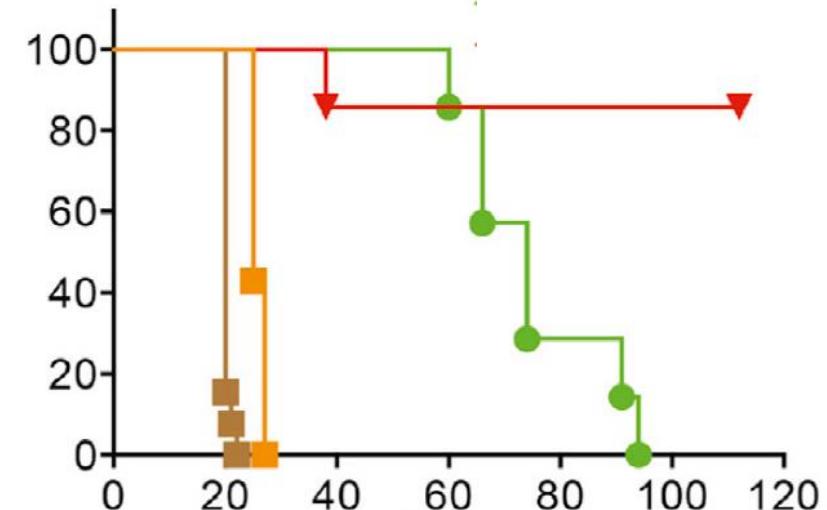
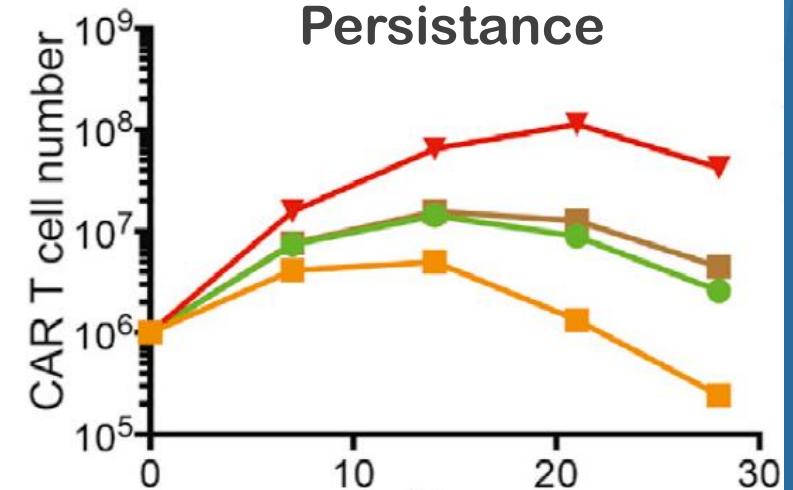
- 1928BBz
- 1928z-41BBL
- 19BBz-CD80
- 19z1-CD80-41BBL

Structural Design of Engineered Costimulation Determines Tumor Rejection Kinetics and Persistence of CAR T Cells

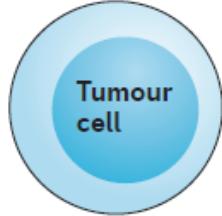
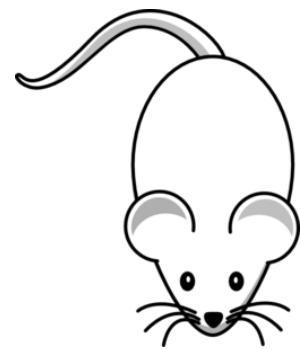


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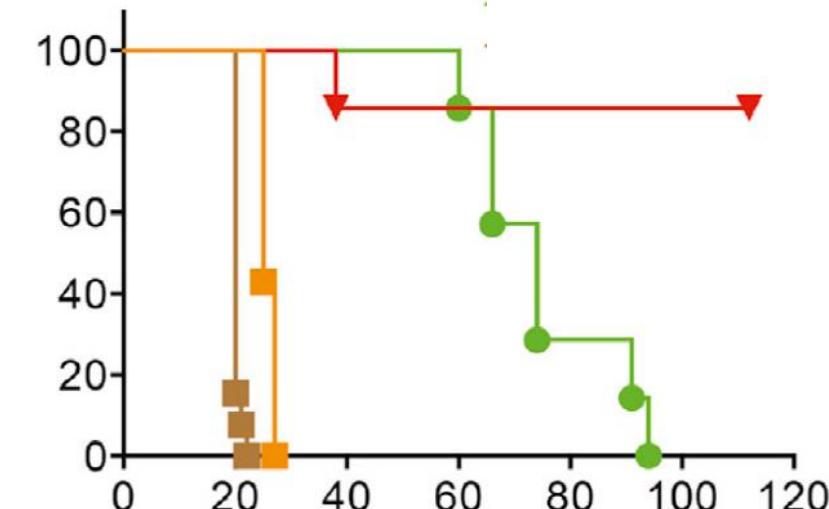
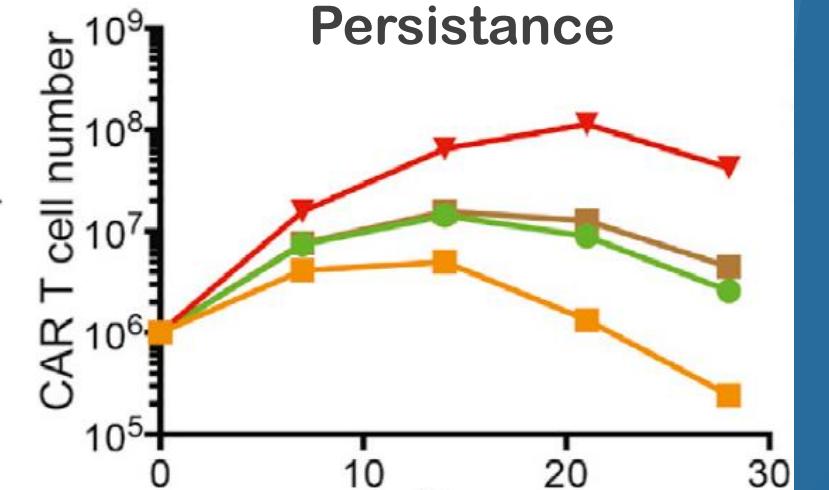
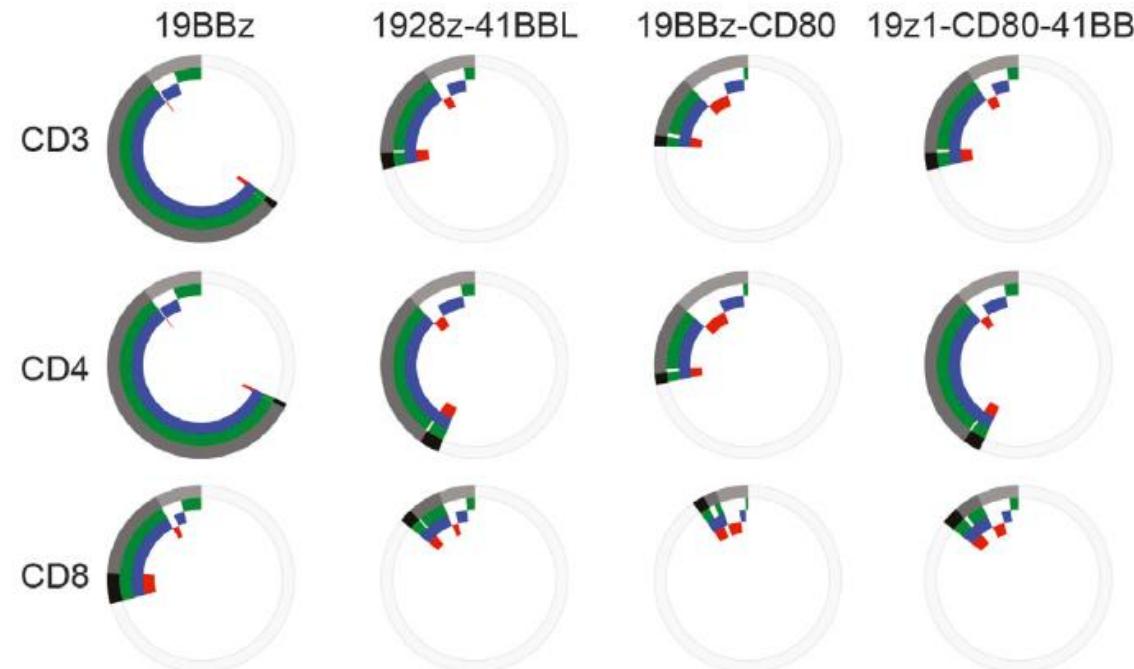


Structural Design of Engineered Costimulation Determines Tumor Rejection Kinetics and Persistence of CAR T Cells



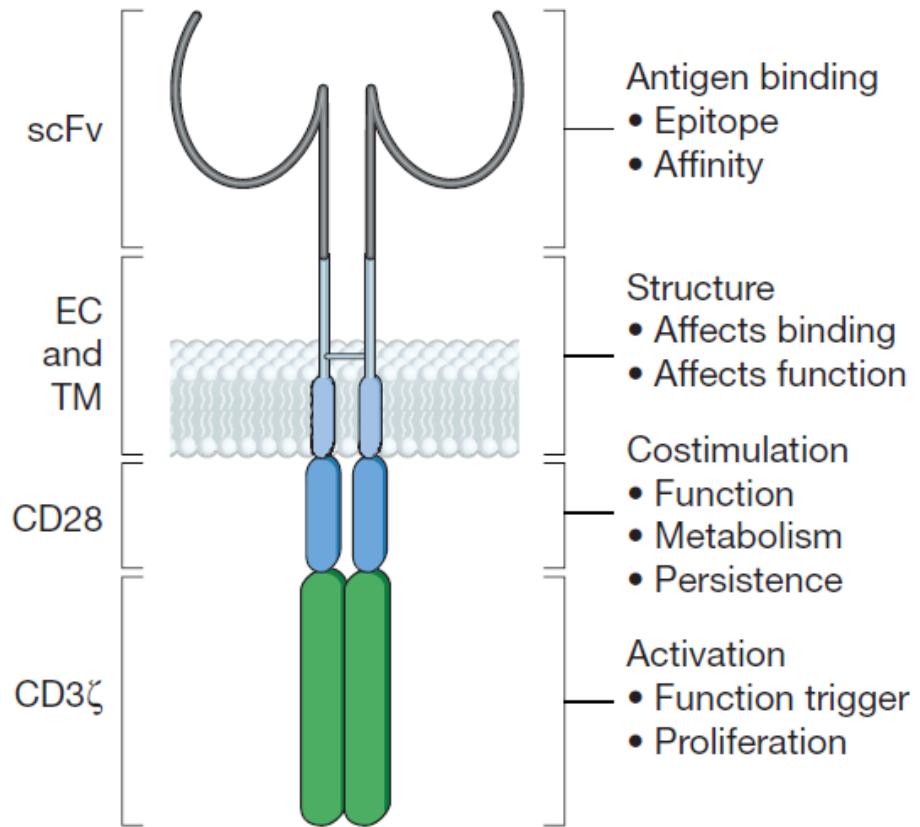
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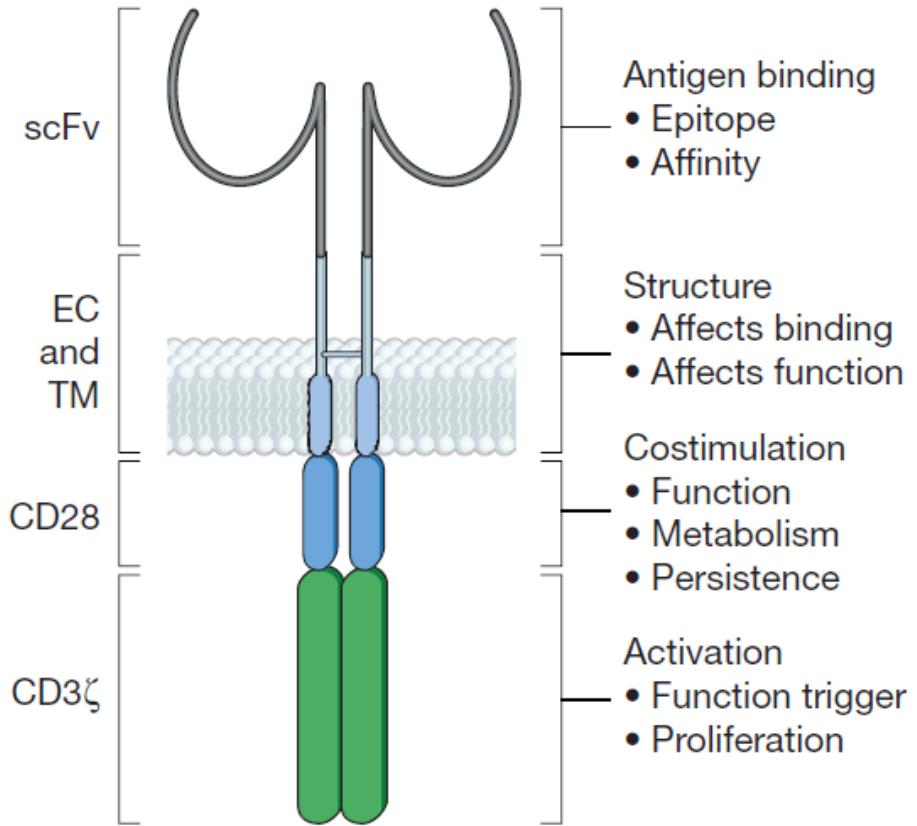
Therapeutic T cell engineering

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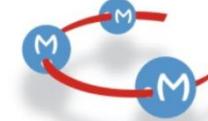


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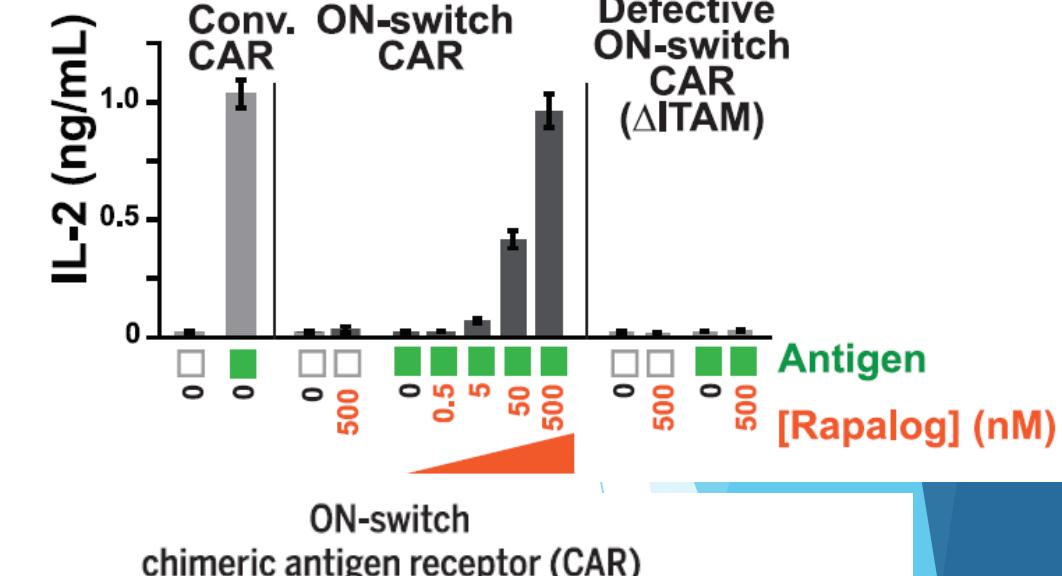
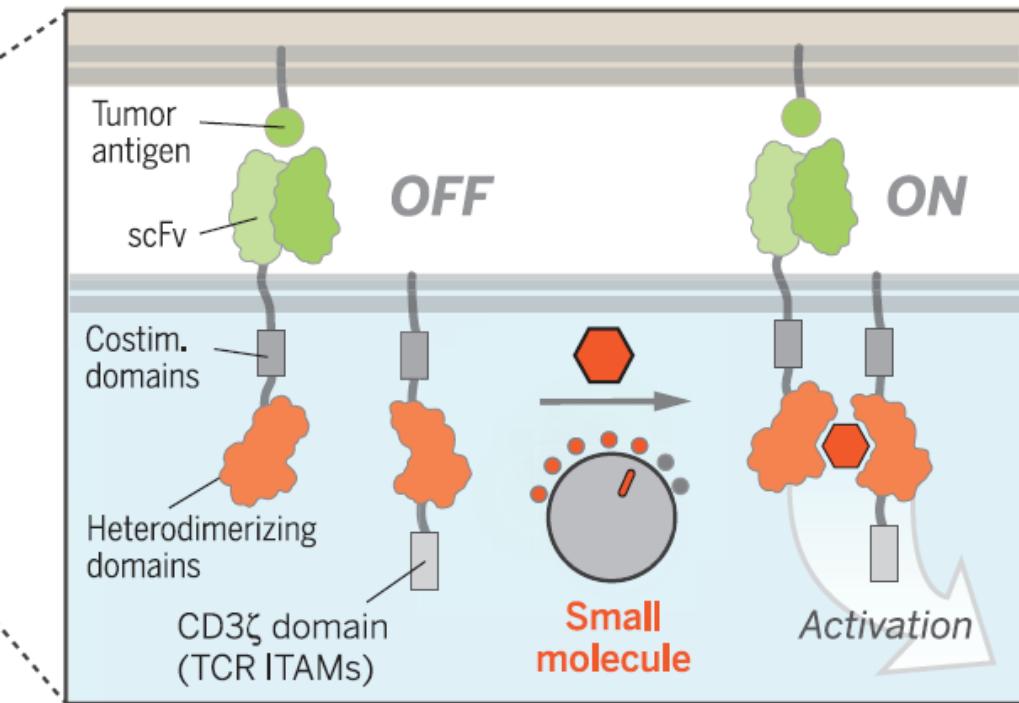
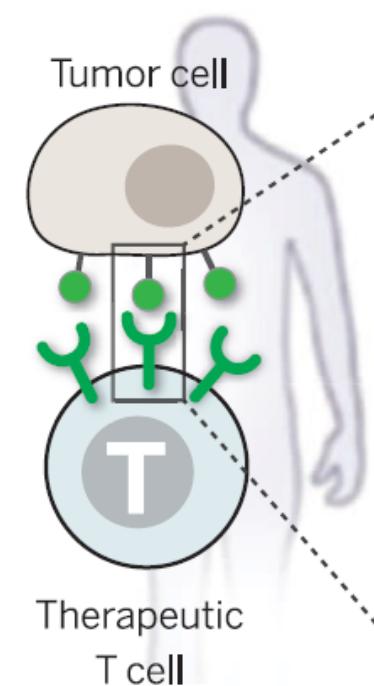
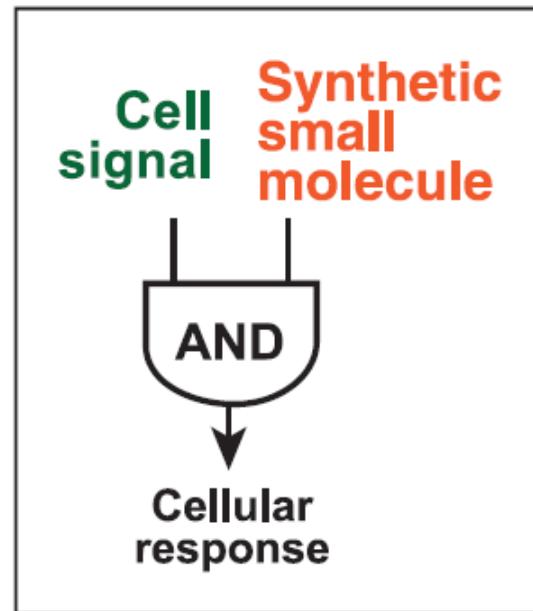
Study	Disease	CAR	V	N	Cond.	T cells	CR rate
Davila, 2014 (ref. 72)	ALL (Ad.)	CD28	γRV	16	CY	Auto	88%
Maude, 2014 (ref. 73)	ALL (Paed.)	4-1BB	LV	25	CF	Auto	90%
Lee, 2015 (ref. 74)	ALL (Paed.)	CD28	γRV	21	CY	Auto	68%
Turtle, 2016 (ref. 75)	ALL (Ad.)	4-1BB	LV	29	CY/CF	1:14/8	93%
Qasim, 2017 (ref. 150)	ALL (Paed.)	4-1BB	LV	2	IC	Allo	100%
Kochenderfer, 2015 (ref. 71)	NHL/CLL	CD28	γRV	15	CF	Auto	53%
Kochenderfer, 2016 (ref. 137)	B-mix	CD28	γRV	20	IC	Allo	30%
Turtle, 2016 (ref. 132)	NHL	4-1BB	LV	32	CY/CF	1:14/8	79%



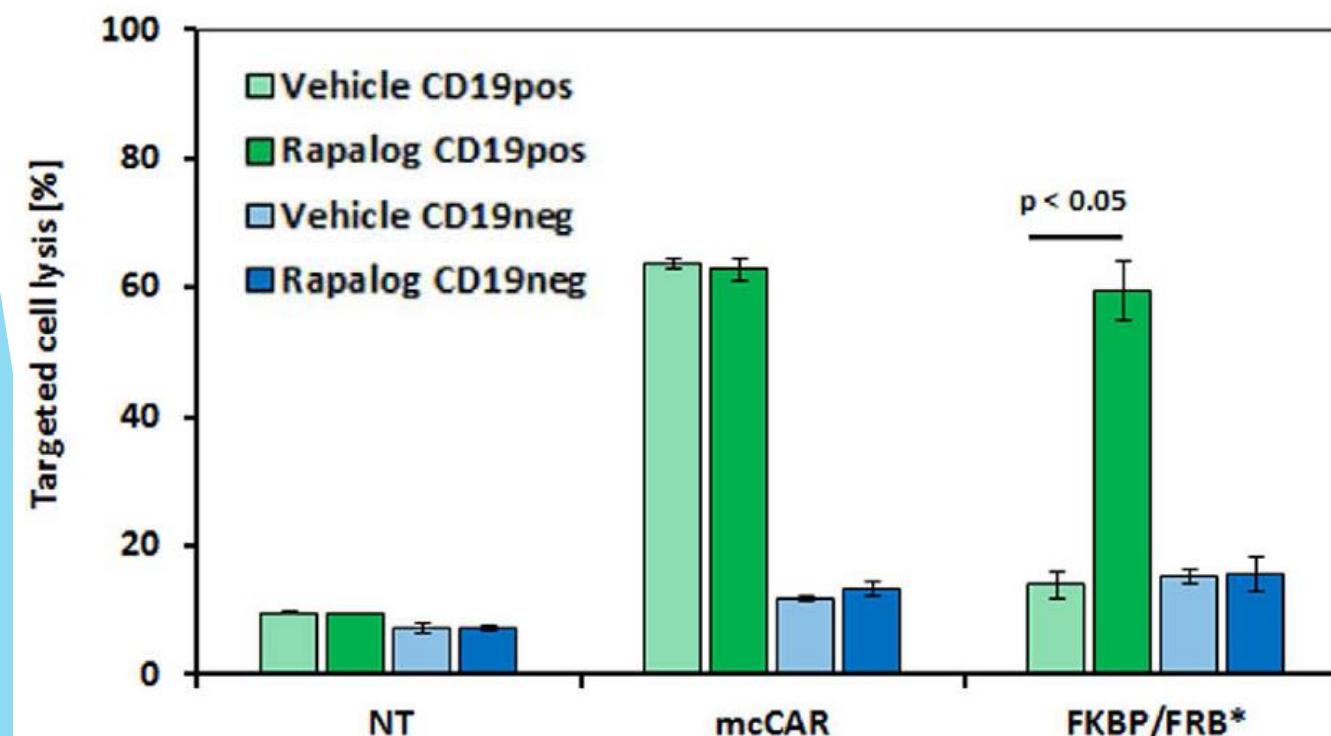
CAR-T cells n^{ième} génération
CAR-T cells « *actionnable* »

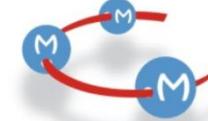
Remote control of therapeutic T cells through a small molecule-gated chimeric receptor

Chia-Yung Wu, Kole T. Roybal, Elias M. Puchner, James Onuffer,*
Wendell A. Lim*



Design of chimeric antigen receptors with integrated controllable transient functions

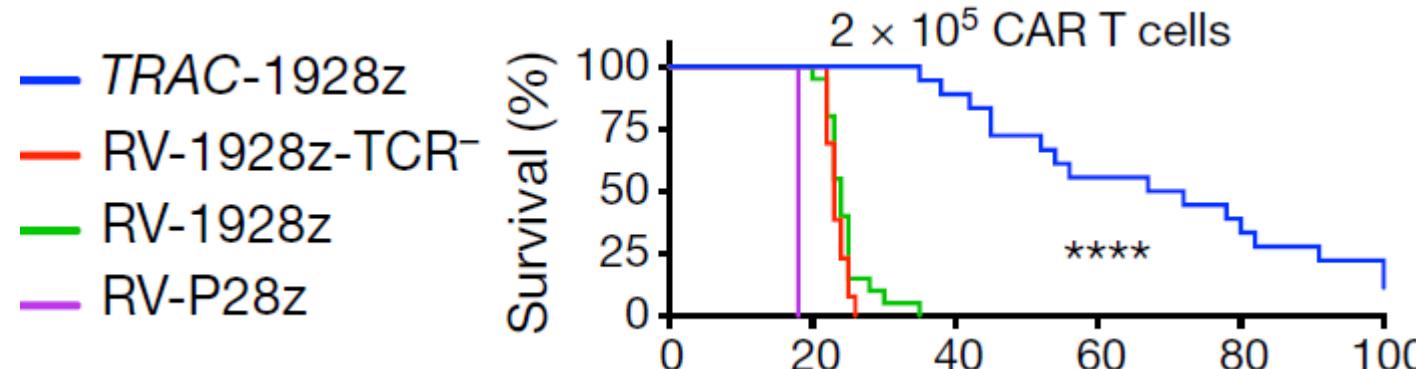
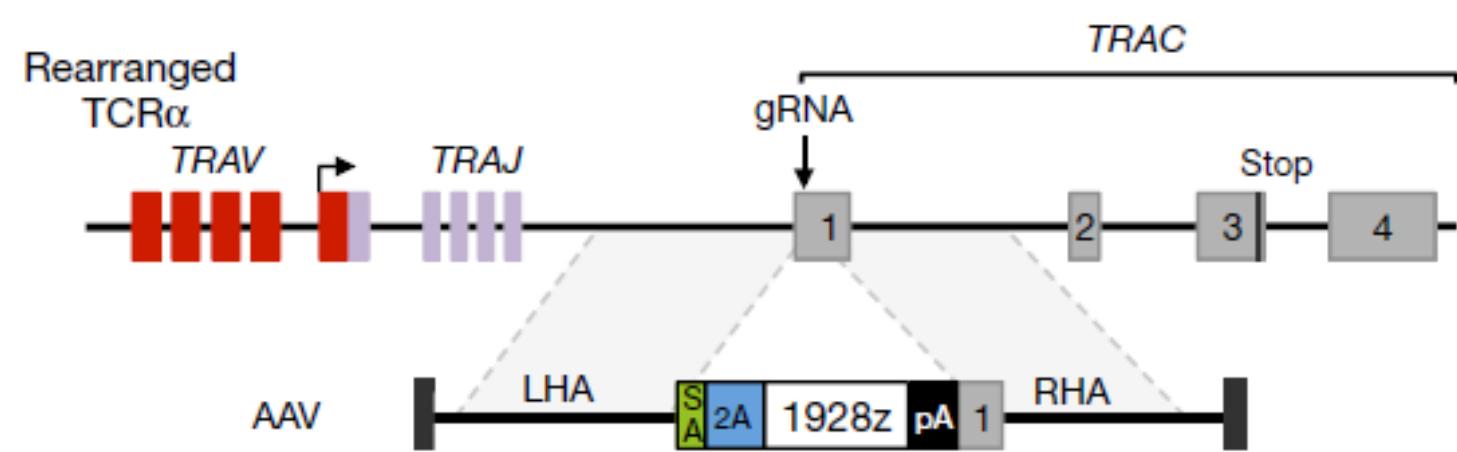


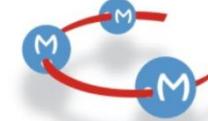


CAR-T cells n^{ième} génération
CAR-T cells « universels »

Targeting a CAR to the *TRAC* locus with CRISPR/Cas9 enhances tumour rejection

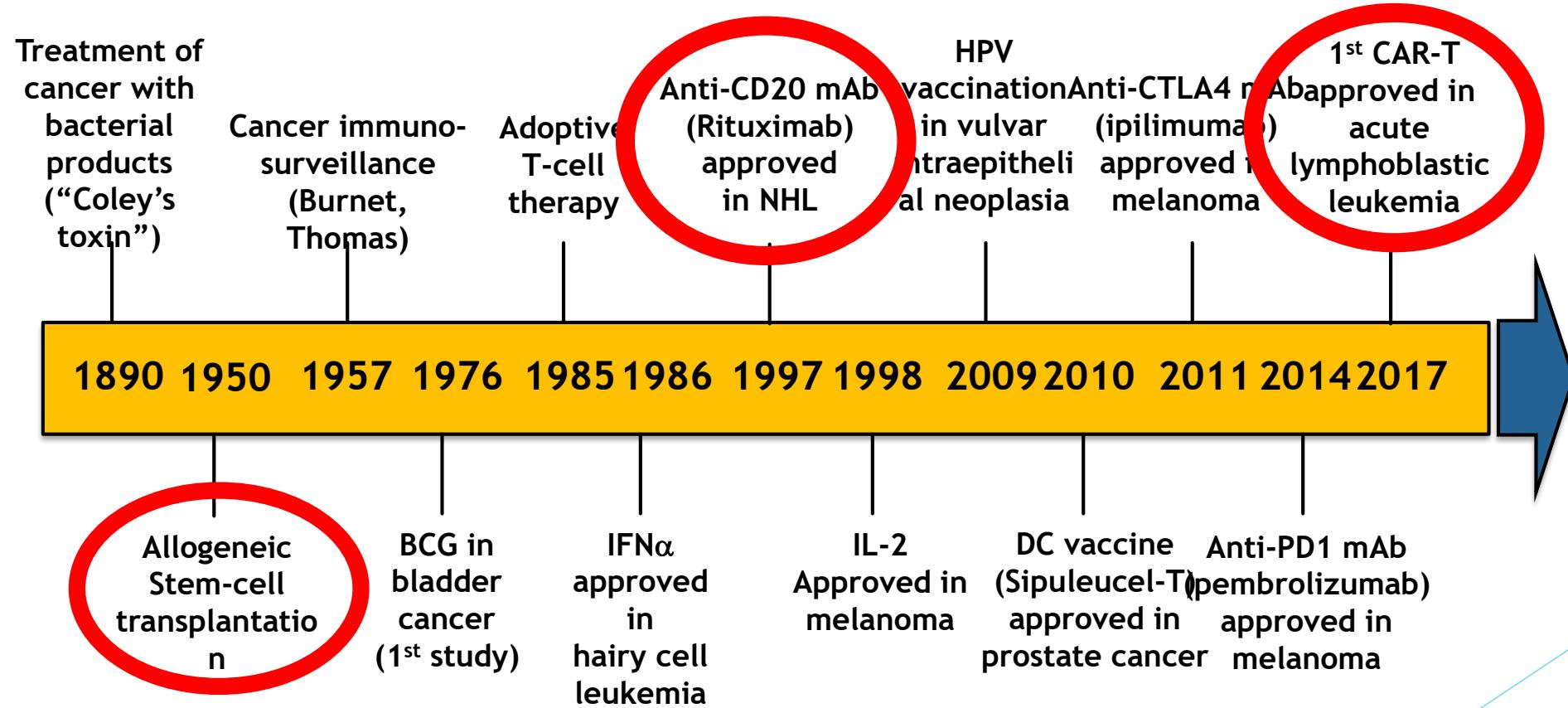
Justin Eyquem^{1*}, Jorge Mansilla-Soto^{1*}, Theodoros Giavridis¹, Sjoukje J. C. van der Stegen¹, Mohamad Hamieh¹, Kristen M. Cunanan², Ashlesha Odak¹, Mithat Gönen² & Michel Sadelain¹

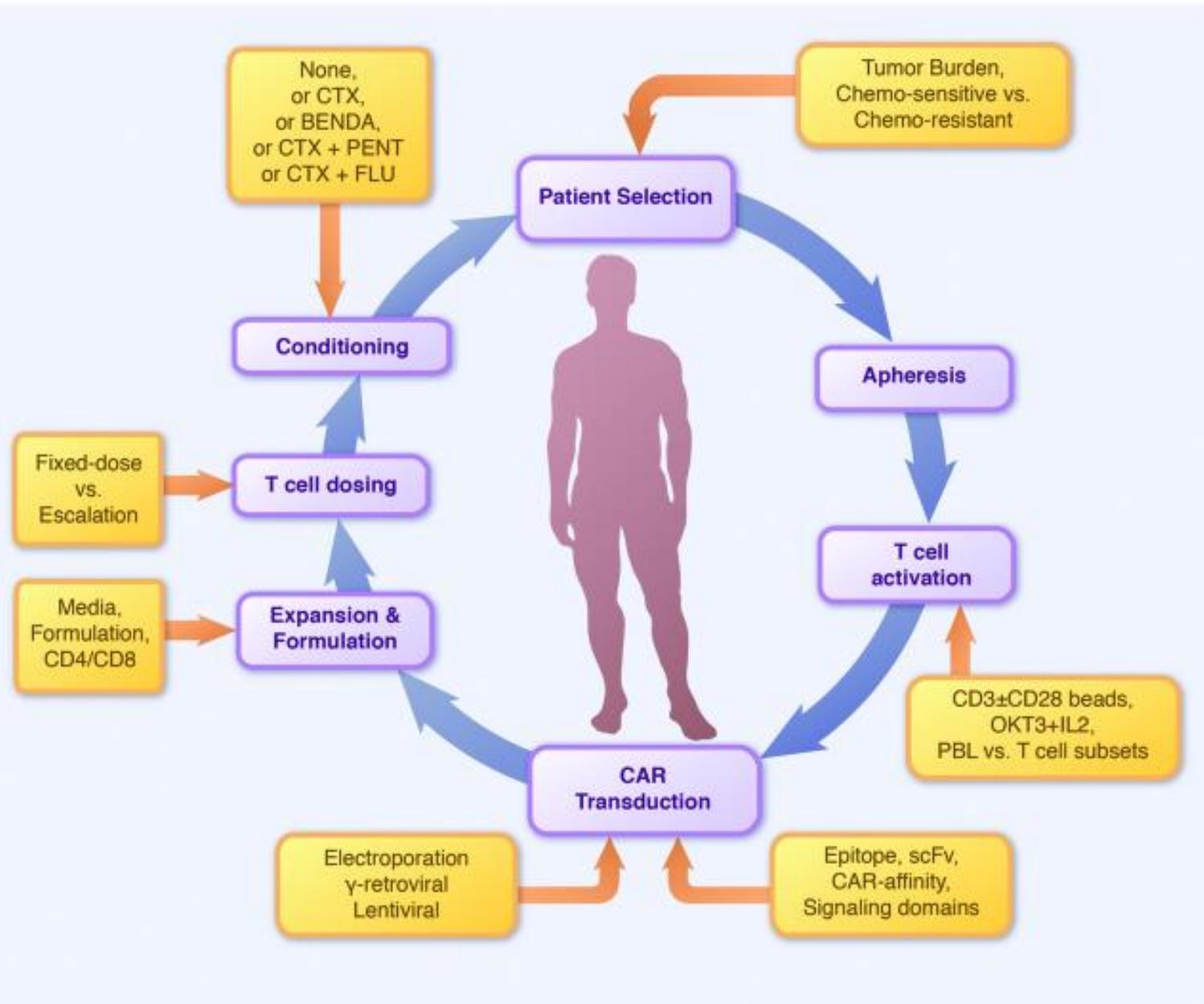




CAR-T cells « en pratique »

Immunotherapy in cancer

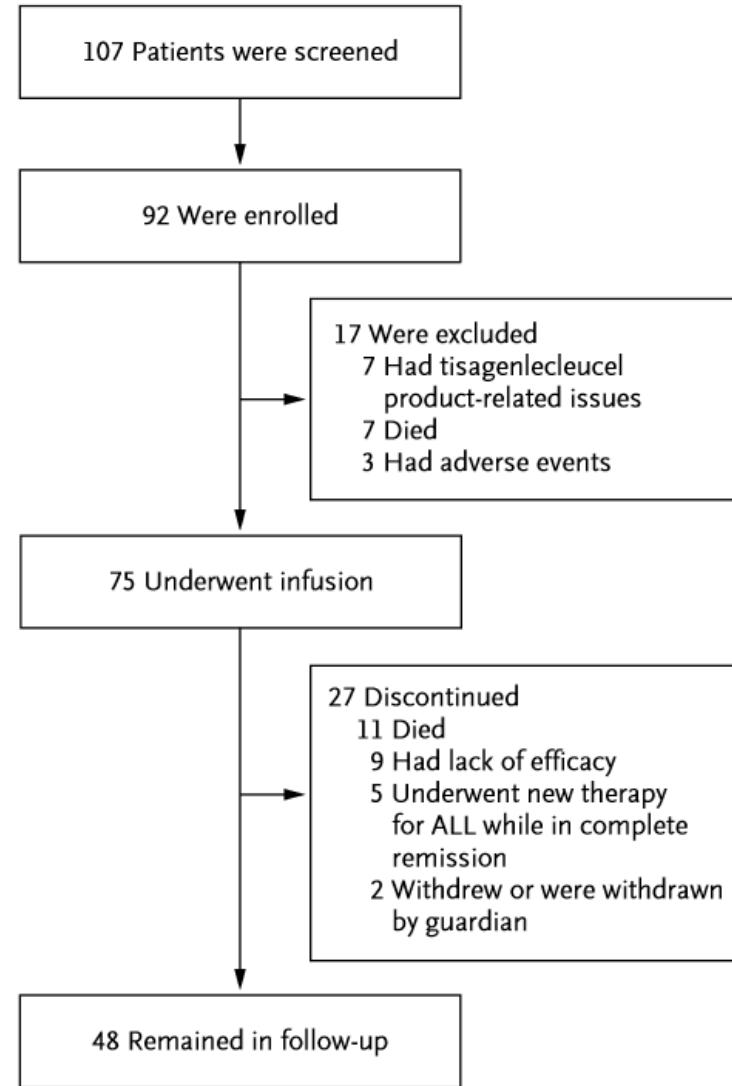




ELIANA-CTL019 global trial: *R/R BCP-ALL*

- ▶ Eligibility criteria
 - ▶ Inclusion : R/R BCP-ALL, age 3-21 years, $\geq 5\%$ BM blasts
 - ▶ Exclusion : isolated extra-medullary relapse, prior CD19-directed therapy
- ▶ Study treatment
 - ▶ Lymphodepleting chemotherapy prior to infusion
 - ▶ Fluda (30 mg/sqm/d IV, 4 days)
 - ▶ Cy (500 mg/sqm/d IV, for 2 days)
 - ▶ Target CTL019 dosing (single infusion)
 - ▶ $2.0 - 5.0 \times 10^6/\text{kg}$ for patients $\leq 50 \text{ kg}$
 - ▶ $1.0 - 2.5 \times 10^8$ for patients $> 50 \text{ kg}$

ELIANA-CTL019 global trial: R/R BCP-ALL

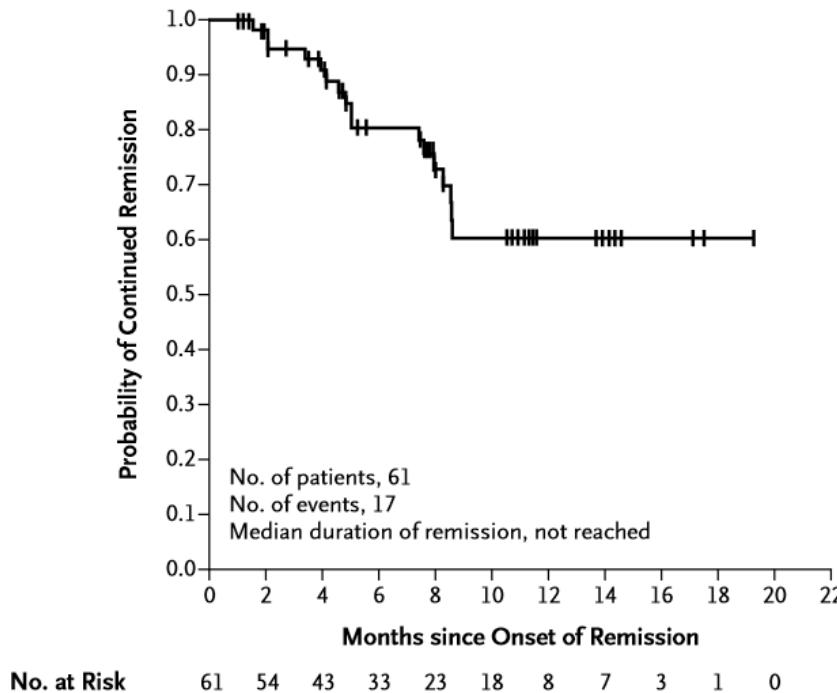


ELIANA-CTL019 global trial: *R/R BCP-ALL*

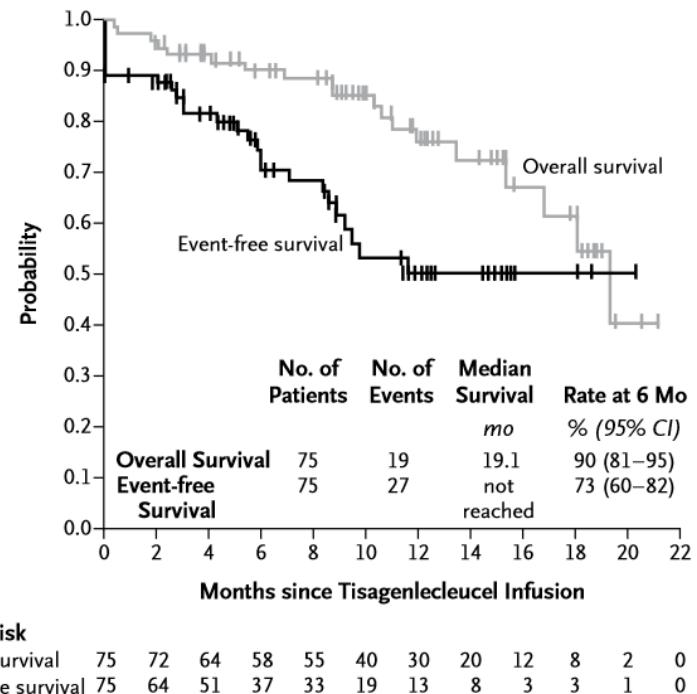
Efficacy	% (n/N)	95%CI	p-value
Primary			
- CR+CRi within 3 months	82% (41/50)	69%-91%	<.0001
- CR	68%		
- Cri	14%		
Secondary			
- Achieved BOR (CR/CRi) with MRD-	82%	69%-91%	<.0001

ELIANA-CTL019 global trial: R/R BCP-ALL

A Duration of Remission



B Event-free and Overall Survival

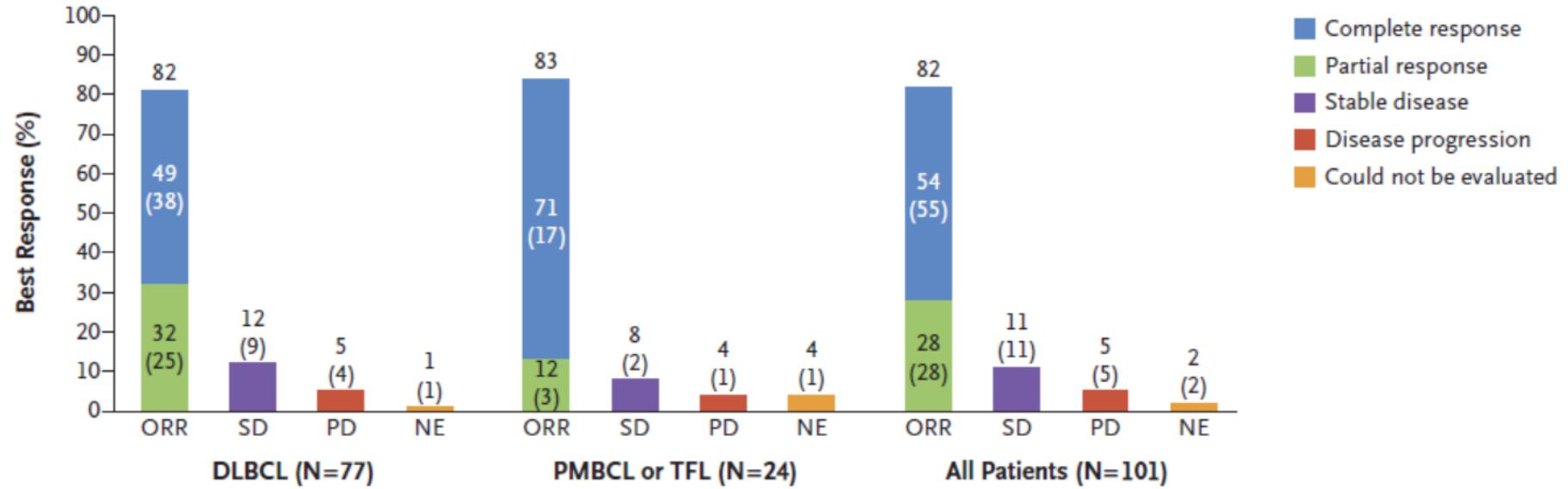


ZUMA-2 trial: *R/R Lymphoma*

- ▶ Eligibility criteria
 - ▶ Inclusion : R/R BCP-Lymphoma, age 18-60 years
- ▶ Study treatment
 - ▶ Lymphodepleting chemotherapy prior to infusion
 - ▶ Fluda (30 mg/sqm/d IV, 3 days)
 - ▶ Cy (500 mg/sqm/d IV, for 3 days)
 - ▶ Target CTL019 dosing (single infusion)
 - ▶ $2.0 \times 10^6/\text{kg}$

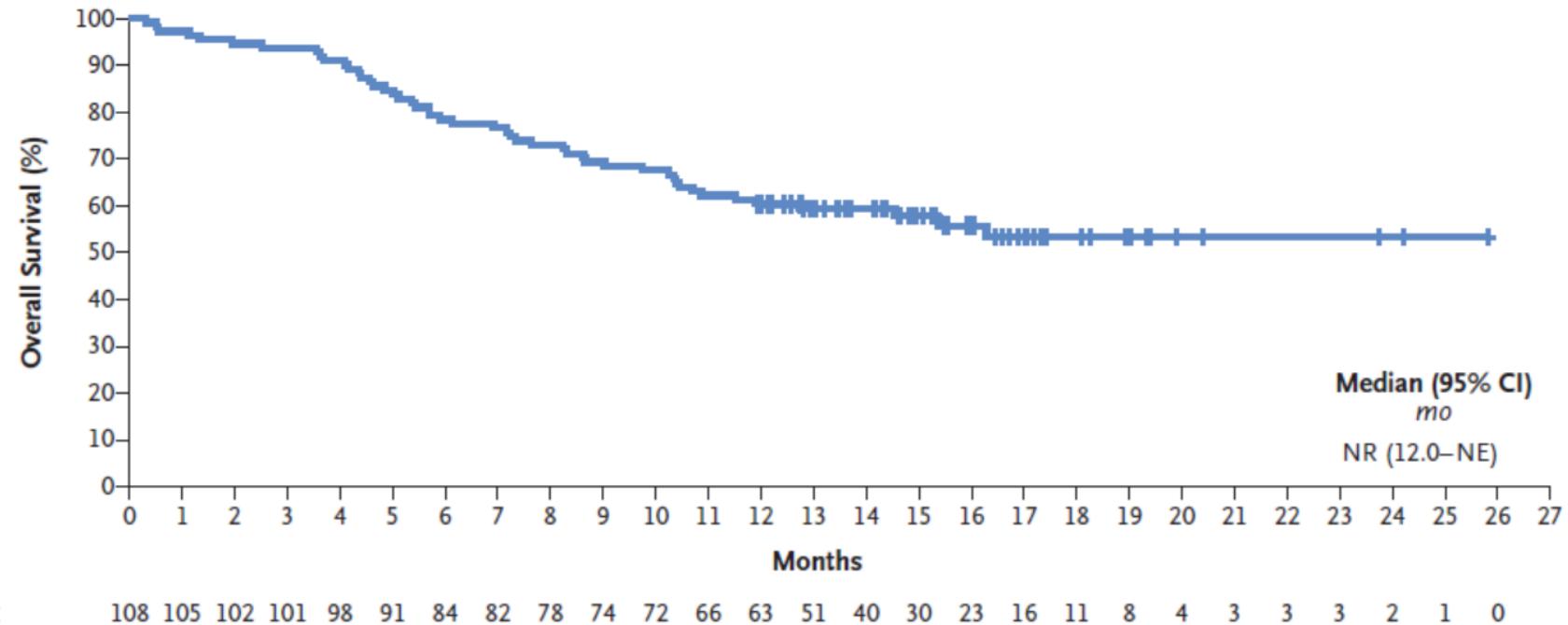
ZUMA-2 trial: *R/R Lymphoma*

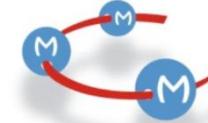
A Objective Response Rate



ZUMA-2 trial: *R/R Lymphoma*

C Overall Survival





CAR-T cells en oncologie

Antigènes cibles

Antigène ciblé	Indications
c-MET	Mélanome, sein
CD133	Foie, pancréas, cerveau
CD171	Neuroblastome
CD70	pancréas, rein, sein
CEA	foie, poumon, colo-rectal, estomac, pancréas
EGFR-VIII	Glioblastome
EpCAM	foie, estomac, nasopharynx, sein, colon, œsophage, pancréas
EphA2	glioblastome
FAP	mésothéliome
GD2	neuroblastome, glioblastome, sarcomes, ostéosarcome, mélanome
GPC3	foie, poumon
HER2	sein, ovaire, poumon, glioblastome, sarcomes
IL-13Ra2	glioblastome
Mésothéline	col de l'utérus, pancréas, ovaire, poumon
MUC1	foie, poumon, pancréas, sein, glioblastome, estomac, colo-rectal
PSCA	pancréas
PSMA	prostate, vessie
ROR1	cancers ROR1 ⁺
VEGFR2	mélanome, rein

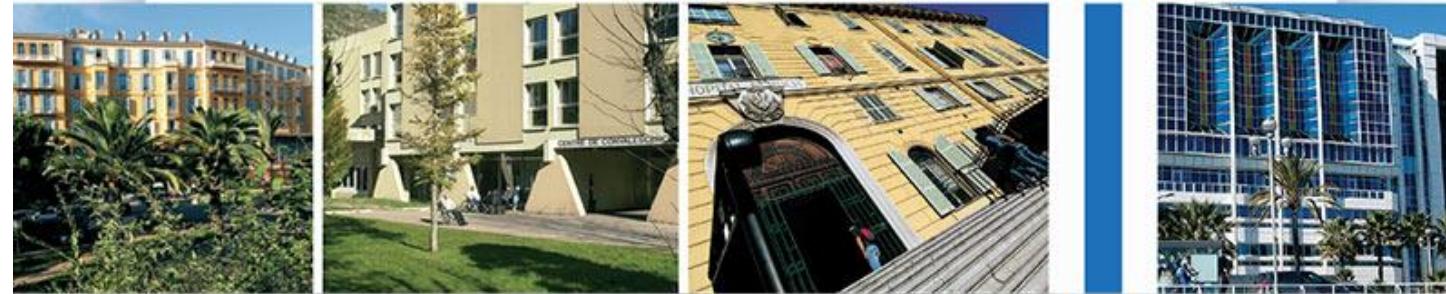
Conclusions et perspectives

- ▶ 2 AMM
 - ▶ Kymriah® dans les LAL et les lymphomes
 - ▶ Yescarta® dans les lymphomes
- ▶ 5 centres qualifiés en France
 - ▶ Pharmacie qualifiée pour MTI
 - ▶ Structure pratiquant l'allogreffe de CSH
 - ▶ Réanimation sur site
 - ▶ ...
- ▶ Nombreux essais cliniques de phase 3 en cours



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Hospitalier
Universitaire
de Nice

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Merci de
votre
attention