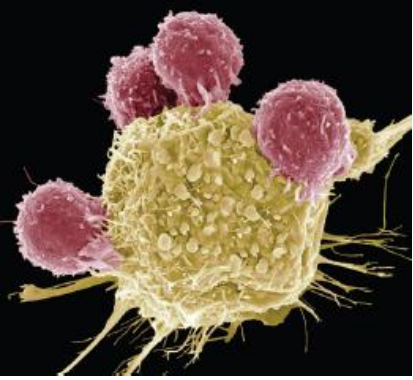
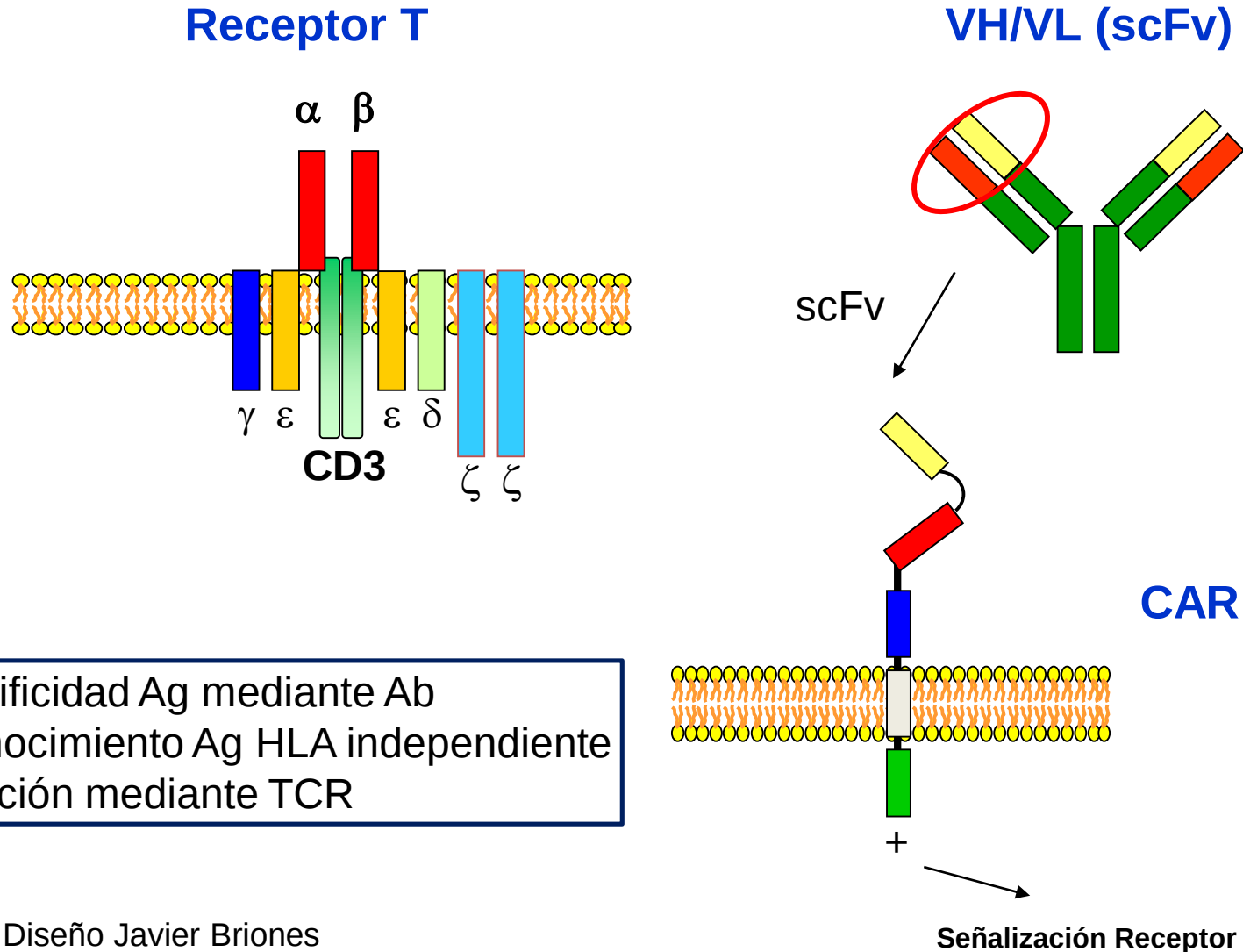




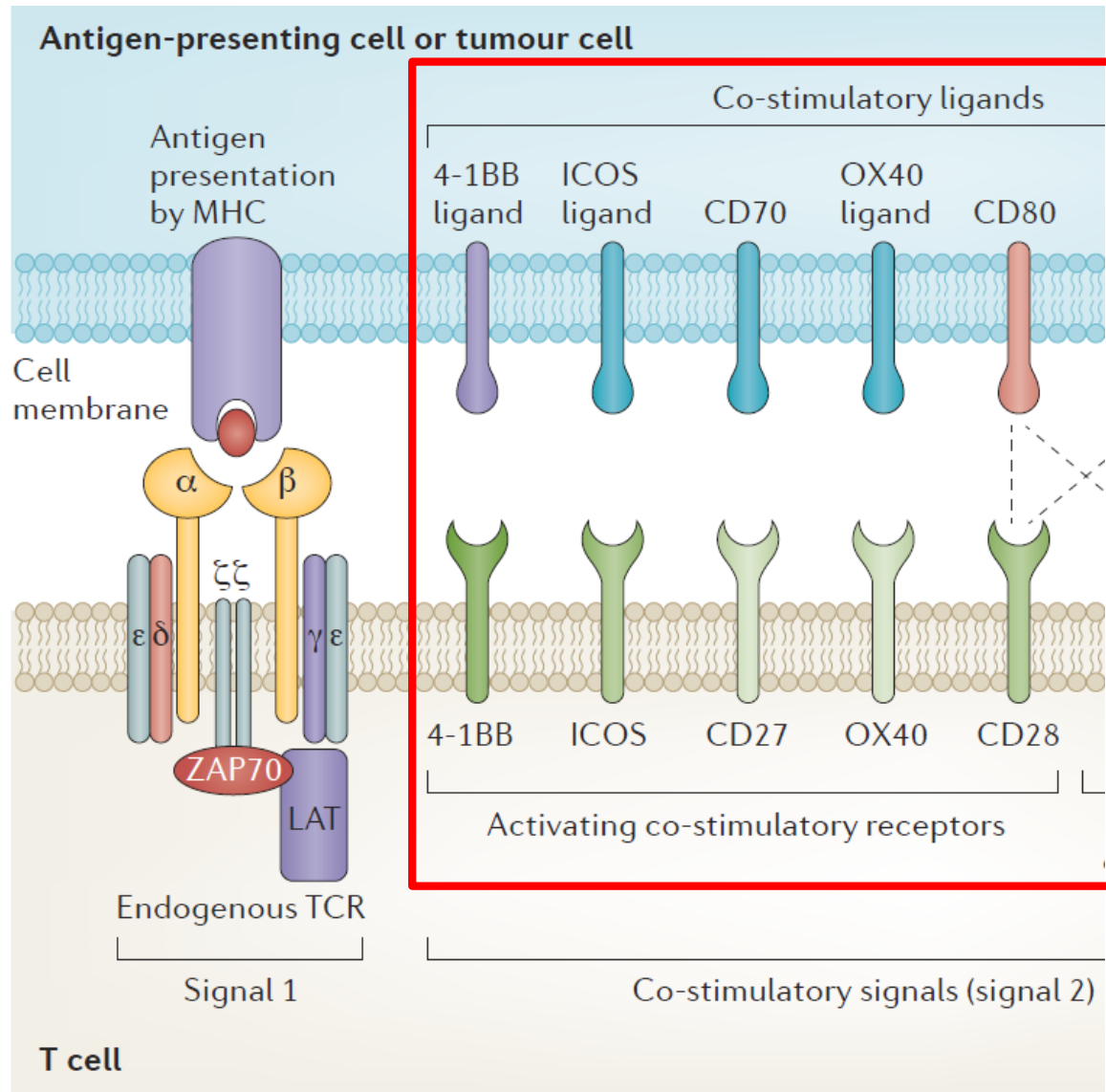
Terapia CART

Javier Briones
Servicio de Hematología
Hospital Santa Creu i Sant Pau
Barcelona

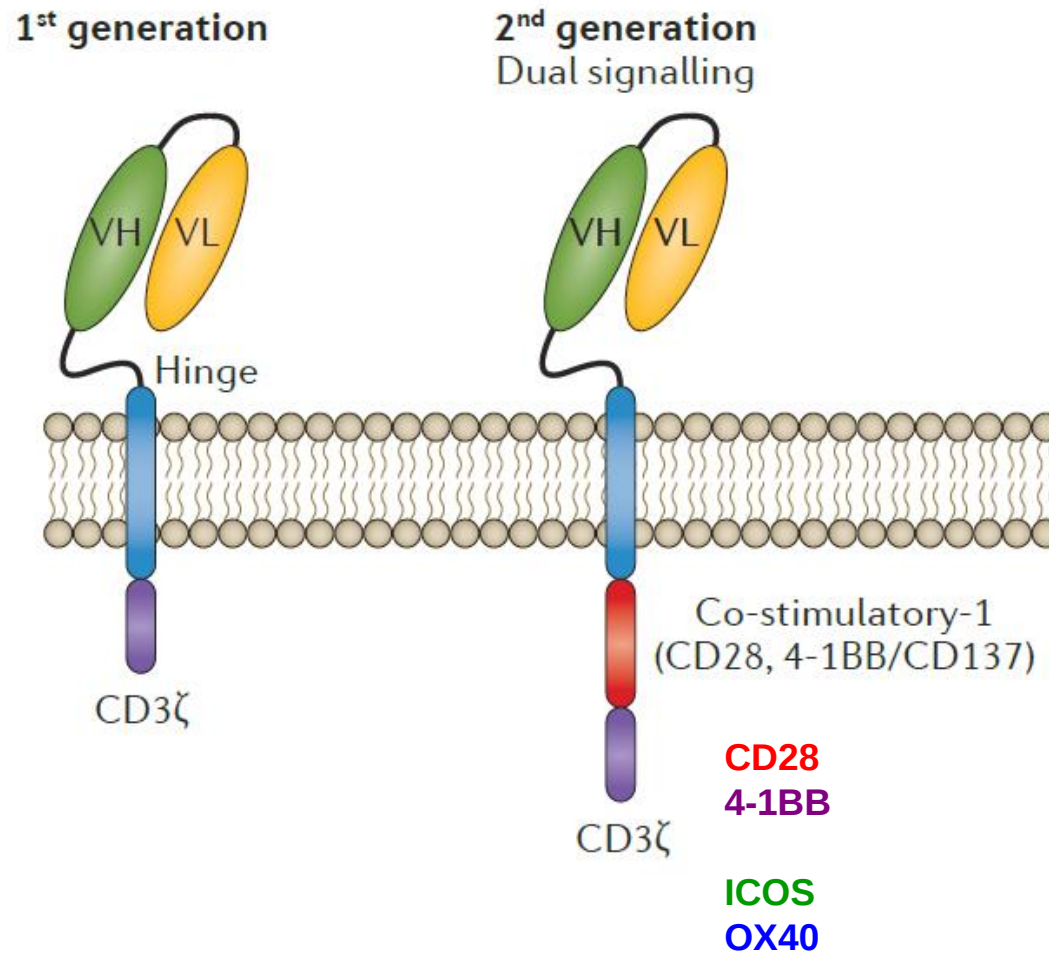
Cels. T con Receptores Quiméricos Antígeno-específicos (CAR)



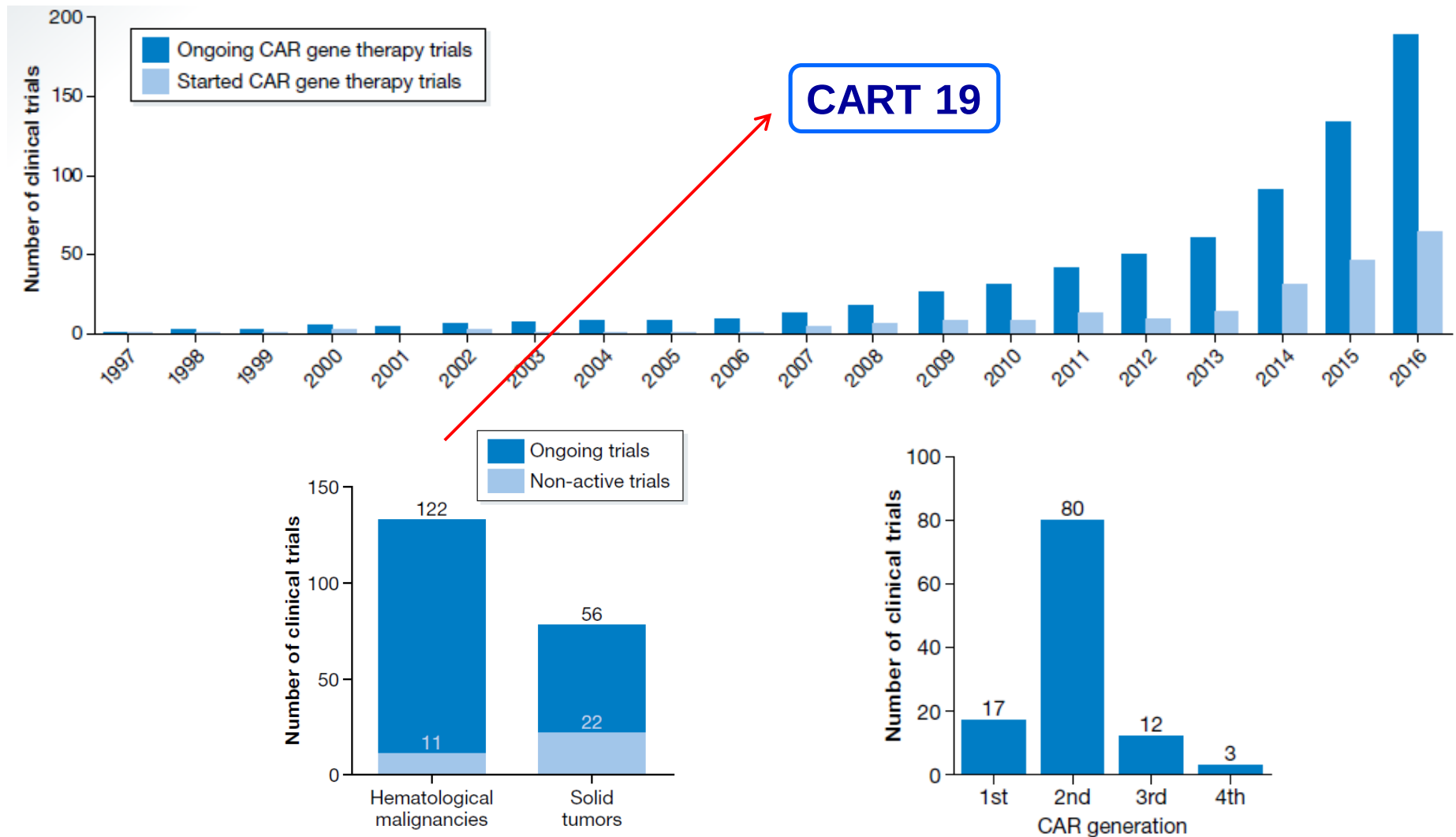
Coestimulación Célula T



CAR: diseño



Ensayos clínicos con cels. CART



CAR19: Indicaciones Clínicas

- **Leucemia aguda linfoblástica B : pediátrico y adultos jóvenes hasta 25 años. Refract/2ª recidiva**
- **Linfoma no Hodgkin difuso cel. grande B: recidiva/refractario a 2 líneas**



4-1BB



CD28

- **Linfoma no Hodgkin difuso cel. grande B: recidiva/refractario a 2 líneas Tx.**
- **Linfoma B Mediastínico primario**

Targets for CAR T cell Immunotherapy for Hematological Malignancies

Target Antigen

Disease

CD19

B lymphoma, B-ALL

CD22

B-ALL

CD20

B lymphoma

CD33

AML

ROR1 γ

Mantle lymphoma, CLL

CD30

Hodgkin

BCMA

Myeloma

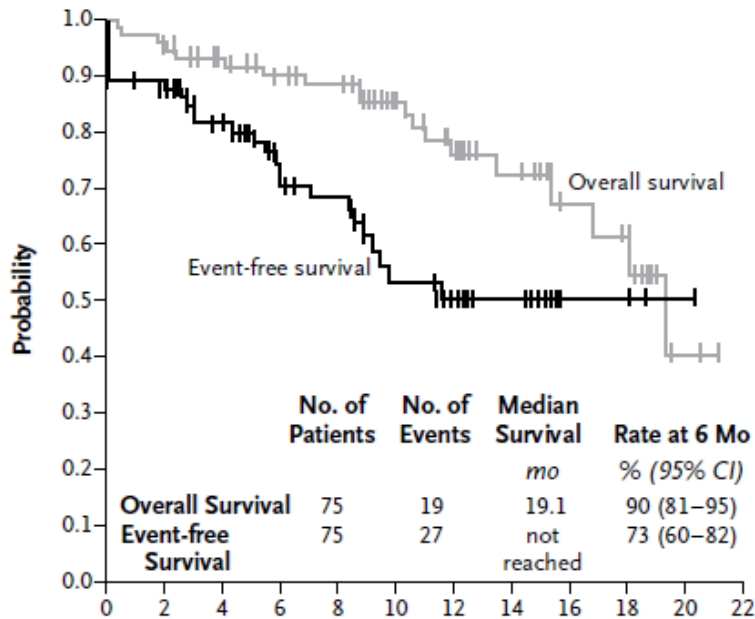
CAR19 en LAL-B: Resultados Clínicos

N	CAR	RC	MRD-	SLP
30 (5 adultos) (UPenn 2014)	4-1BB-z	90%	100%	50% @12m
21 (7 adultos) (NCI 2015)	CD28-z	70%	60%	50% @12m
53 (adultos) (MSKCC 2015)	CD28-z	84%	67%	30% @ 12m
32 (adultos) (FHCRC 2016)	4-1BB-z	100%	93%	60% @ 6m
88 (niños) "Eliana" Global Ph II (2016)	4-1BB-z	83%	82%	60% @ 9m
45 (niños- adult. jóvenes)	4-1BB-z	90%	100%	50% @ 12m

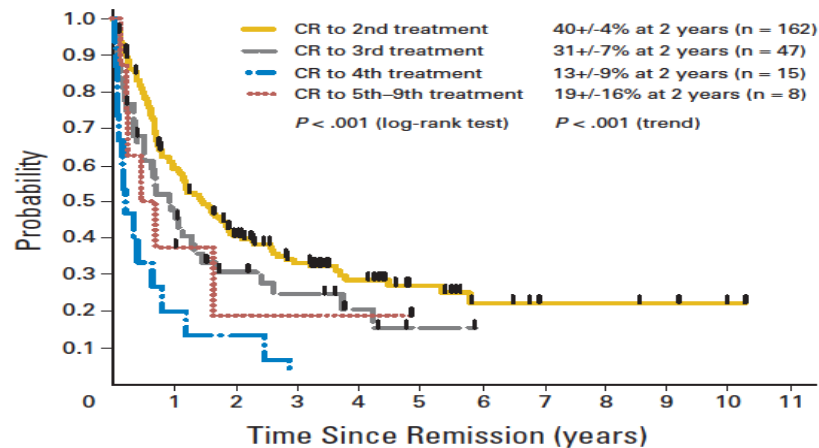
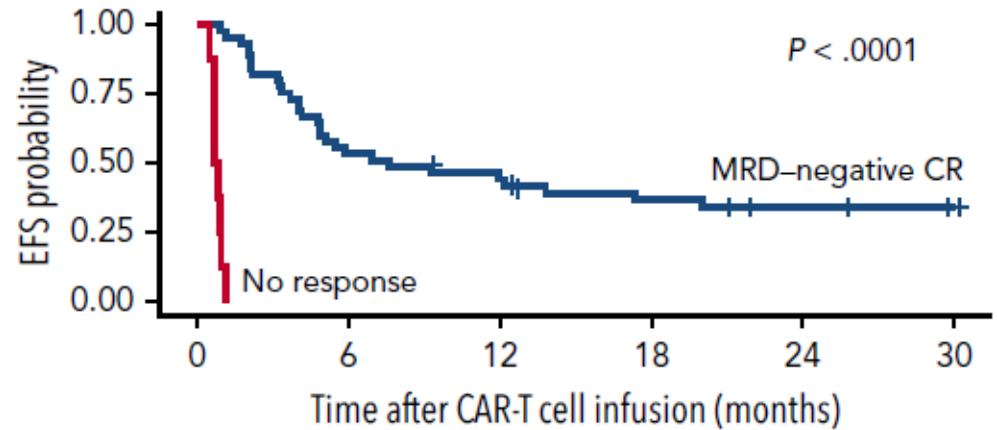
Maude et al. NEJM 2014; Lee et al. Lancet 2015;
 Park et al (MSKCC Meeting) 2017;
 Turtle et al. JCI 2017; Grupp et al. ASH 2016;
 Gardner et al. Blood 2017

CART19 en LAL-B

CAR19 LAL Pediátrica



CAR19 LAL Adultos

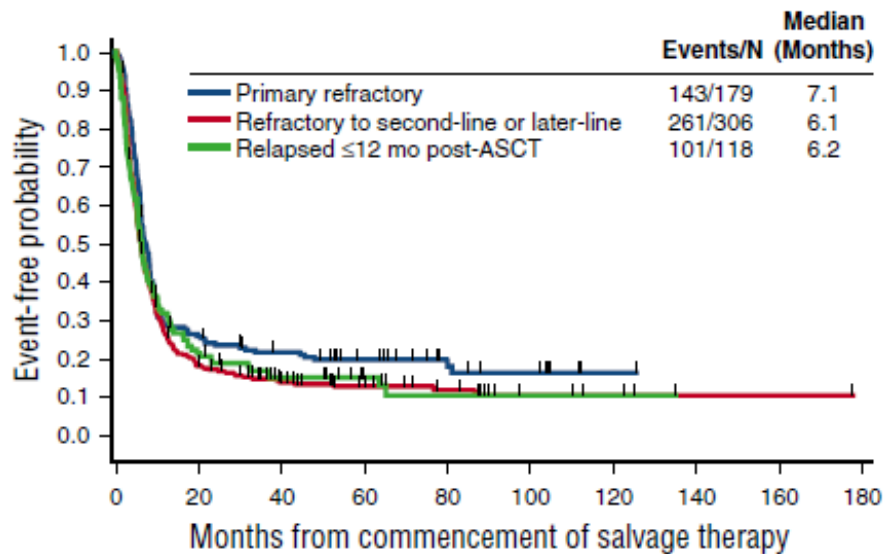
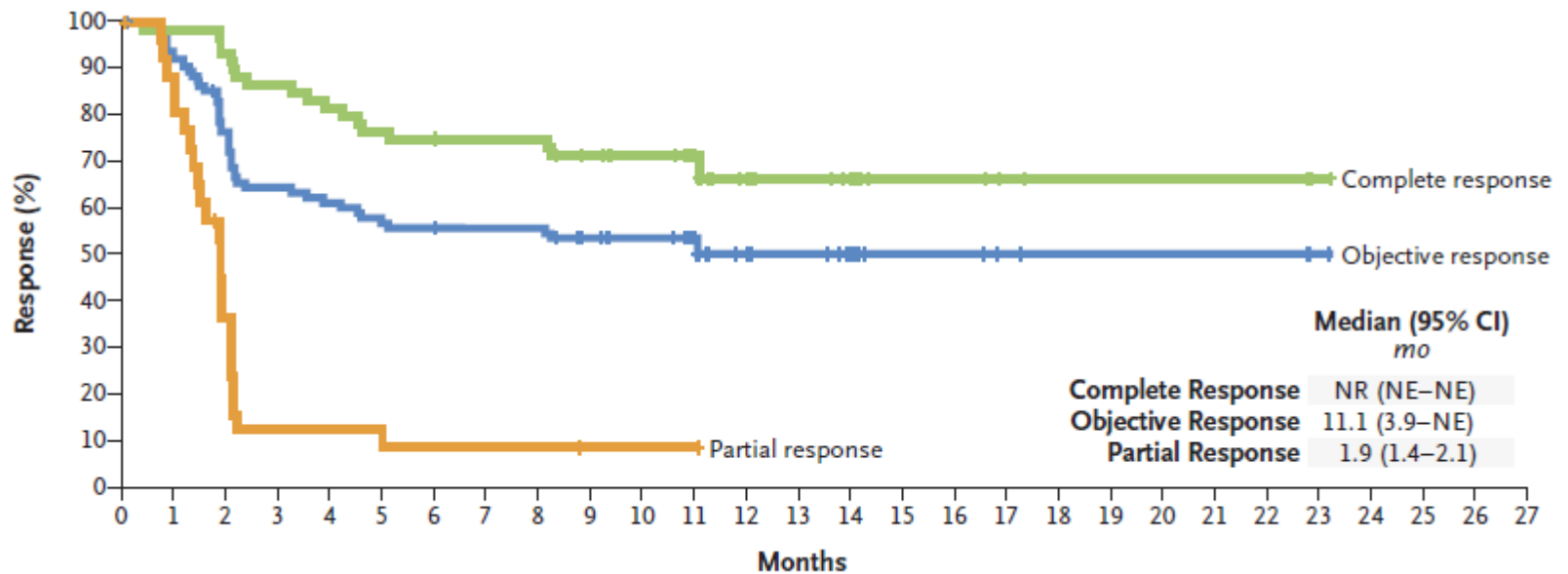


Maude et al. NEJM. 2018
 Park et al. NEJM. 2018
 Ko RH et al. J Clin Oncol. 2010

CART19 en Linfoma no-Hodgkin (LDCGB)

Estudio	N	Histología	CAR	Dosis CAR+/kg	RG (%)	RC (%)	SLP
ZUMA (Kite)	101	LDCGB; LMP, LFt	CD28-z	2×10^6	82	54	44% @ 12m
Transcend (Juno)	74	LDCGB (69); LMP, LFt; LCM	4-1BB-z	5×10^7 - 1×10^8	63	58	45% @ 6m
Juliet (Novartis)	147 (99)	LDCGB	4-1BB-z	$0,1-6 \times 10^8$	53	40	73% @ 6m

Neellapu et al. NEJM. 2018
Turtle et al . Sci Translat Med. 2016
Schuster et al. NEJM. 2018



OR: 25%; CR: < 10%
DOR: 6 months

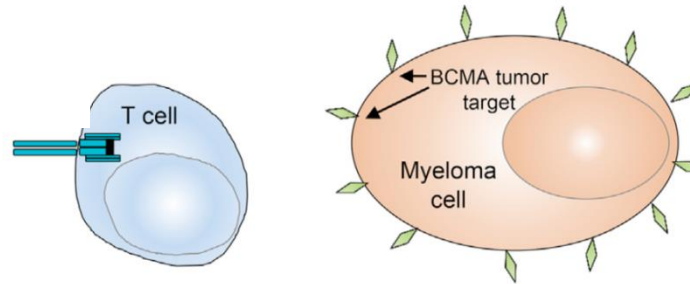
Neellapu et al. NEJM. 2018

Crump et al. Blood. 2017

CART BCMA en Mieloma

T cells are not sufficiently active to control myeloma cell accumulation

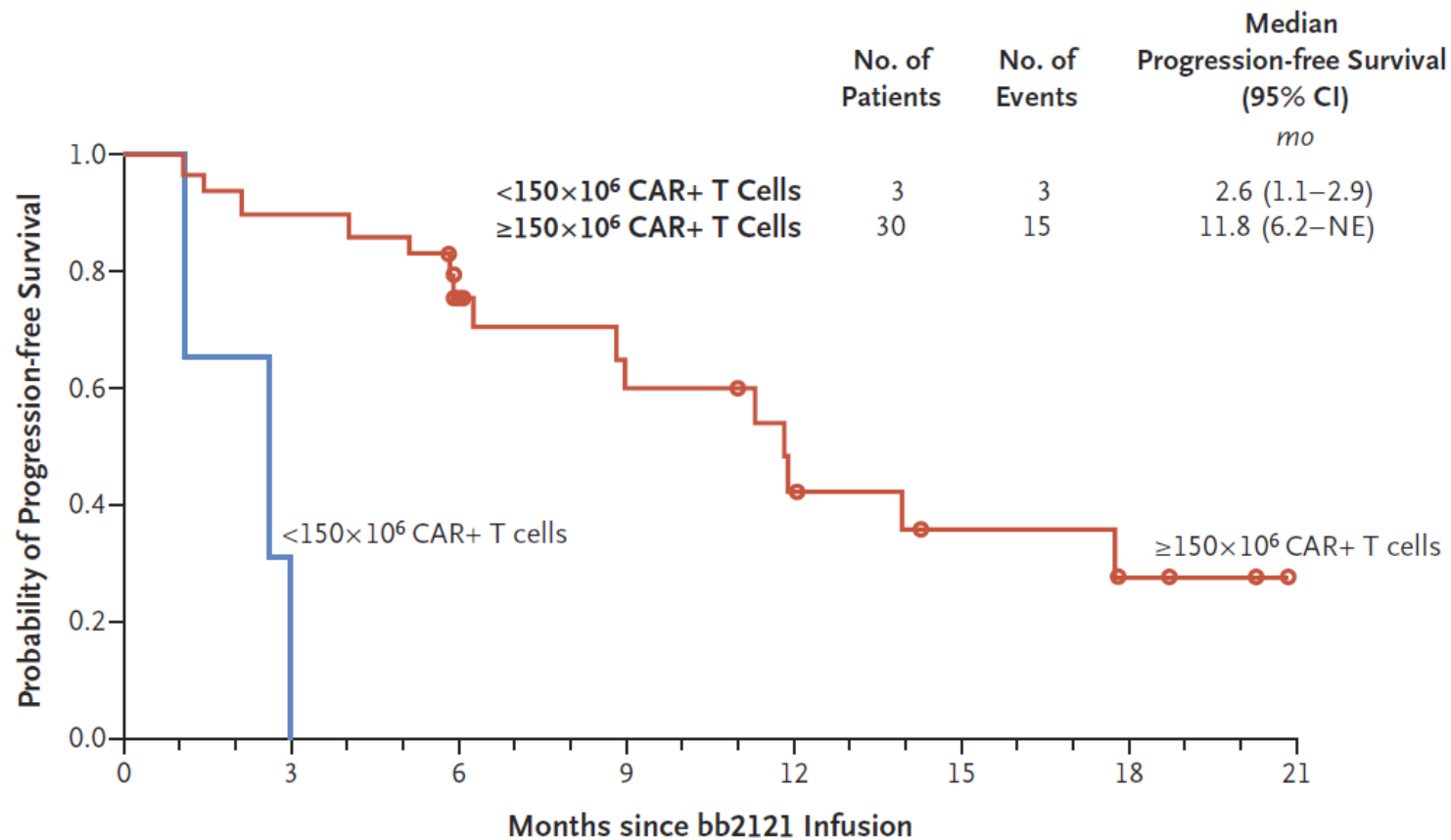
BCMA is expressed on myeloma cells of all patients



Estudio	N	Nº Tx (mediana)	CAR	Dosis (CAR+/kg)	RG (%)	RC/ VGPR (%)
Fase I-II (NCI)	32	7	4-1BB-z	5×10^7 - 8×10^8	94	56/33

Ali et al. Blood 2016
N. Raje et al. NEJM 2019

Ensayo NCI Fase I CART BCMA

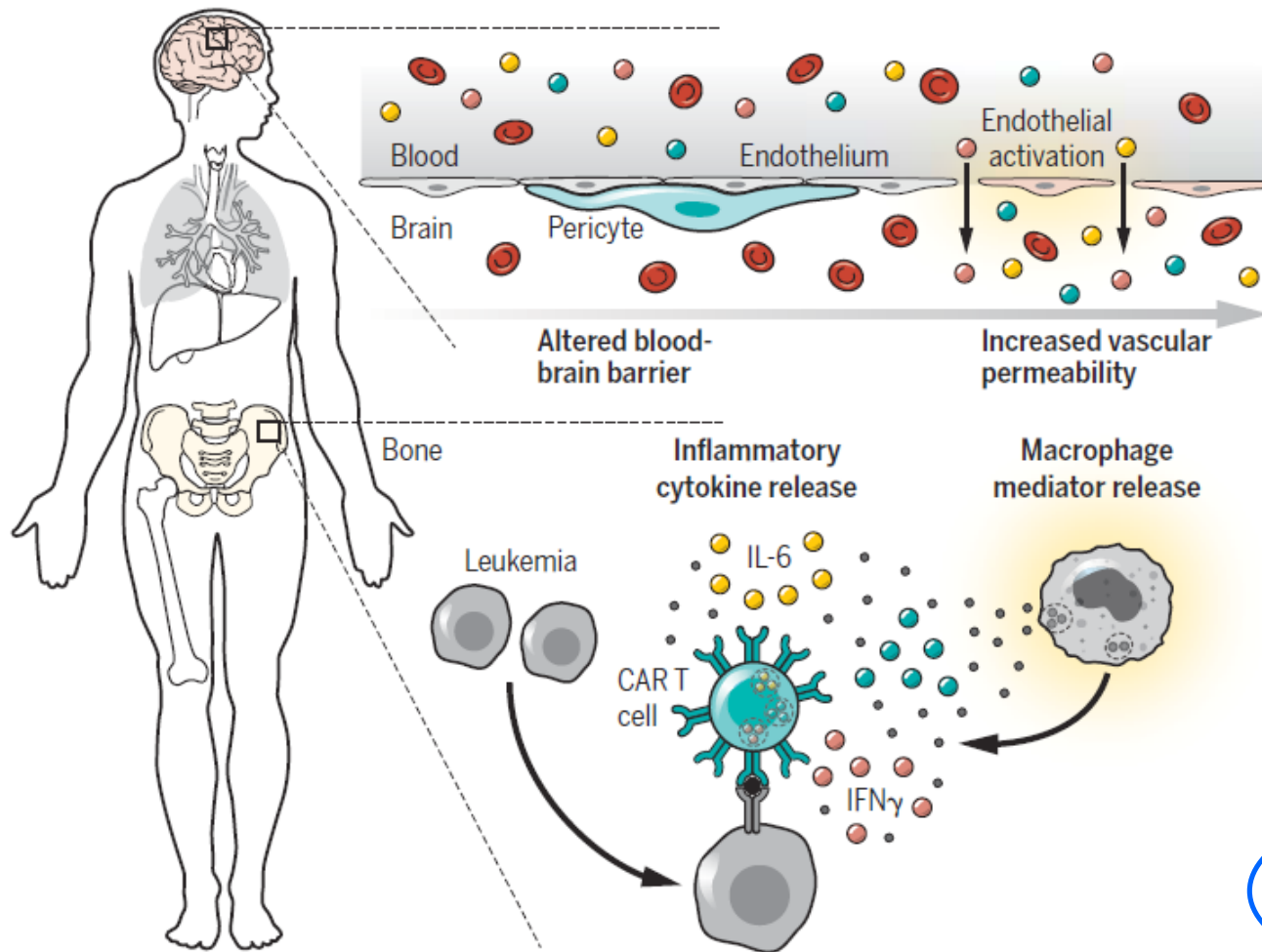


Duración mediana Respuesta : 10,9 m

CAR T: Problemas

- Mejorar eficacia (> 50% pacientes no beneficio)
 - Diseño del CAR
- Persistencia de las cels. CART
 - Cels. T de memoria
- Resistencia inmunosupresión Ambiente tumoral
- Disminución Toxicidad

Inmunoterapia CAR-T: Complicaciones



Neurotoxicidad

- Desorientación
- Afasia
- Delirio
- Convulsiones
- Edema cerebral

IL-1

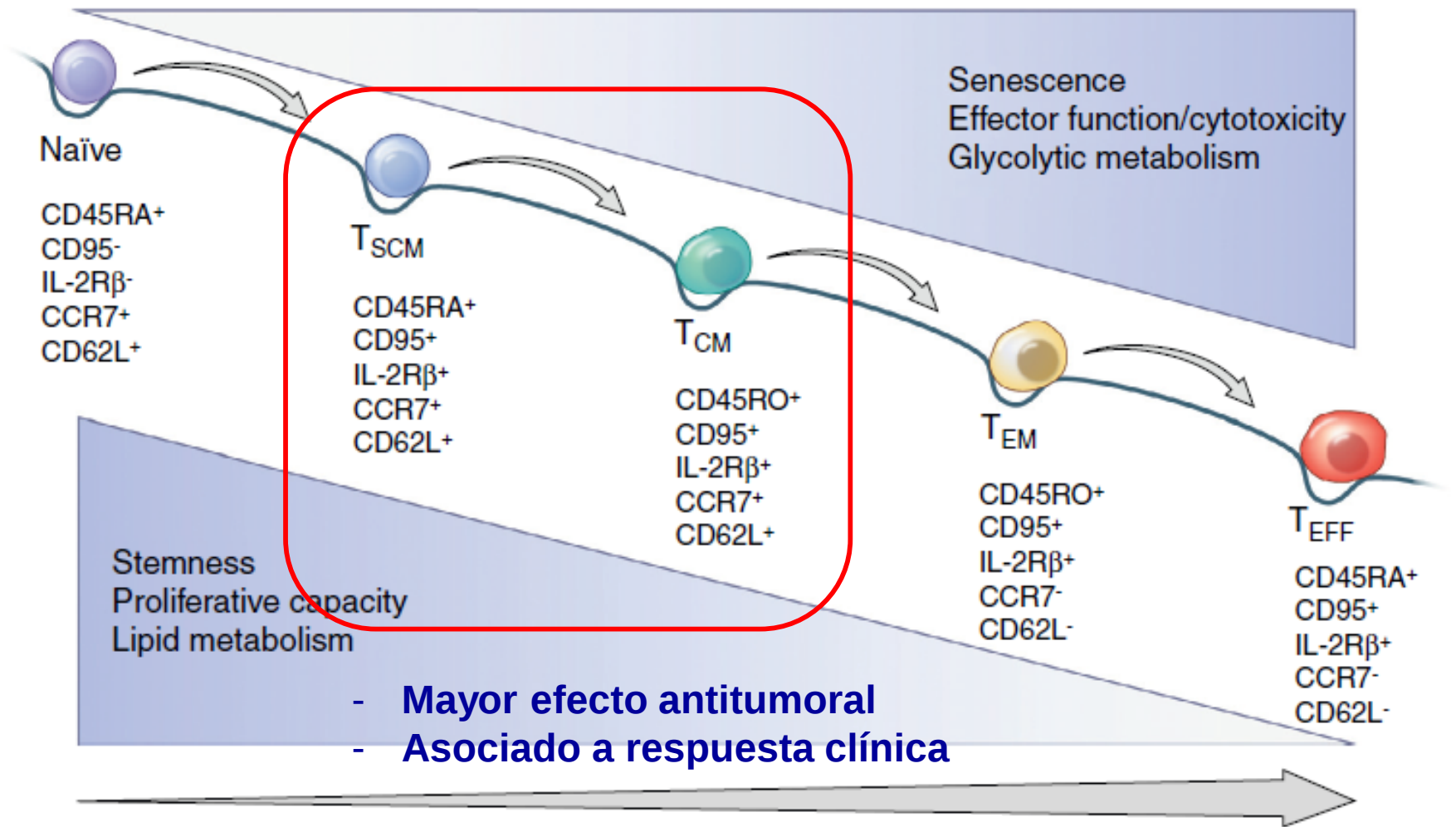
Sind. Liberación Citoquinas

- Fiebre
- Dísnea
- Insuf. Respiratoria
- Hipotensión

IL-6

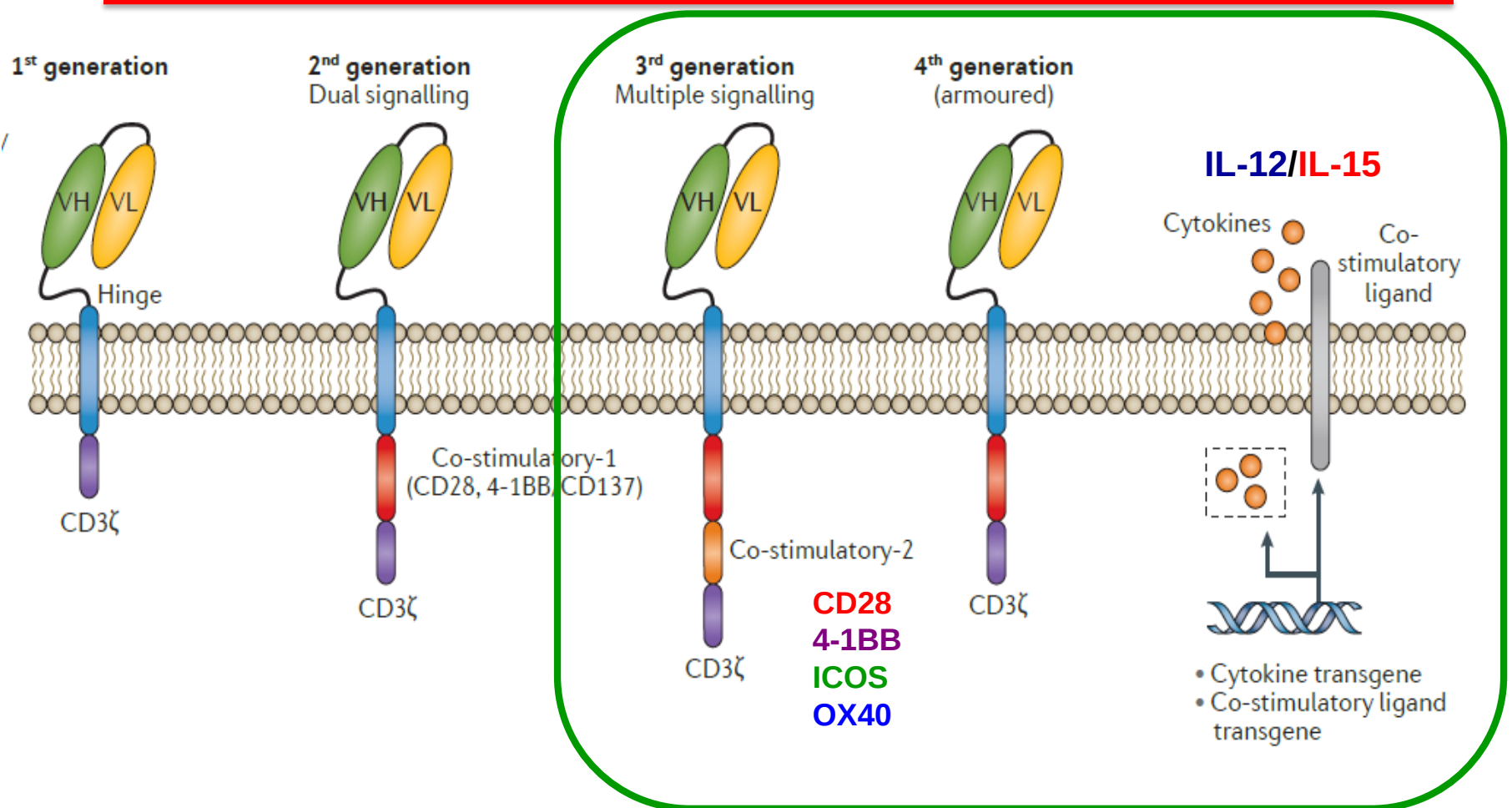
Tocilizumab

CAR T Con Subtipos de células T



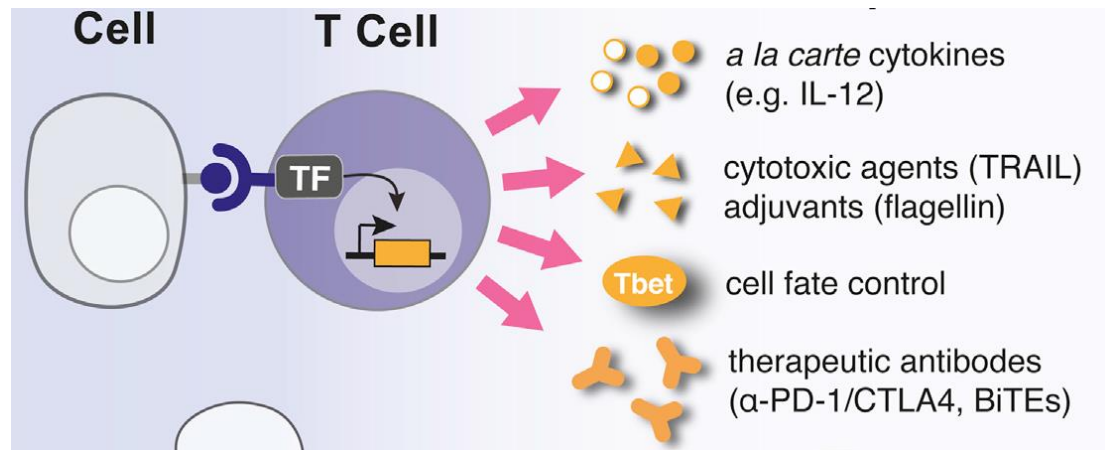
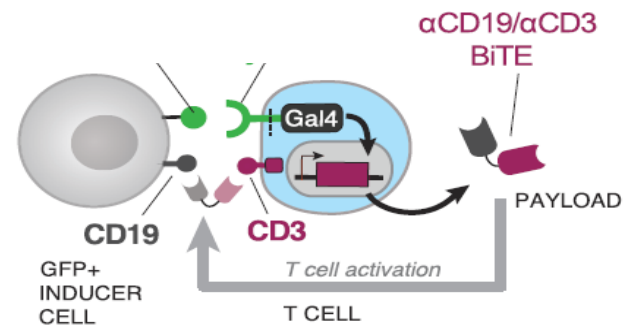
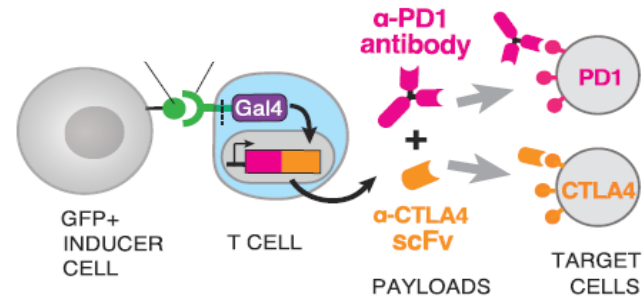
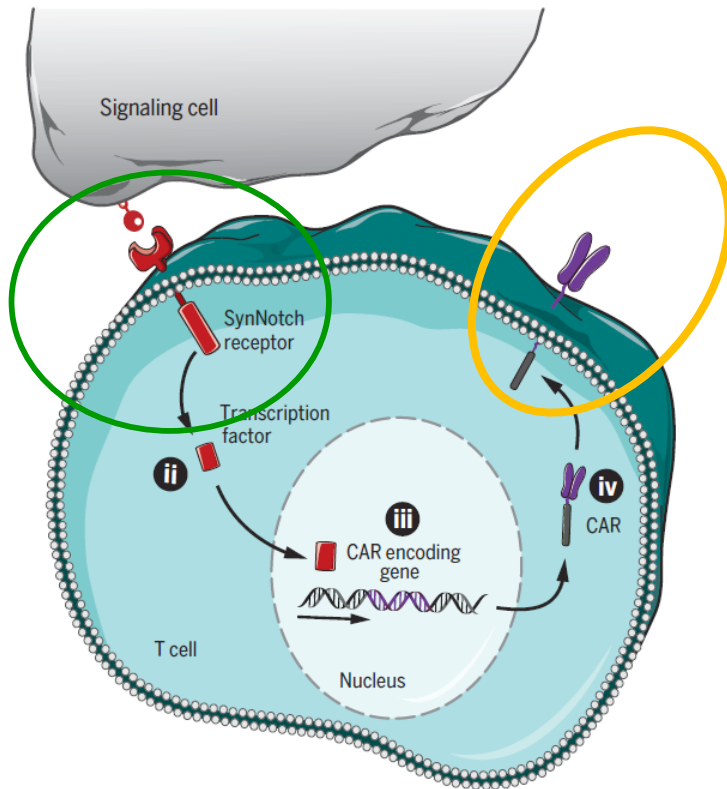
Current Opinion in Immunology

CART: Diseño y Evolución



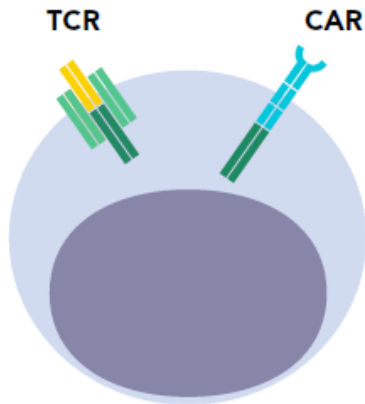
Maus et al. Annu Rev Immunol. 2014
 Brenner et al. Annu Rev Immunol. 2015
 Batlevy et al. Nat Rev Clin Oncol. 2016

CARS Inducibles: “Micro-Farmacias”

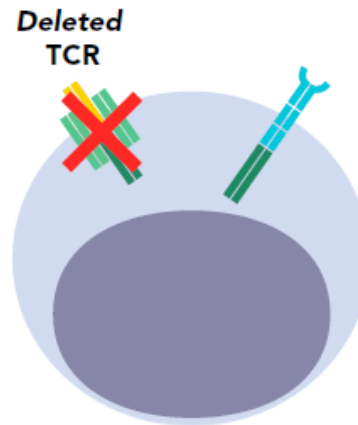


CARs Alogénicos

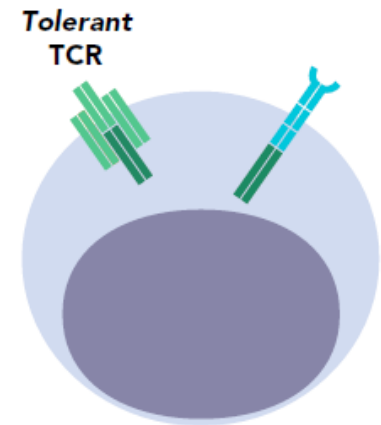
A Dual TCR / CAR T cell



B TCR-less CAR T cell



C Pro-CAR

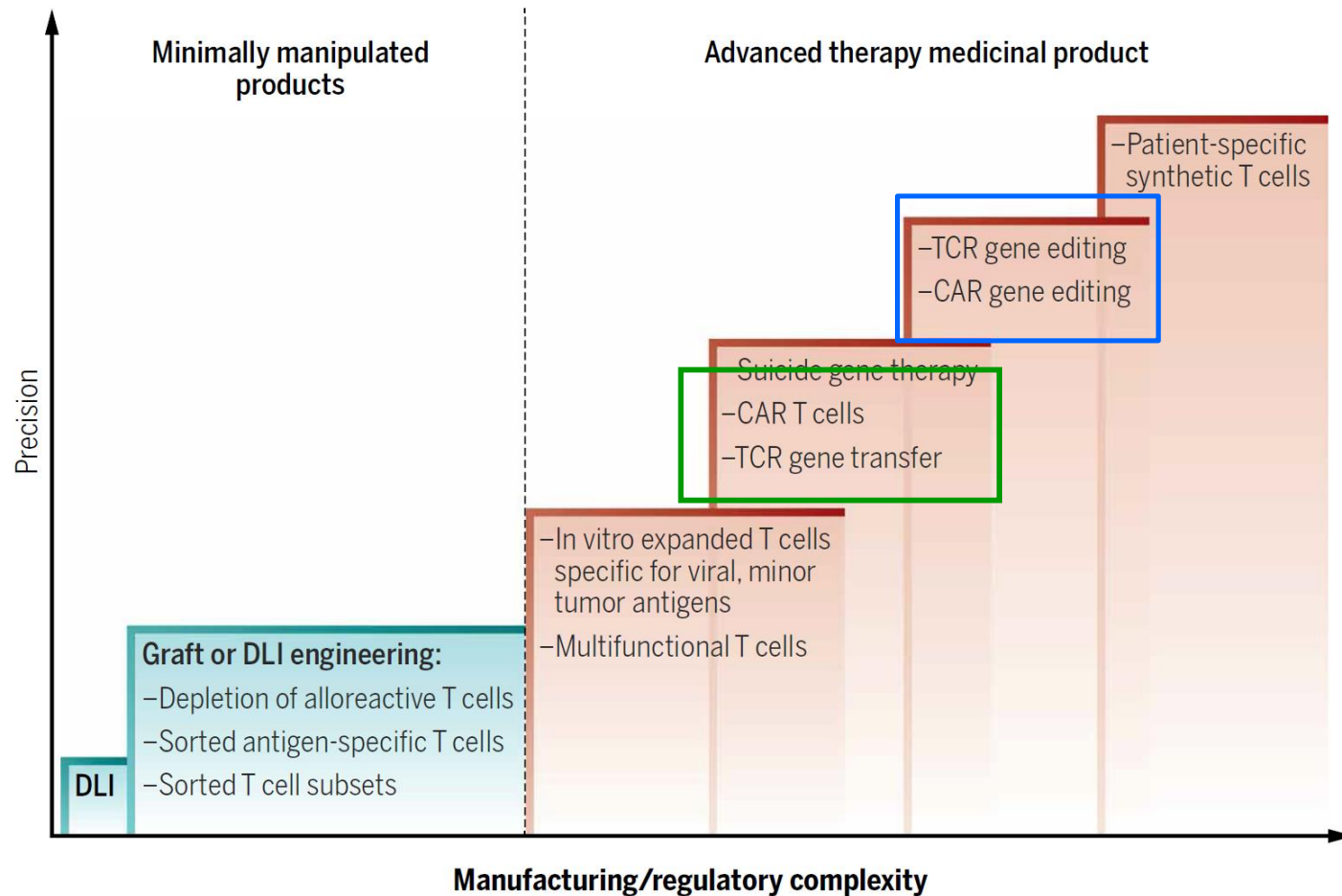


Gene-edited
TALEN, CRISPR
TRAC CAR

Progenitores Linfoides
“Educación Tímica”

EICH

Terapia Celular en la Era de la Medicina Personalizada





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