Current Status of Chimeric and Adoptive T Cell Therapy

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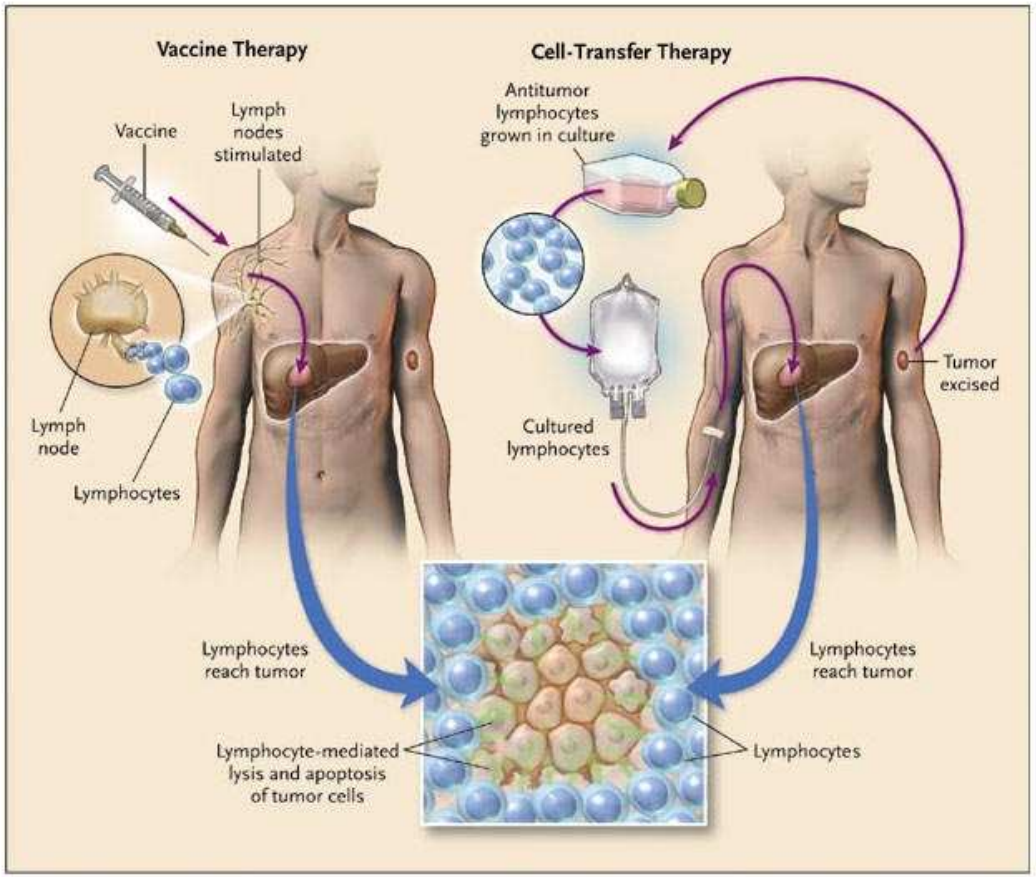
Disclosures

None

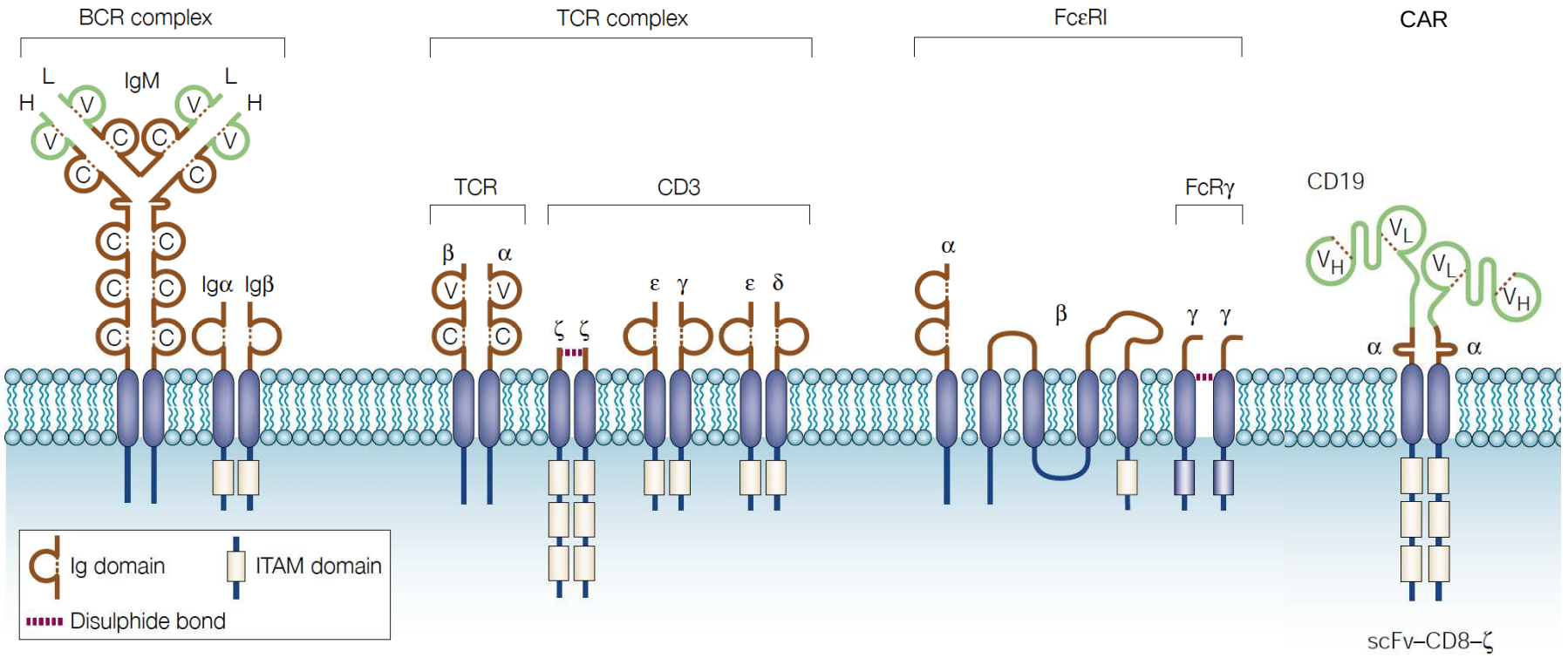
There will be discussion about the use of products for non-FDA approved indications in this presentation.

T cell immunotherapy



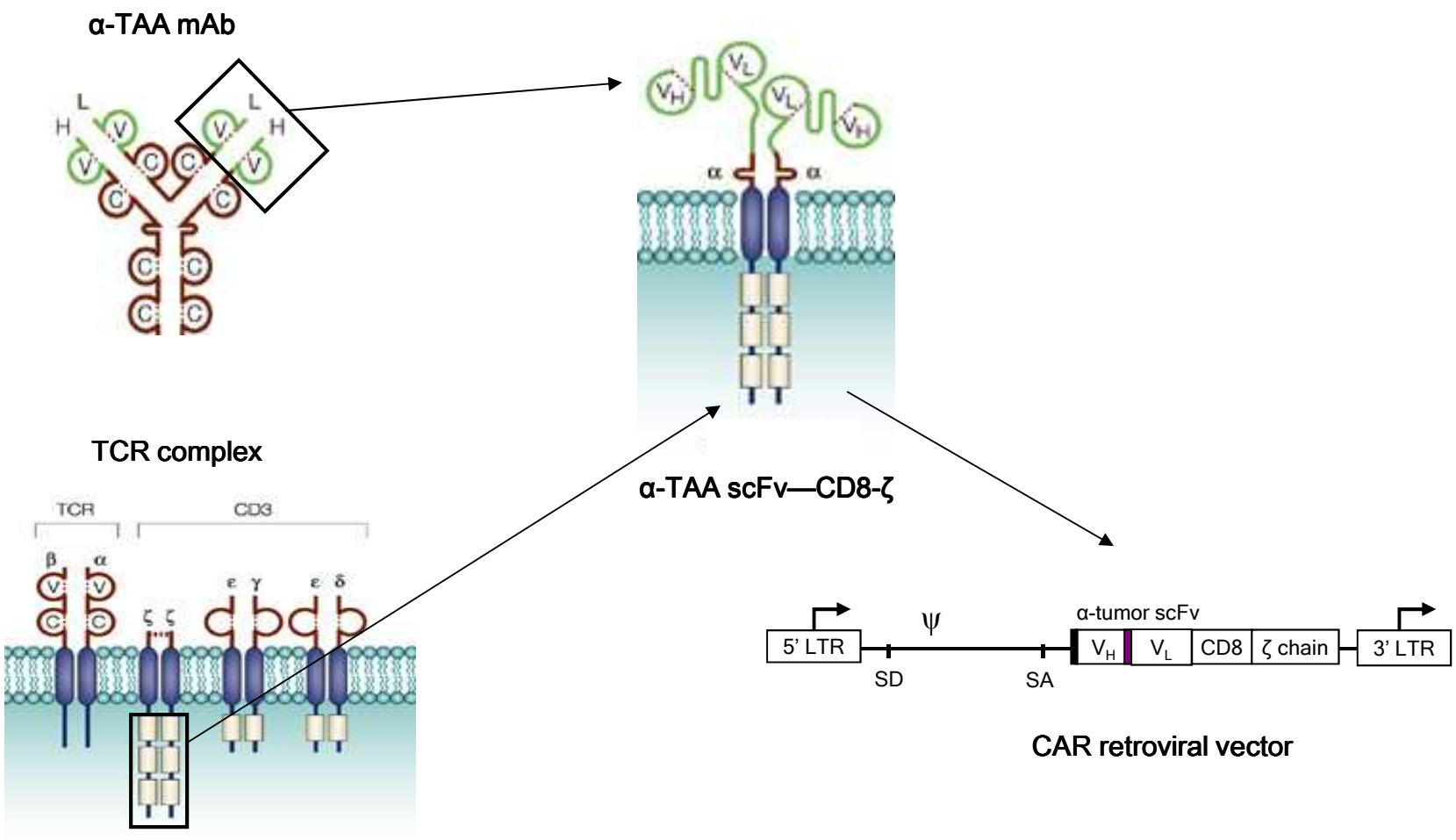
Rosenberg S. N Engl J Med 2004;350:1461-1463

Antigen Receptors

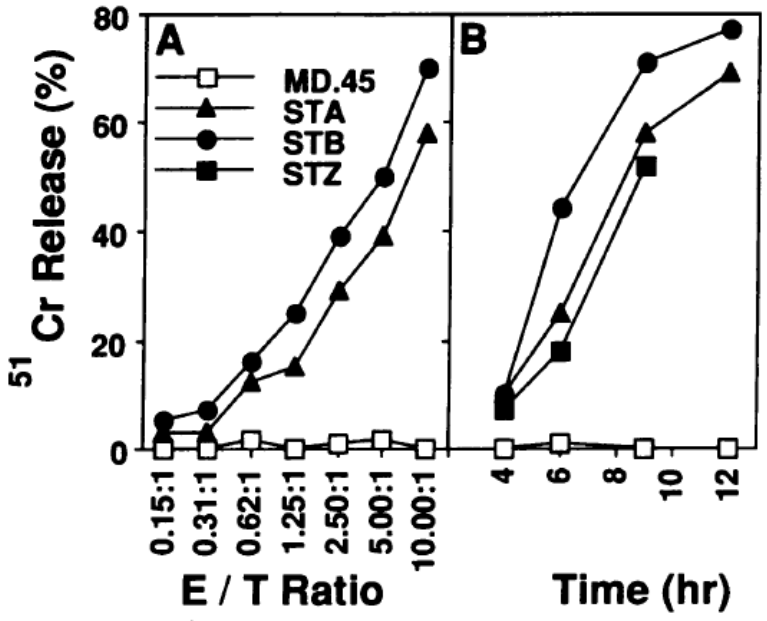


Sadelain et al. *Nat Rev Cancer 2003*

Creation of the Chimeric Antigen Receptor (CAR)



CARs genetically retarget T cells



Proc. Natl. Acad. Sci. USA
Vol. 90, pp. 720–724, January 1993
Immunology

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

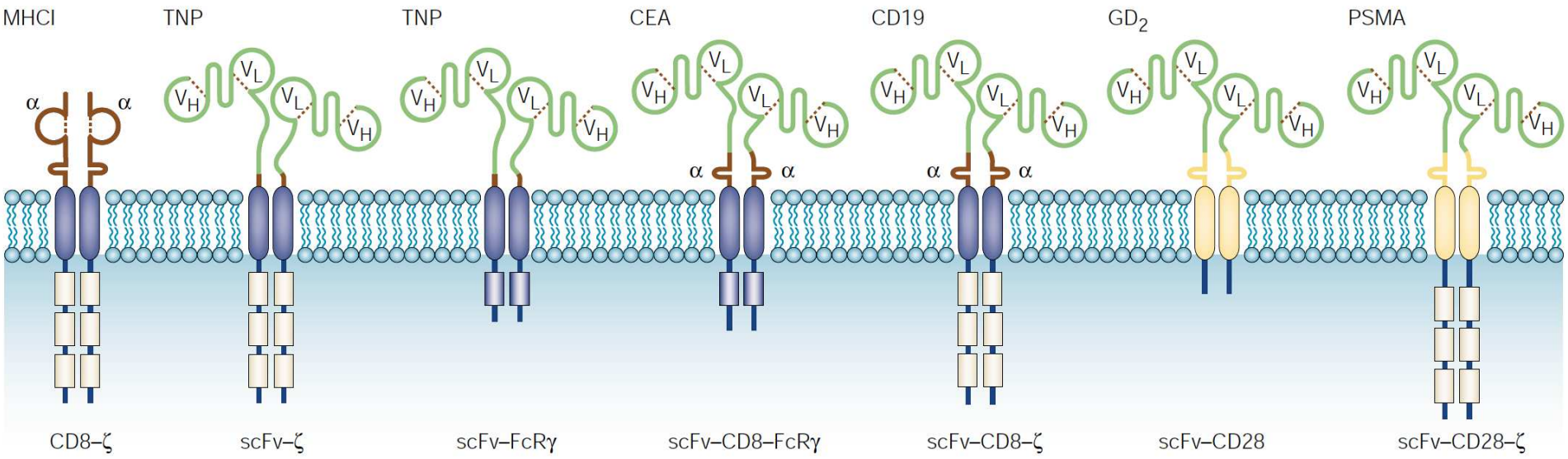
(single-chain Fv domain/chimeric receptors/immunotargeting/T cell)

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

Advantages of CARs

- HLA-independent antigen recognition
- Active in both $CD4^+$ and $CD8^+$ T cells
- Target antigens include proteins, carbohydrates and glycolipids
- Rapid generation of tumor specific T cells
- Minimal risk of autoimmunity or GvHD
- A living drug, single infusion
- Universal application to all patients

Makes & models of CARs



Sadelain et al. *Nat Rev Cancer 2003*

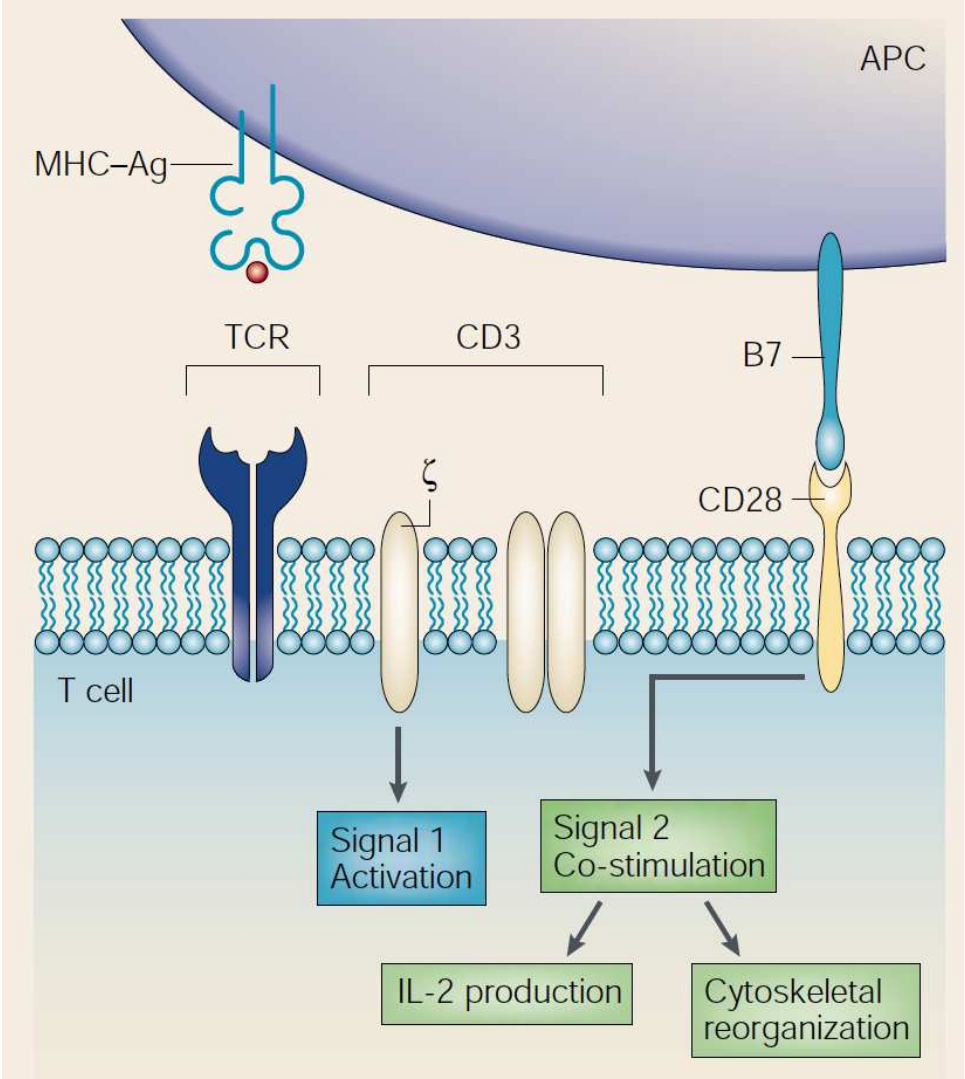
CARs hit a speedbump

Signals through T Cell Receptor–ζ Chain Alone Are Insufficient to Prime Resting T Lymphocytes

By Thomas Brocker and Klaus Karjalainen

From the Basel Institute for Immunology, 4058 Basel, Switzerland

T cell activation requires 2 signals



Sadelain et al. *Nat Rev Cancer 2003*

Next-gen CARs are better in vivo

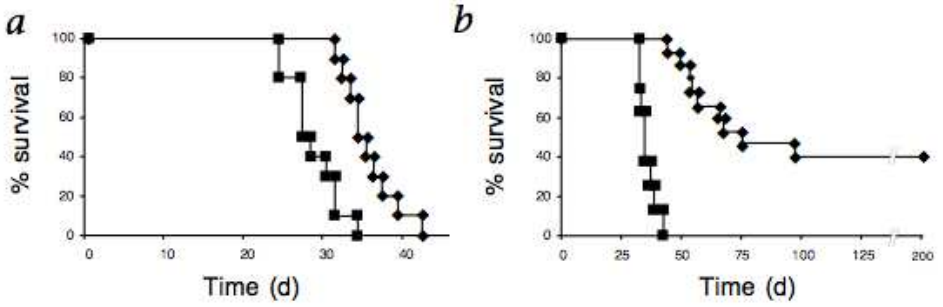
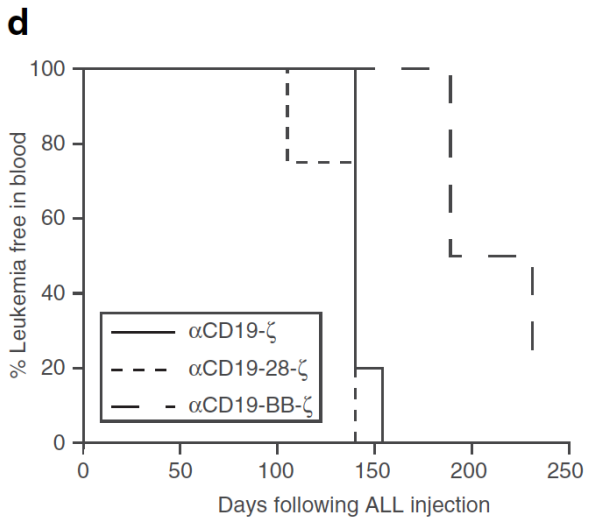


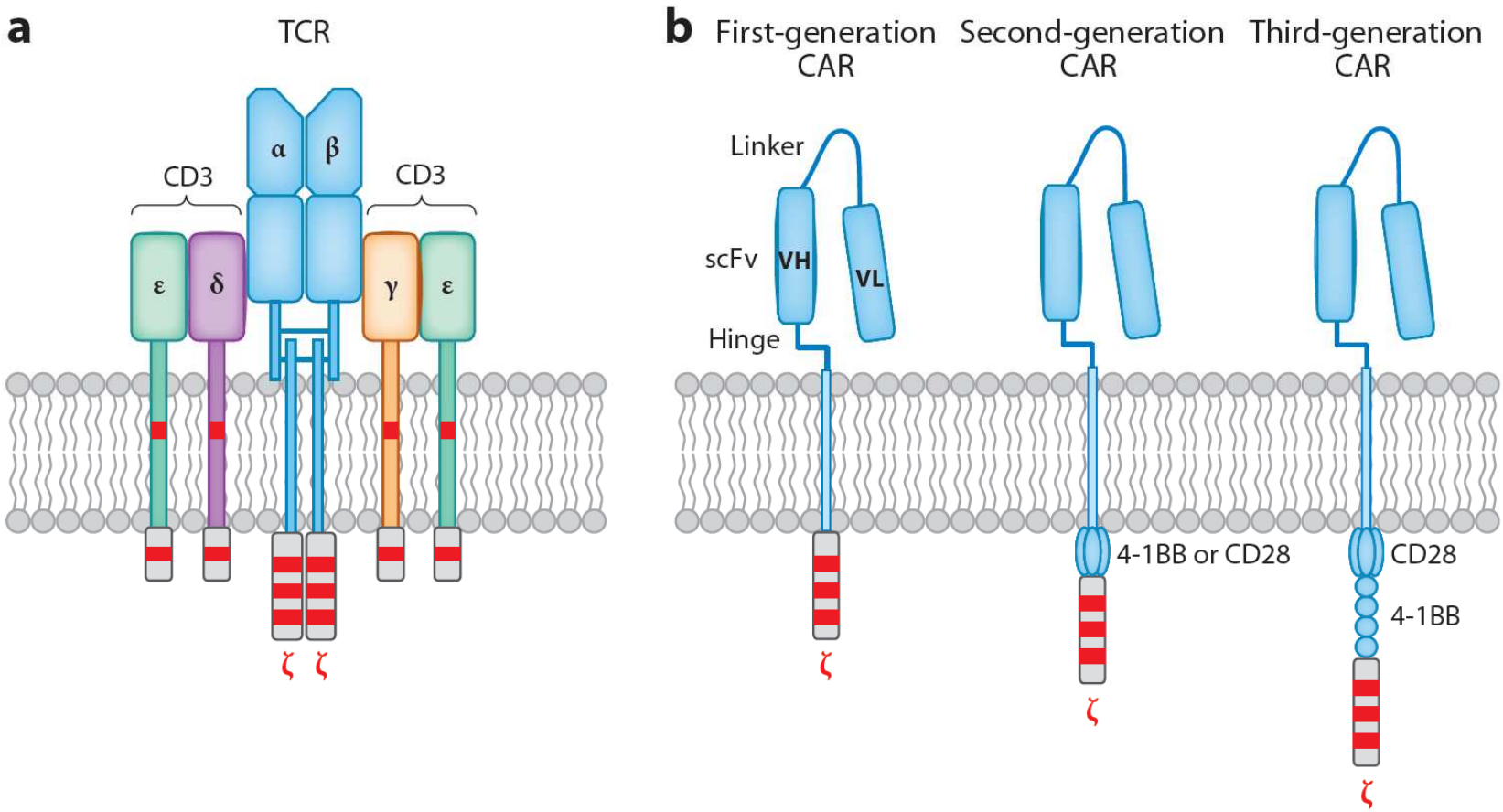
Fig. 4 Tumor cell eradication by 19z1$^+$ T cells is dependent on *in vivo* T-cell co-stimulation. ***a***, Kaplan-Meier survival curve of SCID-Beige mice treated with 1×10^7 19z1$^+$ (◆; $n = 10$) or Pz1$^+$ (■; $n = 10$) T cells 4 and 5 d after NALM-6 tumor cell injection. ***b***, Kaplan-Meier survival curve of SCID-Beige mice treated with 7.5×10^6 19z1$^+$ (◆; $n = 15$) or Pz1$^+$ (■; $n = 8$) transduced T cells 4, 5 and 6 d after NALM-6(CD80$^+$) tumor cell injection. Results represent data pooled from 2 independent experiments.



Brentejens et al. *Nat Med 2003*

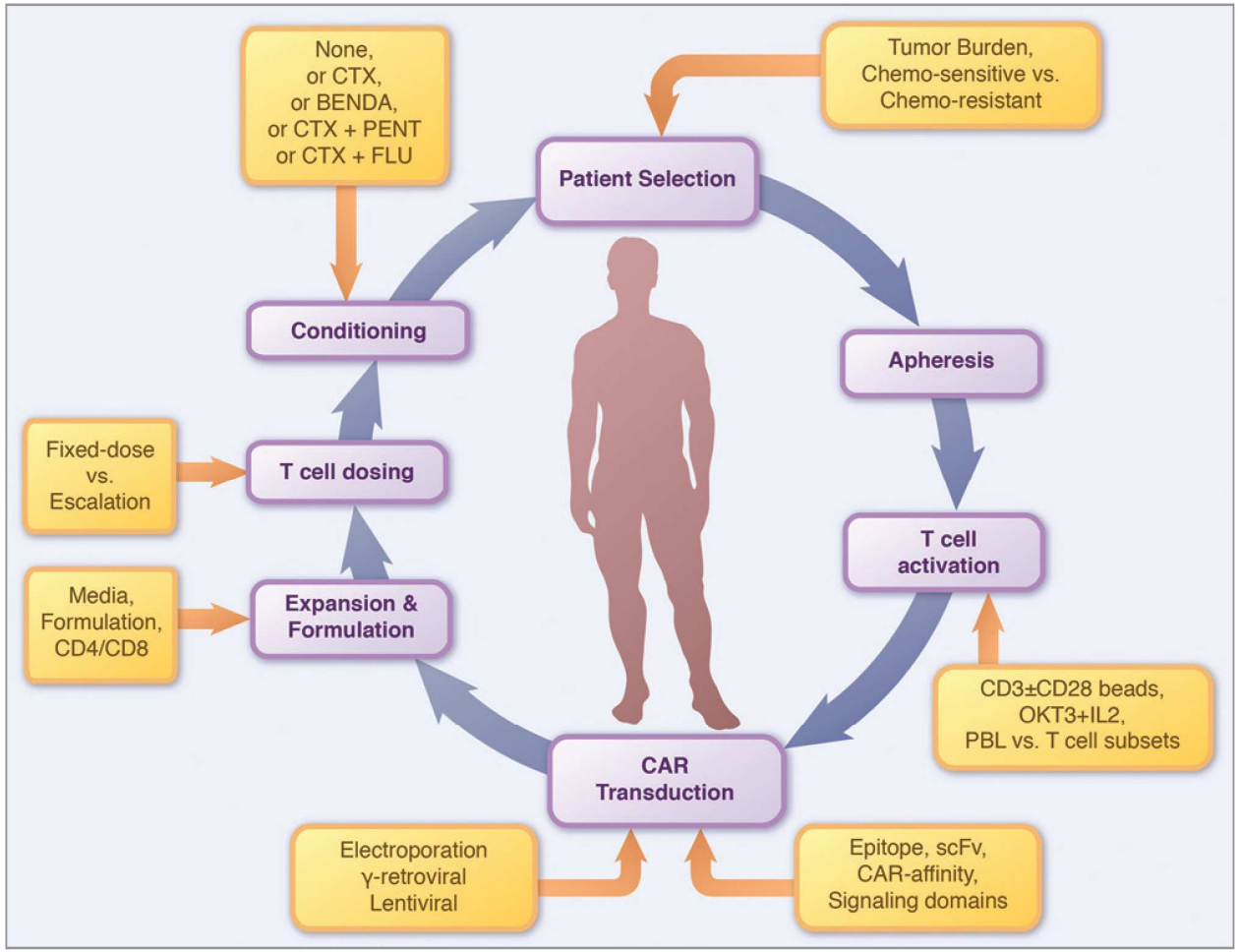
Milone et al. *Molecular Therapy 2009*

Next-gen CARs



Maus et al. *Ann Rev Immunology 2013*

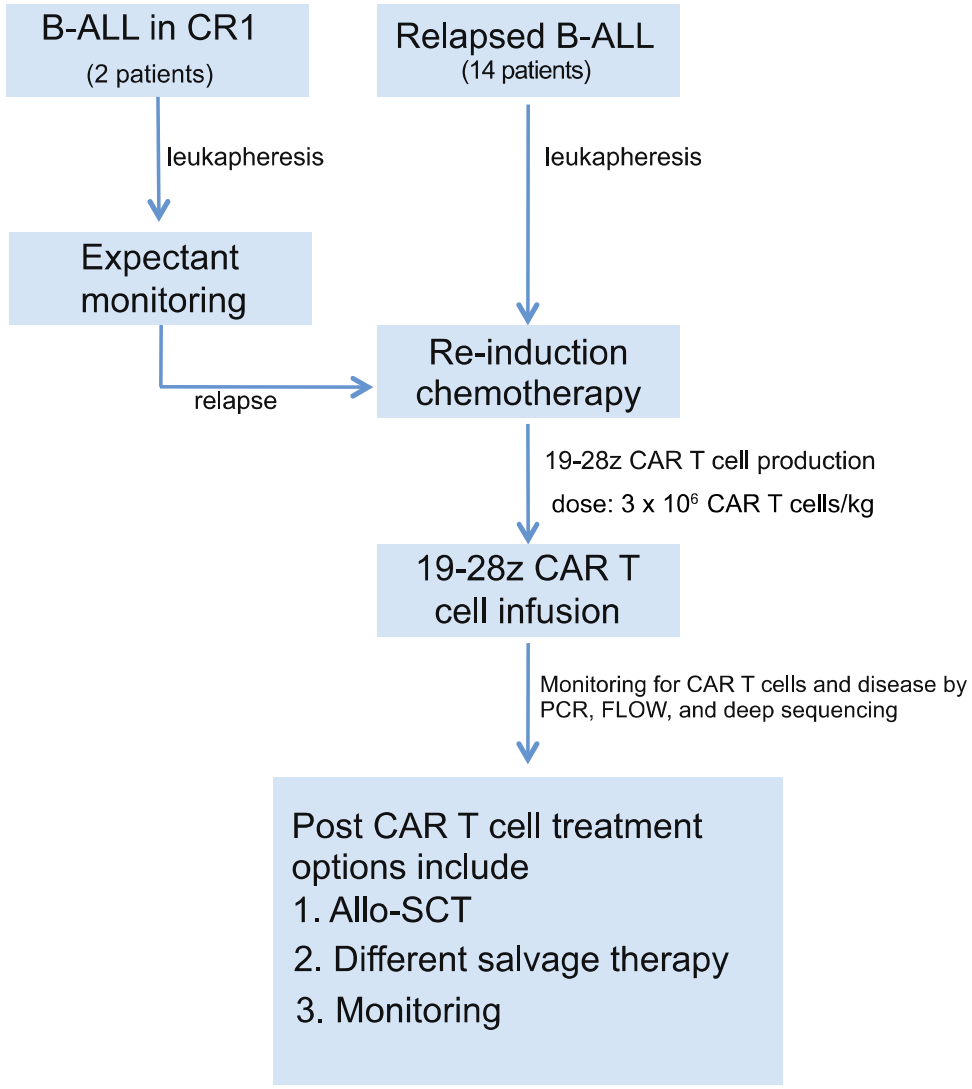
CARs in clinical trials



Davila et al. *Oncoimmunology 2012*

Eligibility and Treatment Schemes

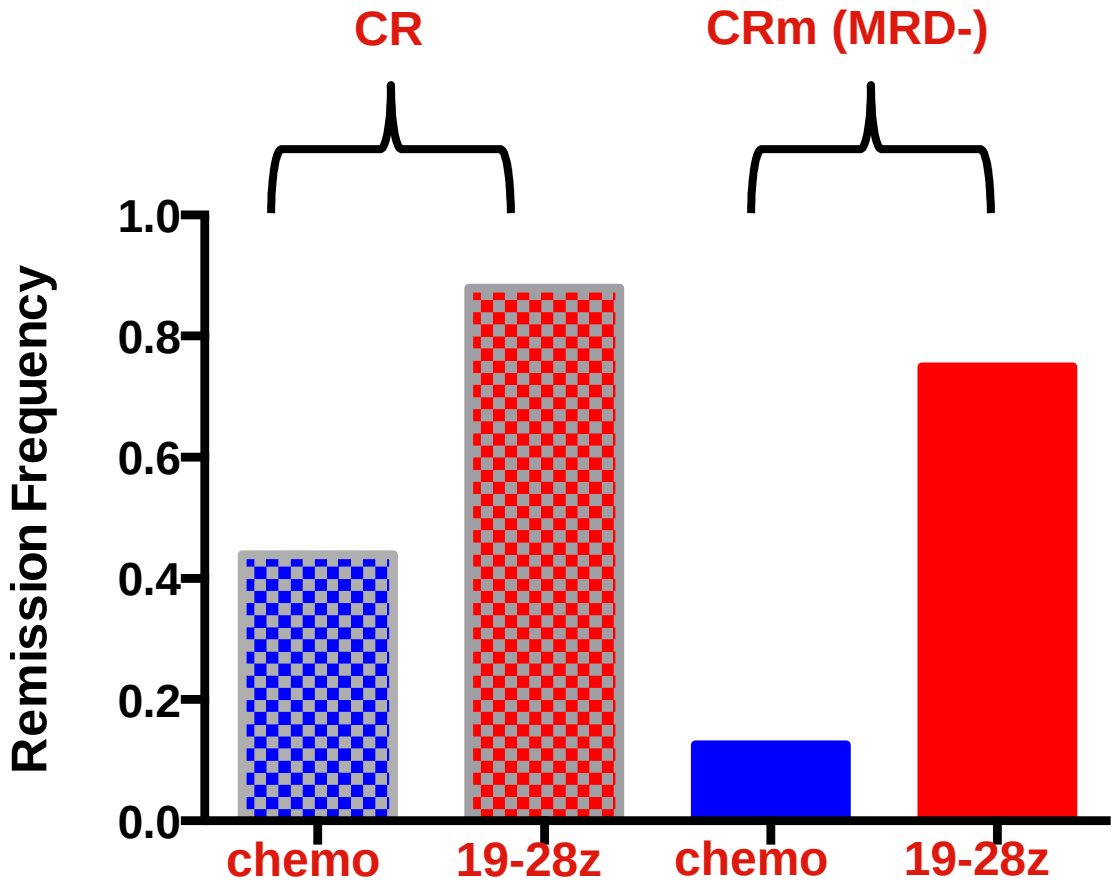
- Adult patients are eligible (>18 year old).
- Patients must have B-ALL refractory, relapsed, MRD+, or in CR1. Ph+, extramedullary disease, CNS Leukemia, and/or relapsed after prior allo- stem cell transplant are all eligible.



Patient and disease characteristics

Patient Characteristics (n=16)	# Patients	%
Age (years)		
Median	50	
Range	23-74	
Baseline tumor cytogenetics		
Unfavorable	7	**44**
Ph+	4	**25**
Other	9	**56**
Prior Allo-SCT		
Yes	4	**25**
No	12	**75**
Refractory to pre-CAR T salvage therapy		
Yes	14	**88**
No	2	**12**
Tumor burden in BM before CAR T cell infusion (n=15)*		
MRD-	2	**13**
MRD+	5	**33**
overt residual disease	8	**53**

19-28z CAR T cells are an effective salvage therapy

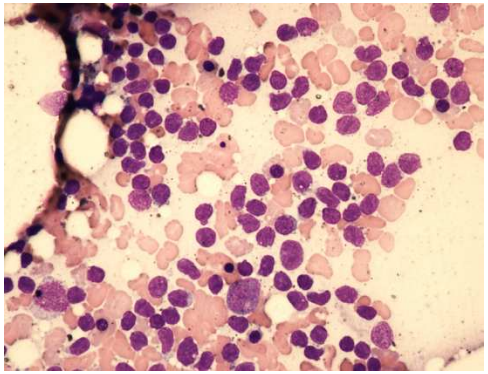
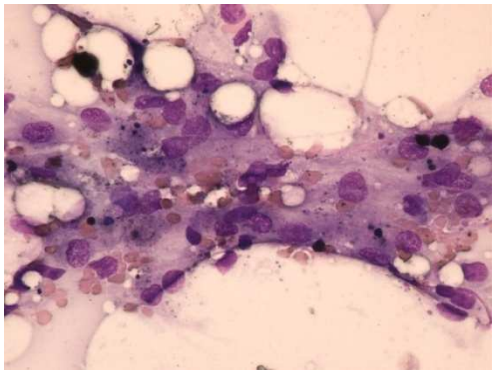
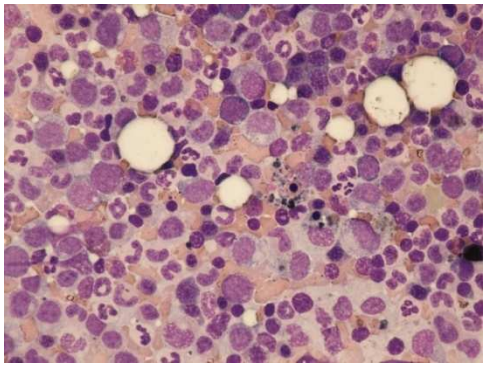
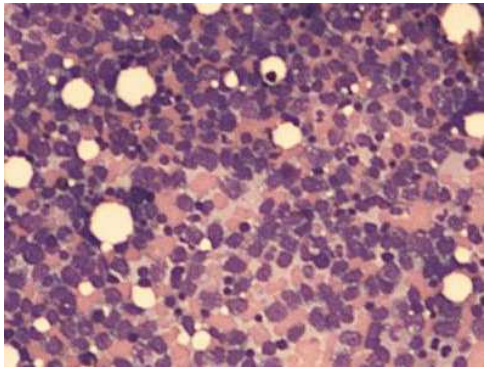
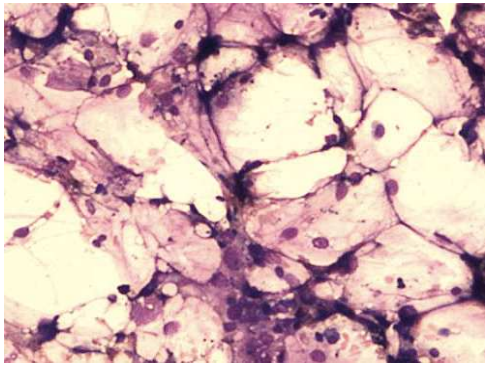
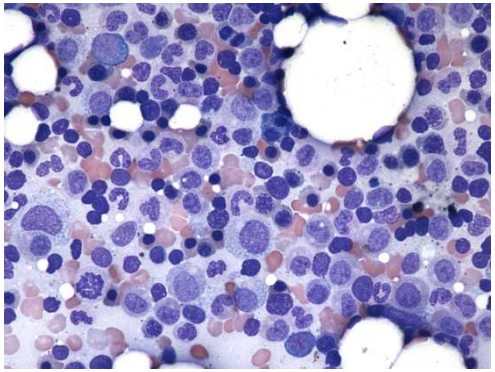


Davila et al. *Sci Trans Med 2014*

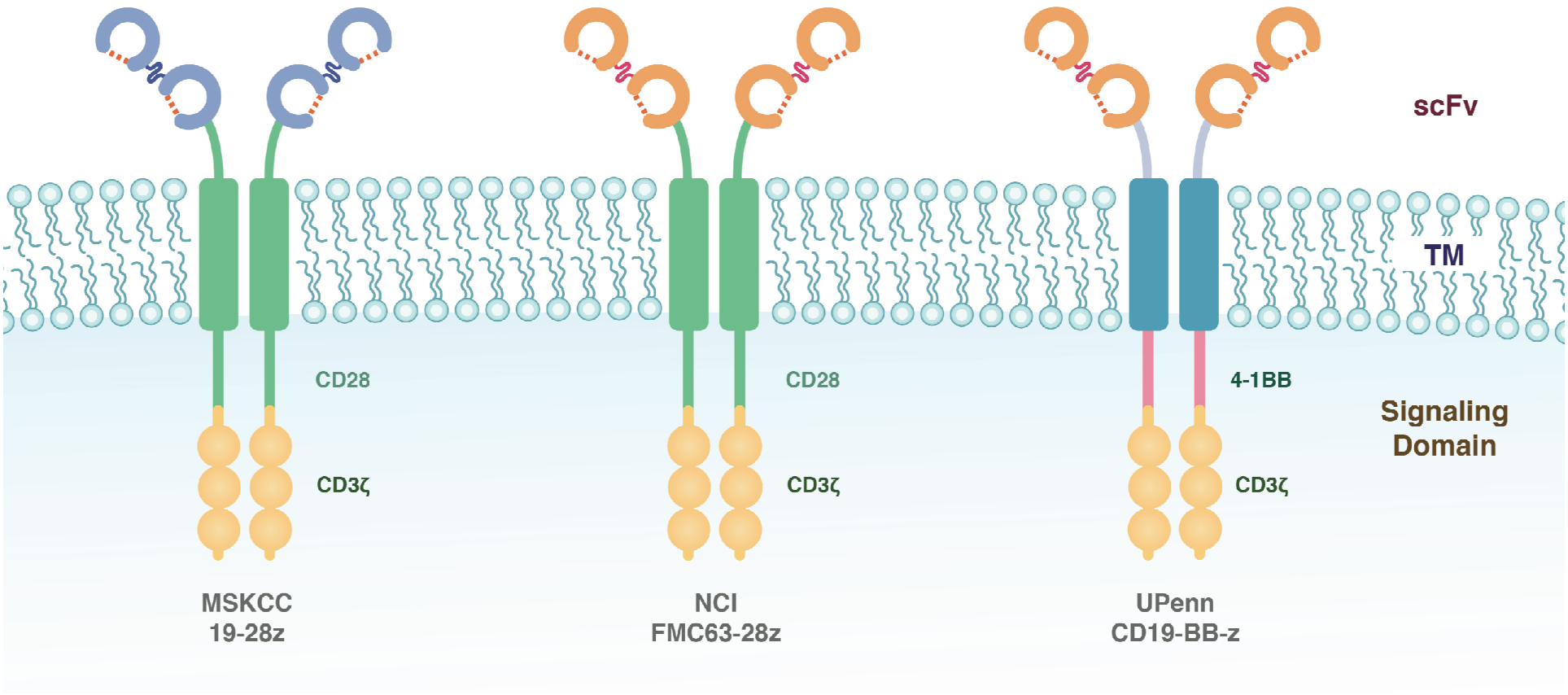
Treatment of chemotherapy refractory B-ALL

- MSK-ALL4
  - 59 yo male with relapsed B-ALL after therapy on ECOG-2993
  - Salvage chemotherapy with vincristine/prednisone
  - 63% blast cells in the BM after re-induction chemotherapy
- MSK-ALL5
  - 56 yo male with relapsed B-ALL after therapy on ECOG-2993
  - Salvage chemo with high dose AraC and mitoxantrone
  - 70% BM blasts after re-induction chemotherapy

Rapid Morphological Remissions Following CAR Modified T cell Infusions

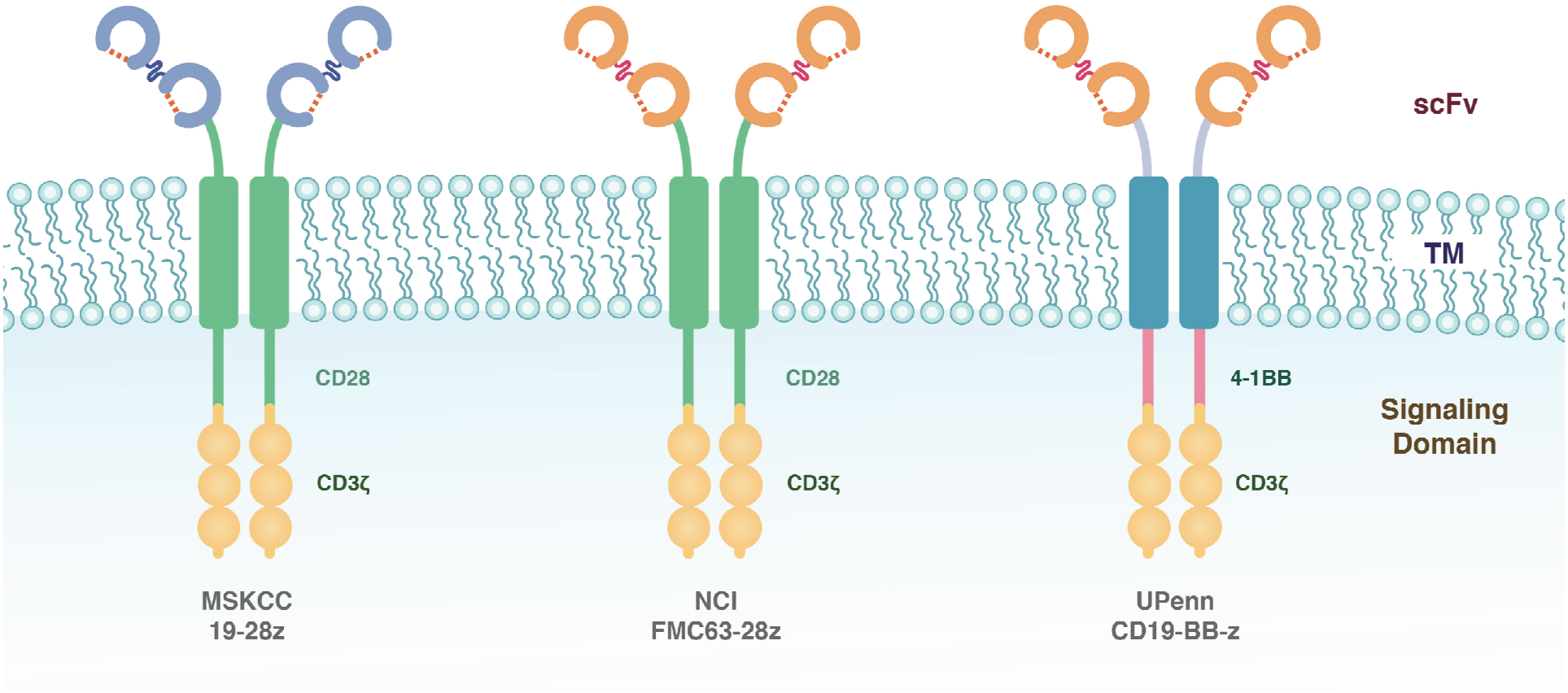
	A	B	C
MSK-ALL04			
MSK-ALL05			

CD19-targeted CAR T cell therapy for B-ALL: Similar efficacies



Davila et al. *Oncoimmunology 2012*

CD19-targeted CAR T cell therapy for B-ALL: Similar efficacies

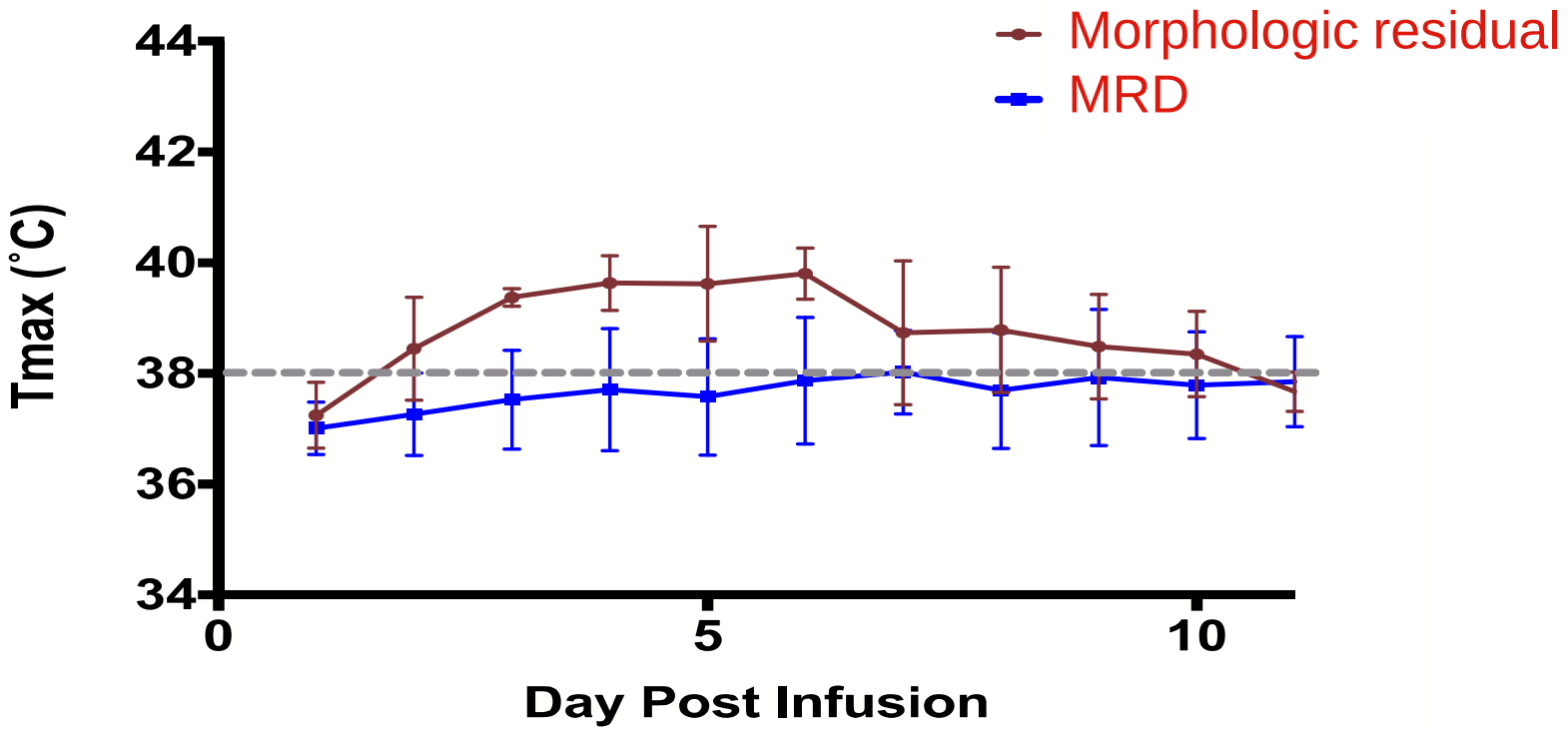


CR:	88% (n=16)	67% (n=21)	90% (n=30)
	Davila, et al Science Trans Med 2014	Lee et al, Lancet 2014	Maude et al, NEJM 2014

Adverse Events

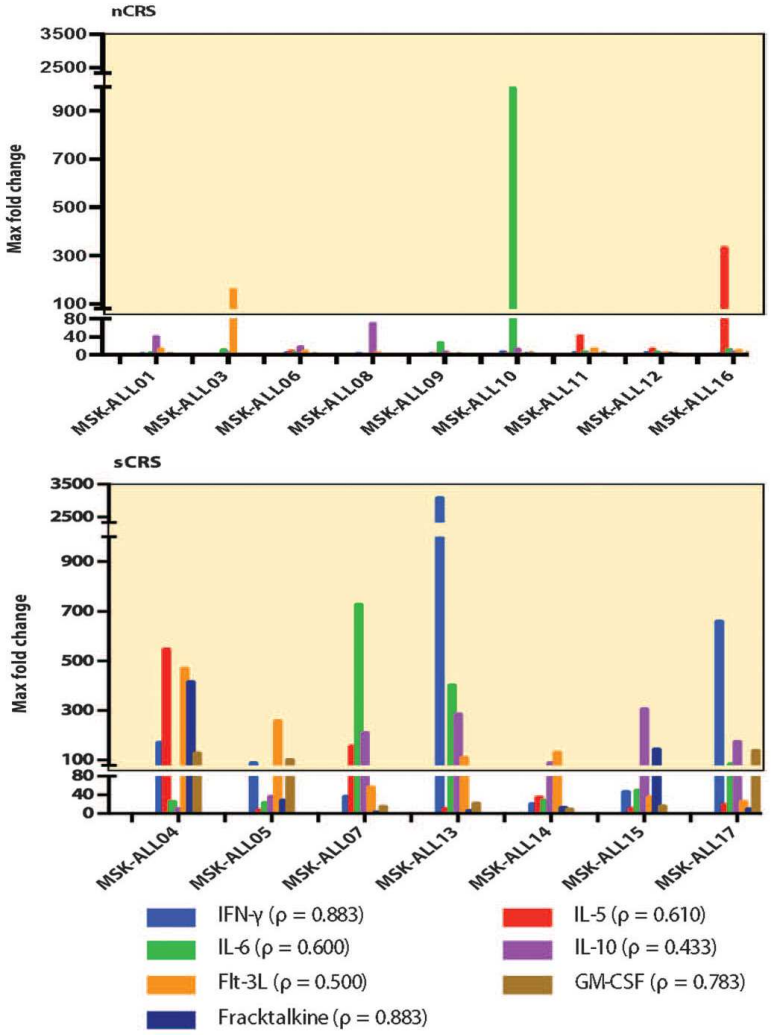
- Fevers
- Hypotension
- Hypoxia
- Neurologic changes
  mental status change, obtundation, seizures
- Malaise

Fevers post CAR T cell infusion



Davila et al. *Sci Trans Med 2014*

The toxicities are due to a cytokine release syndrome (CRS)



No CRS

CRS

Davila et al. *Sci Trans Med 2014*

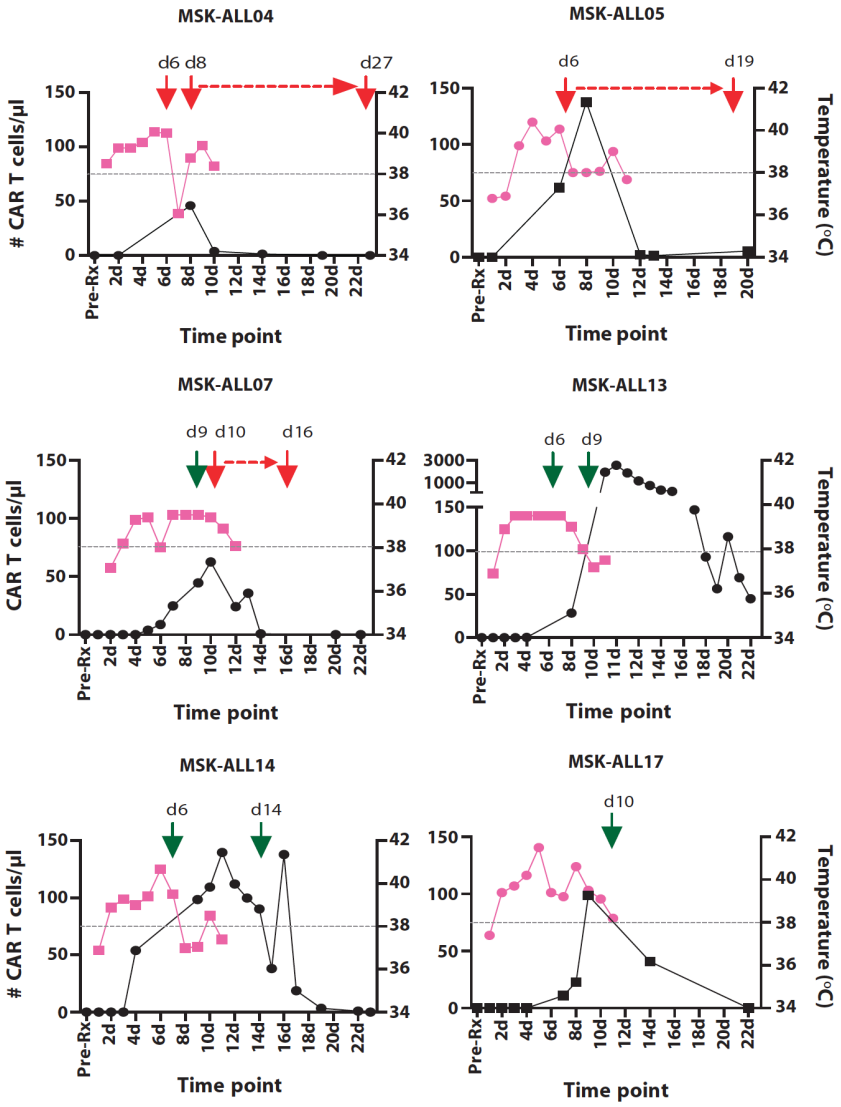
Pharmacologic management for CRS

CART cells/μl

T_{max}

Steroids administered

Tocilizumab administered



Davila et al. *Sci Trans Med 2014*

Summary

- Equivalent high complete response rate in patients with chemotherapy refractory disease
- Patients can be transitioned to an allo-SCT
- Steroids are effective at ameliorating the CRS but at the cost of lymphotoxicity, resulting in eventual relapses
- Tocilizumab is effective at treating the CRS without lymphotoxicity.
- Neurologic toxicities, which are self-limiting, are associated with CAR T cell detection in the CNS
- CD19-negative escape leads to relapses

Initial clinical trials using CD19 targeted T cells in low grade B cell malignancies

Comparison of trials using CD19 CAR-targeted T cells in patients with indolent B cell malignancies

Center	T-cell activation	Gene delivery and expression methods	EOP T-cell phenotype	Range days in culture
UPenn	Anti-CD3/Anti-CD28 stimulation	Lentiviral vector (EF-1α promoter)	NA	10–14
NCI	Anti-CD3 (OKT3) + autologous PBMCs	MSCV-Gammaretroviral vector	CD45RA+ (5–26%), CD62L+ (4–35%) CCR7+ (5–37%)	24
MSKCC	Anti-CD3/Anti-CD28 stimulation	SFG-Gammaretroviral vector	CD62L+ (9–78%) CCR7+ (1–36%) CD28+ (43–94%) CD25+CD4+ FOXP3+ (0.6–2.4%)	11–19
Baylor	Anti-CD3 (OKT3)	SFG-Gammaretroviral vector	CD45RA+ (0–15%) CD62L+ (15–90%) CCR7+ (0%) CD28+ (15–90%)	6–18
City of Hope	Anti-CD3 (OKT3) + PBMCs/lymphoblastoid cell lines	Plasmid electroporation and hygromycin B selection	NA	≥ 55

EOP, end of production; NA, not available; PBMC, peripheral blood mononuclear cell.

Davila et al. *Oncoimmunology 2012*

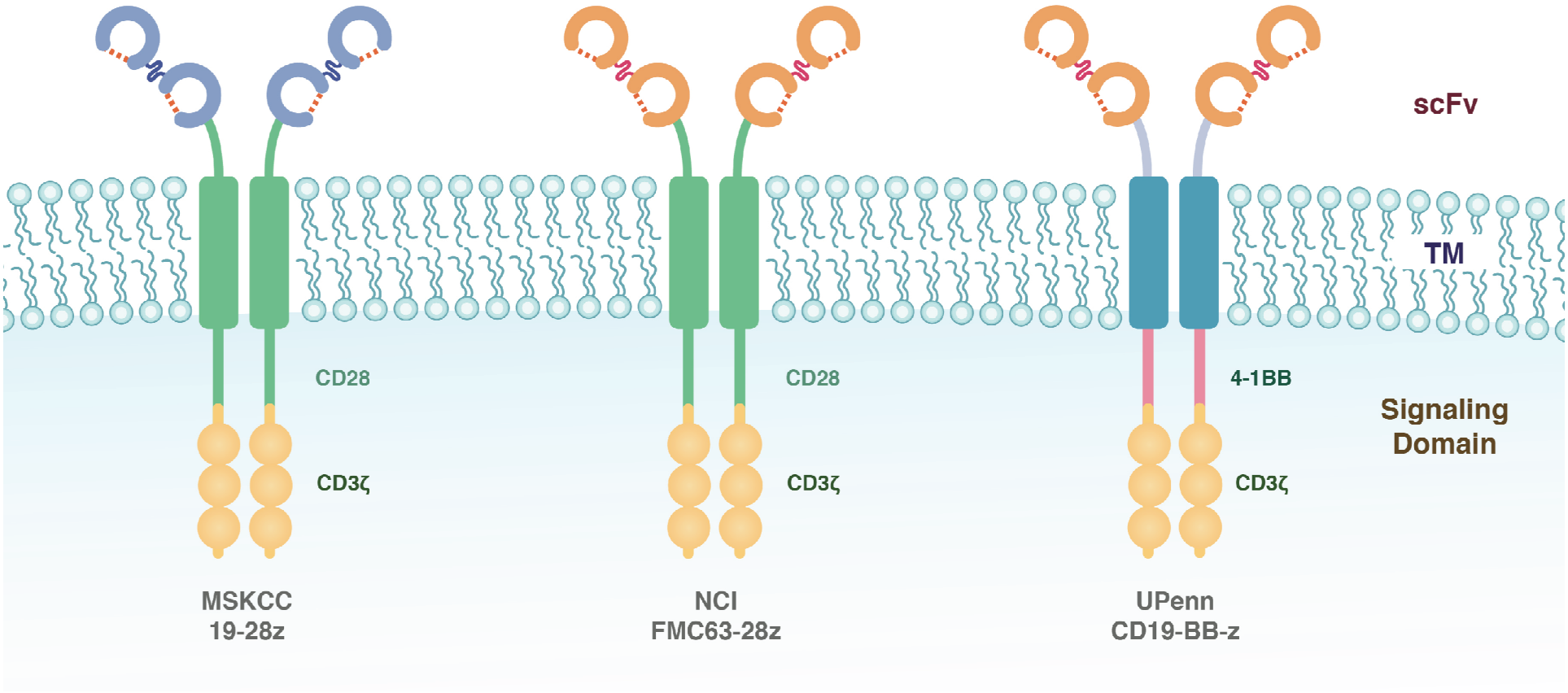
Comparisons of published clinical data

Patient*	CAR$^+$ T-cell dose (per kg)	CD4$^+$/CD8$^+$ ratio	Tumor burden**	E:T ratio***	Outcome	Max VCN (per μg DNA)	Peak CAR detection (day)
MSKCC01	31×10^6	94/5	4.2×10^{12}	6.0×10^{-4}	PD	43	14
MSKCC02	15×10^6	96/5	****	****	PD	0	NE
MSKCC03	15×10^6	93/8	2.9×10^{12}	3.7×10^{-4}	PD	0	NE
MSKCC05	5.2×10^6	87/12	2.0×10^{12}	2.0×10^{-4}	LN reduction	257	6
MSKCC06	4.6×10^6	79/21	2.9×10^{12}	1.4×10^{-4}	PD	14	1
MSKCC07	8.1×10^6	58/27	6.6×10^{11}	1.1×10^{-3}	SD	6143	8
MSKCC08	11×10^6	92/8	1.2×10^{12}	1.1×10^{-3}	SD	1143	1
UPENN01	16×10^6	NR	1.7×10^{12}	6.5×10^{-4}	CR	200000	15
UPENN02	10×10^6	NR	3.5×10^{12}	1.7×10^{-4}	PR	1000	110
UPENN03	0.2×10^6	NR	8.8×10^{11}	1.6×10^{-5}	CR	10000	23
NCI03	11×10^6	35/53	NR		CR	NR	7
NCI05	3×10^6	87/12	NR		SD	NR	7
NCI06	17×10^6	37/57	NR		PR	NR	7
NCI07	28×10^6	58/41	NR		PR	NR	9

*CLL, UPENN, and NCI refer to patients treated at MSKCC, UPenn, and NCI, respectively. Two CLL patients have been excluded from this table: one due to a history of Epstein-Barr virus (EBV)$^+$ non-Hodgkin's lymphoma,[20] and one owing to early death.[9] **Tumor burden for bone marrow and blood is calculated as described by Kalos et al.[7] ***The E:T ratio is calculated as the number of infused anti-CD19 T cells divided by the tumor burden. ****Bone marrow aspirate and biopsy did not include cellularity so tumor burden could not be calculated. Abbreviations: CR, complete remission; NE, not evaluable; NR, not reported; PD, progressive disease; PR, partial remission; SD, stable disease.

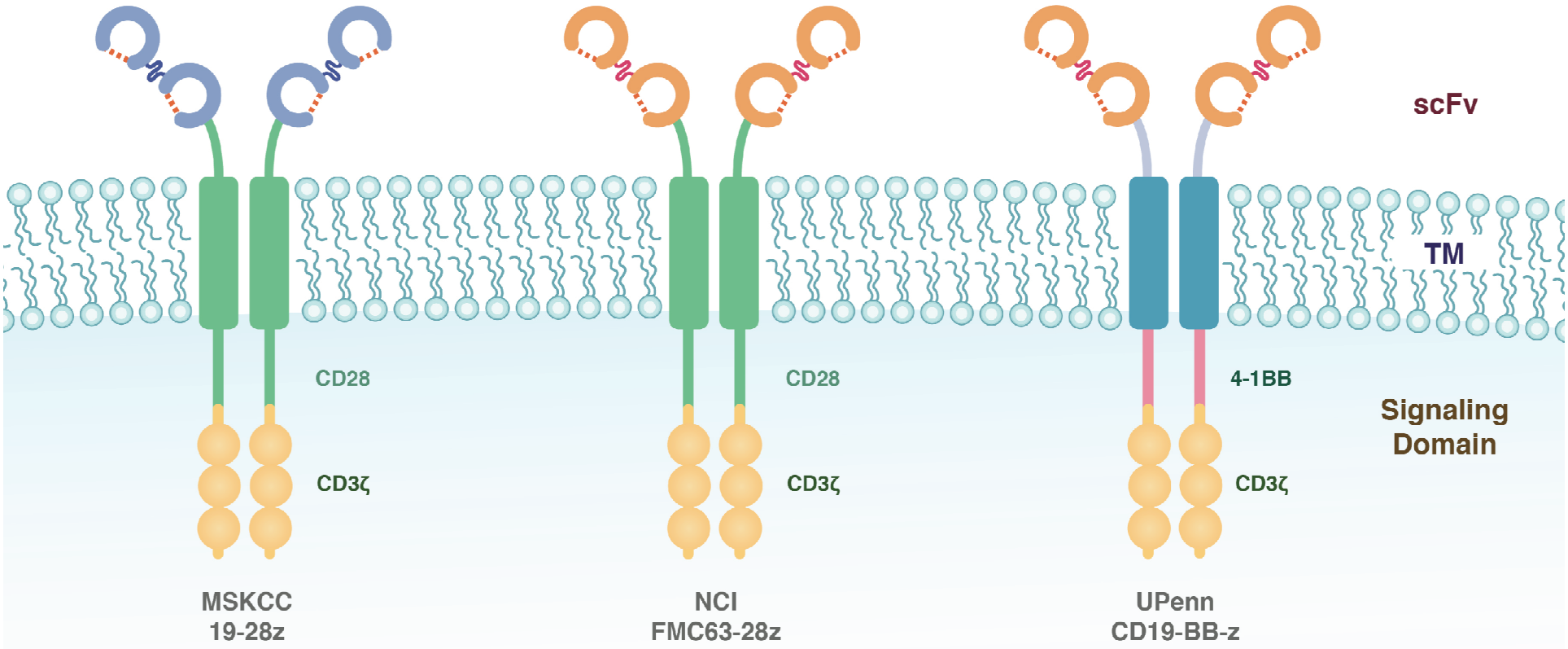
Davila et al. *Oncoimmunology 2012*

CD19-targeted CAR T cell therapy for CLL: Limited efficacies



Davila et al. *Oncoimmunology 2012*

CD19-targeted CAR T cell therapy for CLL: Limited efficacies



CR:	0% (n=8)	43% (n=7)	29% (n=14)
	Brentjens et al. Blood 2011	Kochenderfer et al, Blood 2011 Kochenderfer et al, JCO 2014	Porter et al, Sc Trans Med 2015

Future Directions

- Phase II trials for B-ALL
- Definition of the CRS, as well as further management optimization
- Why are acute leukemias so much more sensitive than NHL?
- Modification of CD19-targeted to prevent tumor escape
- Targets other than CD19. What are the next success stories in hematologic malignancies or solid tumors?