CAR-T Cells and Other Cell Based Therapies

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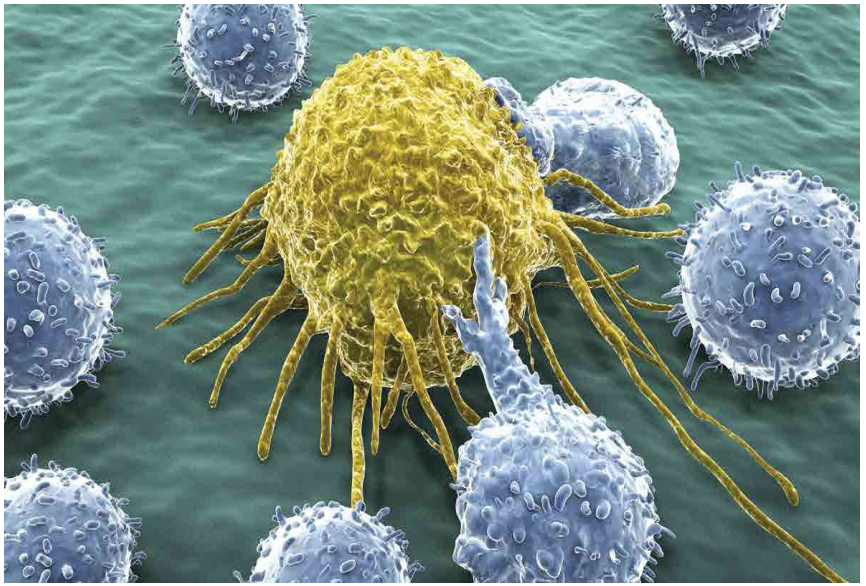
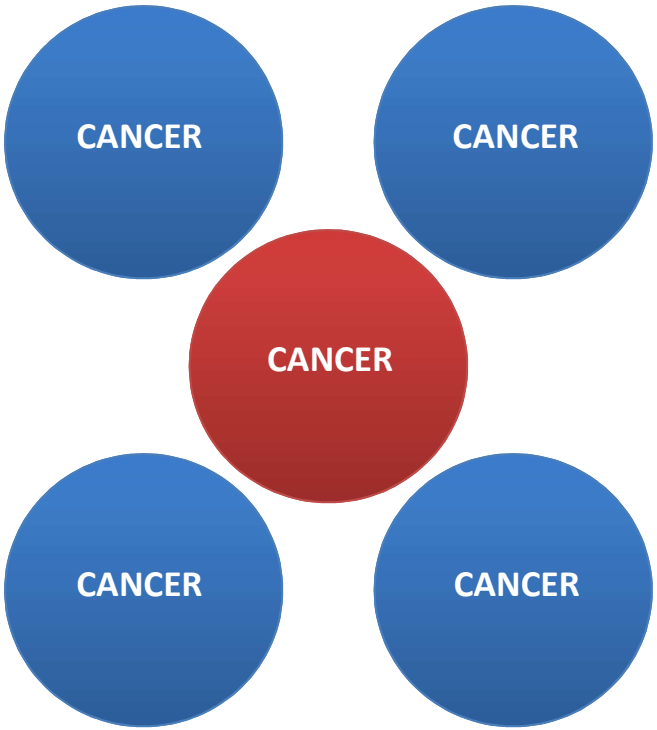
Director, Alpha Clinic For Stem Cell Therapy

Professor of Medicine

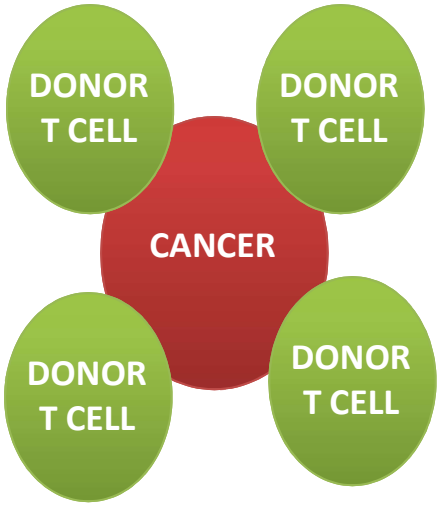
UC Davis Medical Center



We have been doing cell therapy for a long time!



CHEMOTHERAPY



ALLOGENEIC (DONOR) TRANSPLANT

Graft Versus Leukemia (GVL)

CHEMOTHERAPY SENSITIVE

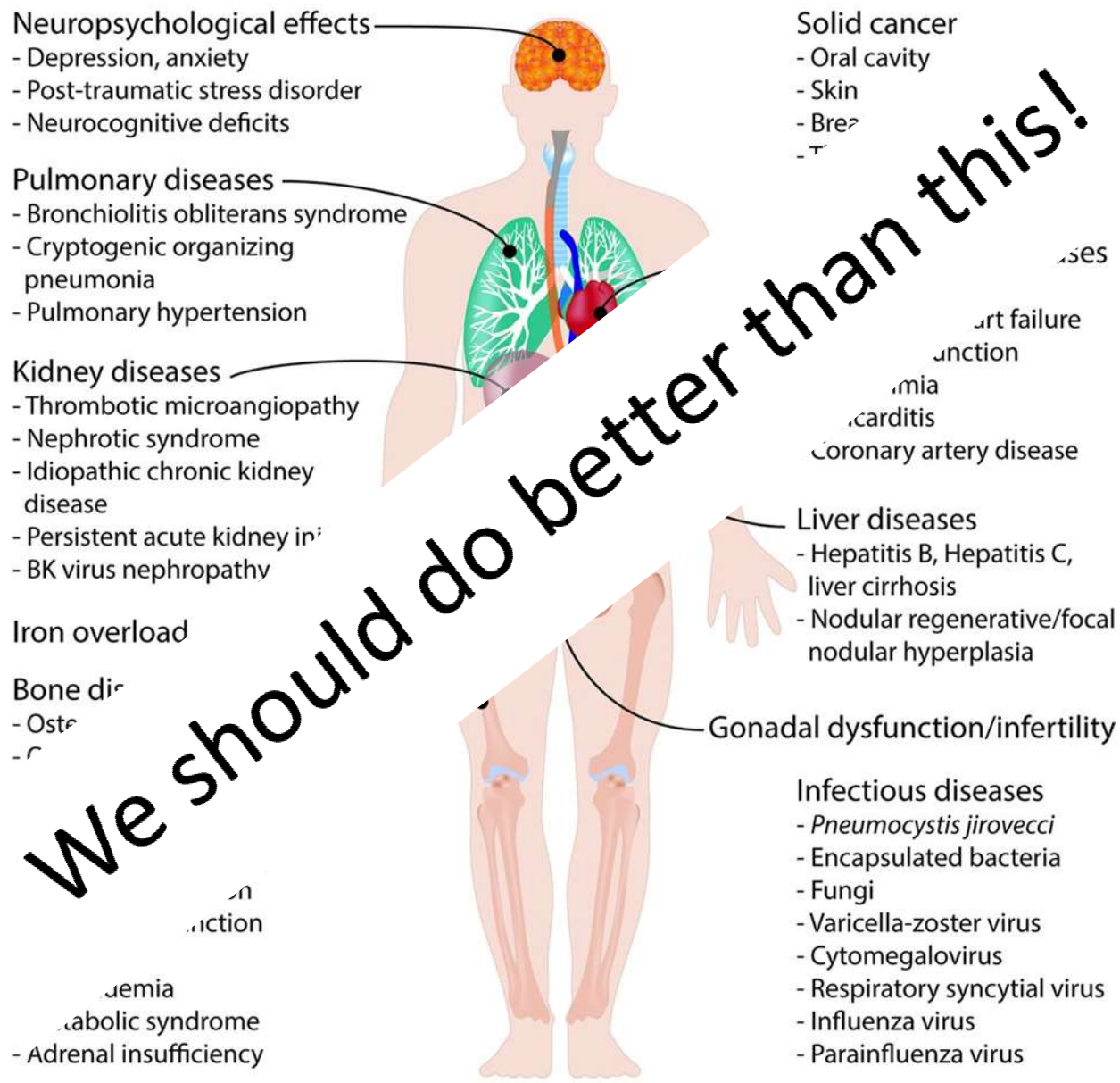
CHEMOTHERAPY RESISTANT

Donor Lymphocyte Infusion (DLI)

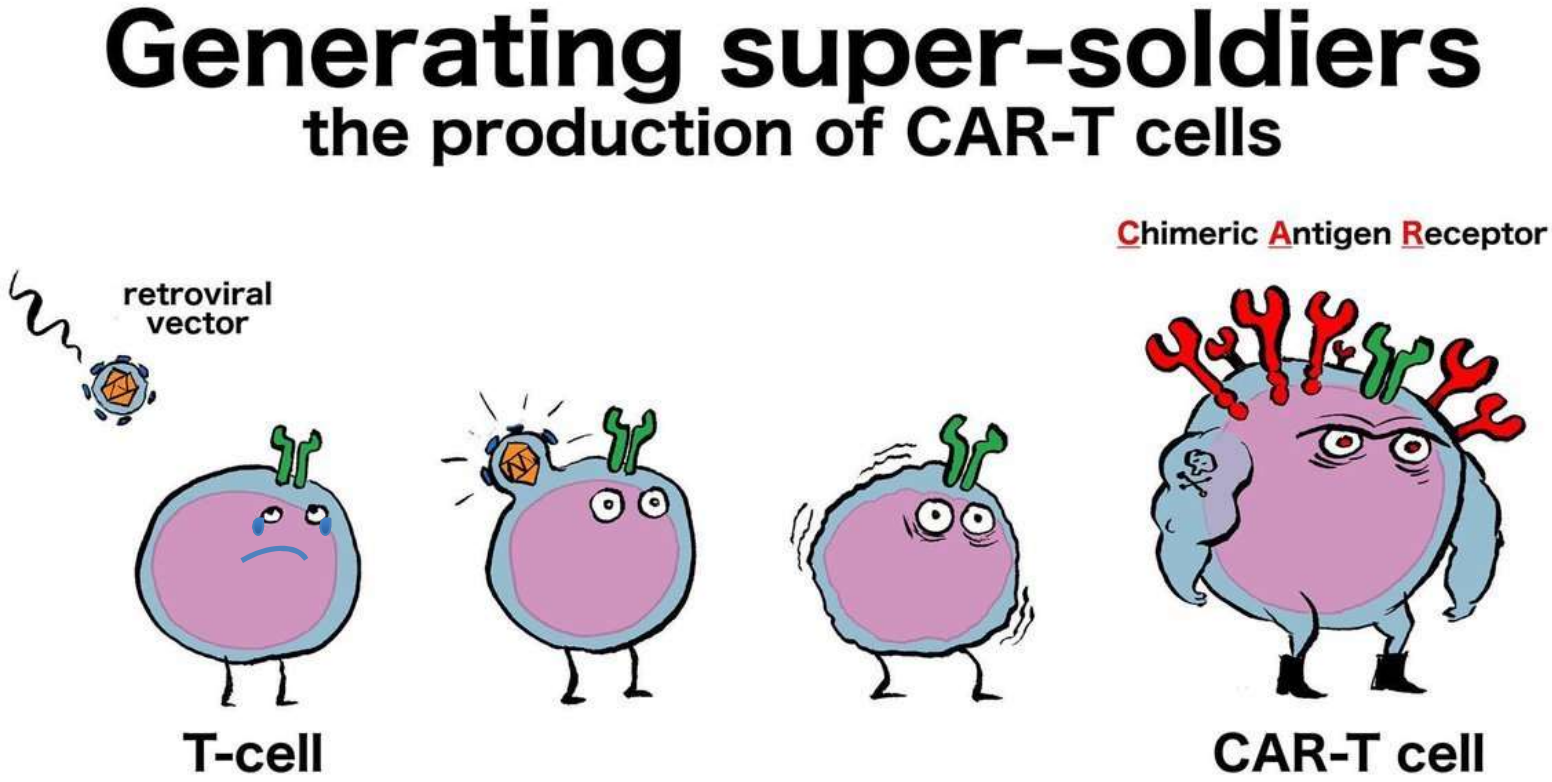
DLI is a proof of principal for the effectiveness of cell therapy

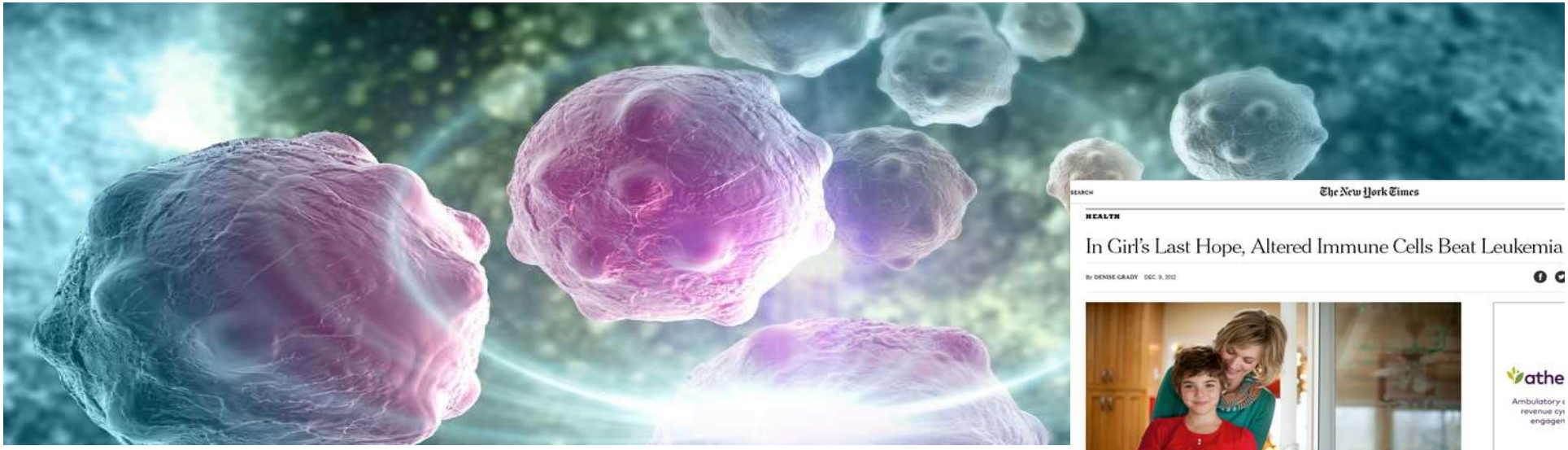
DIAGNOSIS		INCIDENCES OF COMPLETE RESPONSES AFTER DLI
Chronic myeloid leukaemia:	Overall	60%[9]
	Chronic phase	76%
	Accelerated phase	33%
	Blastic phase	17%
Acute myeloid leukaemia/myelodysplastic syndrome		15-26%[9,18]
Acute lymphoblastic leukaemia		3-15%[9,18]
Chronic lymphocytic leukaemia		29%[60]
Multiple myeloma		5-29%[18,67]

Side effects of blood and marrow transplantation



Cellular Immunotherapy





The New York Times

Patient's Cells Deployed to Attack Aggressive Cancer

A Sickened Body as Cancer Weapon

Harnessing the Power of the Immune System

THE NEW YORKER

MEDICAL DISPATCHES | APRIL 23, 2012 ISSUE

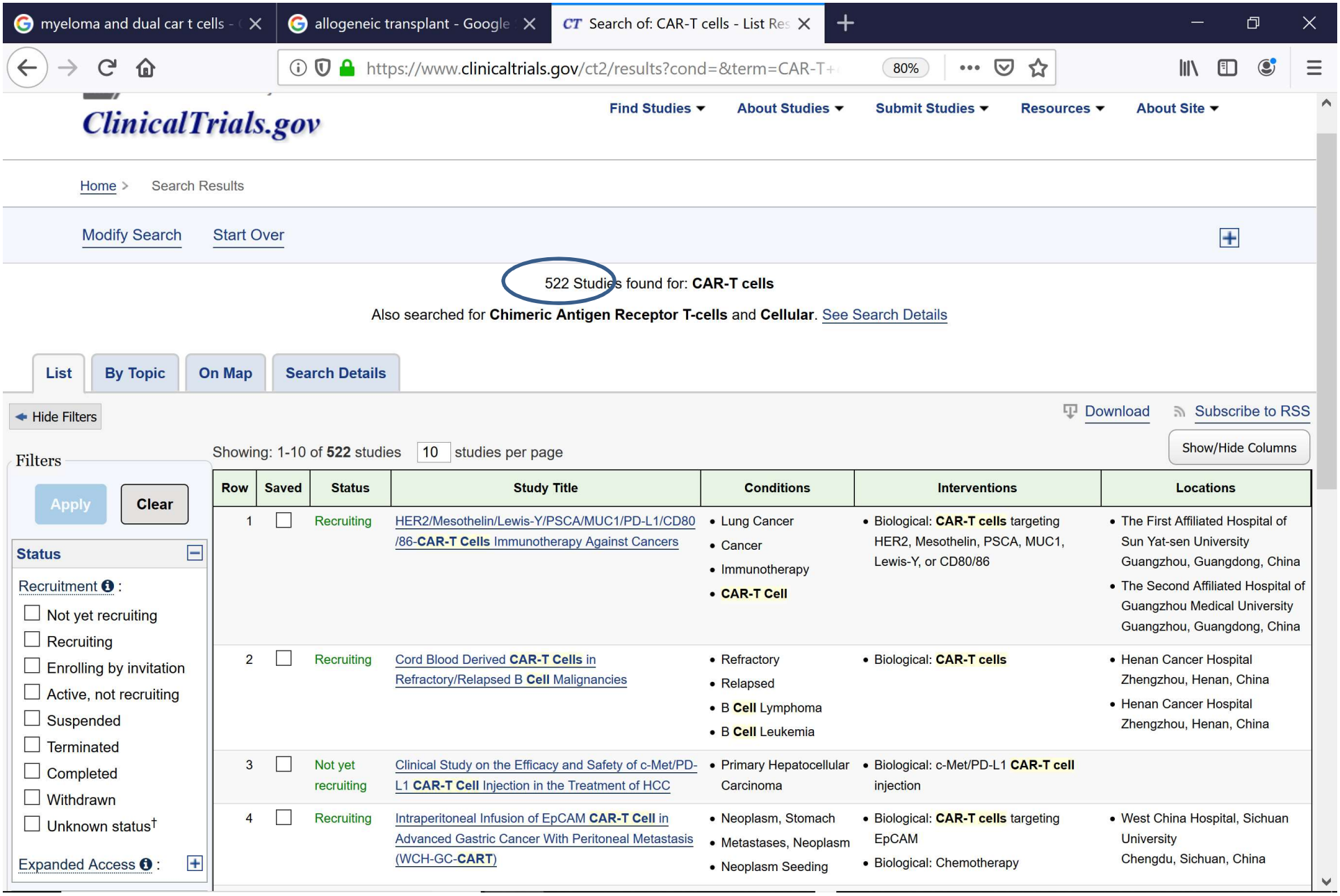
THE T-CELL ARMY

Can the body's immune response help treat cancer?

The Washington Post

Health & Science

New therapies raise hope for a breakthrough in tackling cancer


myeloma and dual car t cells -
allogeneic transplant - Google
CT Search of: CAR-T cells - List Res
https://www.clinicaltrials.gov/ct2/results?cond=&term=CAR-T+
80%
ClinicalTrials.gov
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Resources
About Site
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Modify Search
Start Over
522 Studies found for: CAR-T cells
Also searched for Chimeric Antigen Receptor T-cells and Cellular. See Search Details
List
By Topic
On Map
Search Details
Hide Filters
Download
Subscribe to RSS
Filters
Apply
Clear
Showing: 1-10 of 522 studies
10
studies per page
Show/Hide Columns
Status
Recruitment :
Not yet recruiting
Recruiting
Enrolling by invitation
Active, not recruiting
Suspended
Terminated
Completed
Withdrawn
Unknown status†
Expanded Access :
Row
Saved
Status
Study Title
Conditions
Interventions
Locations
1
Recruiting
HER2/Mesothelin/Lewis-Y/PSCA/MUC1/PD-L1/CD80/86-CAR-T Cells Immunotherapy Against Cancers
Lung Cancer
Cancer
Immunotherapy
CAR-T Cell
Biological: CAR-T cells targeting HER2, Mesothelin, PSCA, MUC1, Lewis-Y, or CD80/86
The First Affiliated Hospital of Sun Yat-sen University Guangzhou, Guangdong, China
The Second Affiliated Hospital of Guangzhou Medical University Guangzhou, Guangdong, China
2
Recruiting
Cord Blood Derived CAR-T Cells in Refractory/Relapsed B Cell Malignancies
Refractory
Relapsed
B Cell Lymphoma
B Cell Leukemia
Biological: CAR-T cells
Henan Cancer Hospital Zhengzhou, Henan, China
Henan Cancer Hospital Zhengzhou, Henan, China
3
Not yet recruiting
Clinical Study on the Efficacy and Safety of c-Met/PD-L1 CAR-T Cell Injection in the Treatment of HCC
Primary Hepatocellular Carcinoma
Biological: c-Met/PD-L1 CAR-T cell injection
4
Recruiting
Intraperitoneal Infusion of EpCAM CAR-T Cell in Advanced Gastric Cancer With Peritoneal Metastasis (WCH-GC-CART)
Neoplasm, Stomach
Metastases, Neoplasm
Neoplasm Seeding
Biological: CAR-T cells targeting EpCAM
Biological: Chemotherapy
West China Hospital, Sichuan University Chengdu, Sichuan, China

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https://www.ncbi.nlm.nih.gov/pubmed/?term=car-t+cell

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Best matches for car-t cell:

CAR T Cell Therapy for Solid Tumors.
Newick K et al. Annu Rev Med. (2017)

CAR T-cell therapy for pancreatic cancer.
DeSelm CJ et al. J Surg Oncol. (2017)

CAR T-Cell Therapy: Progress and Prospects.
Wilkins O et al. Hum Gene Ther Methods. (2017)

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1. ROR1-**CAR T-cells** are effective against lung and breast cancer in advanced microphysiologic 3D tumor models.
Wallstabe L, Göttlich C, Nelke LC, Kühnemundt J, Schwarz T, Nerreter T, Einsele H, Walles H, Dandekar G, Nietzer SL, Hudecek M.
JCI Insight. 2019 Aug 15. pii: 126345. doi: 10.1172/jci.insight.126345. [Epub ahead of print]
PMID: 31415244
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2. Anti-CAR-engineered T **cells** for epitope-based elimination of autologous **CAR T cells**.
Koristka S, Ziller-Walter P, Bergmann R, Arndt C, Feldmann A, Kegler A, Cartellieri M,

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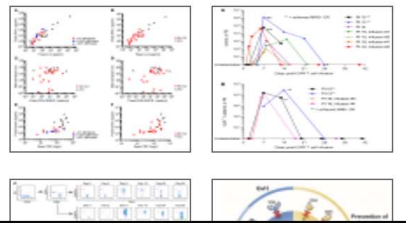


Type of cellular therapy

T cell therapy

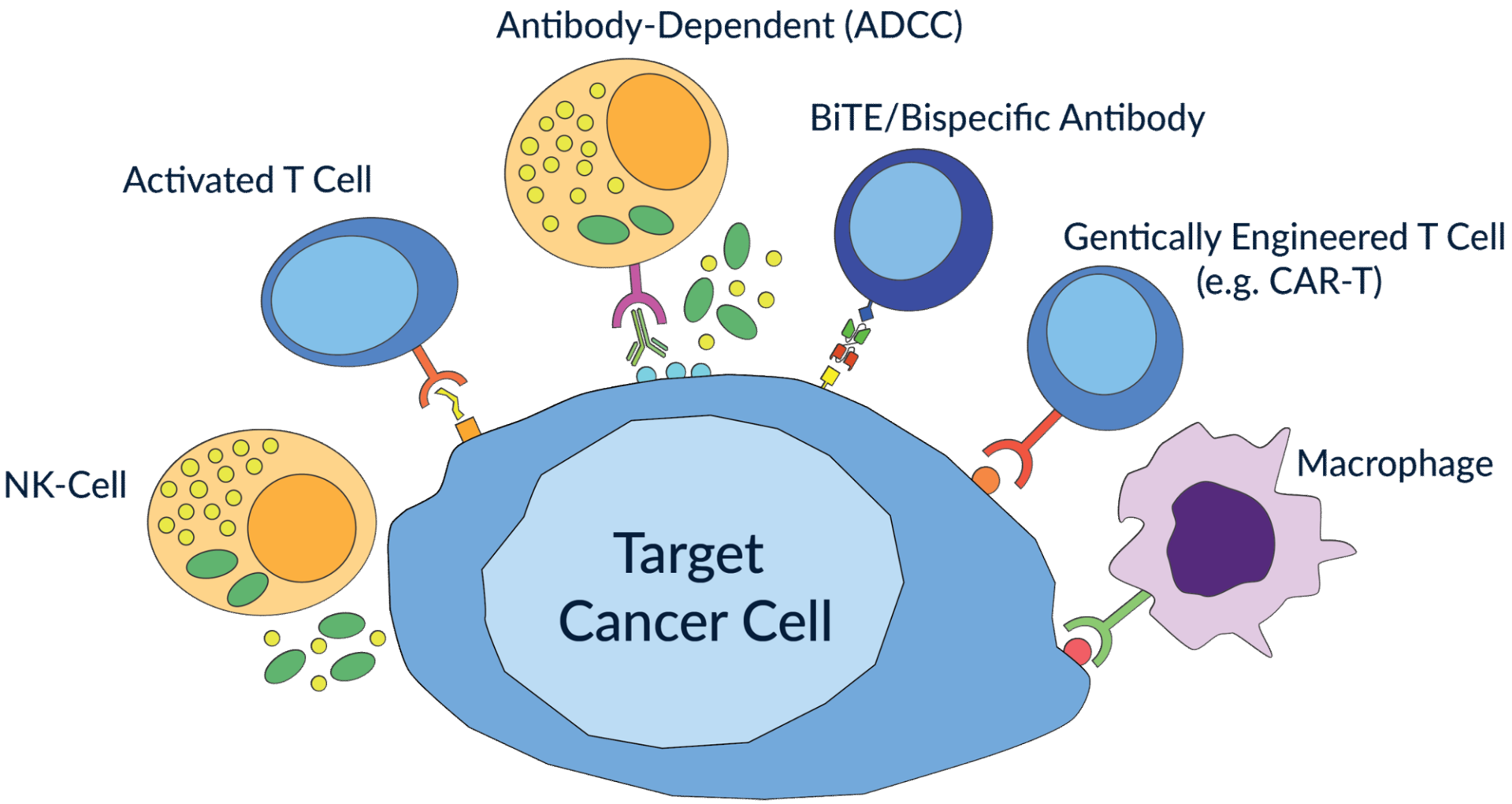
NK Cell therapy

Stem cell therapy

Dendritic cell therapy

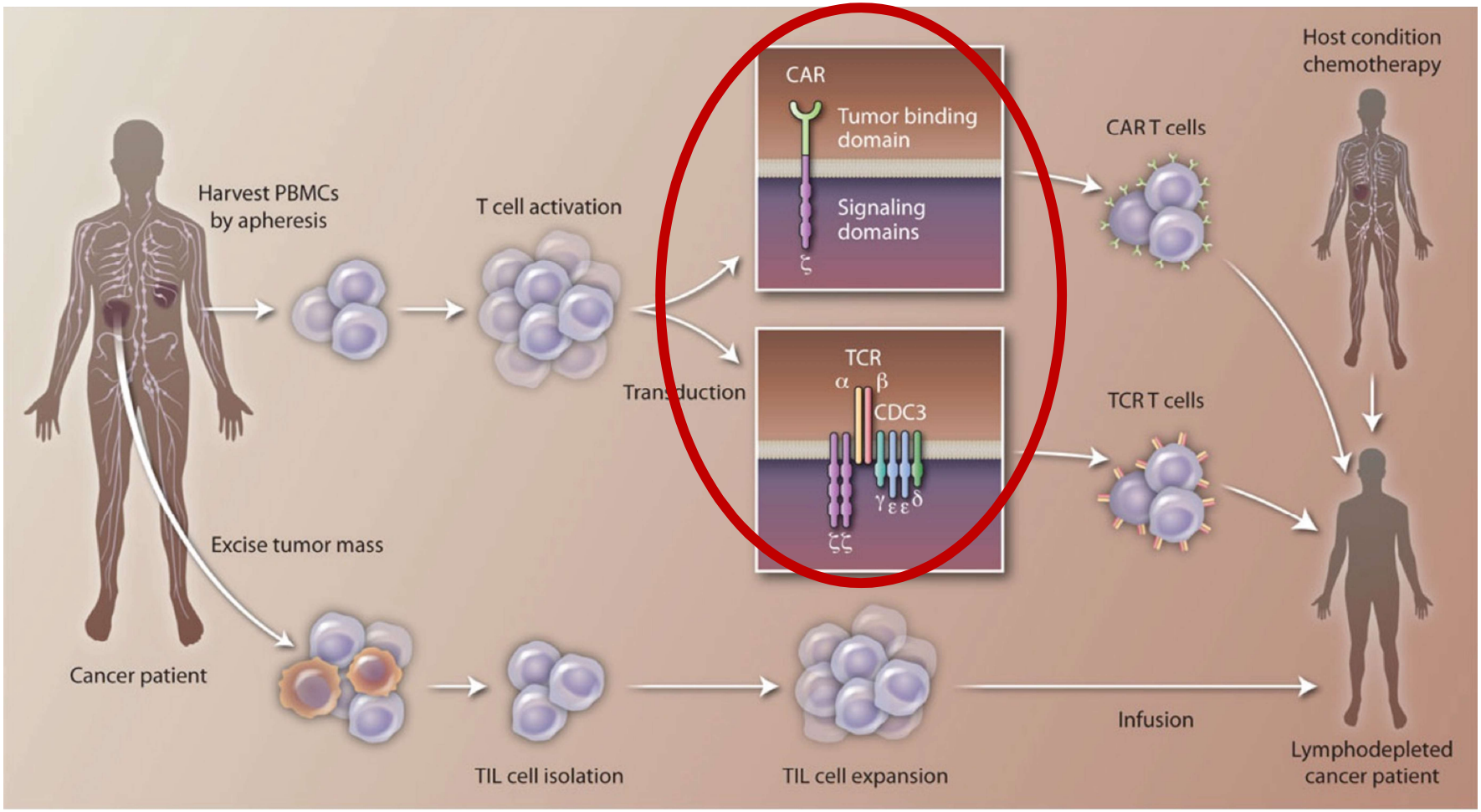
Mesenchymal Cell Therapy

Harnessing the Immune System to Attack Tumors



https://aceabio.com

Adoptive Cell Therapy Approaches



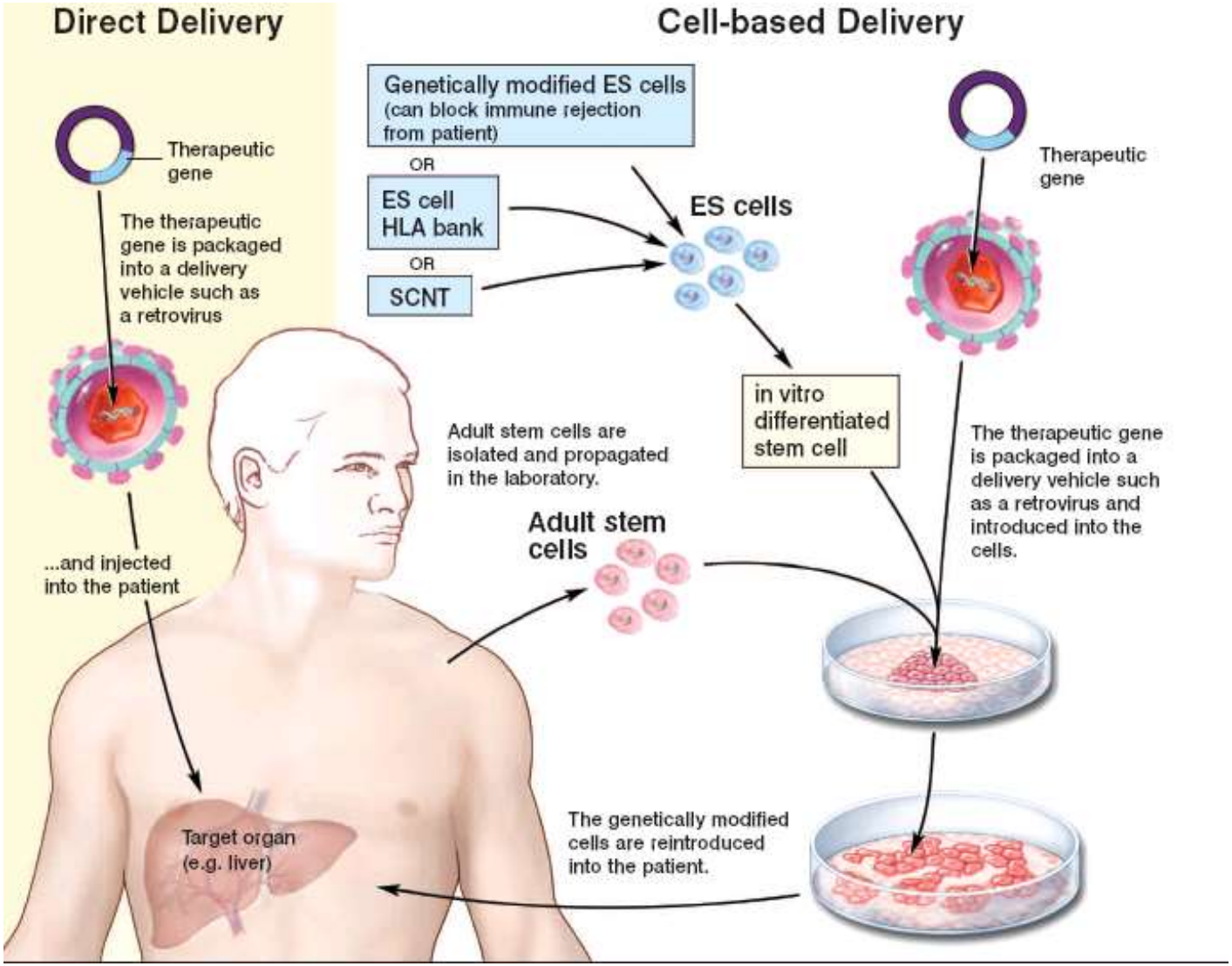
June, Riddell, and Schumacher
Science Transl Med 2015

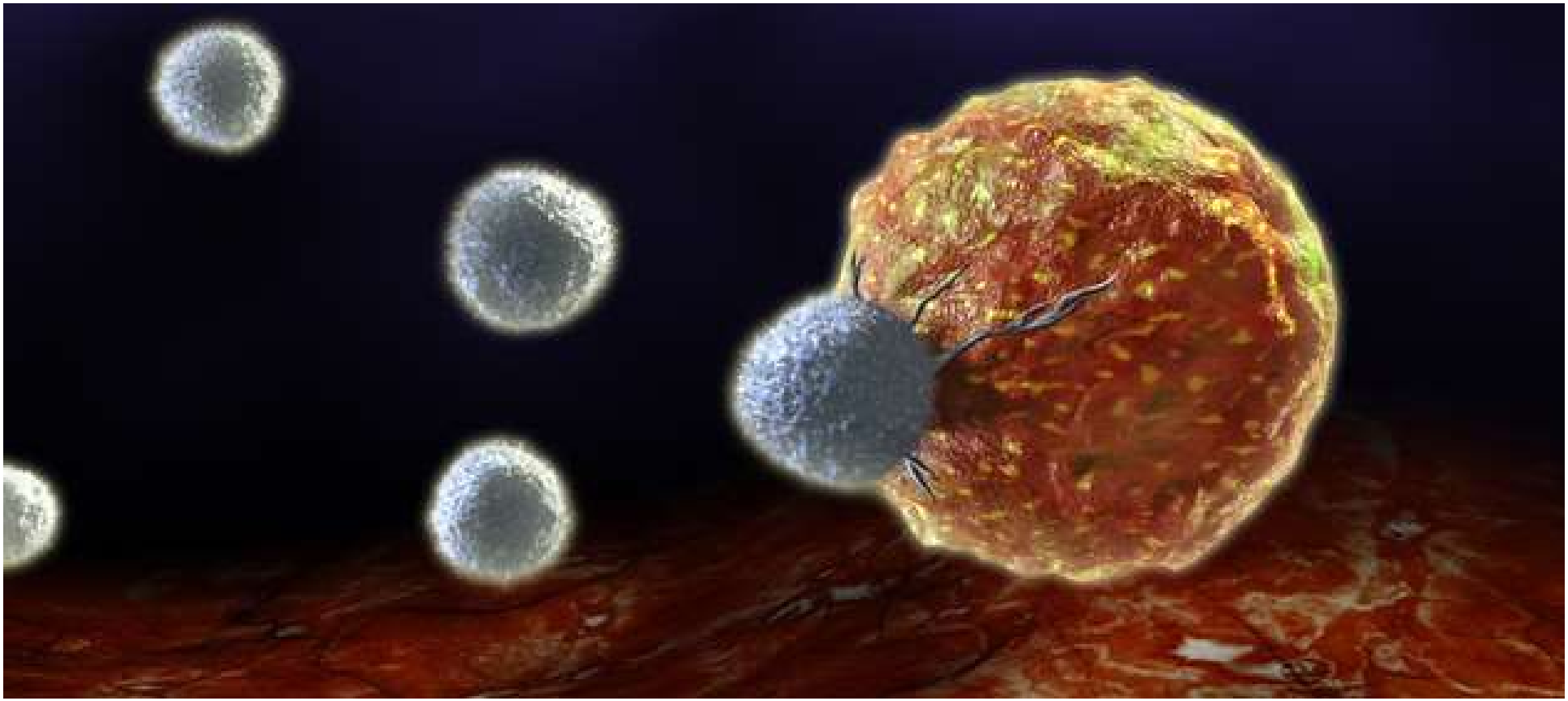
Cellular and Gene Therapy

This used to be a risky business.

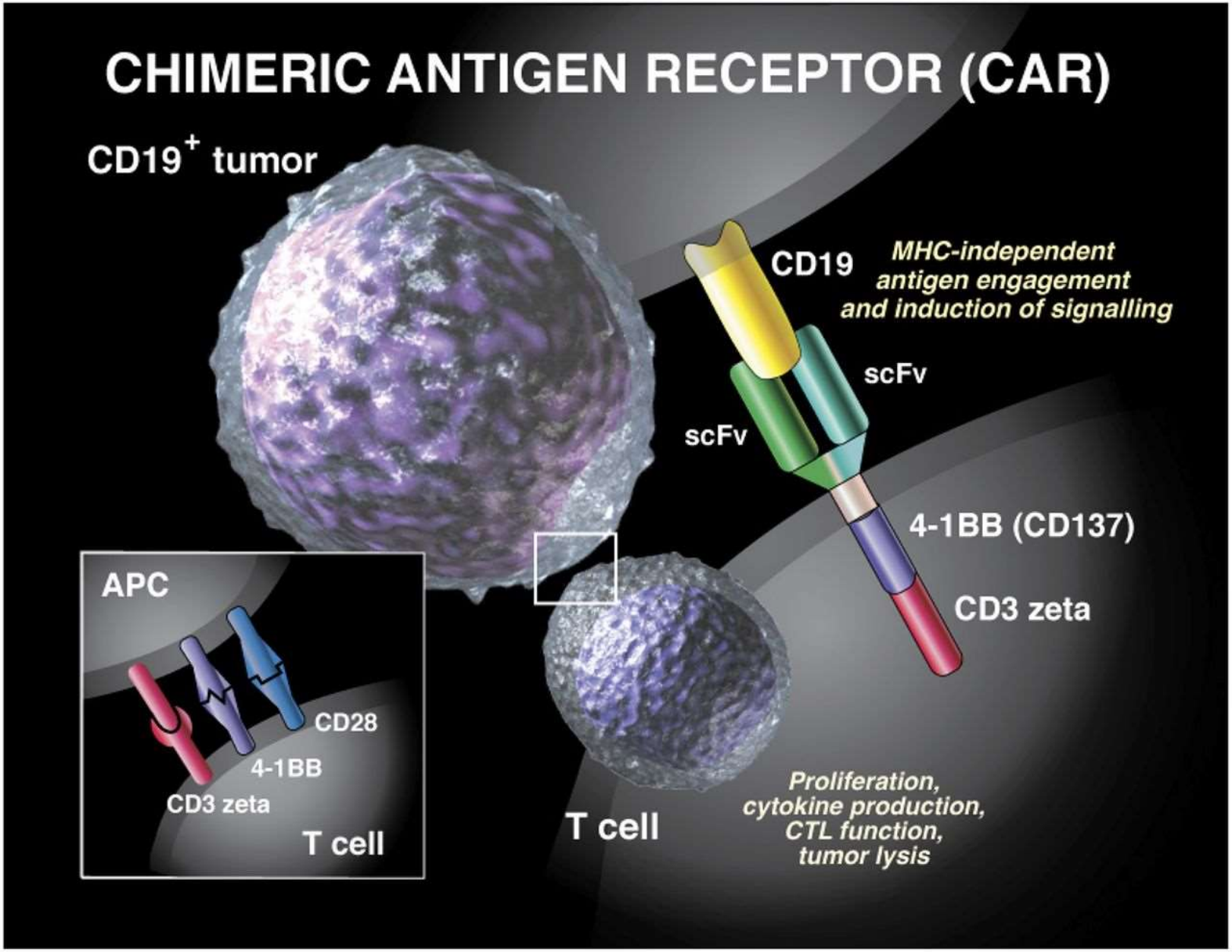

DWAYNE JOHNSON
RAMPAGE

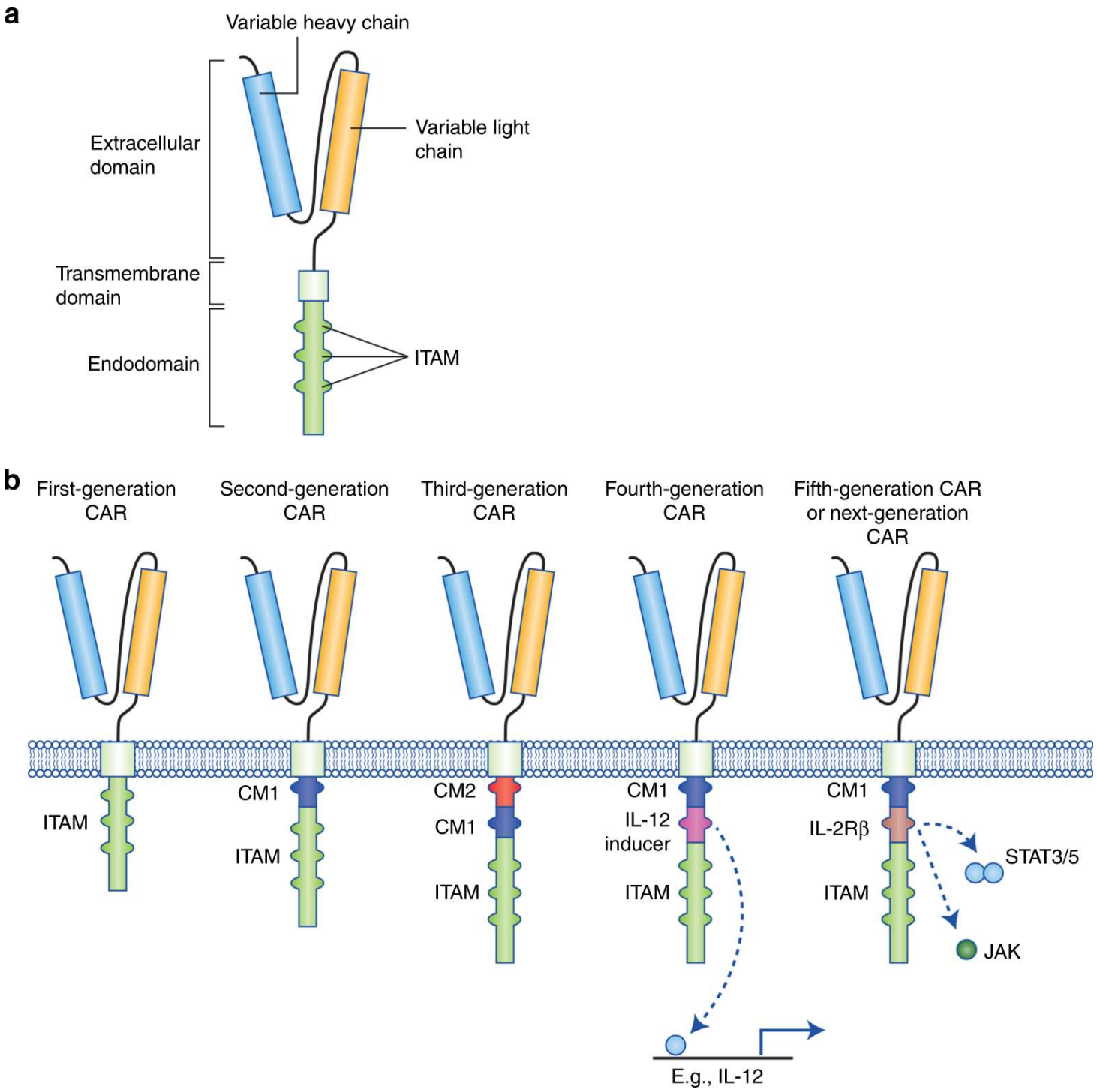
Delivering desired Genes



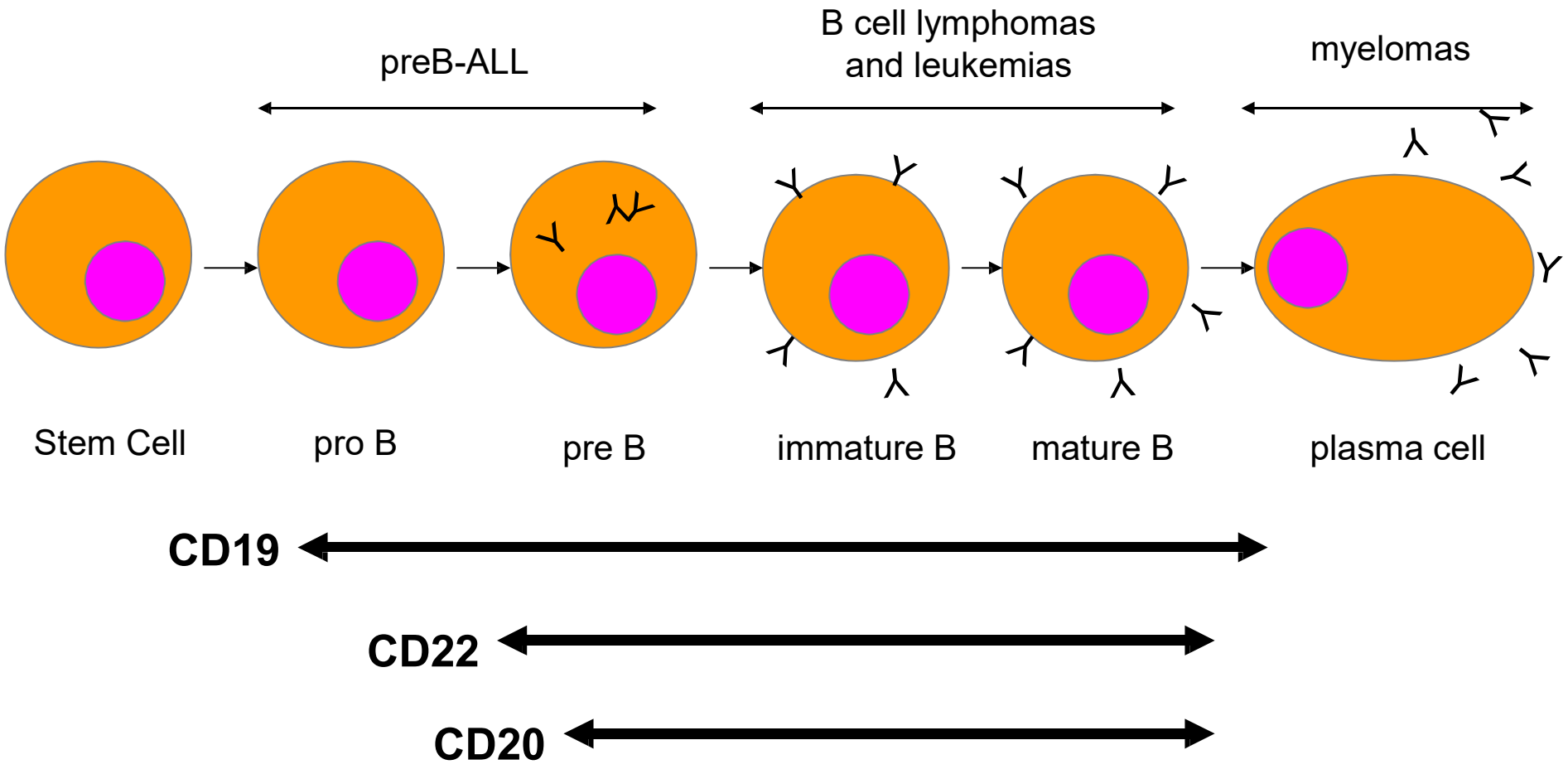


Chimeric **A**ntigen **R**eceptor (**CAR**) **T** Cells

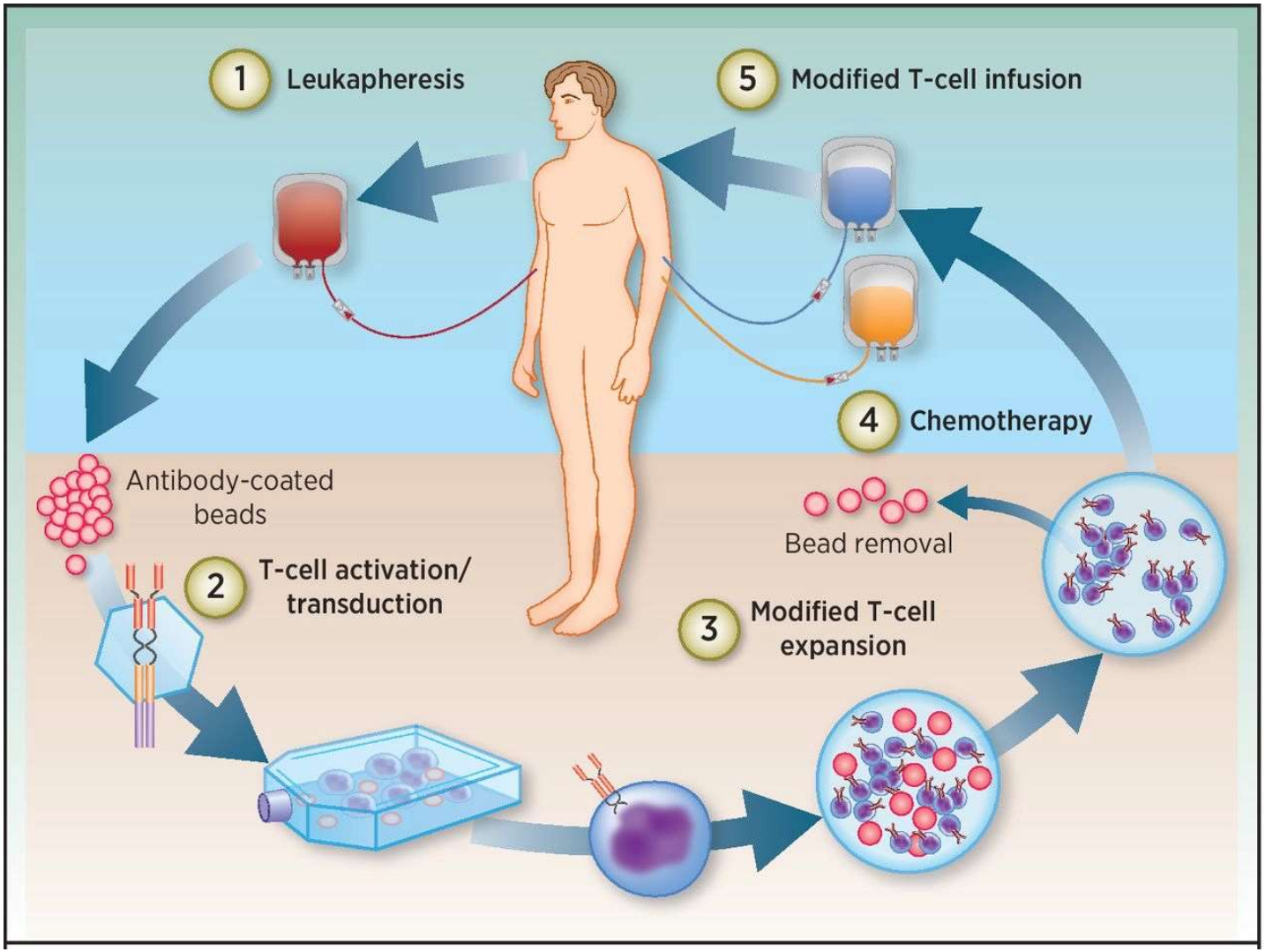

CHIMERIC ANTIGEN RECEPTOR (CAR)
CD19+ tumor
CD19
MHC-independent
antigen engagement
and induction of signalling
scFv
scFv
4-1BB (CD137)
CD3 zeta
APC
CD28
4-1BB
CD3 zeta
T cell
T cell
Proliferation,
cytokine production,
CTL function,
tumor lysis


a
Variable heavy chain
Variable light chain
Extracellular domain
Transmembrane domain
Endodomain
ITAM
b
First-generation CAR
Second-generation CAR
Third-generation CAR
Fourth-generation CAR
Fifth-generation CAR or next-generation CAR
ITAM
CM1
ITAM
CM2
CM1
ITAM
CM1
IL-12 inducer
ITAM
CM1
IL-2Rβ
ITAM
STAT3/5
JAK
E.g., IL-12

Target is critical!



Cellular Immunotherapy
CAR T Cells



Importance of lymphodepletion

Table 1: Response Rates in Evaluable NHL Patients Receiving CAR T-Cell Treatment

Patients	Objective Response Rate	Complete Response Rate
All evaluable patients (n = 39)	26 (67%)	13 (33%)
Cy or Cy/E (n = 12)	6 (50%)	1 (8%)
Cy/Flu (all dose levels; n = 27)	20 (74%)	12 (44%)
Cy/Flu (dose level 2; n = 20)	16 (80%)	10 (50%)
Aggressive subtype (n = 16)	13 (81%)	8 (50%)

CAR = chimeric antigen receptor; Cy = cyclophosphamide; E = etoposide; Flu = fludarabine; NHL = non-Hodgkin lymphoma.

CAR T cells for ALL

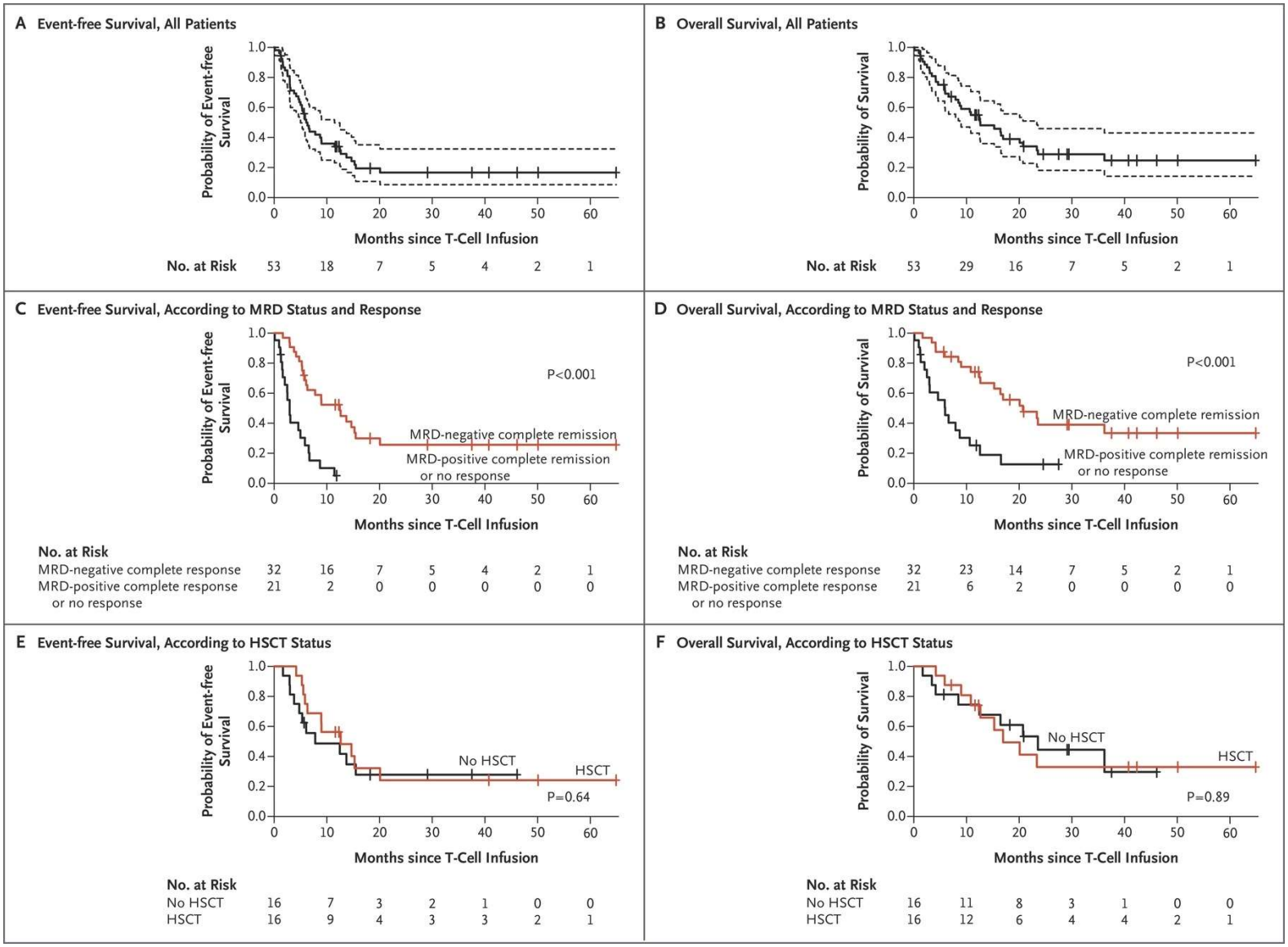
CD19-specific-CAR T-cell therapy outcomes in patients with B-ALL

Table 1 | **CD19-specific-CAR T-cell therapy outcomes in patients with B-ALL**

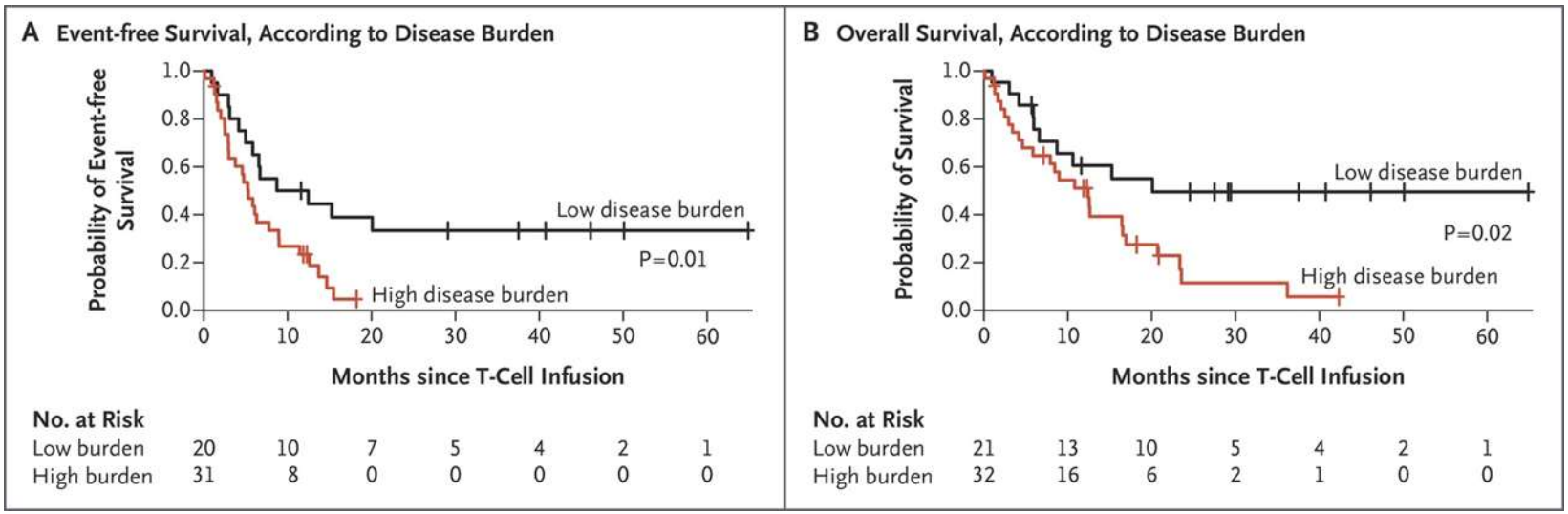
Institution	CAR design	Patient population	Outcome	Toxicities	Reference
MSKCC	CD28, CD3ζ	• *n* = 32 adults • R/R B-ALL	91% CR	• B-cell aplasia • CRS	NCT01044069 (REF. 13)
UPenn/ CHOP	4-1BB, CD3ζ	• *n* = 30 children and young adults • B-ALL	90% CR	• B-cell aplasia • CRS	NCT01626495 (REF. 15)
NCI	CD28, CD3ζ	• *n* = 20 children and young adults • B-ALL	70% CR	• B-cell aplasia • CRS	NCT01593696 (REF. 17)
Fred Hutchinson	4-1BB, CD3ζ	• *n* = 20 adults • B-ALL	83% CR	CRS	NCT01865617 (REF. 18)

Jackson, H. J. *et al.* (2016) Driving CAR T-cells forward *Nat. Rev. Clin. Oncol.*

Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia



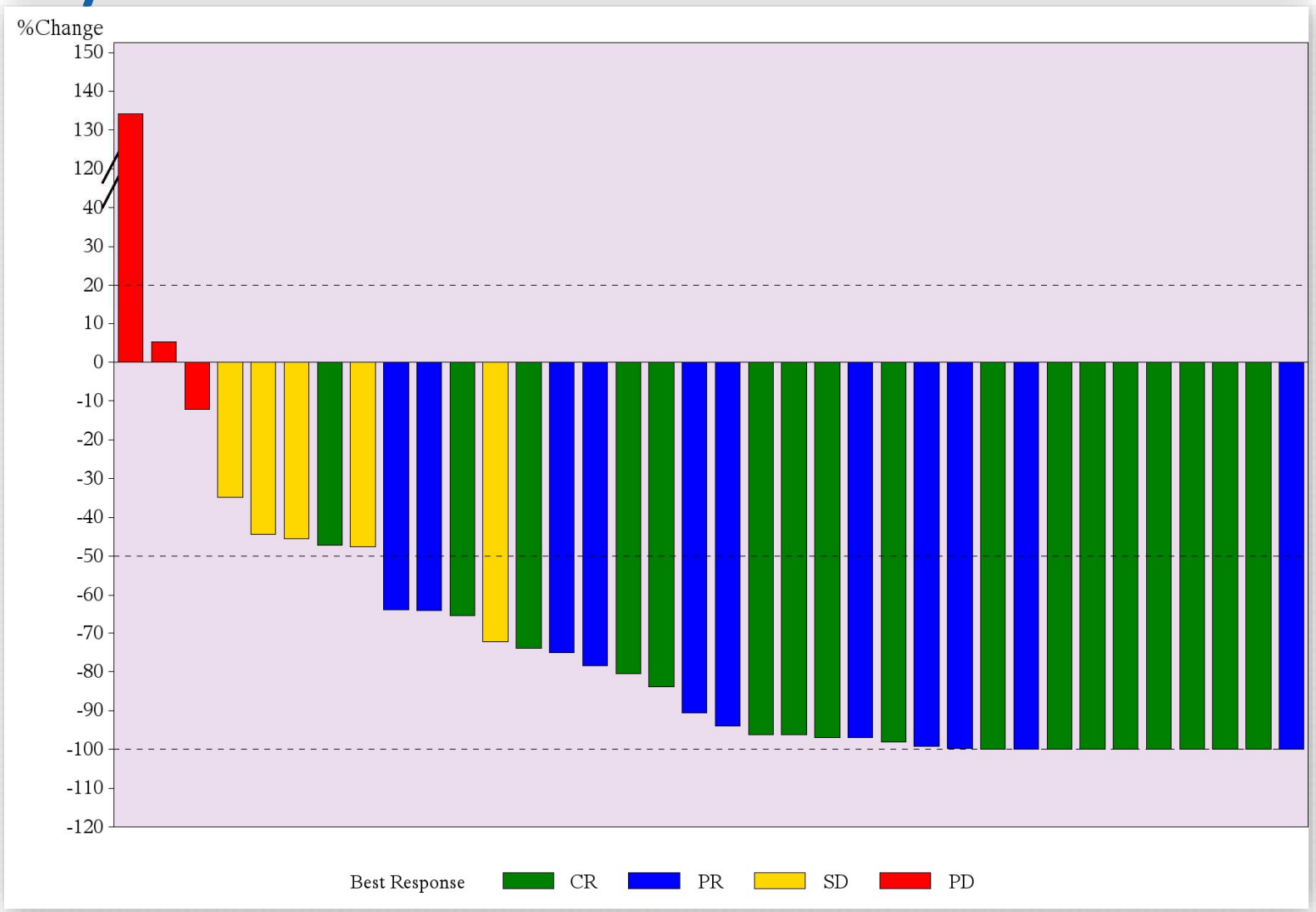
Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia



Commonly used CAR T cells for lymphomas

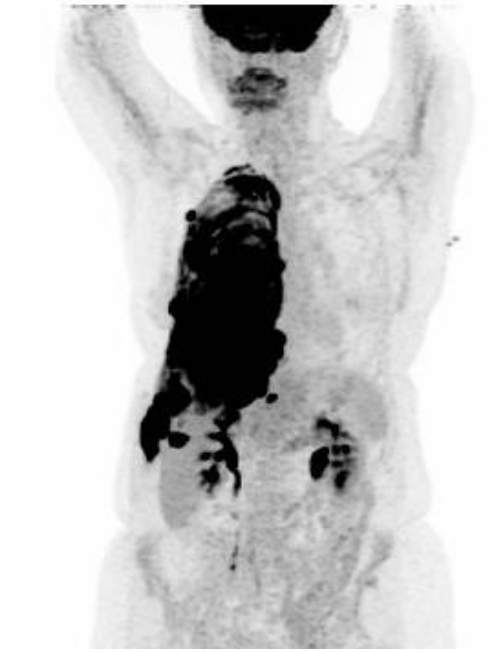
Company		Juno		Novartis		Gilead	
Product		JCAR017		KYMRIAH Tisagenlecleucel		YESCARTA Axicabtagene ciloleucel	
US Status		P1-2		BLA Filed		Approved	
Trial		Transcend		Juliet		ZUMA-1	
Efficacy	Follow-Up	3 Mon	6 Mon	3 Mon	6 Mon	3 Mon	6 Mon
	Patients	N=19	N=14	N=81		N=101	
	Objective Response Rate (ORR)	74%	50%	38%	37%	54%	41%
	Complete Response (CR)	**68%**	**50%**	**32%**	**30%**	**36%**	**36%**
Safety	Patients	N=67		N=81		N=101	
	Cytokine Release Syndrome (CRS)	**1% Severe** 40% Any		**23% Severe** 58% Any		**13% Severe** 94% Any	
	Neurotoxicity	15% Severe		12% Severe		31% Severe	

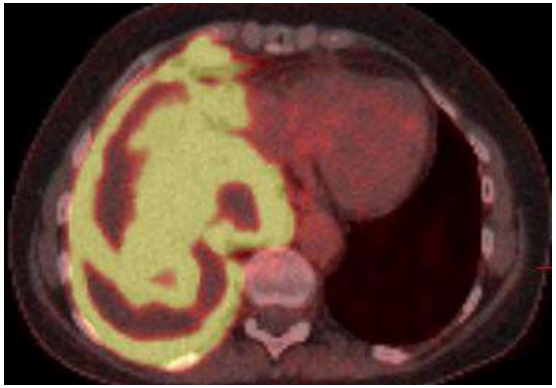
Depth of Best Response in NCI B Cell Lymphoma Study



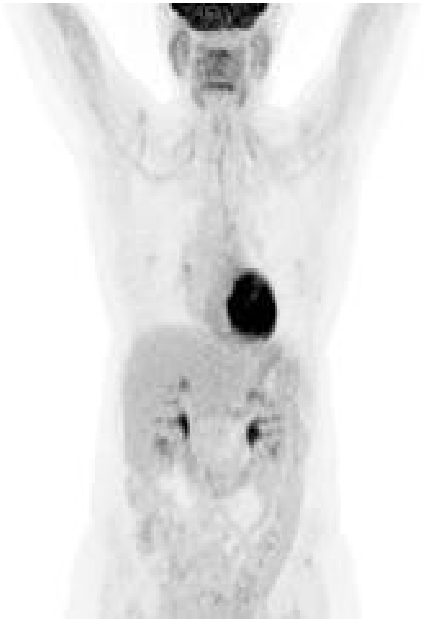
Response in Patient with Refractory DLBCL

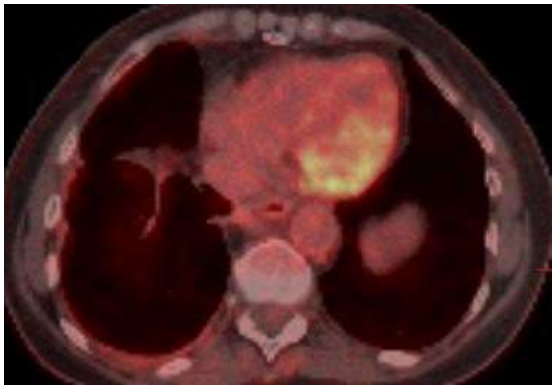
Before treatment





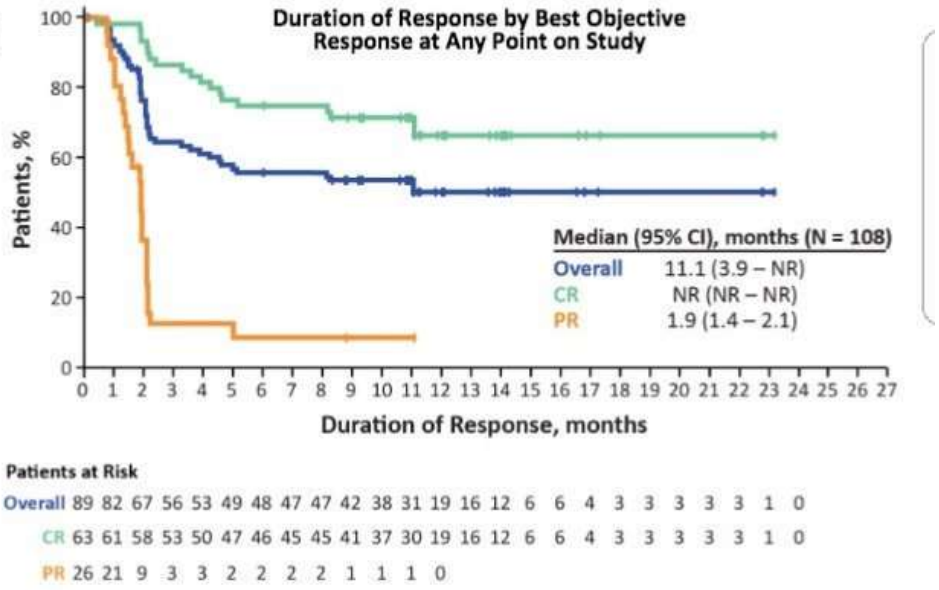
6 months after treatment





ZUMA-1 Long-Term Follow-Up

- Long-term follow-up (median 15.4 mo) of both Phase 1 and 2 (N = 108) demonstrated[1]:
  - ORR = 82%; CR rate = 58%
    - Ongoing responses in 42% (40% CRs)
  - Median OS = not reached
- 12% Grade ≥ 3 CRS; 31% Grade ≥ 3 neurologic events



CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PR, partial response.

1. From Neelapu SS and Locke FL, et al. *N Engl J Med*. 2017;277:2531-2544.

TABLE 1 Summary of landmark CD19-targeted CAR T-cell approaches for ALL and NHL

	Author (trial)	Sites	Phase	Costim	T-cell subset	Vector	Time[a]	Enrolled	Treated	Population	LD[b]	CRS[c] (grade 3+)[d]	NT[c] (grade 3+)[d]	Response[e]	Analysis
Pre-B-ALL	Maude (ELIANA)[1]	Multicenter	II	4-1BB	Unselected	Lentivirus	45 d (S)	92	75	Pediatric	95% Flu/ CPM	77% (48%)	40% (13%)	81%	Of treated
	Lee[5]	NCI	I	CD28	Unselected	γ-Retrovirus	7-11 d (M)	21	21	Pediatric	Flu/CPM or other	76% (29%)	29% (5%)	70%	Intent to treat
	Gardner[82]	SCRI	I/II	4-1BB	CD4 and CD8	Lentivirus	15 d (M), 53 d (S)	45	43	Pediatric	Prefer Flu/ CPM	93% (23%)	49% (21%)	89%	Intent to treat
	Hay[84]	FHCRC	I/II	4-1BB	CD4 and TcmCD8	Lentivirus	19 d (M)	61	53	Adult	CPM +/− Flu	75% (19%)	(28%)	85%	Of treated
	Park[3]	MSKCC	I	CD28	Unselected	γ-Retrovirus	Unknown	83	53	Adult	CPM +/− Flu	85% (26%)	(42%)	83%	Of treated
	Jacoby[86]	Israel	Ib/II	CD28	Unselected	γ-Retrovirus	9-10 d (M)	21	20	Pediatric	Flu/CPM	80% (20%)	55% (30%)	90%	Of treated
NHL	Schuster (Juliet)[97]	Multicenter	II	4-1BB	Unspecified	Lentivirus	54 d (S)	165	111	Adult, DLBCL	73% Flu/ CPM	58% (22%)	21% (12%)	3 mo: RR 52%, CR 40%	Of treated
	Neelapu[2] (Zuma)	Multicenter	I/II	CD28	Unspecified	γ-Retrovirus	17 days (S)	111	101	Adult, NHL	Flu/CPM	93% (13%)	64% (28%)	6 mo: RR 82%, CR 54%	Modified intent to treat
	Abramson[98] (Transcend)	Multicenter	I	4-1BB	CD4 and CD8	Lentivirus	Unknown	39	14	Adult, NHL	Flu/CPM	21% (0%)	(14%)	1 mo: RR 82%, CR73%	Of treated

Abbreviations: CAR, chimeric antigen receptor; NCI, National Cancer Institute; SCR, Seattle Children's Research Institute; FHCRC, Fred Hutchison Cancer Research Center; MSKCC, Memorial Sloan Kettering Cancer Center.

[a]M = manufacturing time; S = time from enrollment or consent to infusion.

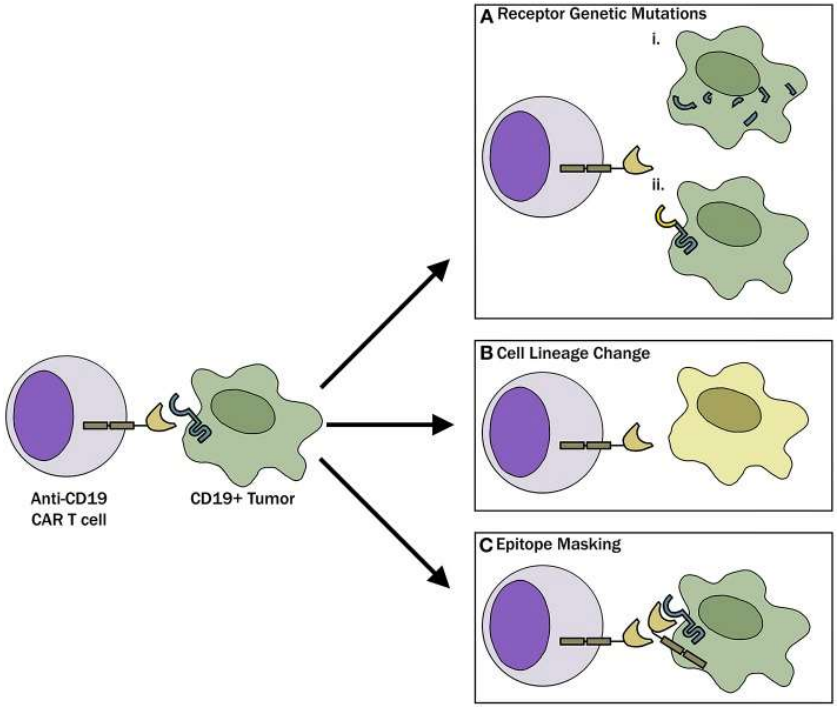
[b]LD = lymphodepletion; Flu = fludarabine; CPM = cyclophosphamide.

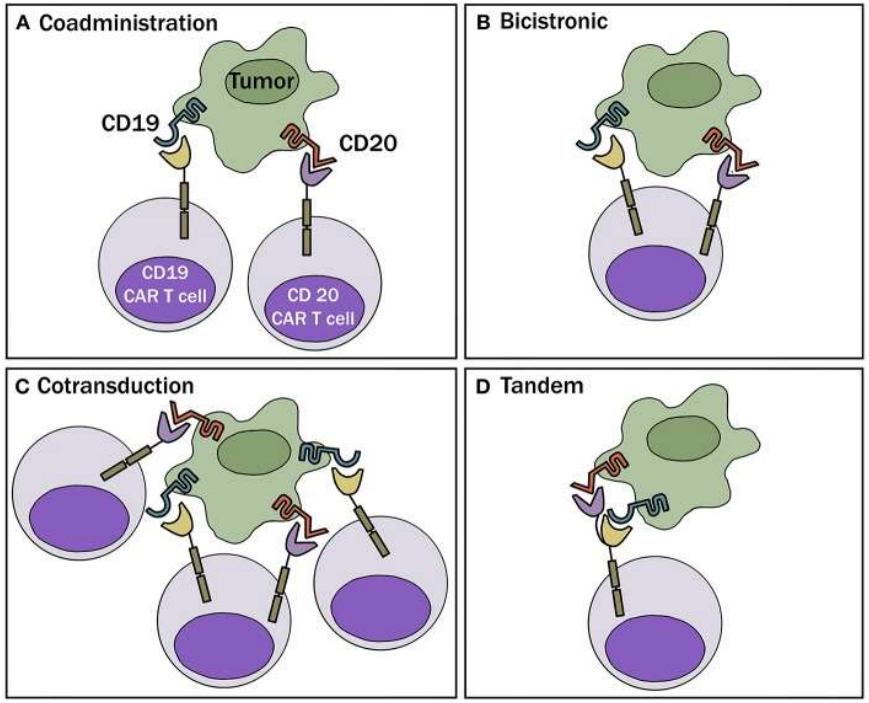
[c]CRS = cytokine release syndrome; NT = neurotoxicity.

[d]Any (Grade 3+), except for Jacoby et al, for which grading is reported as Grade 2+.

[e]RR = response rate; CR = complete response. For pre-B-ALL, response percentages reflect MRD-negative response.

Antigen Escape





Early results of phase I CD19/CD20 CAR T cells in DLBCL from Medical College of Wisconcin:

- Fourteen of 17 patients had a response,(11 CR, 3 PR).
- Eleven patients were treated at the target dose of 2.5 x 10^6 cells/kg, 9 had a CR and 1 PR

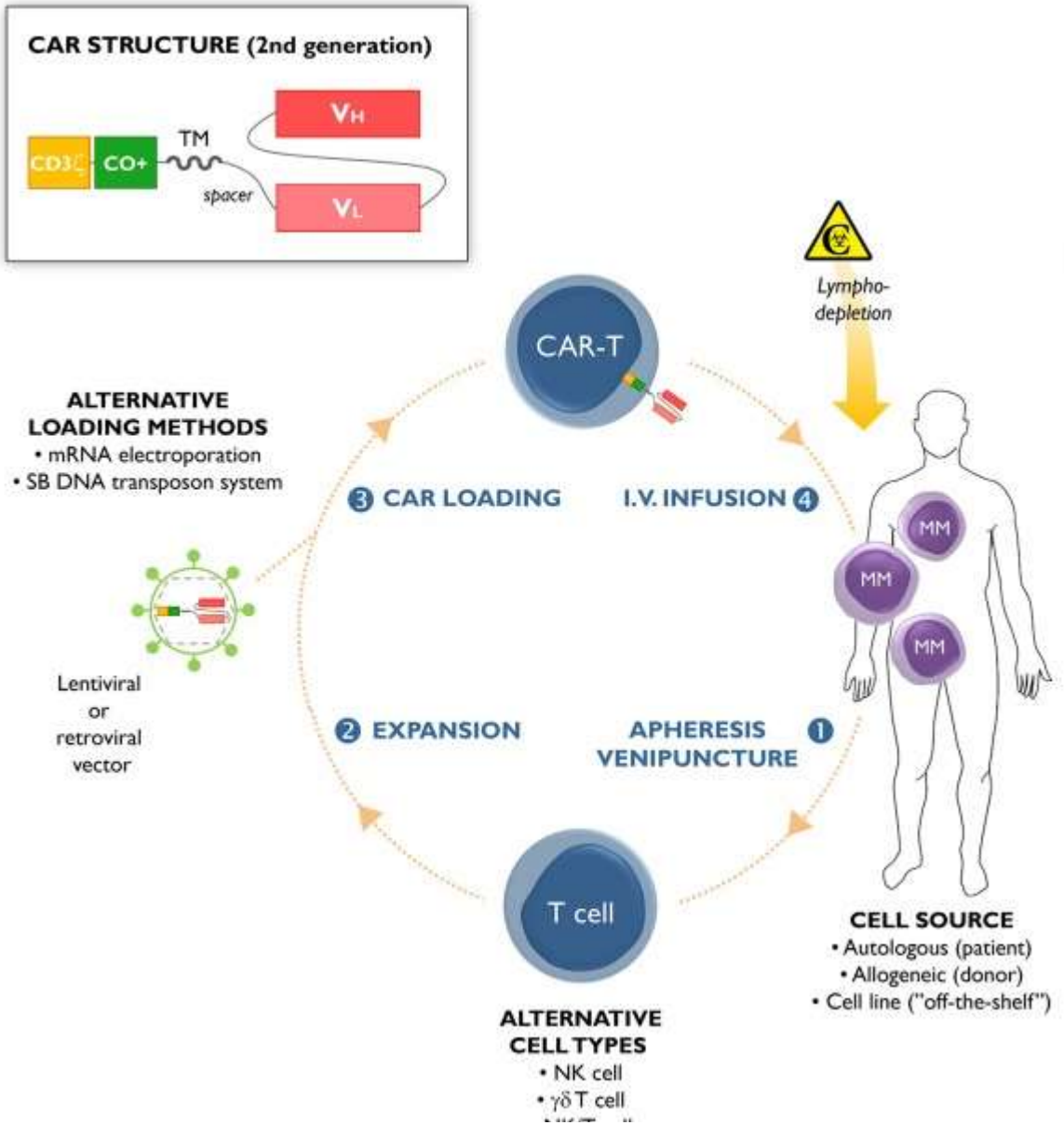
Shah NN et al. ASCO 2019.

CAR T Cells for CLL

	Clinical context						CAR T characteristics					Efficacy
Reference/ year	Number of CLL patients	Clinical situation	Prior ttmt with ibrutinib	Prior ttmt with venetoclax	TP53 alterations	Complex karyotype	Targeted Ag	Co-stimulation	Cell source	Lymphodepletion	Treatment combination	Responses
[8] / 2011	1	R/R	0	0	1/1	0	CD19	4-1BB	Autologous	P + C	None	CR
[9] / 2011	8	R/R	0	0	2/8	1/8	CD19	CD28	Autologous	None or C	None	3/8 SD
[10] / 2011	3	R/R	0	0	2/3	0	CD19	4-1BB	Autologous	B + R or P + C	None	3/3 ORR 2/3 CR
[11] / 2012	4	R/R	0	0	ND	ND	CD19	CD28	Autologous	F + C	IL2 IV for 5 d	3/4 ORR 1 CR
[12] / 2013	4 2 Richter	Recurrence after allogeneic treatment	0	0	2/4	ND	CD19	CD28	Allogeneic	None	None	1/4 ORR 1 PR 1 SD
[13] / 2015	5 1 Richter	R/R	ND	ND	ND	ND	CD19	CD28	Autologous	F + C	None	5/5 ORR 3 CR 2 PR
[14] / 2015	14	R/R	1/14	0	6/14	ND	CD19	4-1BB	Autologous	B or P+ C or F + C	None	8/14 ORR (57%) 4/14 CR (28%) 4/14 PR (28%) 4 MRD neg
[15] / 2016	3	R/R	3/3	0	3/3	2/3	CD19	4-1BB	Autologous	ND	Ibrutinib stopped just before leukapheresis	3/3 ORR 1 CR 2 PR
[16] / 2016	5	Recurrence after allogeneic treatment	ND	ND	ND	ND	CD19	CD28	Allogeneic	None	None	2/5 ORR 1 CR 1 PR
[17] / 2016	2	R/R	0	0	ND	ND	Kappa	CD28	Autologous	None	None	0 ORR 1 SD
[18] / 2017	24 5 Richter	R/R post-ibrutinib 25% post venetoclax	24/24	6/24	23/24	16/24	CD19	4-1BB	Autologous	F + C mostly, or F or C	None	71% ORR 21% CR 43% PR 58% MRD neg
[19] / 2018	8	1st line P + FC	0	0	0	0	CD19	CD28	Autologous	C	None	3/8 ORR (38%) 2/8 CR
[20] / 2018	19 4 Richter	R/R post-ibrutinib	19/19	11/19	14/19	14/19	CD19	4-1BB	Autologous	F + C	Concomitant ibrutinib	15/18 ORR (83%) 11/13 CR BM with MRD neg
[21] / 2018	19	R/R ×14 +1st line ibrutinib ×5	5 in 1st line	0	11/19	ND	CD19	4-1BB	Autologous	ND"chemotherapy"	Concomitant ibrutinib	10/11 ORR 94 CR BM with 78% MRD neg
[22] / 2018	16	R/R post-ibrutinib	16/16	8/16	10/16	8/16	CD19	4-1BB	Autologous	F + C	None	81.3% ORR 7 CR 6 PR

Lemal et al Journal for ImmunoTherapy of Cancer. (2019) 7:202

CAR T Cells for Myeloma



ANTIGEN TARGETS

Clinical (published)
- BCMA
- CD138
- CD19
- NKG2D ligands
- Light chains

Clinical (ongoing)
- CD38
- SLAMF7/CS1
- CD44v6
- CD56
- GPRC5D
- TACI
- Lewis Y
- NY-ESO-1

Preclinical
- CD229
- Integrin β7
- CD70
- CD1d

Table 1

Published clinical results of multiple myeloma CAR-T cell clinical trials targeting BCMA.

CAR-T cell product (ref.)	*n* =	ORR (*n* =)	median PFS (95% CI)
bb2121 (22)	33	85% (28)	11.8 months (6.2–n.e.)[$]
CART-BCMA Upenn (23)	25	48% (12)	2.0 months (ND)
NCI CAR BCMA-T (24)[#]	10	20% (2)	1.5 months (ND)
NCI CAR BCMA-T (25)*	16	81% (13)	7.25 months (ND)
LCAR-B38M (26)	17	88% (15)	12.2 months (ND)
LCAR-B38M (27)	57	88% (50)	15.0 months (11.0–n.e.)

Only fully published clinical studies were included (last search: May 1, 2019). (ref.), bibliography reference; n =, number of patients; ORR, objective response rate, defined as the sum of complete responses and (very good) partial responses; PFS, progression-free survival; 95% CI, 95% confidence interval; n.e., not estimable, ND, no data;

[$]*PFS calculated for 30 patients treated with active doses of bb2121 only (i.e., ≥150 × 10^6 CAR-T cells);* [#]*lower dose cohorts (i.e., 0.3-1-3 × 10^6 CAR-T cells/kg), *highest dose cohort (i.e., 9 × 10^6 CAR-T cells/kg).*

Outcome of bb2121 CAR T-Cell Therapy in Myeloma

TABLE Response Outcomes in Efficacy-Evaluable Patients

	50x106 (n=3)	150x106 (n=14)	>150x106 (n=22)
Median follow-up (range)	84 days (59-94)	87 days (36-638)	194 days (46-556)
Overall response	33.3%	57.1%	95.5%
Complete response	0%	42.9%	50%
Very good partial response	0%	7.1%	36.4%
Median duration of response	1.9 months	Not estimable	10.8 months

Clinical Results of Non-BCMA CAR T cells for Myeloma

n = (ref.)	Antigen	Signaling domains	Cell source/type	Transfer method	Conditioning	T-cell dosage	Therapy-related side effects	Clinical effects
n = 1 (31)	CD138	ND	Autologous T cells	ND	CP/Flu	1.5×10^8	• CRS gr. 2 (1)	• PR (1)
n = 5 (32)	CD138	4-1BB/CD3ζ	Autologous T cells	Lentiviral	PCD, CP or VAD	0.756×10^7/kg	• Infusion-related fever (4) • Nausea and vomiting (3) • ↑ Liver function tests (1) • Possible TLS (1)	• SD > 3 m (4) • ↓ circulating PCL cells (1)
n = 10 (33)	CD19	4-1BB/CD3ζ	Autologous T cells	Lentiviral	HDM + ASCT	$1–5 \times 10^7$	• Hypogammaglobulinemia (1) • Autologous GvHD (1) • Mucositis (1)	• CR (1) • VGPR (6/10) at d100 post-ASCT • PR (2/10) at d100 post-ASCT
n = 5/8 (34)	CD19 + BCMA	OX40/CD28	Autologous or allogeneic T cells	Lentiviral	CP/Flu	1×10^7/kg	• CRS gr. 1–2 (7), gr.≥3 (1) • Prolonged cytopenias (5/5) • Coagulopathy (5) • ↑ Liver function tests (4) • Pulmonary edema (3) • Pleural effusion and ascites (1)	• sCR (1/5) • VGPR (1/5) • PR (2/5) • SD (1/5)
n = 10 (35)	CD19 + BCMA	OX40/CD28	Autologous T cells	Lentiviral	Bu-CP + ASCT	1×10^7/kg	• CRS gr. 1–2 (10) • Coagulopathy (7) • ↑ Troponin levels (4) • Atrial flutter (1)	• CR (7/10) • VGPR (3/10)
n = 5 (36)	NKG2D ligands	CD3ζ	Autologous T cells	Retroviral	None	$1–3 \times 10^{6–7}$	• None	• None
n = 7 (37)	κLC	CD28/CD3ζ	Autologous T cells	Retroviral	CP (4) or none (3)	$0.92–1.9 \times 10^8$/m²	• Lymphopenia gr. 3 (1)	• SD 6 wk–24m (4)

THE LANCET
Haematology

ARTICLES | ONLINE FIRST

A combination of humanised anti-CD19 and anti-BCMA CAR T cells in patients with relapsed or refractory multiple myeloma: a single-arm, phase 2 trial

Zhiling Yan, MD * • Jiang Cao, MD * • Hai Cheng, MD • Prof Jianlin Qiao, PhD • Huanxin Zhang, MD • Ying Wang, MD • et al.

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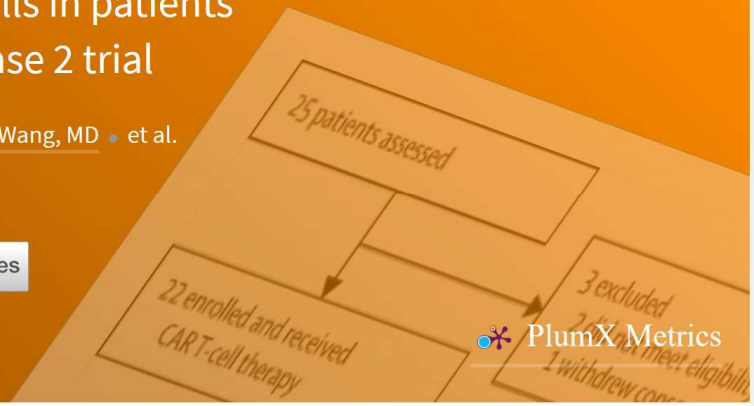
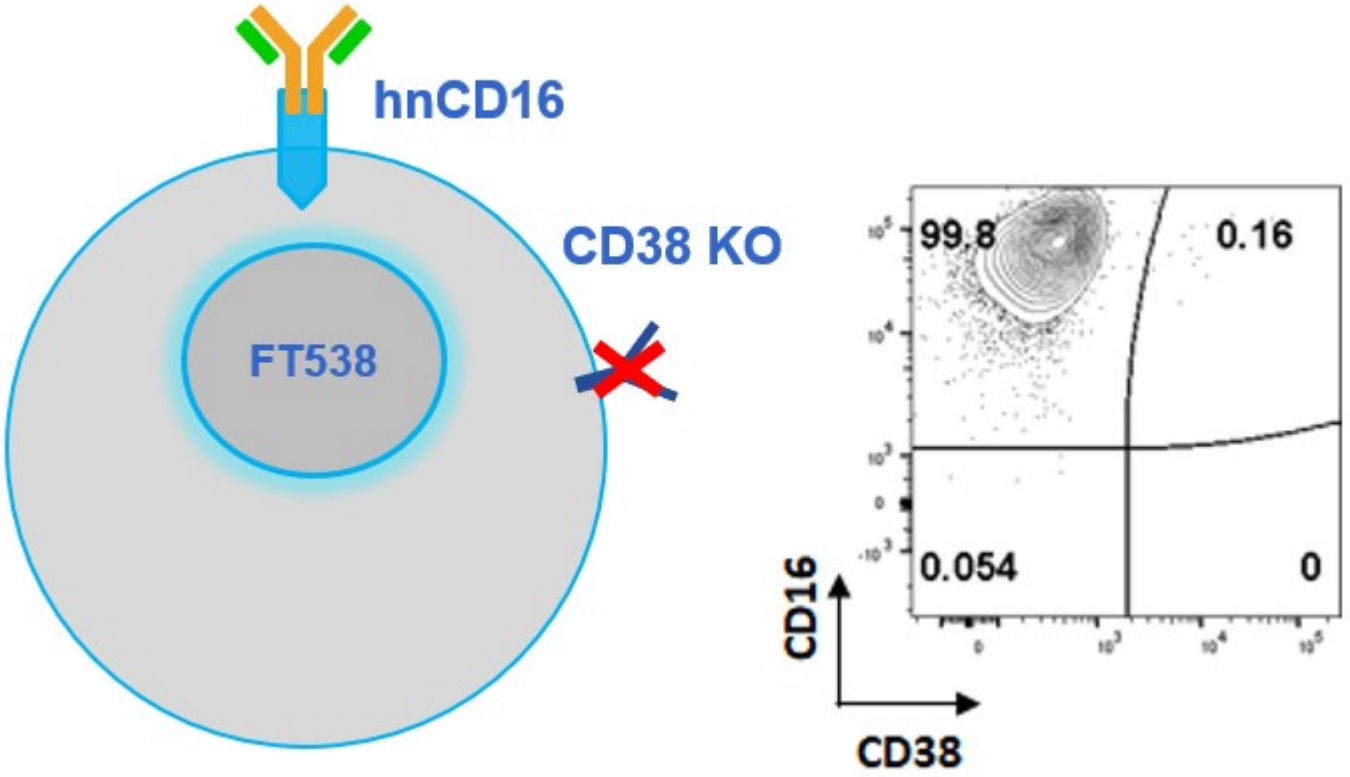
Published: August 01, 2019 • DOI: https://doi.org/10.1016/S2352-3026(19)30115-2 •



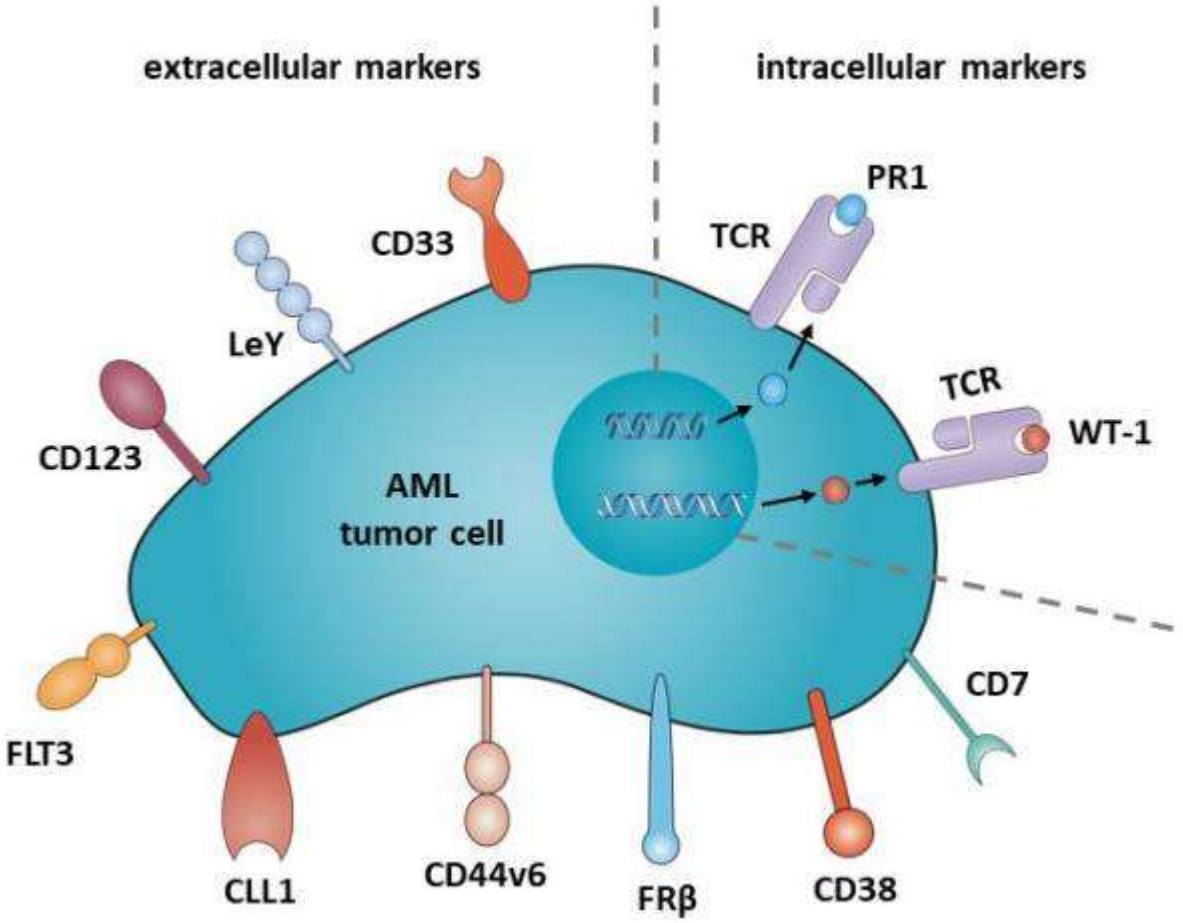
- 22 patients were enrolled and 21 received an infusion of CAR T cells and were evaluable for safety and activity analyses.
- At a median follow-up of 179 days, 20 (95%) of 21 patients had an overall response, including nine (43%) stringent complete responses, three (14%) complete responses, five (24%) VGPR, and three (14%) PR.
- The most common adverse events included CRS (19 [90%] of 21), including 18 patients (86%) with grade 1–2 cytokine release syndrome.
- No death was reported

Engineered NK cells for myeloma



Woan et al. Blood 2018 132:3224

CAR T cells in AML



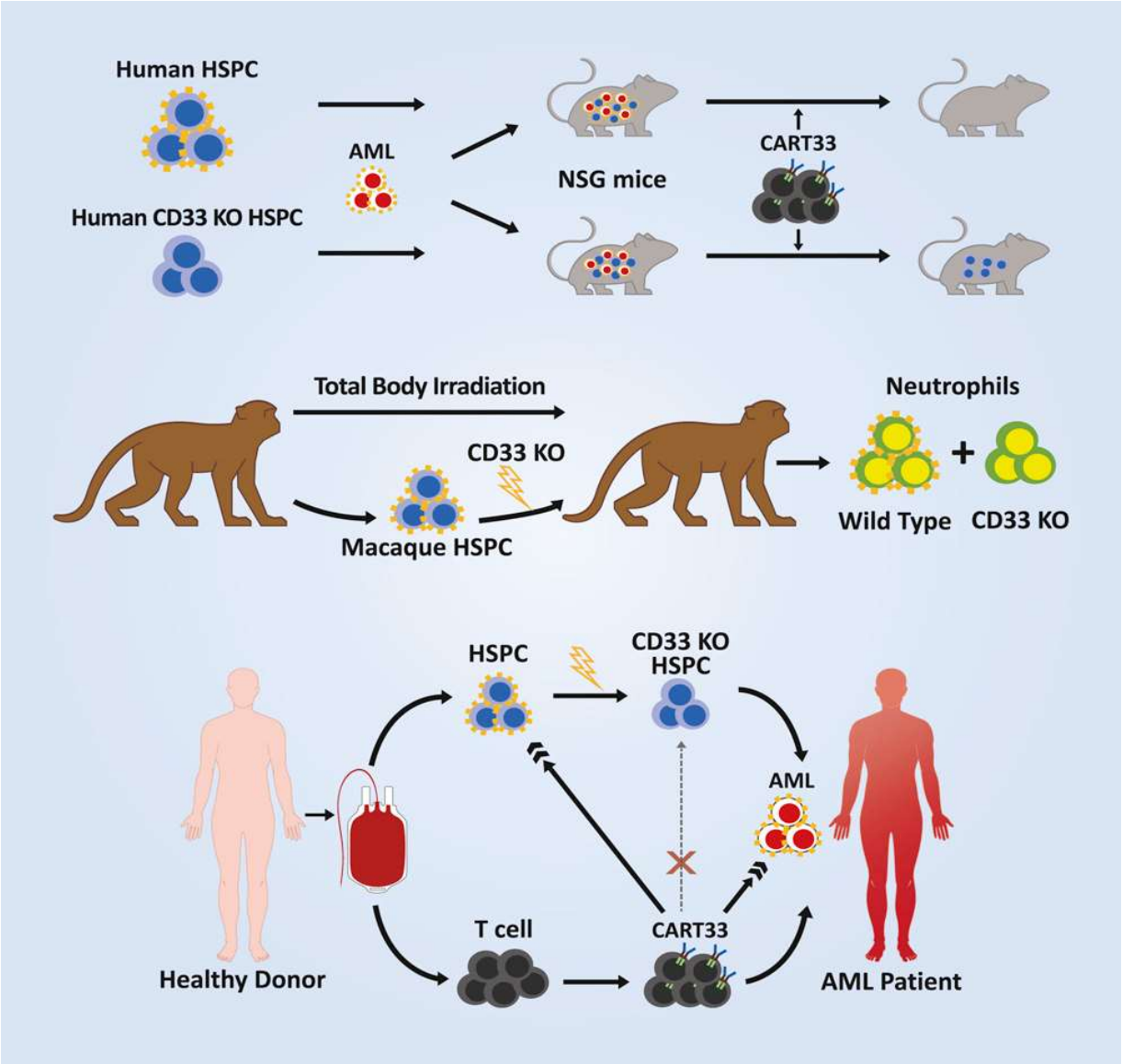
Hoffman, et al. J Clin Med. 2019 Feb; 8(2): 200

CAR T Cells Clinical Trials for AML

Trial ID	Status	Phase	Target	Indication	Institution
NCT03585517	R	I	CD123	CD123+ AML	Xian Lu, Beijing, China
NCT03114670	R	I	CD123	recurred AML after allo	Fengtai District, Beijing Shi, China
NCT03556982	R	I/II	CD123	R/R AML	307 Hospital of PLA, Beijing, Beijing, China
NCT02623582	terminated	I	CD123	R/R AML	Abramson Cancer Center of the University of Pennsylvania, Philadelphia, Pennsylvania, United States
NCT02159495	R	I	CD123	R/R AML, Persistent/Recurrent Blastic Plasmacytoid Dendritic Cell Neoplasm	City of Hope Medical Center, Duarte, California, United States
NCT03672851	R	I	CD123	R/R AML	Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China
NCT03766126	R	I	CD123	R/R AML	University of Pennsylvania, Philadelphia, Pennsylvania, United States
NCT01864902	R	I	UCART 123	R/R AML, newly diagnosed high-risk AML	Weill Cornell Medical College, New York, New York, United States MD Anderson Cancer Center, Houston, Texas, United States
NCT03631576	R	II/III	CD123/CLL1	R/R AML	Fujian Medical University Union Hospital, Fuzhou, Fujian, China
NCT03126864	R	I	CD33	R/R CD33+ AML	University of Texas MD Anderson Cancer Center, Houston, Texas, United States
NCT02799680	unknown	I	CD33	R/R AML	Affiliated Hospital of Academy of Military Medical Sciences, Beijing, Beijing, China | Chinese PLA General Hospital, Beijing, Beijing, China
NCT01864902	unknown	I/II	CD33	R/R AML	Biotherapeutic Department and Pediatrics Department of Chinese PLA General Hospital, Hematological Department, Affiliated Hospital of Changzhi Medical College, Beijing, Beijing, China
NCT02944162	unknown	I/II	anti-CD33 NK CAR	R/R CD33+ AML	PersonGen BioTherapeutics (Suzhou) Co., Ltd., Suzhou, Jiangsu, China

Hoffman, et al. J Clin Med. 2019 Feb; 8(2): 200

Genetic Inactivation of CD33 in Hematopoietic Stem Cells to Enable CAR T Cell Immunotherapy for Acute Myeloid Leukemia



Cell 2018 173, 1439-1453.e19DOI: (10.1016/j.cell.2018.05.013)

Dual targeting CARs for AML

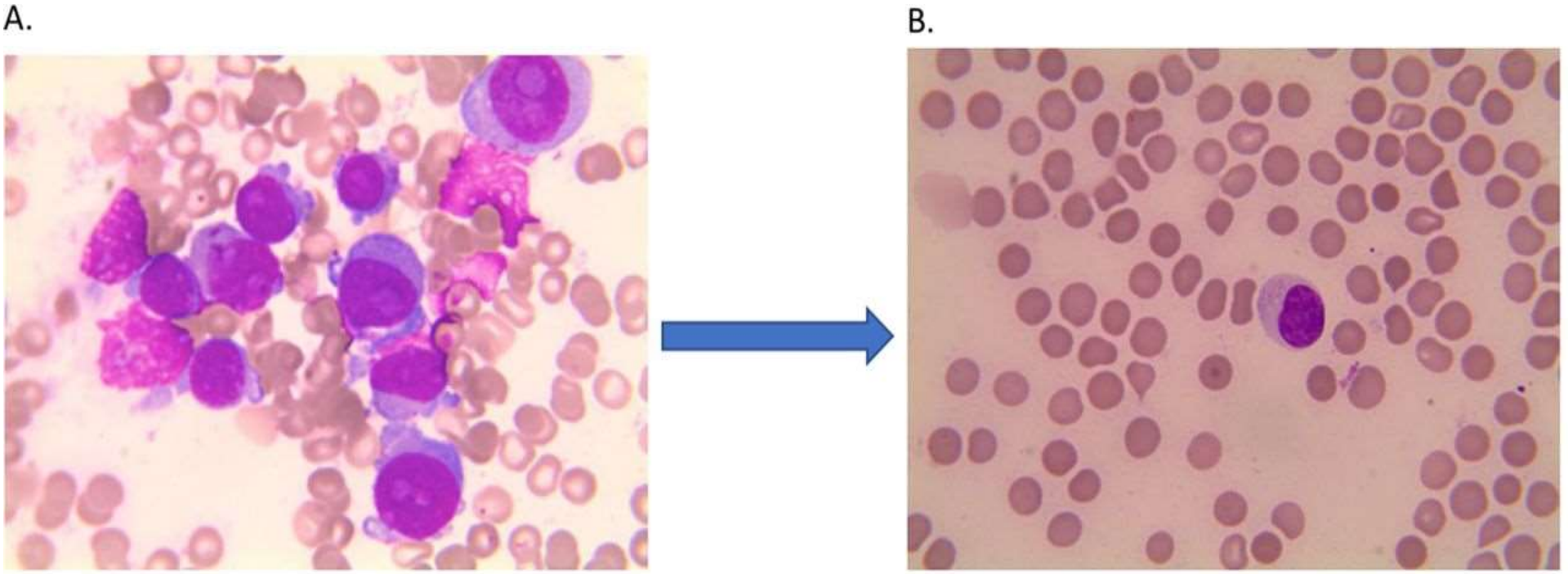


Figure 1. Patient treated with cCAR achieved complete remission. A. 12 days post cCAR infusion, leukemia blasts comprised 98% of the bone marrow. **B.** 19 days post cCAR infusion, total myeloid ablation had taken place in patient's bone marrow with only CAR T cells existing. Results were confirmed by flow cytometry showing the absence of blasts. Sternal bone marrow aspiration also showed similar findings.

Liu, et al. Blood 2018 132:901

How about solid tumors

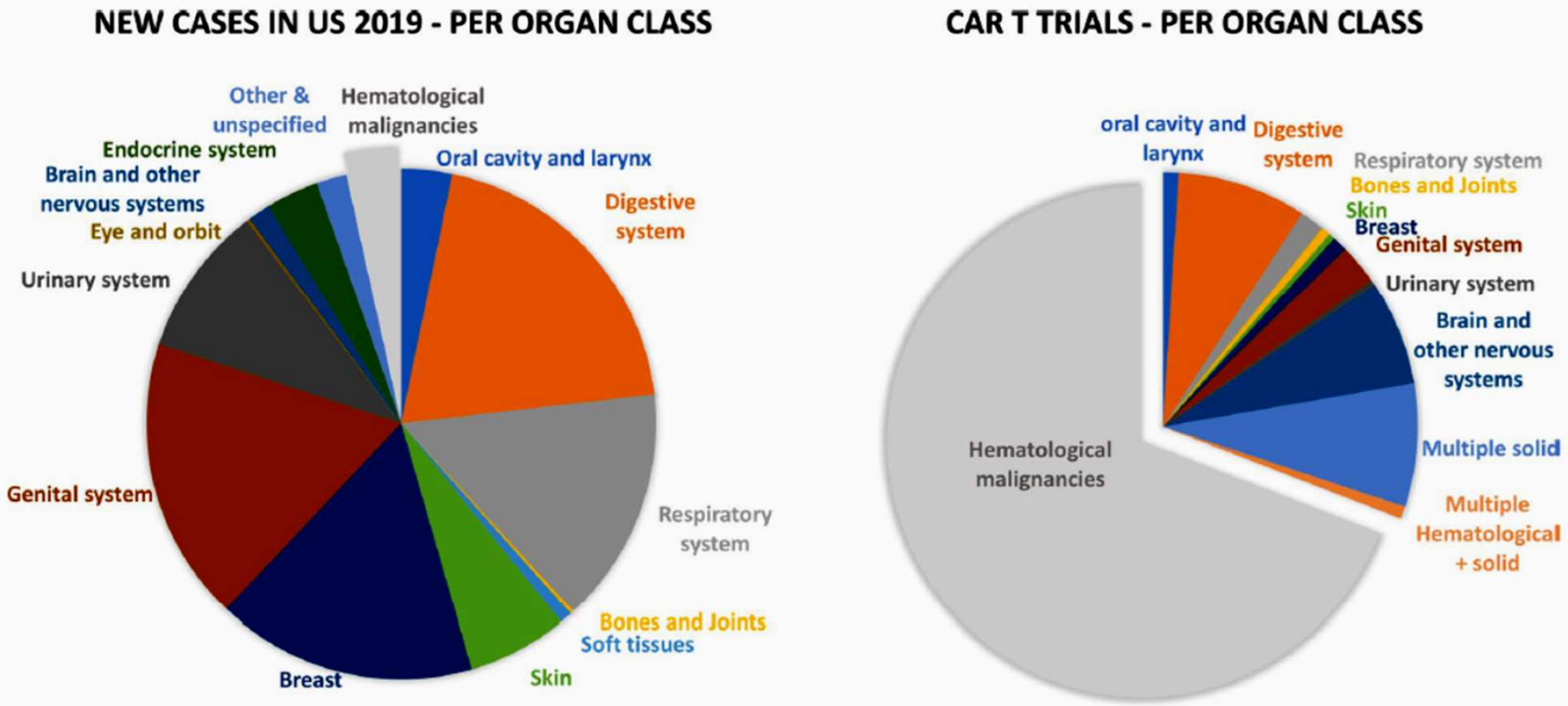
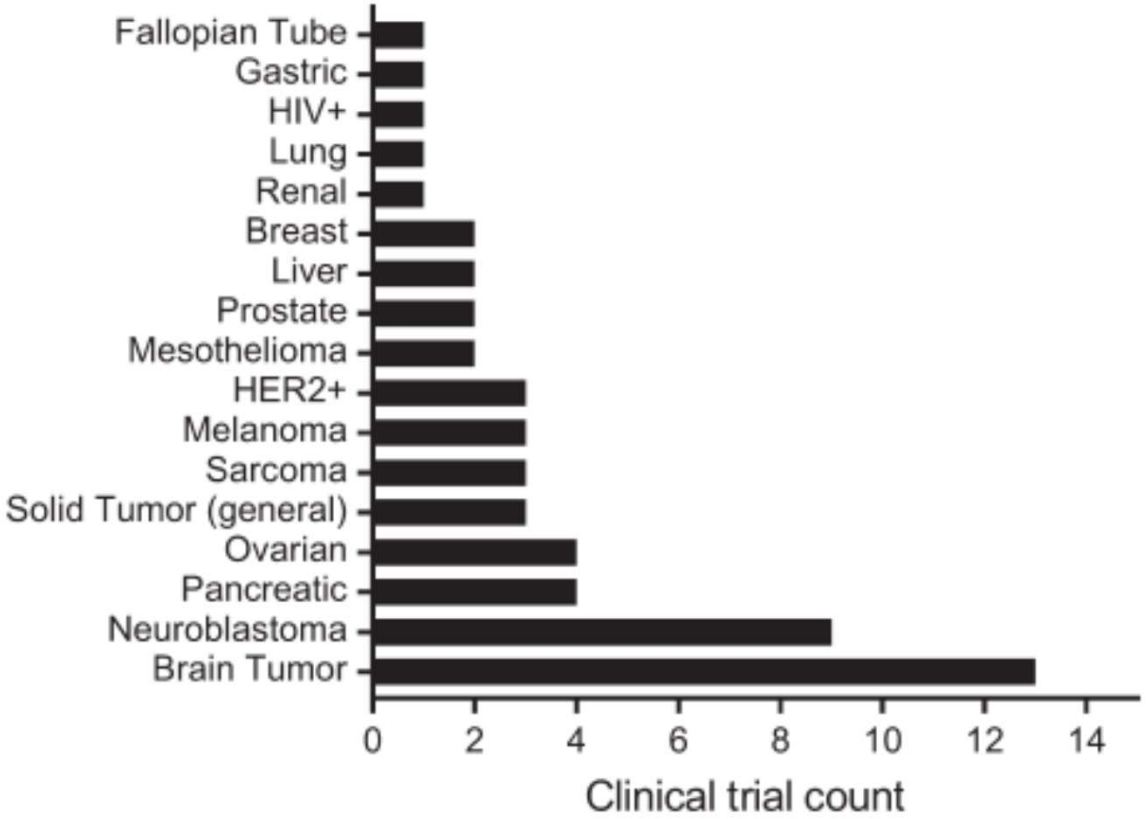


Fig. 1 Estimated proportion of new cancer cases in the USA in 2019 (left) and CAR-T clinical trials per organ class (right). Based on Cancer Facts and Figures, 2019 (American Cancer Society) [129] and the U.S. National Library of Medicine (ClinicalTrials.gov; excluding long-term follow-up and retrospective studies). *CAR-T* chimeric antigen receptor T cell

Chimeric antigen receptor (CAR) T cell trials for solid tumors.



Current Clinical Trials in Glioblastoma

Antigen	Expression on brain tumors	Expression on normal tissues	Preclinical investigation of CAR targeting the brain TAA
B7-H3	Highly expressed in high-grade gliomas and other brain tumors	Liver, lung, bladder, testis, prostate, breast, placenta, and lymphoid organs	118
CD133	Glioma tumor-initiating cancer stem cells	Hematopoetic stem cells, endothelial progenitor cells, neuronal stem cells	123
CSPG4	Uniform in GBMs (67% high expression)	Chondroblasts, pericytes, cardiomyocytes	119
EGFRvIII	Most common EGFR mutation in GBM; approximately 30% of GBMs	Restricted	77,82
EphA2	Uniform in high-grade glioma with various levels	Epithelial tissue	111,261
GD2	Uniform in DIPGs; low in high-grade gliomas	Central nervous system, peripheral nerves, and skin melanocytes	112
HER2	Moderate expression on GBM; highly expressed on other solid tumors that metastasize to the brain	Epithelial tissue, skin and muscle	93,95
IL13Rα2	Majority of GBM and other high-grade gliomas	Testis	60,70,262

Table 1 Published human CAR T-cell trials in glioblastoma

CAR Target	CAR Generation[a] (number of subjects)	Biomarker Inclusion Criteria	Mode of Administration	Grade 3/4 Adverse Events Possibly Related to CART cells	Efficacy Measures
IL-13 Rα2[25,45]	First ($N = 3$) Second ($N = 1$)	None Tumor IL-13 Rα2+ by IHC[b]	Postresection intracavitary infusions × 12 (catheter device; $N = 3$) Direct intratumoral infusions × 5 (catheter device; $N = 1$) Postresection intracavitary infusions × 6 (catheter device) Intraventricular infusions × 10 (catheter device)	Headache ($N = 2$) Neurologic (shuffling gait, tongue deviation) ($N = 1$) Leukopenia ($N = 1$) Fatigue ($N = 1$) None	Median overall survival ~11 months No tumor recurrence at border of resection cavity Complete response of intracranial and spinal disease lasting 7.5 months
HER2 (virus-specific)[49]	Second ($N = 17$)	Tumor HER2+ by IHC, CMV seropositivity	Peripheral infusions: 1 infusion ($N = 10$) 2 infusions ($N = 4$) 3 infusions ($N = 1$) 4 infusions ($N =$) 6 infusions ($N = 1$)	Lymphopenia ($N = 2$) Headache ($N = 2$) Neutropenia ($N = 1$) Fatigue ($N = 1$) Weakness ($N = 1$) Cerebral edema ($N = 1$) Hydrocephalus ($N = 1$) Hyponatremia ($N = 1$)	Median overall survival ~11 months One patient with partial response more than 9 months Three patients with durable stable disease during 24–29 months of follow-up
EGFRvIII[26]	Second ($N = 10$)	Tumor EGFRvIII+ by RNA-based next-generation sequencing	Single peripheral infusion	Extremity or facial muscle weakness ($N = 2$) Cerebral edema ($N = 2$) Seizure ($N = 2$) LV systolic dysfunction ($N = 1$) Headache ($N = 1$) Intracranial hemorrhage ($N = 1$)	Median overall survival ~8 months One patient remains alive (33 months post CART-cell infusion) at time of this review article

[a] First generation: CD3 ξ-chain only.
Second generation: CD3 ξ-chain plus 1 co-stimulation domain (4-1BB or CD28).
Third generation: CD3 ξ-chain plus 2 co-stimulation domains (4-1BB and CD28).
[b] IHC: immunohistochemistry.

Moving Forward with CAR-T Cells

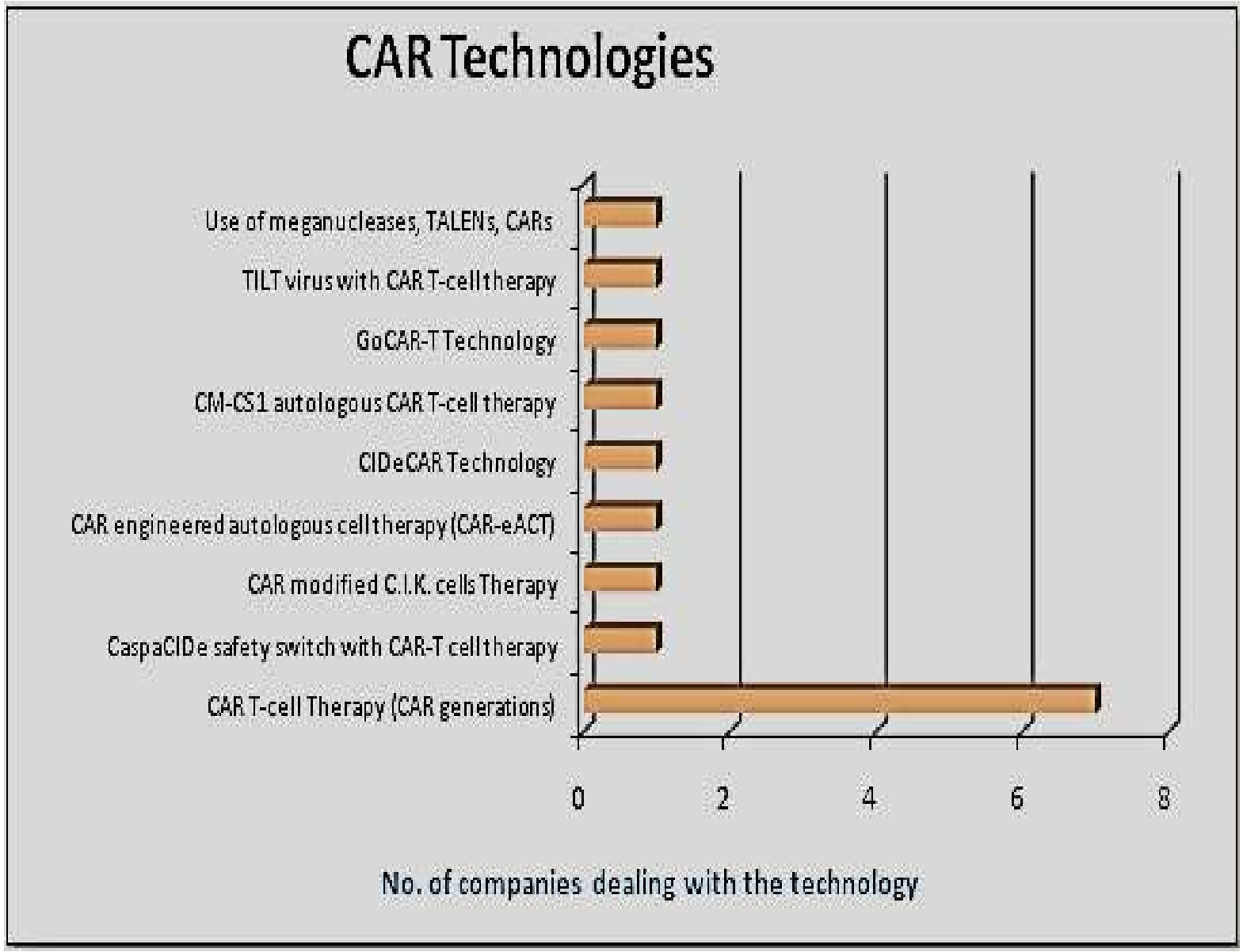
Determinants of successful ACT: CAR-T cells

- **Tumor target**
  - Target antigen is critical determinant for efficacy & safety
  - Ideal target uniquely express on tumor cells or on cells which are not essential for survival

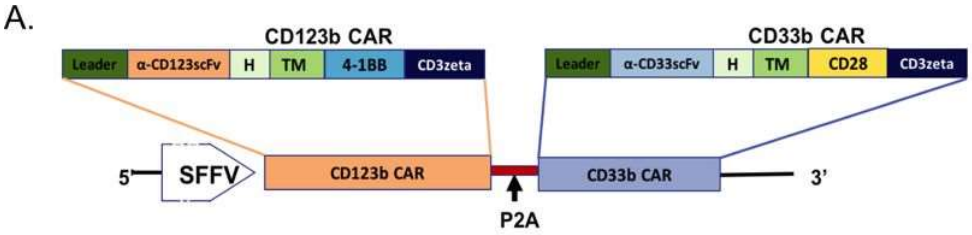
- **Efficacy & Long-term persistence**
  - Subtypes of CD4+T cells (Th1, Th2, Th17, Th9 cells),
  - CD8+T cells
    - naïve, central memory; long-term
    - effector; active but short lived

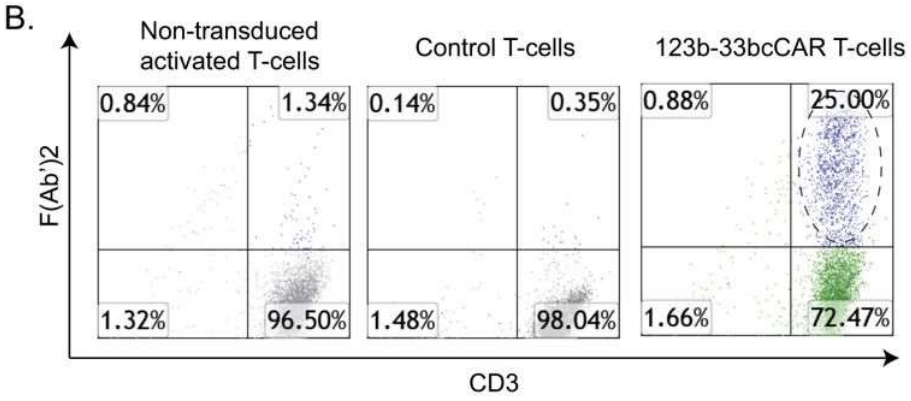
- **Trafficking of CAR T cells to tumor**
  - Expression of addressins
  - Route of CAR-T cell infusion
    - Intra-tumoral/intravenous
  - Optimal co-stimulation of T cells

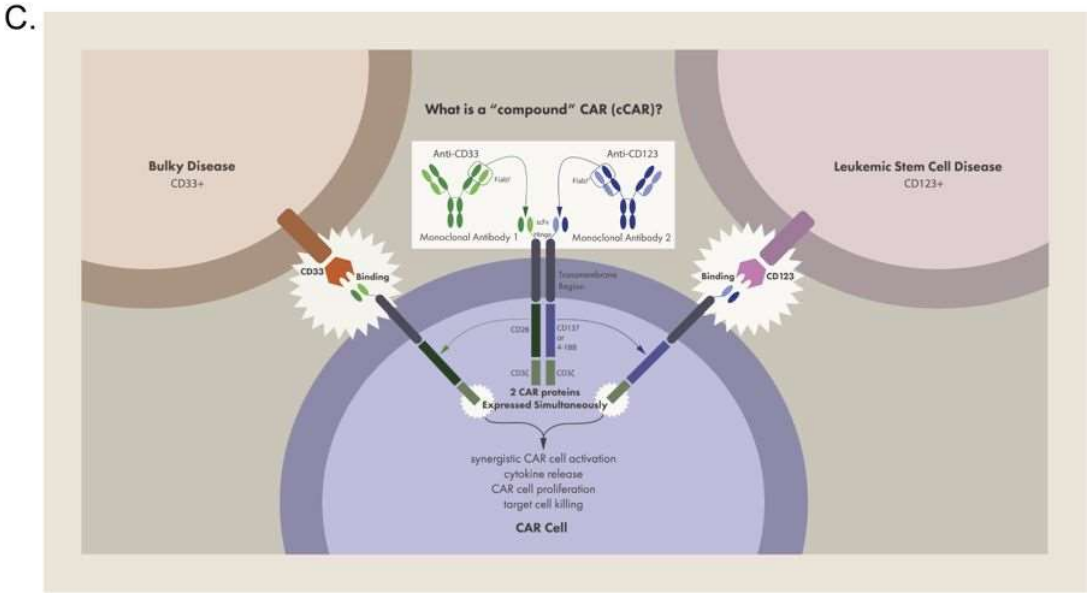
- **Patient conditioning before ACT**
  - Reduced-intensity or non-myeloablative
  - Increased intensity myelo ablative


CAR Technologies
Use of meganucleases, TALENs, CARs
TILT virus with CAR T-cell therapy
GoCAR-T Technology
CM-CS1 autologous CAR T-cell therapy
CIDeCAR Technology
CAR engineered autologous cell therapy (CAR-eACT)
CAR modified C.I.K. cells Therapy
CaspaCIDe safety switch with CAR-T cell therapy
CAR T-cell Therapy (CAR generations)
0
2
4
6
8
No. of companies dealing with the technology

Compound CAR T cells

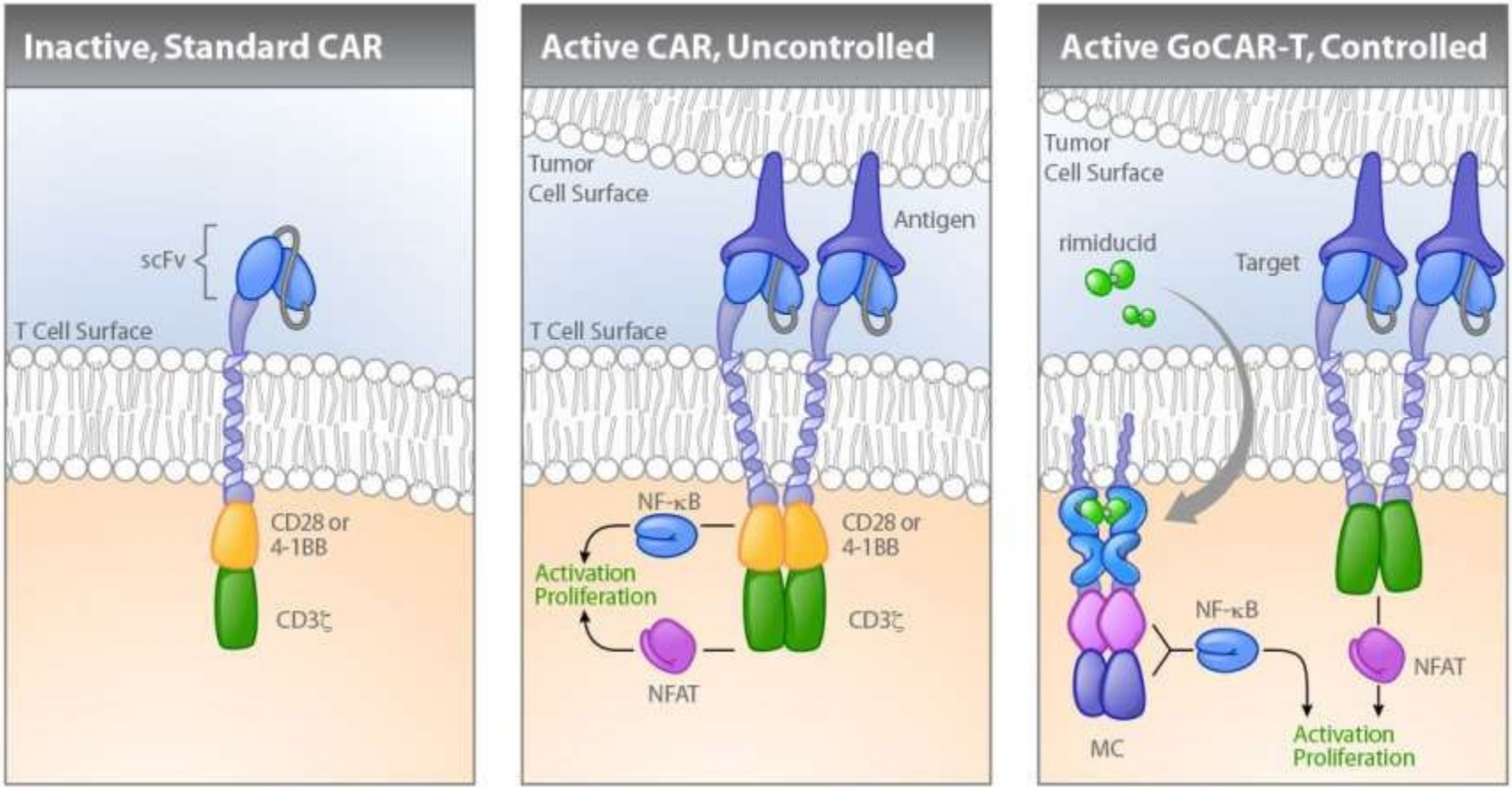


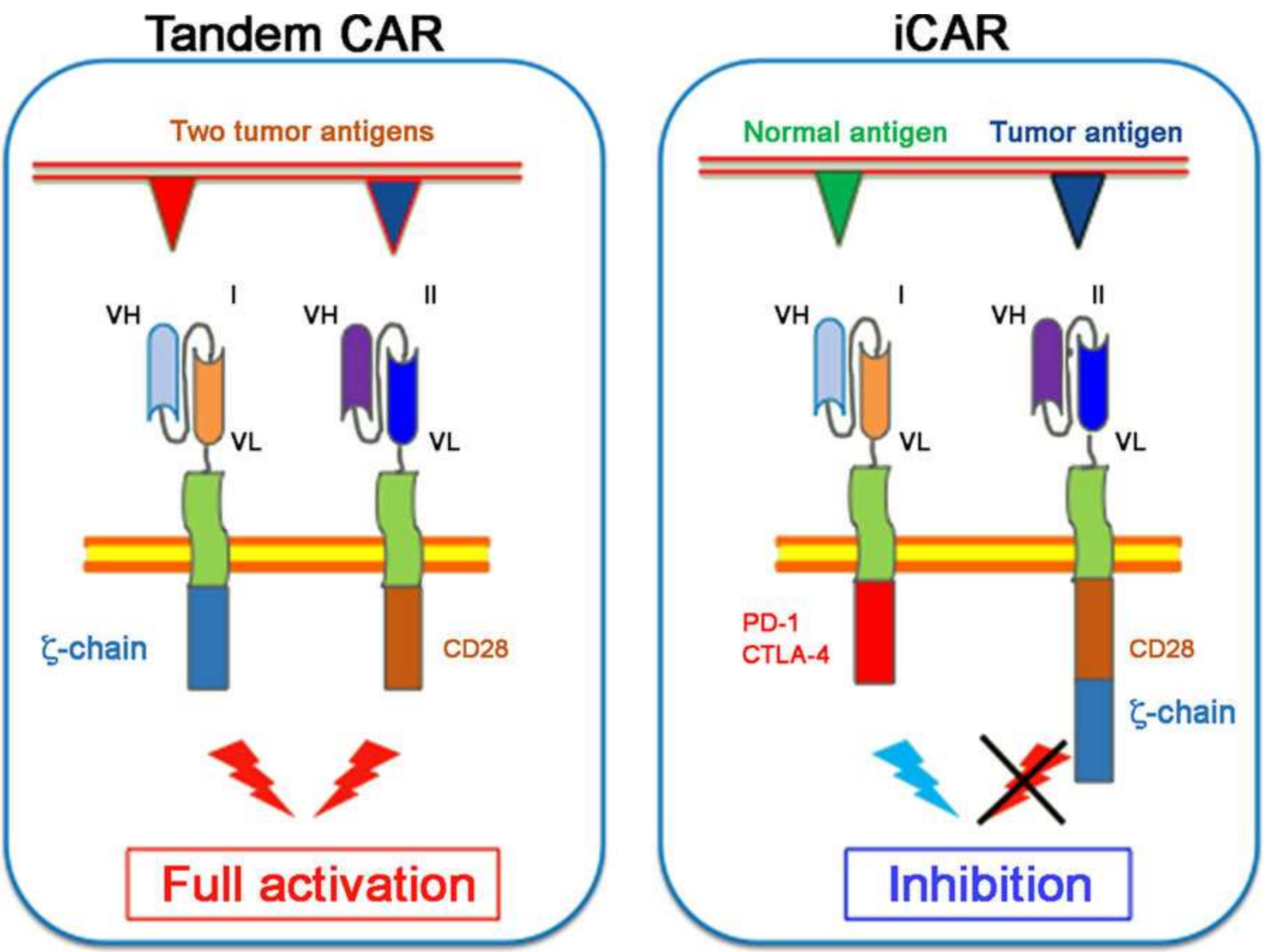




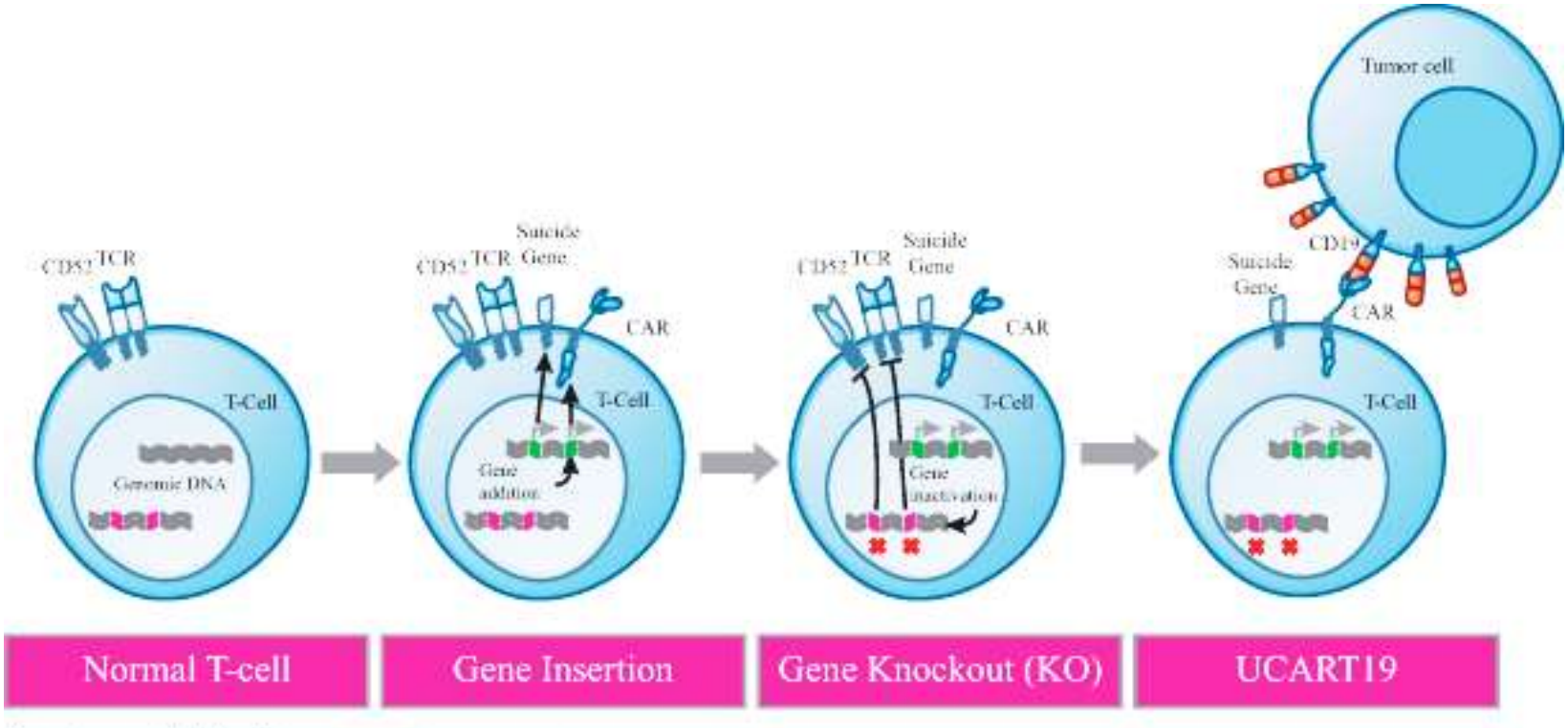
Leukemia (2018) 32:1317 –1326

Conventional CAR-T Technology *vs.* GoCAR-T



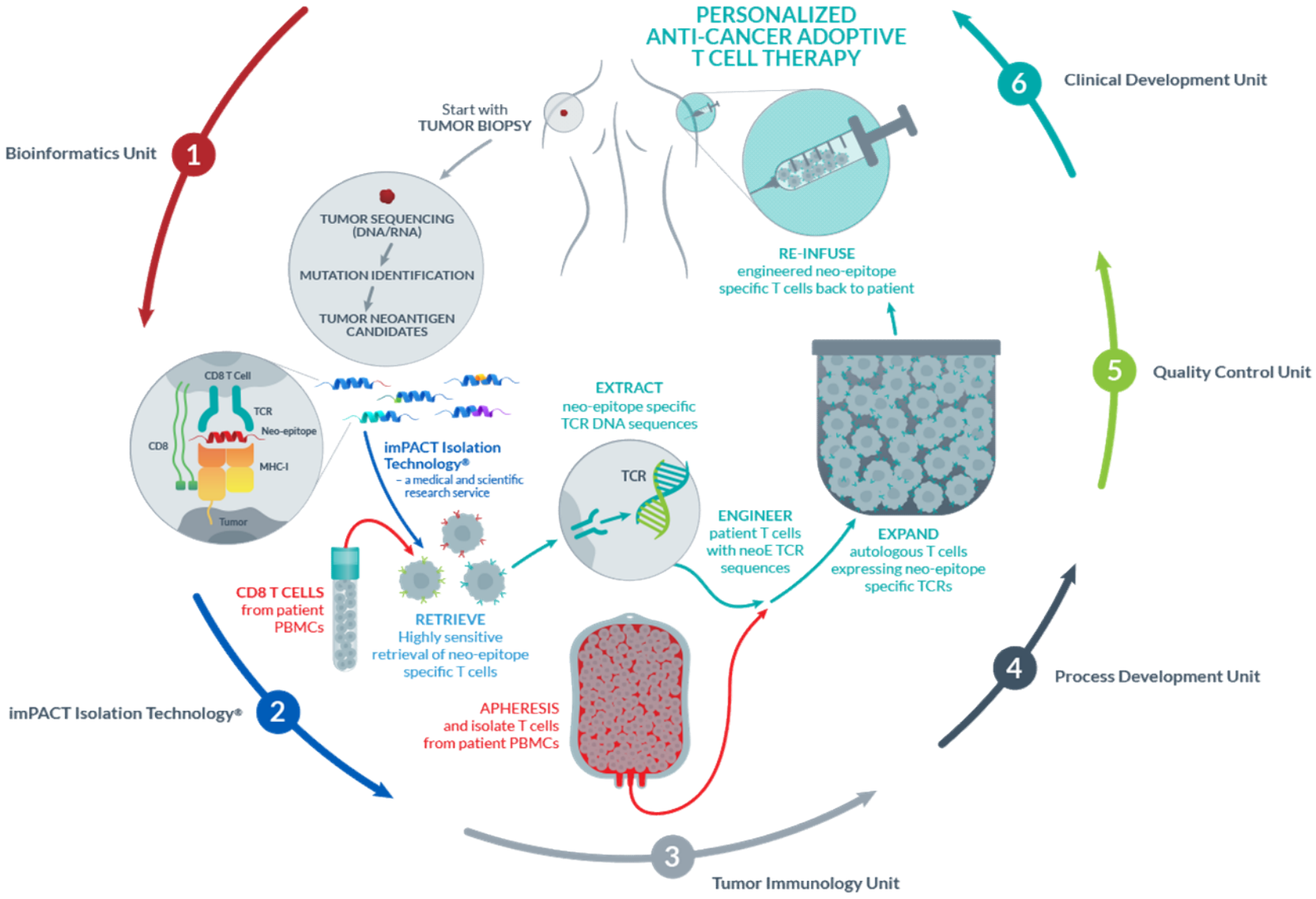

Tandem CAR
Two tumor antigens
VH
I
VL
VH
II
VL
ζ-chain
CD28
Full activation
iCAR
Normal antigen
Tumor antigen
VH
I
VL
VH
II
VL
PD-1
CTLA-4
CD28
ζ-chain
Inhibition

UCARs: Universal Chimeric Antigen Receptors



Trial	Patients Enrolled/ Treated	CR/CRi with FCA	CR/CRi Overall	G1 GvHD	G3 or 4 CRS	G4 Prolonged Cytopenia[1]	G3 or 4 Viral Infection	G3 or 4 Neurotoxicity
PALL	7	100% (6/6)	86% (6/7)	14% (1/7)	14% (1/7)	43% (3/7)	57% (4/7)	0% (0/7)
CALM	14	73% (8/11)	57% (8/14)	7% (1/14)	14% (2/14)	21% (3/14)	7% (1/14)	0% (0/14)
Pooled	21	82% (14/17)	67% (14/21)	10% (2/21)	14% (3/21)	29% (6/21)	24% (5/21)	0% (0/21)

Based on the Data cut-off date October 23, 2018



Rizvi et Science 2015
Desrichard et al clinical Cancer Research 2016

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