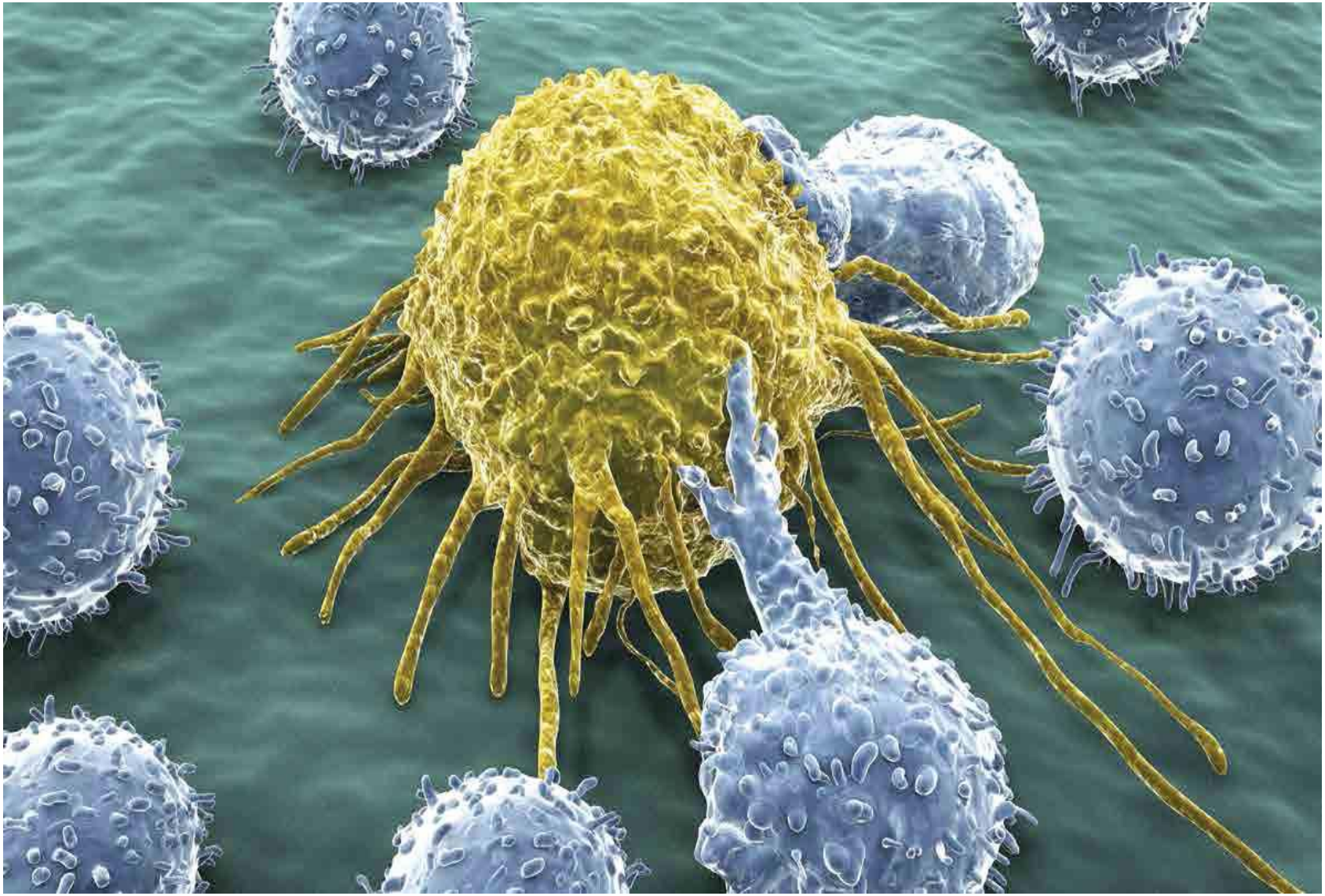
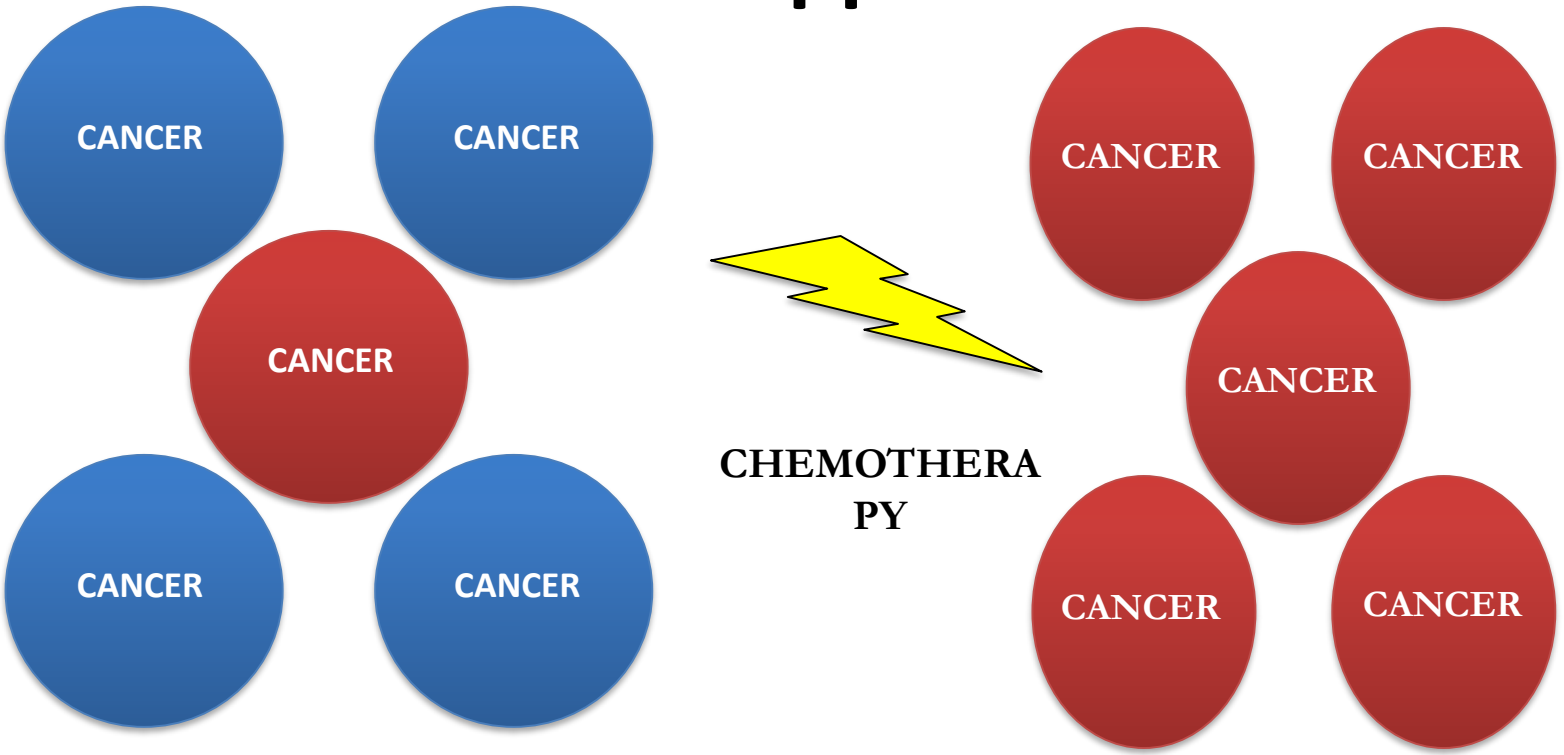
Advances in Cellular Therapy

Mehrdad Abedi MD
Director, Alpha Clinic For Stem Cell Therapy
Professor of Medicine
UC Davis Medical Center



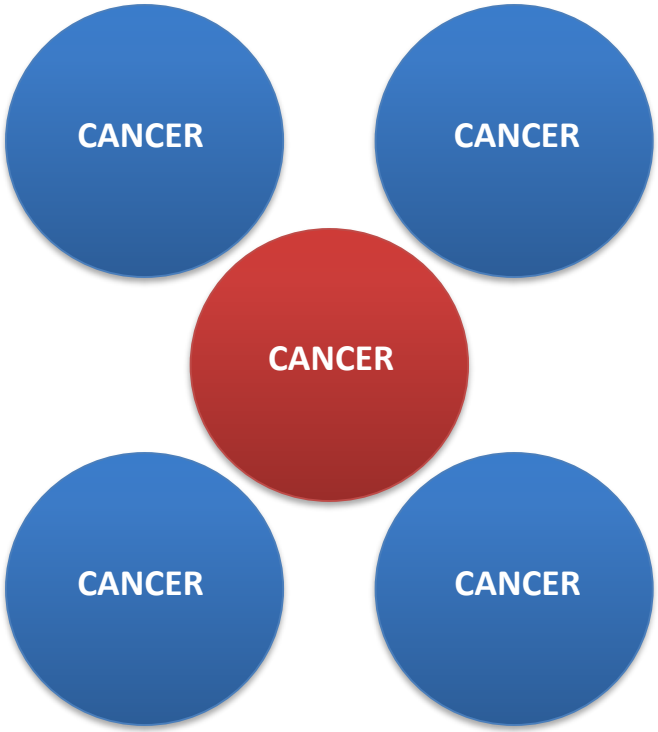
Why does leukemia relapse happen?



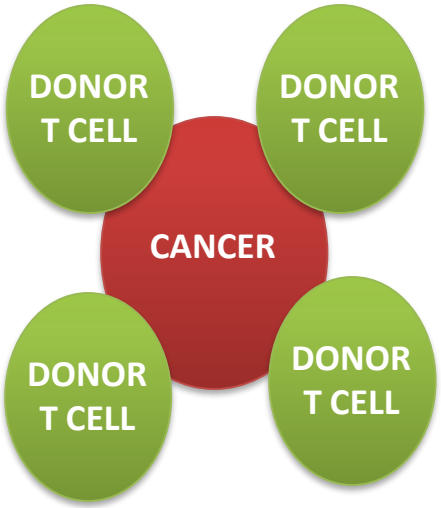
CHEMOTHERAPY SENSITIVE

CHEMOTHERAPY RESISTANT

Principles of Bone Marrow Transplant



CHEMOTHERAPY



ALLOGENEIC (DONOR) TRANSPLANT

Graft Versus Leukemia (GVL)

CHEMOTHERAPY SENSITIVE

CHEMOTHERAPY RESISTANT

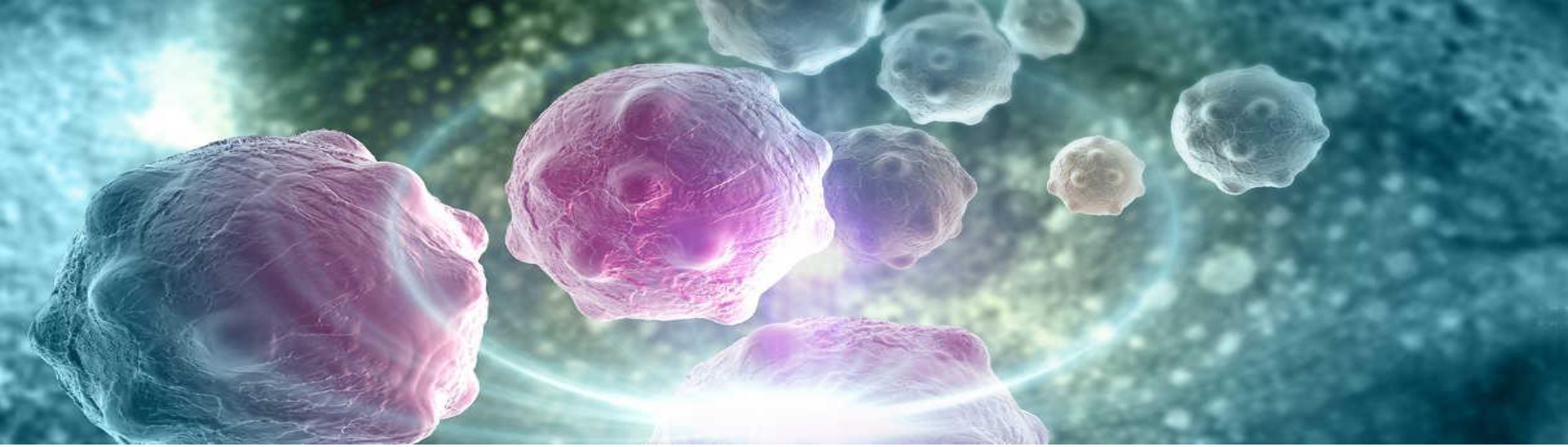
Donor Lymphocyte Infusion (DLI)

DLI is one of the earliest form of T cell therapy and proof of principal for GVL effect

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]

Cellular and Gene Therapy used to be a dangerous business.


Science
20 December 2013 | 342
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
AAAS



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

The New York Times

HEALTH

In Girl's Last Hope, Altered Immune Cells Beat Leukemia

By DENISE GRADY DEC. 9, 2012

Emma Whitehead, with her mother, Kari. Last spring, Emma was near death from acute lymphoblastic leukemia but is now in remission after an experimental treatment at the Children's Hospital of Philadelphia.
Jeff Swensen for The New York Times

384 Studies found for: **car t cells**

Also searched for **Chimeric antigen receptor**, **T lymphocyte**, and **Cellular**. See Search Details

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Hide Filters

Showing: 1 10 of **384** studies 10 studies per page

Filters

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Recruitment Status

Clinical Study :

- Not yet recruiting
- Recruiting
- Enrolling by invitation
- Active, not recruiting
- Suspended
- Terminated
- Completed
- Withdrawn
- Unknown status†

Expanded Access :

Eligibility Criteria

Age :

years OR

Age Group :

- Child (birth–17)
- Adult (18–65)
- Senior (66+)

Row	Saved	Status	Study Title	Conditions	
1		Recruiting	A Clinical Research of **CAR T Cells** Targeting EpCAM Positive Cancer	• Colon Cancer • Esophageal Carcinoma • Pancreatic Cancer • (and 3 more...)	• Biological: **CAR-T**
2		Completed	**CAR-T Cell** Immunotherapy for GD2 Positive Glioma Patients	• GD2 Positive Glioma • **CAR-T Cell** Immunotherapy	• Biological: **CAR-T**
3		Completed	**CAR-T Cell** Immunotherapy for EphA2 Positive Malignant Glioma Patients	• EphA2 Positive Malignant Glioma • **CAR-T Cell** Immunotherapy	• Biological: **CAR-T**
4		Recruiting	Safety and Efficacy Evaluation of 4th Generation Safety-engineered **CAR T Cells** Targeting Sarcomas	• Sarcoma • Osteoid Sarcoma • Ewing Sarcoma	• Biological: Sarcom
5		Not yet recruiting	**CAR-T Cell** Immunotherapy for Advanced Lung Cancer	• Advanced Lung Cancer	• Biological: **CAR-T**
6		Completed	CD19-targeting **CAR T Cells** for B **Cell** Lymphoma	• B **Cell** Lymphoma	• Biological: CD19-t
7		Recruiting	PSCA/MUC1/PD-L1/CD80/86-**CAR-T Cells** Immunotherapy Against Cancers	• Lung Cancer • Cancer • Immunotherapy • **CAR-T Cell**	• Genetic: PSCA,MU **CAR-T cells**
8		Recruiting	CD19 **CAR T Cells** in Patients With Relapsed or Refractory CD19 Positive B-**cell** Lymphoma	• Lymphomas Non-Hodgkin's B-**Cell**	• Biological: CD19 C

Article types
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Best matches for car-t cell therapy:

CAR T-cell therapy: toxicity and the relevance of preclinical models.
Kalaitsidou M et al. Immunotherapy. (2015)

Challenges to chimeric antigen receptor (CAR)-T **cell therapy** for cancer.
Magee MS et al. Discov Med. (2014)

Regional delivery of mesothelin-targeted **CAR T cell therapy** generates potent and long-lasting CD4-dependent tumor immunity.
Adusumilli PS et al. Sci Transl Med. (2014)

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1. CRISPR/Cas9 genome editing: Fueling the revolution in cancer immunotherapy.
Liu X, Zhao Y.
Curr Res Transl Med. 2018 Apr 21. pii: S2452-3186(18)30024-2. doi: 10.1016/j.retram.2018.04.003. [Epub ahead of print] Review.
PMID: 29691200
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2. Enhanced Expression of Anti-CD19 Chimeric Antigen Receptor in *piggyBac* Transposon-Engineered T Cells.
Morita D, Nishio N, Saito S, Tanaka M, Kawashima N, Okuno Y, Suzuki S, Matsuda K, Maeda Y, Wilson MH, Dotti G, Rooney CM, Takahashi Y, Nakazawa Y.
Mol Ther Methods Clin Dev. 2017 Dec 22;8:131-140. doi: 10.1016/j.omtm.2017.12.003. eCollection 2018 Mar 16.
PMID: 29687032
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3. Clinical units to set up chimeric antigen receptor T-**cell therapy** (**CAR T**-cells): Based on the recommendations of the Francophone Society of Bone Marrow Transplantation and Cellular **Therapy** (SFGM-TC).
Yakoub-Agha I.
Curr Res Transl Med. 2018 Apr 20. pii: S2452-3186(18)30022-9. doi: 10.1016/j.retram.2018.04.001. [Epub ahead of print]
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4. Cellular therapies: Day by day, all the way.
Atilla E, Kilic P, Gurman G.
Transfus Apher Sci. 2018 Apr 18. pii: S1473-0502(18)30146-0. doi: 10.1016/j.transci.2018.04.019. [Epub ahead of print] Review.
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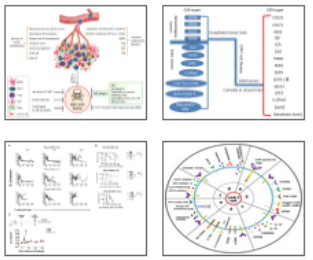

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Type of cellular therapy

T cell therapy

NK Cell therapy

Stem cell therapy

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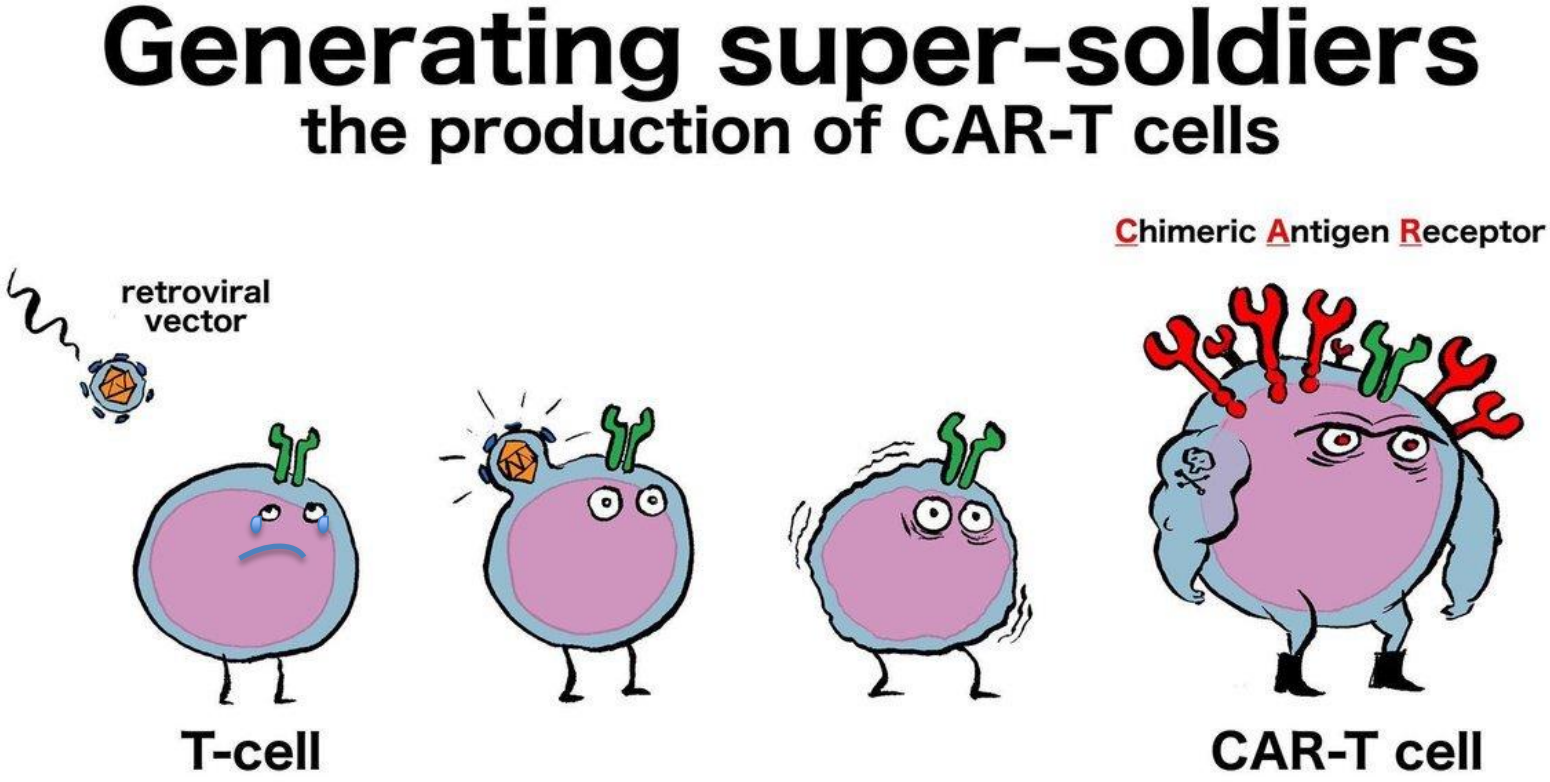
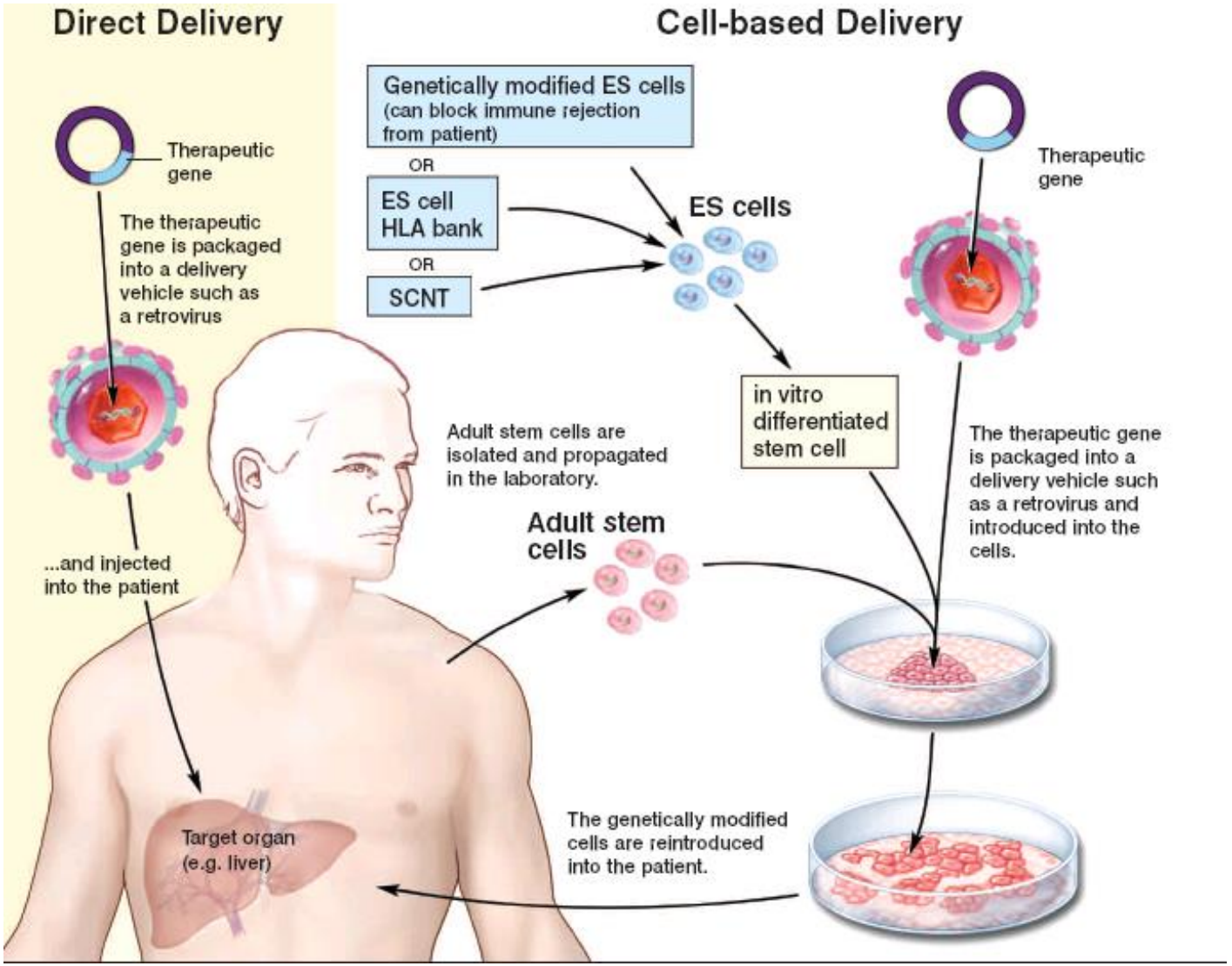
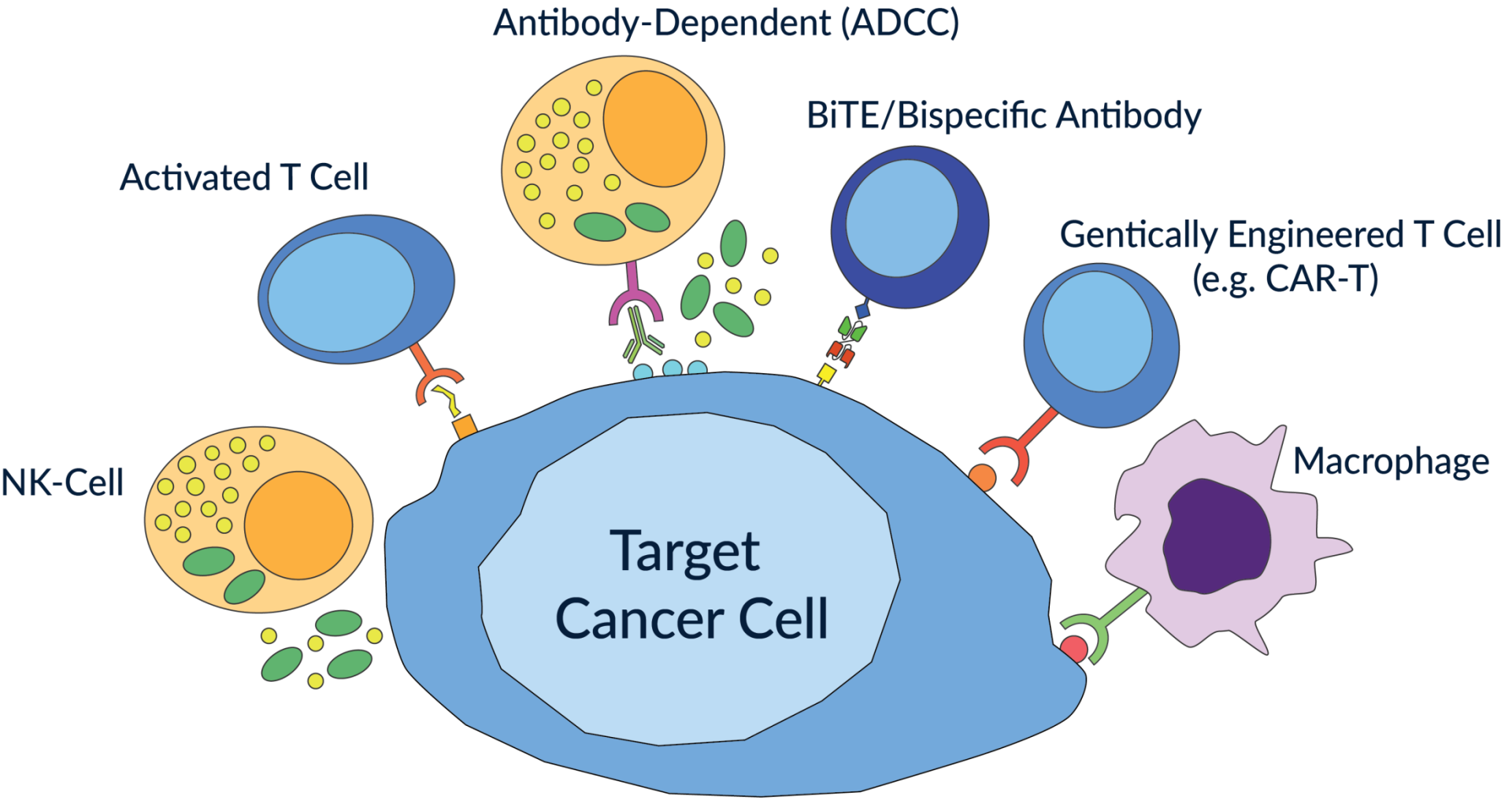
CAR T Cells



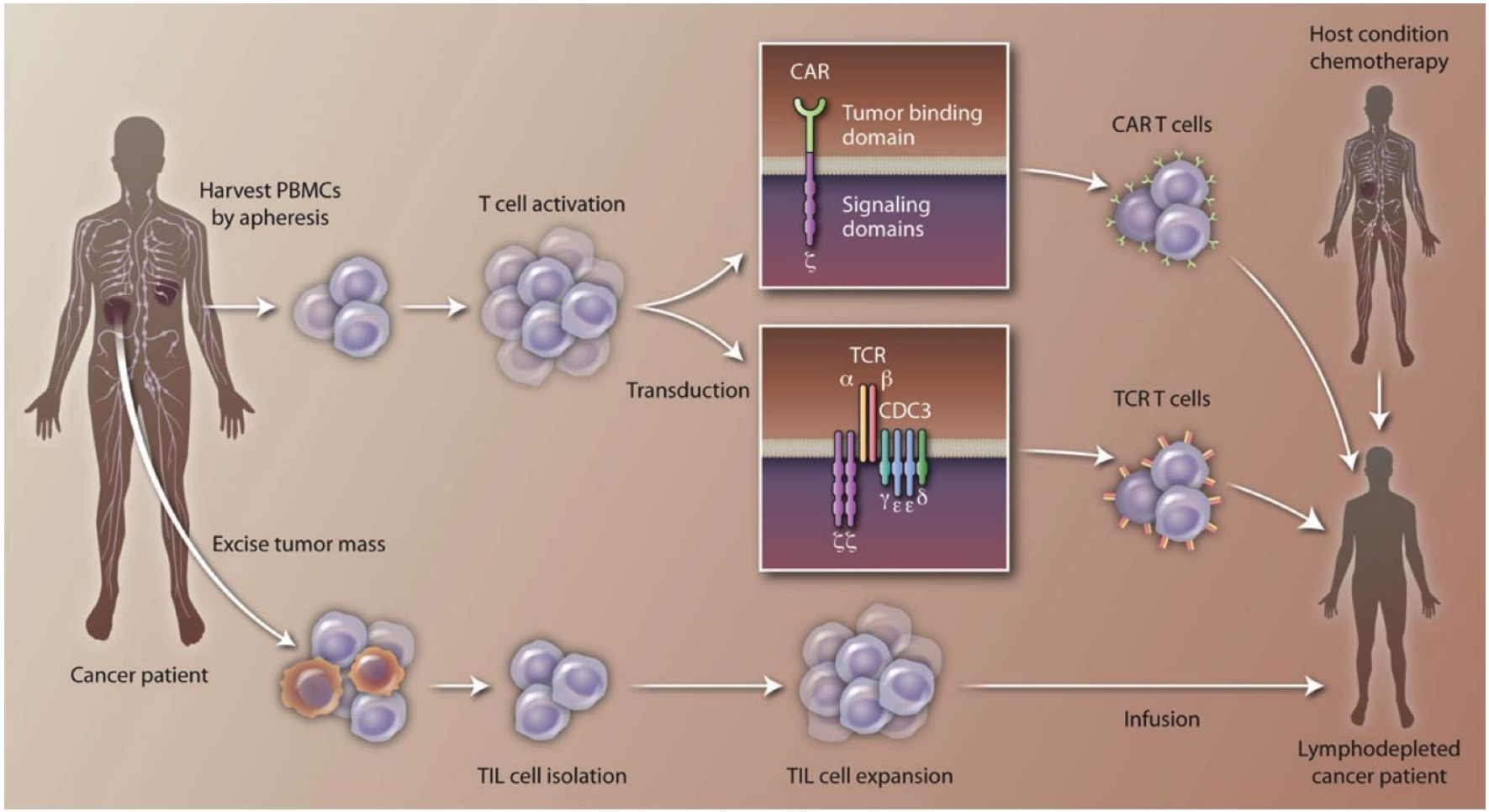
Delivering desired Genes



Harnessing the Immune System to Attack Tumors



Adoptive Cell Therapy Approaches

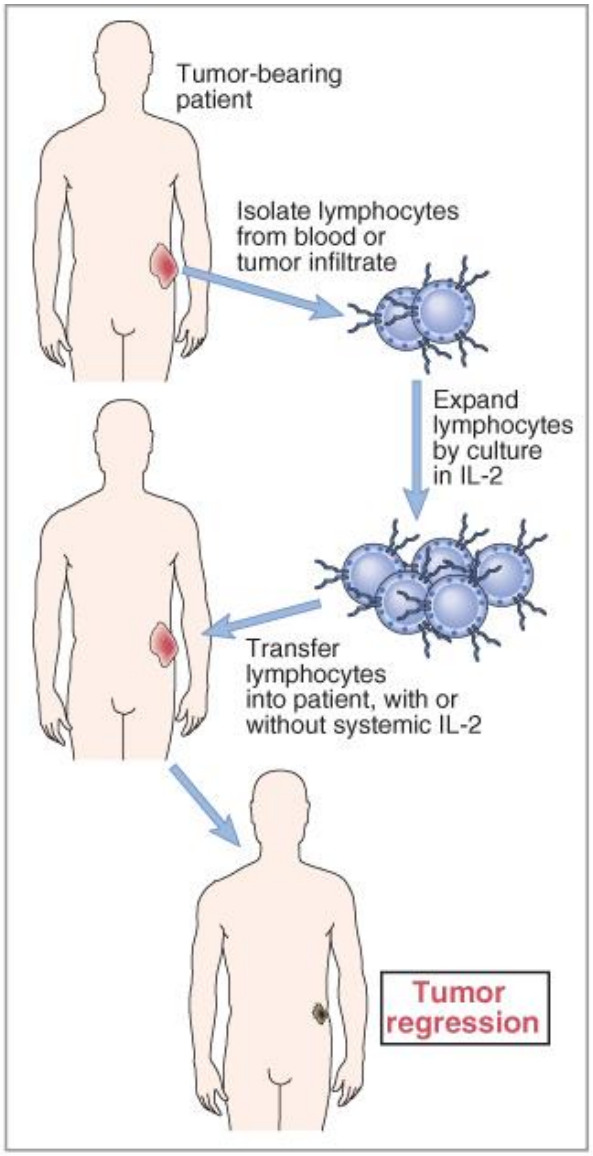


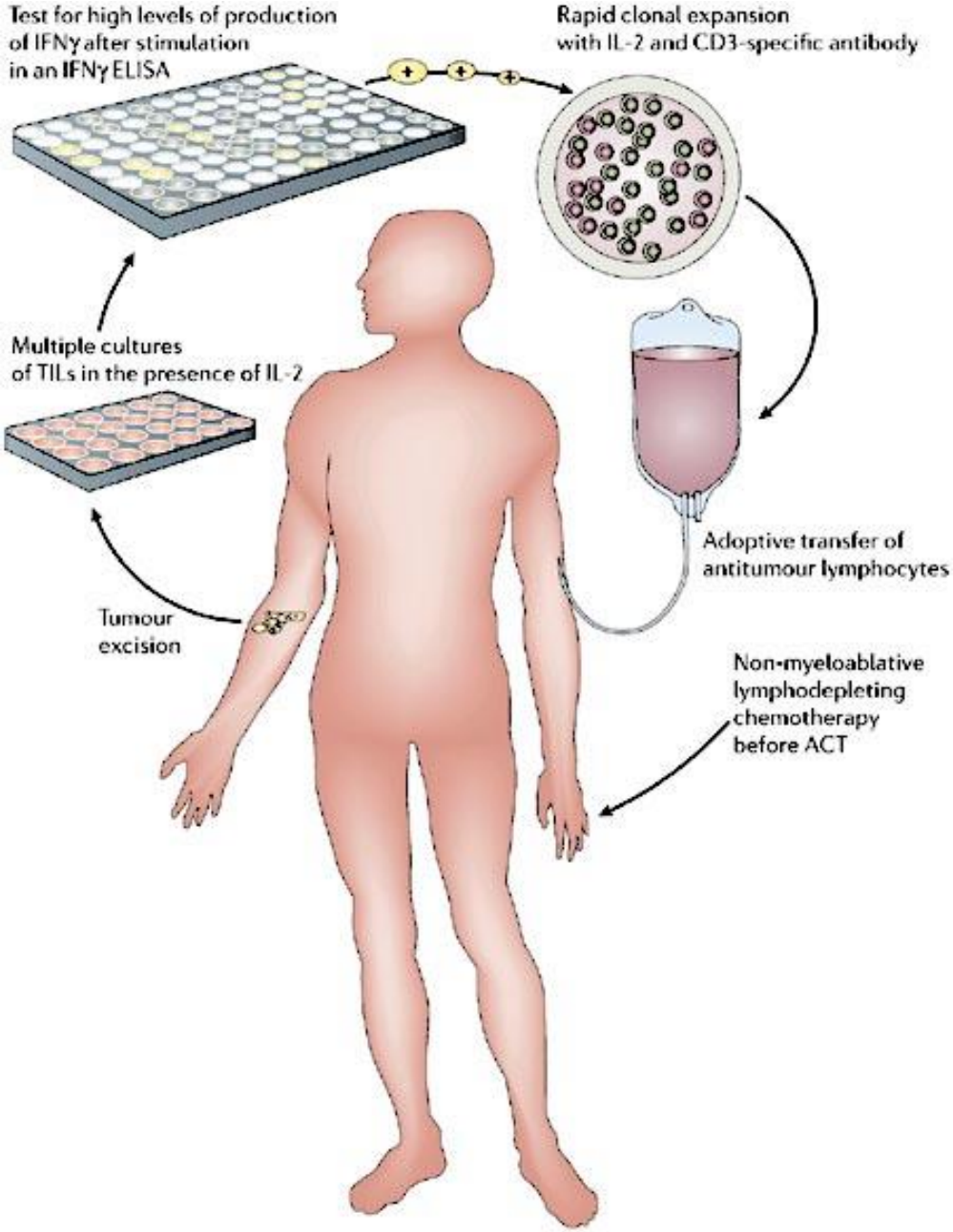
June, Riddell, and Schumacher
Science Transl Med 2015

T cell therapies

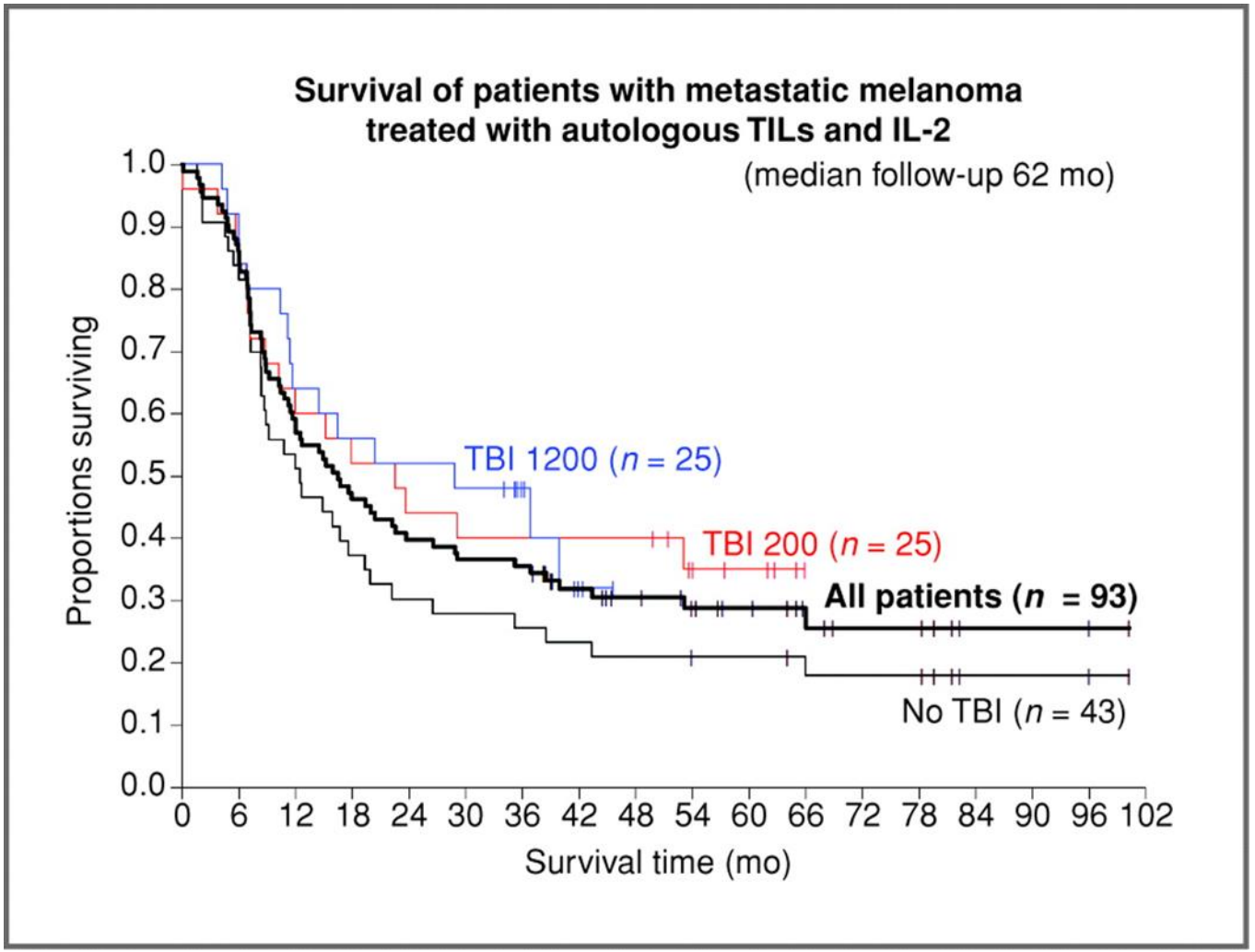
- Bispecific antibody armed T cells
- In vitro activated T cells (including dendritic pulse cells)
- **TIL**(Tumor infiltration T-lymphocytes) and **MIL** (marrow infiltrating lymphocytes) therapies
- **TCR** (T-cell receptor therapy)
- **CAR-T** (Chimeric antigen receptor T-cell therapy)

Adoptive cellular therapy



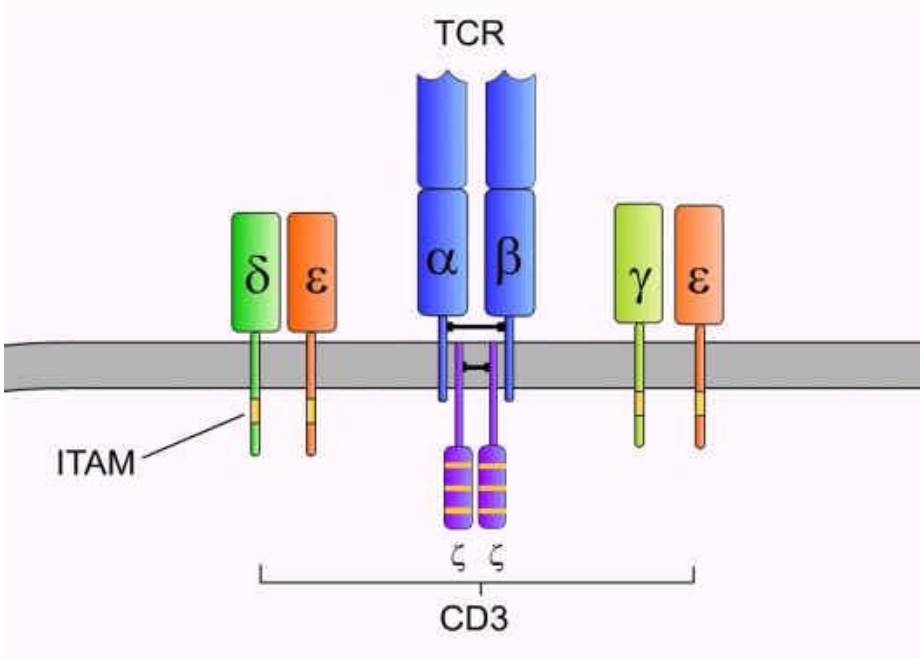

Test for high levels of production of IFNγ after stimulation in an IFNγ ELISA
Rapid clonal expansion with IL-2 and CD3-specific antibody
Multiple cultures of TILs in the presence of IL-2
Adoptive transfer of antitumour lymphocytes
Tumour excision
Non-myeloablative lymphodepleting chemotherapy before ACT

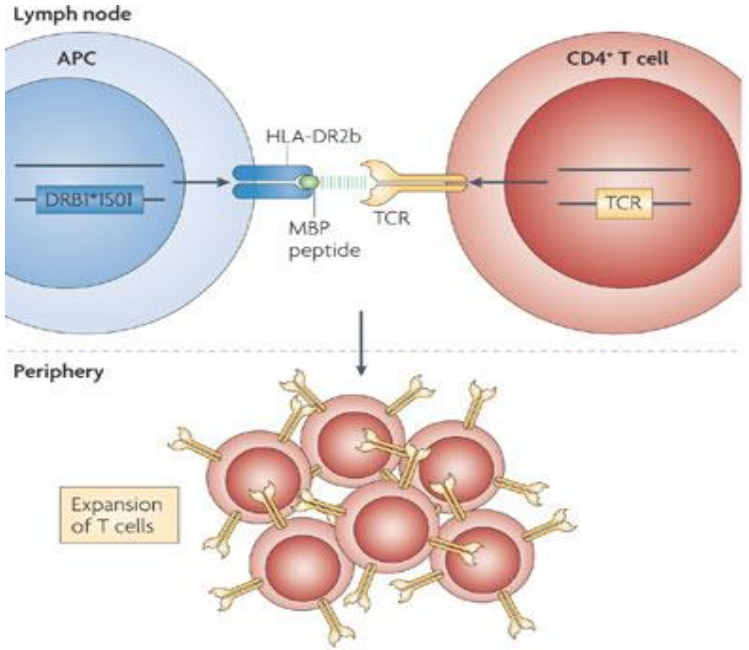
TIL



Rosenberg, S. A.et al.Use of tumor infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. Preliminary report. **N. Engl. J. Med. 319, 1676–1680 (1988).**

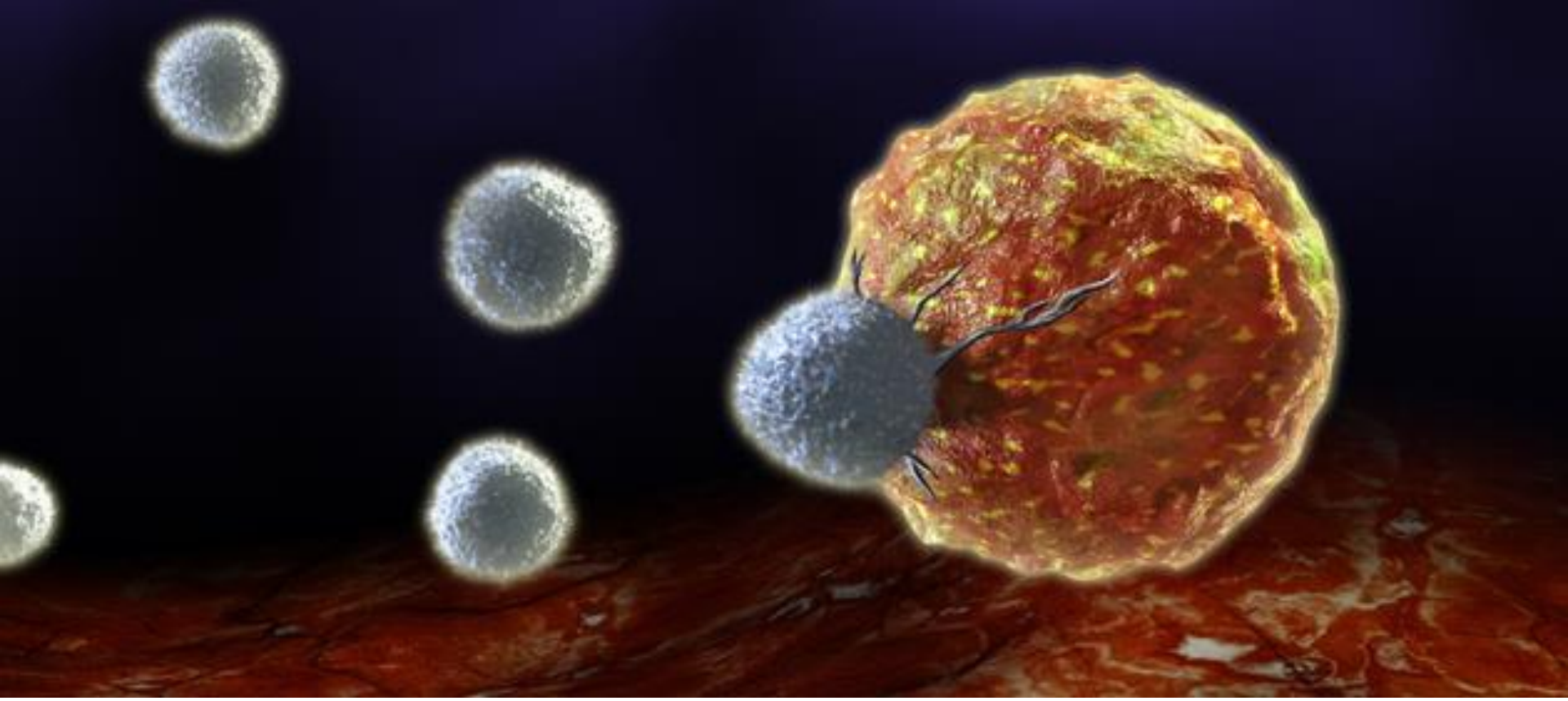
TCR


TCR
δ
ε
α
β
γ
ε
ITAM
ζ ζ
CD3

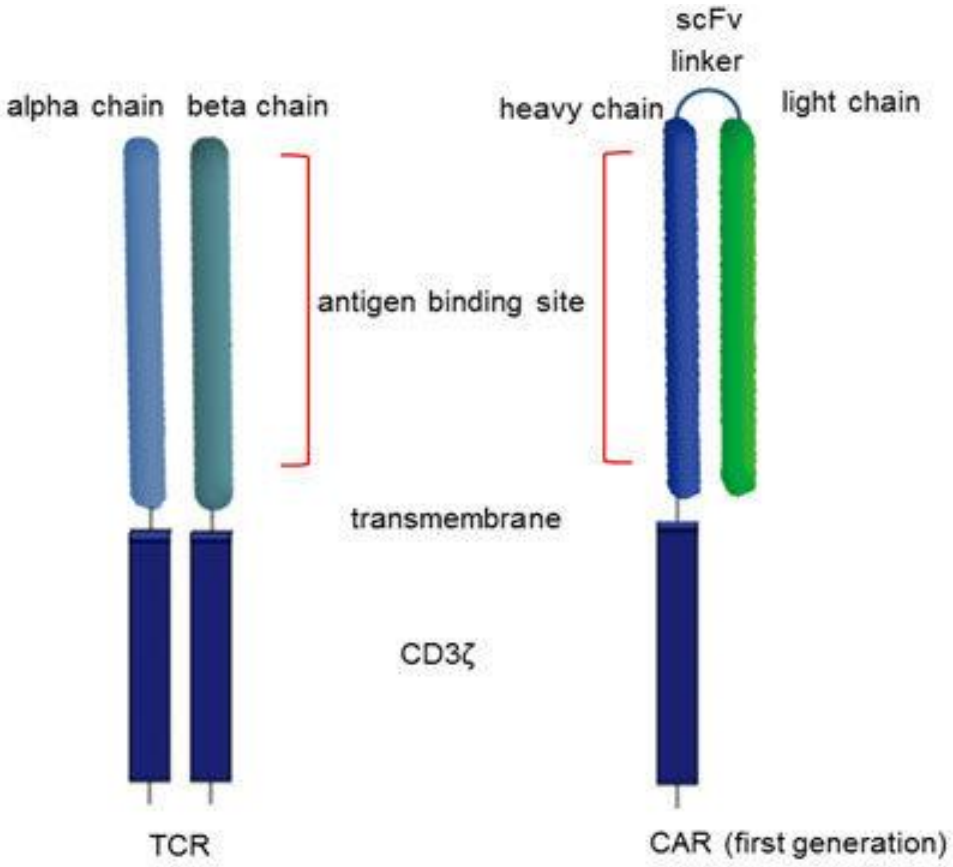

Lymph node
APC
CD4⁺ T cell
HLA-DR2b
DRB1*1501
MBP
peptide
TCR
TCR
Periphery
Expansion
of T cells

TCR based cell therapy problems:

- Problems with target specificity
- Need HLA co-presentation
- Restricted to processed peptide antigens
- Most of the TCRs Requires costimulation.

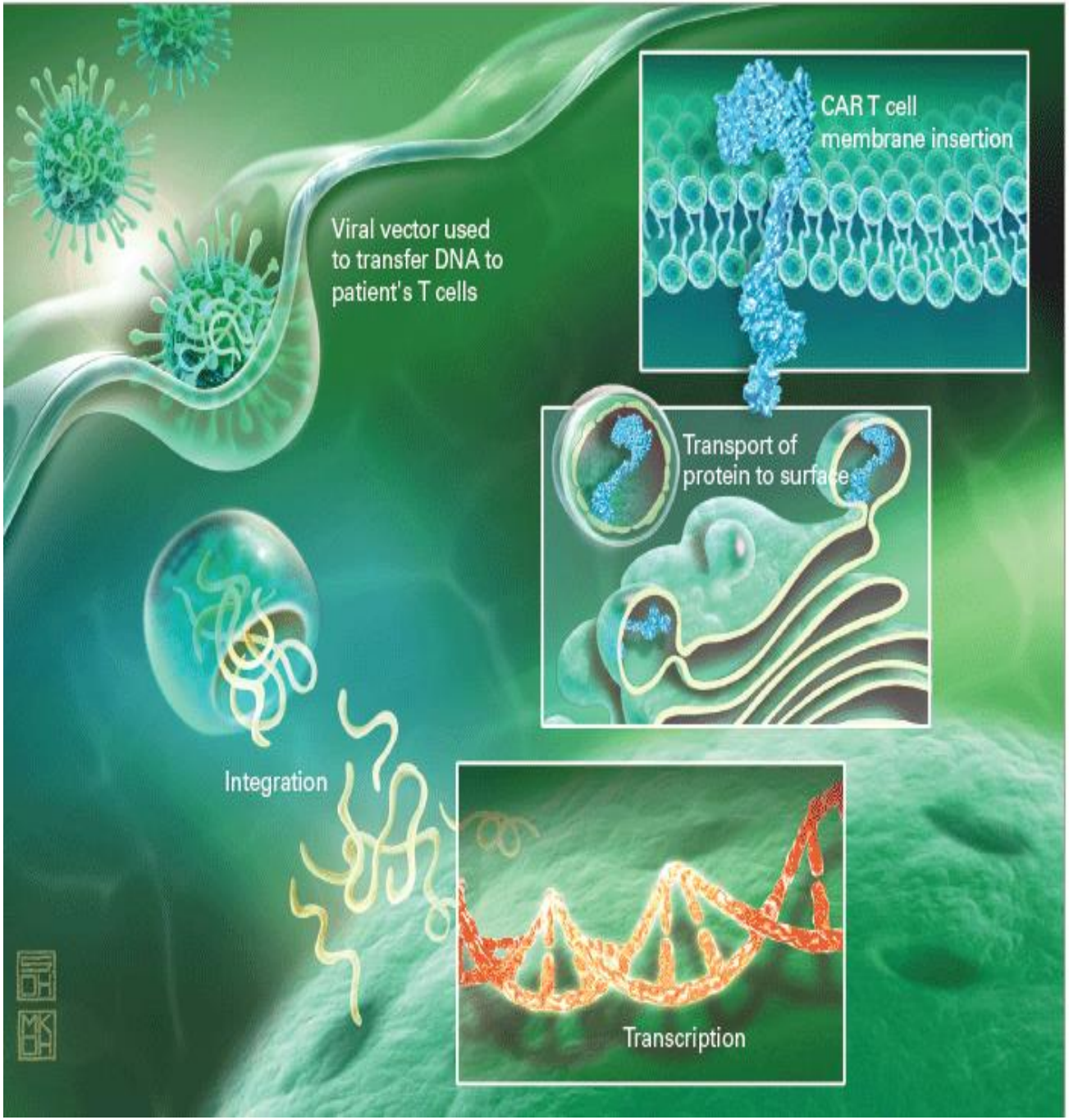


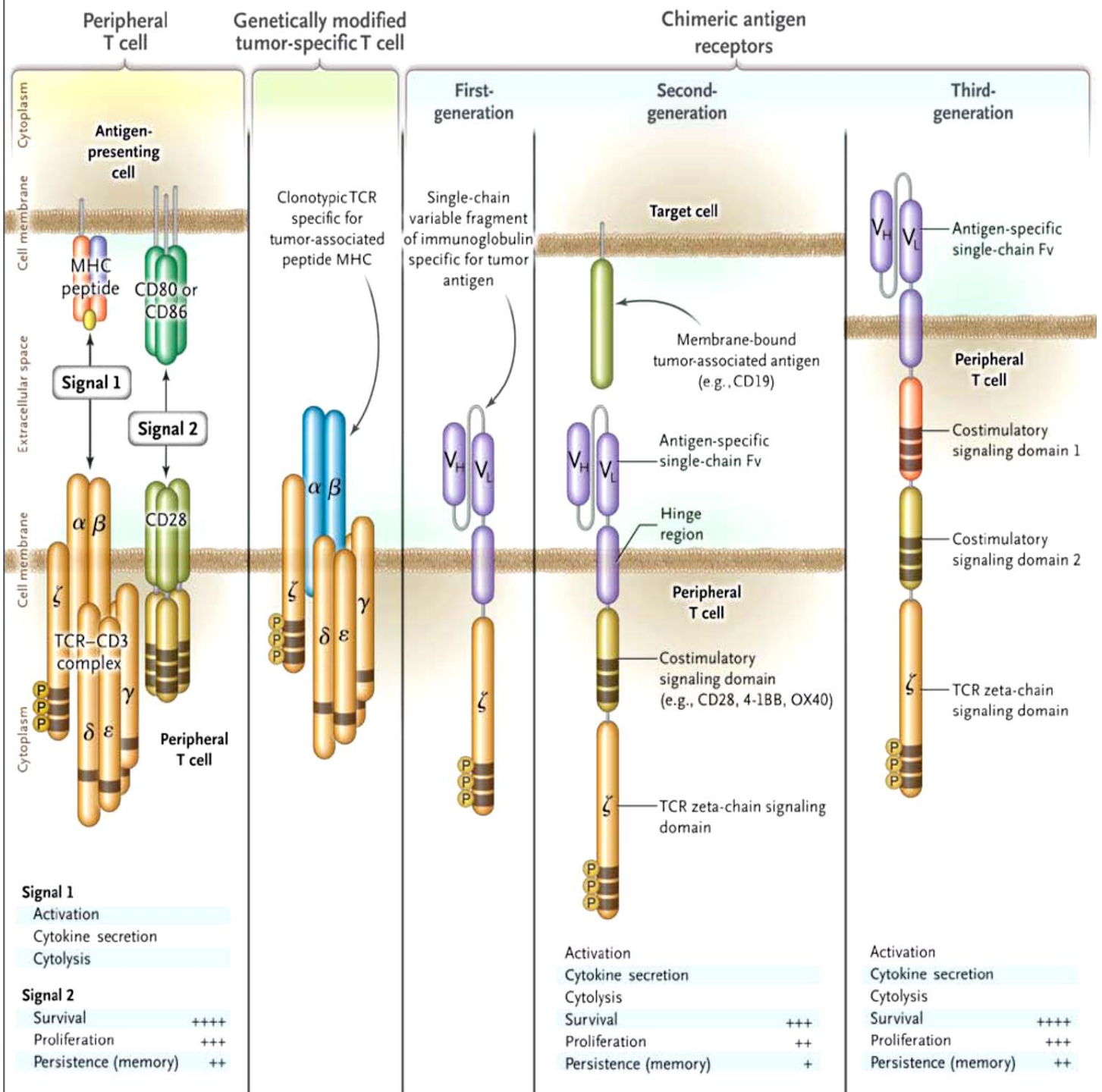
Chimeric **A**ntigen **R**eceptor (**CAR**) **T** Cells

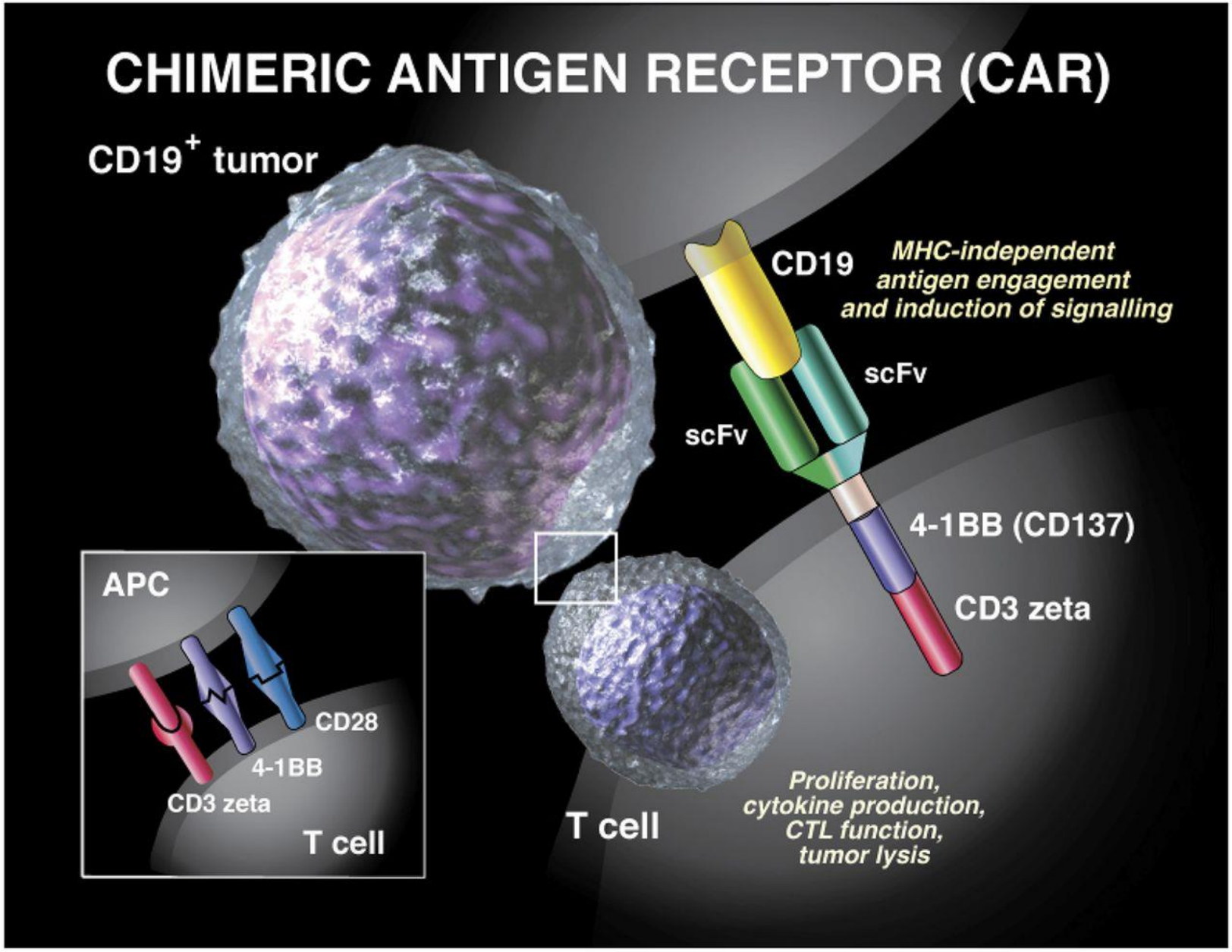

scFv
linker
alpha chain
beta chain
heavy chain
light chain
antigen binding site
transmembrane
CD3ζ
TCR
CAR (first generation)

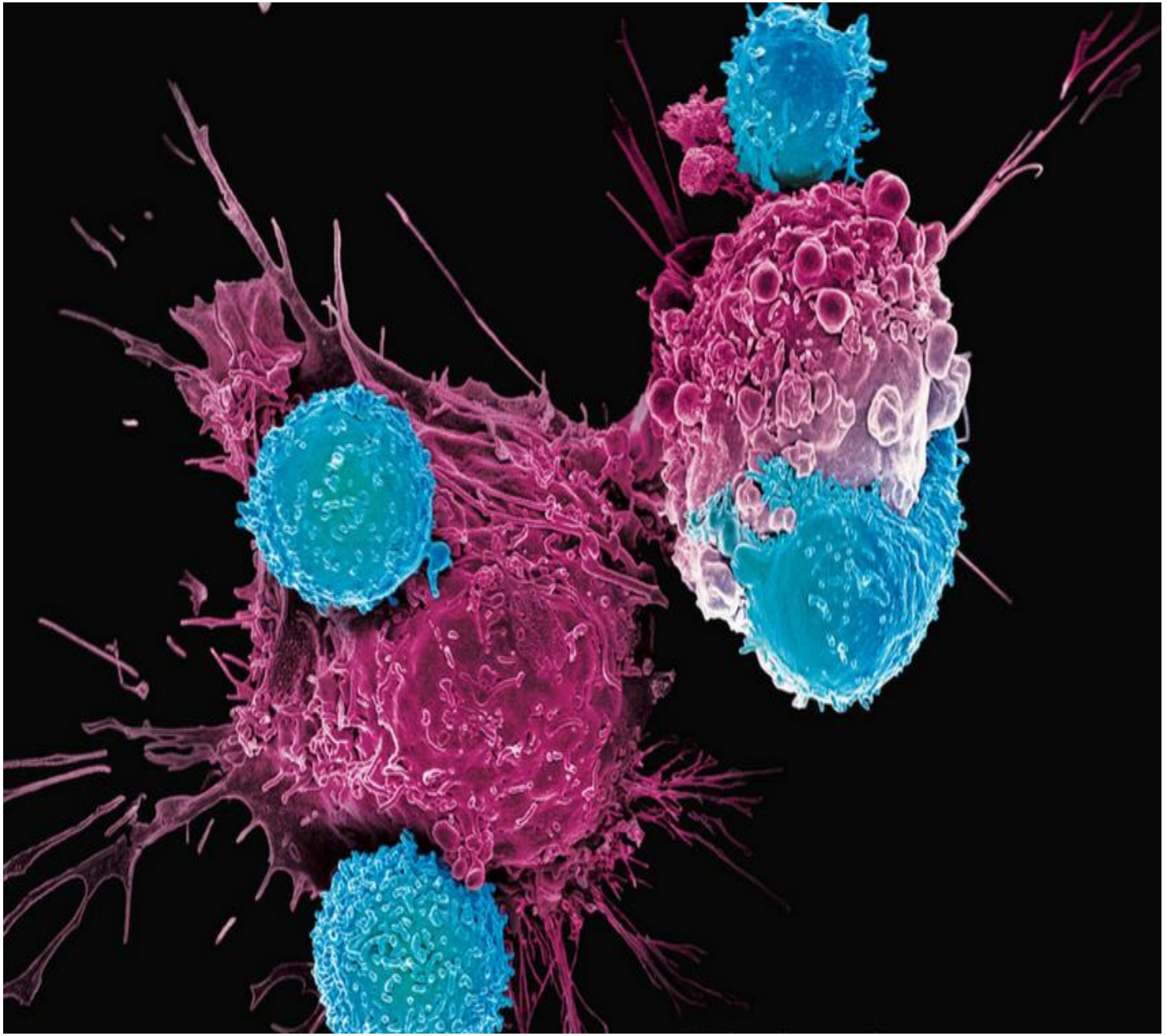
The history of CARs

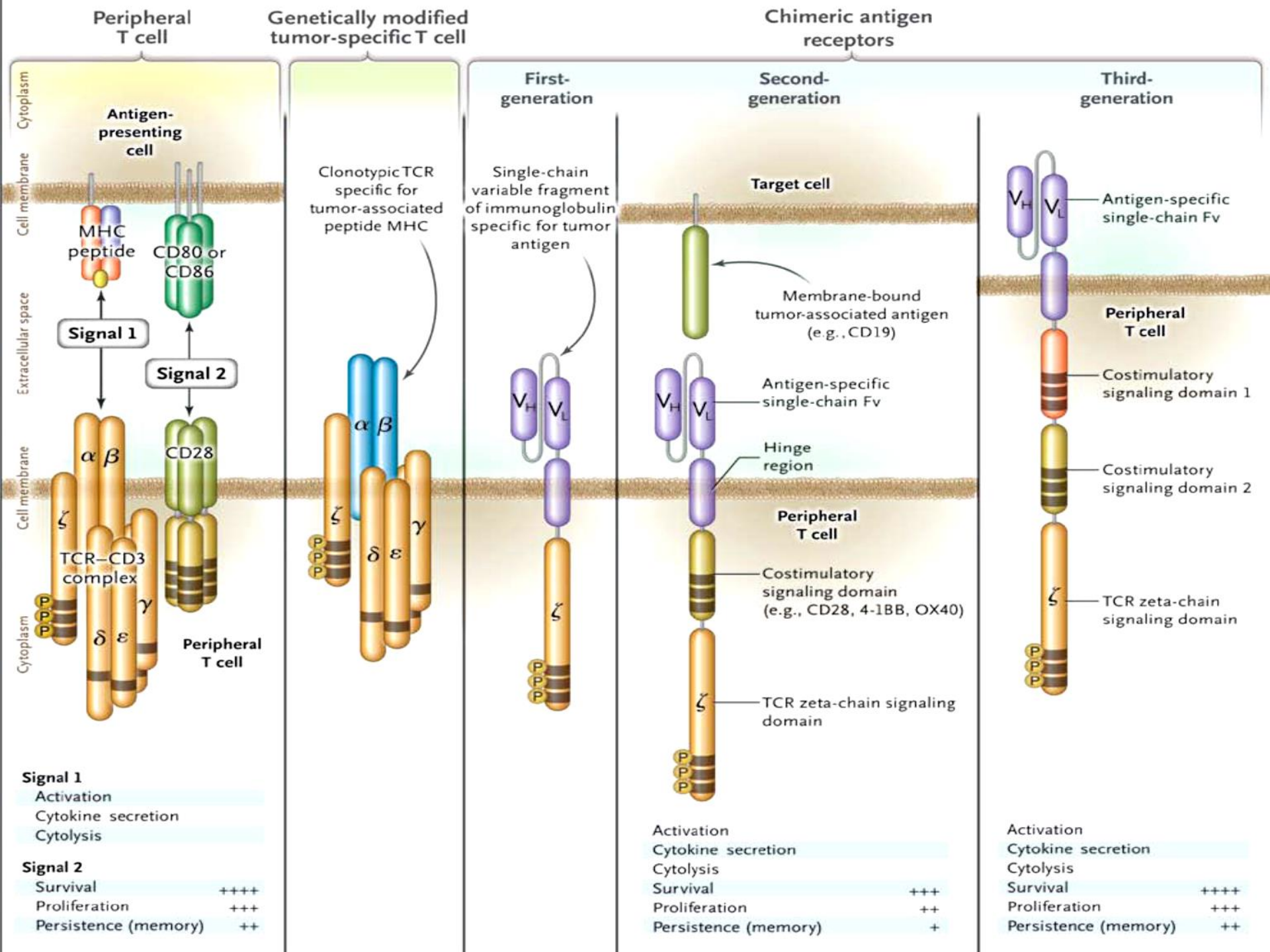
- The birth of CAR technology occurred 25 years ago when it was shown that antibody variable light (V L) or heavy (V H) gene segments can transfer specificity for native antigen.
- It was Eshhar who realized the Translational potential of such non-HLA-restricted T cell recognition.


CAR T cell
membrane insertion
Viral vector used
to transfer DNA to
patient's T cells
Transport of
protein to surface
Integration
Transcription


Peripheral T cell
Genetically modified tumor-specific T cell
Chimeric antigen receptors
Cytoplasm
Cell membrane
Extracellular space
Cell membrane
Cytoplasm
Antigen-presenting cell
MHC peptide
CD80 or CD86
Signal 1
Signal 2
CD28
TCR–CD3 complex
Peripheral T cell
Clonotypic TCR specific for tumor-associated peptide MHC
First-generation
Single-chain variable fragment of immunoglobulin specific for tumor antigen
Second-generation
Target cell
Membrane-bound tumor-associated antigen (e.g., CD19)
Antigen-specific single-chain Fv
Hinge region
Peripheral T cell
Costimulatory signaling domain (e.g., CD28, 4-1BB, OX40)
TCR zeta-chain signaling domain
Third-generation
Antigen-specific single-chain Fv
Peripheral T cell
Costimulatory signaling domain 1
Costimulatory signaling domain 2
TCR zeta-chain signaling domain
Signal 1
Activation
Cytokine secretion
Cytolysis
Signal 2
Survival ++++
Proliferation +++
Persistence (memory) ++
Activation
Cytokine secretion
Cytolysis
Survival +++
Proliferation ++
Persistence (memory) +
Activation
Cytokine secretion
Cytolysis
Survival ++++
Proliferation +++
Persistence (memory) ++


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




Peripheral T cell
Genetically modified tumor-specific T cell
Chimeric antigen receptors
Cytoplasm
Cell membrane
Extracellular space
Cell membrane
Cytoplasm
Antigen-presenting cell
MHC peptide
CD80 or CD86
Signal 1
Signal 2
CD28
TCR–CD3 complex
Peripheral T cell
Clonotypic TCR specific for tumor-associated peptide MHC
First-generation
Single-chain variable fragment of immunoglobulin specific for tumor antigen
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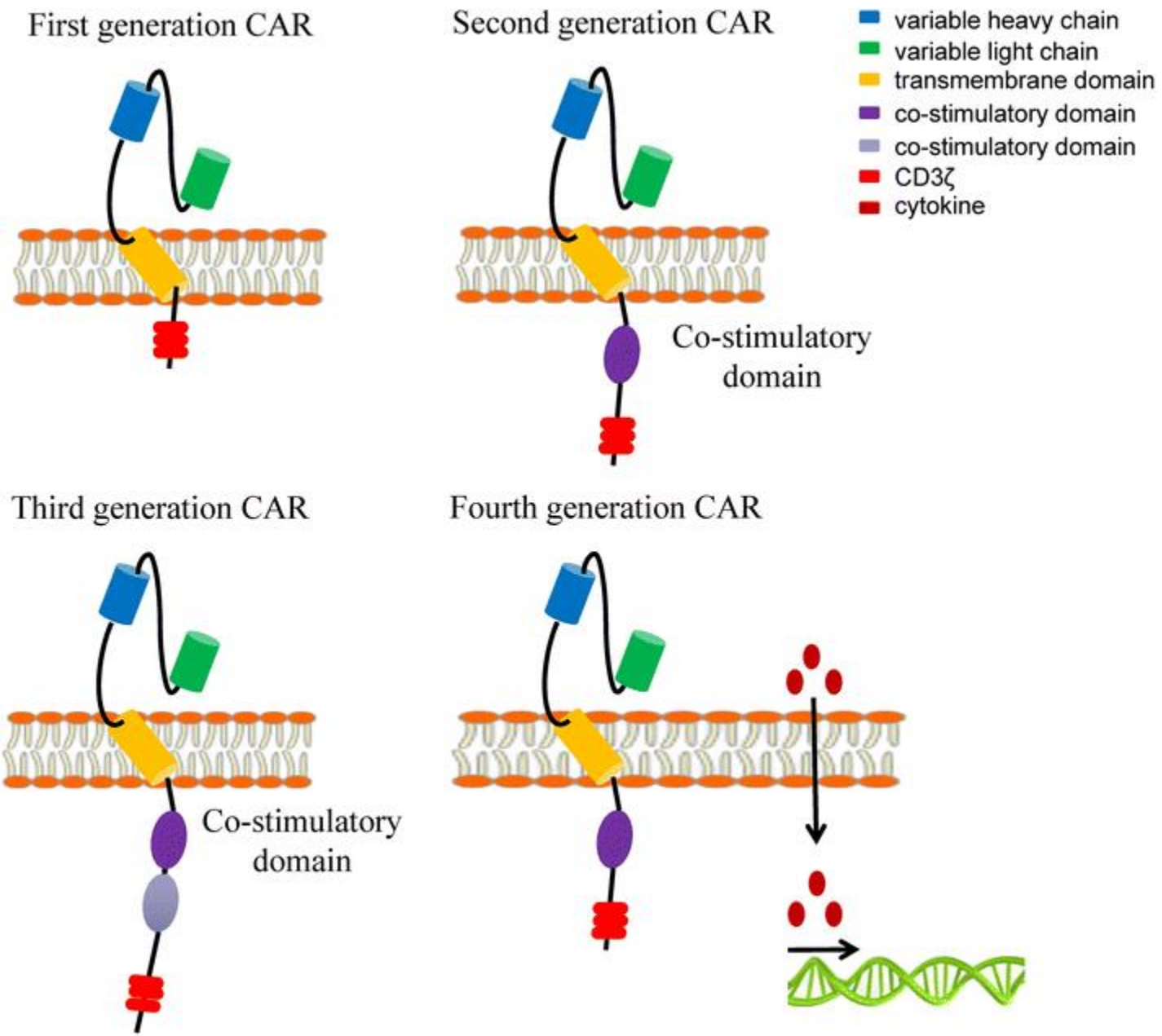
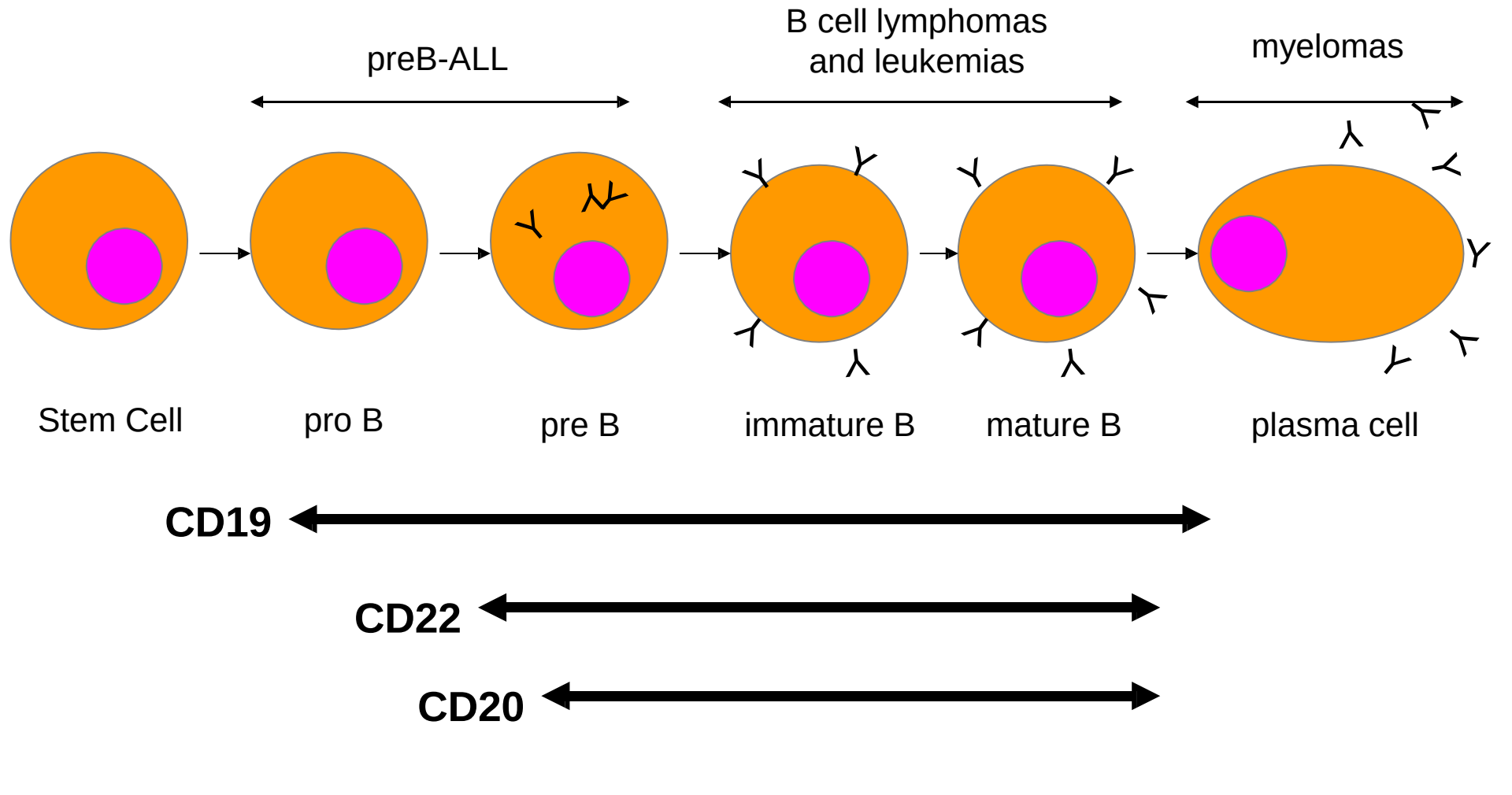
Antigen-specific single-chain Fv
Peripheral T cell
Costimulatory signaling domain 1
Costimulatory signaling domain 2
TCR zeta-chain signaling domain
Signal 1
Activation
Cytokine secretion
Cytolysis
Signal 2
Survival ++++
Proliferation +++
Persistence (memory) ++
Activation
Cytokine secretion
Cytolysis
Survival +++
Proliferation ++
Persistence (memory) +
Activation
Cytokine secretion
Cytolysis
Survival ++++
Proliferation +++
Persistence (memory) ++

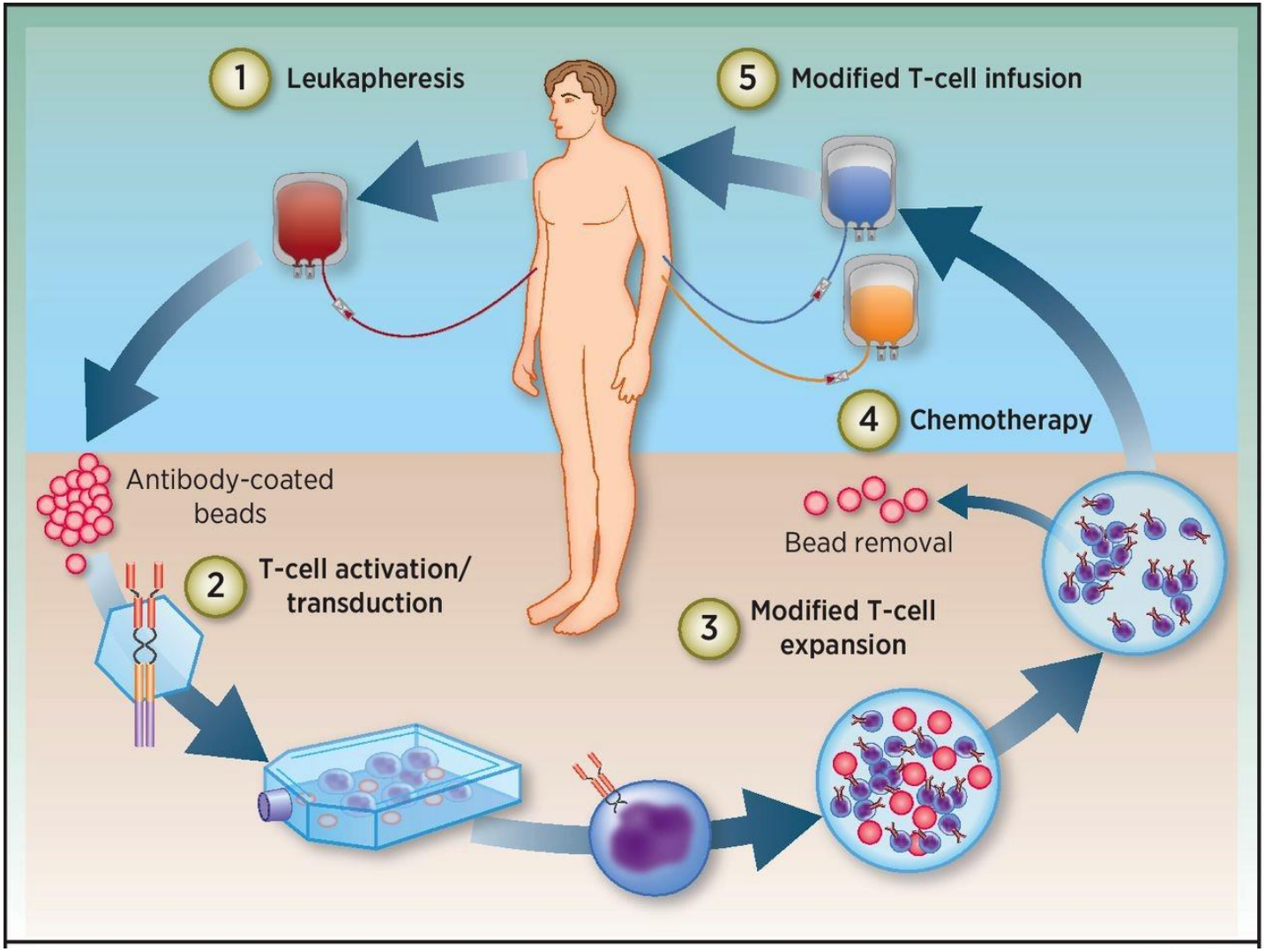

First generation CAR
Second generation CAR
variable heavy chain
variable light chain
transmembrane domain
co-stimulatory domain
co-stimulatory domain
CD3ζ
cytokine
Co-stimulatory domain
Third generation CAR
Co-stimulatory domain
Fourth generation CAR

Expression of CD19 and other B cell markers on B lineage cells



Cellular Immunotherapy

CAR T Cells



Target antigen	Disease	CAR signaling domain	ClinicalTrial.gov identifier	Clinical center
CD19	B-CLL	CD28-CD3ζ	NCT00466531	MSKCC
CD19	B-ALL	CD28-CD3ζ	NCT01044069	MSKCC
CD19	Leukemia	CD28-CD3ζ	NCT01416974	MSKCC
CD19	Leukemia/lymphoma	CD28-CD3ζ	NCT00924326	NCI
CD19	Leukemia/lymphoma	CD28-CD3ζ	NCT01087294	NCI
CD19	Leukemia/lymphoma	CD28-CD3ζ vs. CD3ζ	NCT00586391	BCM
CD19	B-NHL/CLL	CD28-CD3ζ vs. CD3ζ	NCT00608270	BCM
CD19	Advanced B-NHL/CLL	CD28-CD3ζ vs. CD3ζ	NCT00709033	BCM
CD19	ALL post-HSCT	CD28-CD3ζ	NCT00840853	BCM
CD19	Leukemia/lymphoma	CD137-CD3ζ	NCT01029366	UP
CD19	B-lymphoid malignancies	CD28-CD3ζ	NCT00968760	MDACC
CD19	B-lineage malignancies	CD28-CD3ζ	NCT01362452	MDACC
CD20	Mantle cell lymphoma/indolent B-NHL	CD28-CD137-CD3ζ	NCT00621452	FHCRC
PMSA	Prostate cancer	CD28-CD3ζ	NCT01140373	MSKCC
CEA	Breast cancer	CD28-CD3ζ	NCT00673829	RWMC
CEA	Colorectal cancer	CD28-CD3ζ	NCT00673322	RWMC
Her2/neu	Lung cancer	CD28-CD3ζ	NCT00889954	BCM
Her2/neu	Osteosarcoma	CD28-CD3ζ	NCT00902044	BCM
Her2/neu	Glioblastoma	CD28-CD3ζ	NCT01109095	BCM
Kappa light chain	B-NHL and B-CLL	CD28-CD3ζ vs. CD3ζ	NCT00881920	BCM

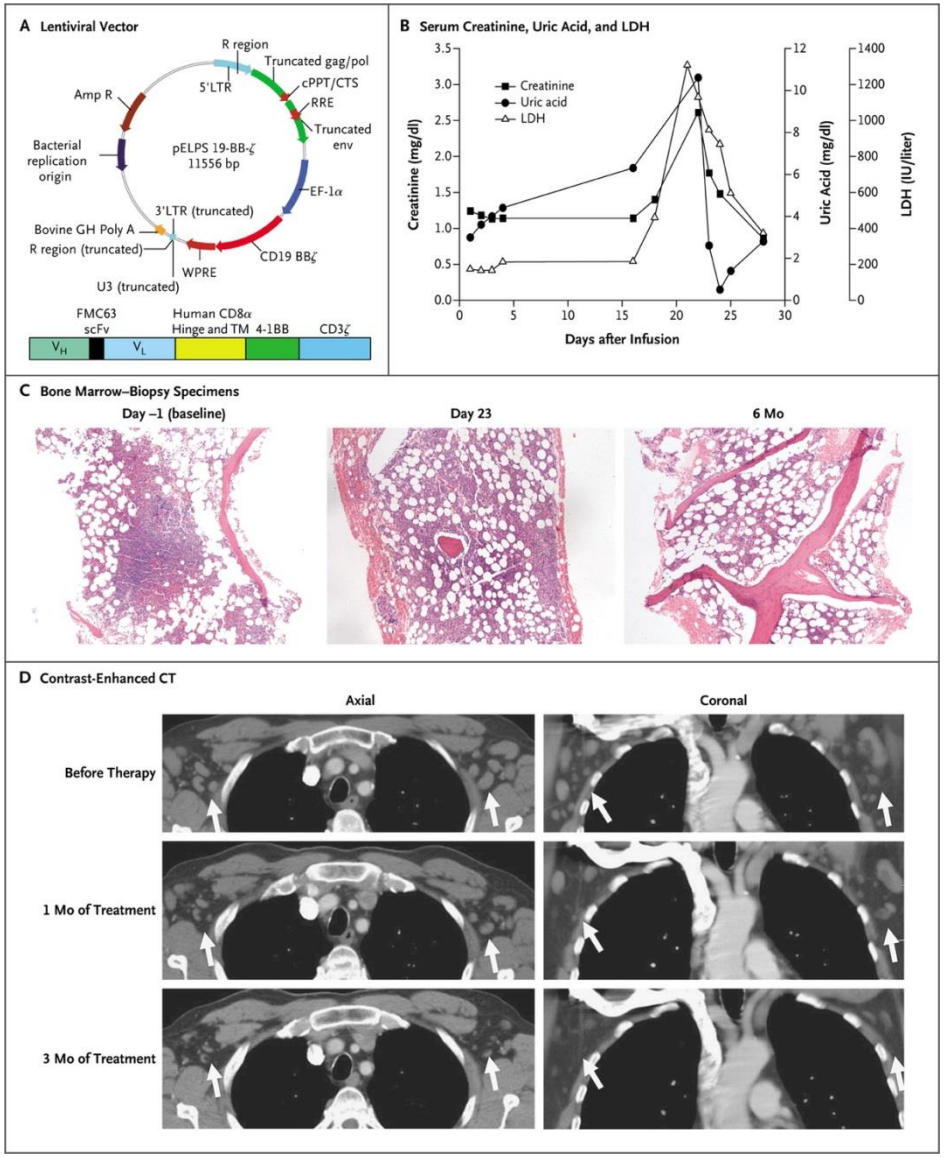
MSKCC, Memorial Sloan-Kettering Cancer Center; NCI, National Cancer Institute; BCM, Baylor College of Medicine; RWMC, Roger Williams Medical Center; UP, University of Pennsylvania; MDACC, M.D. Anderson Cancer Center; FHCRC, Fred Hutchinson Cancer Research Center.

The NEW ENGLAND JOURNAL of MEDICINE

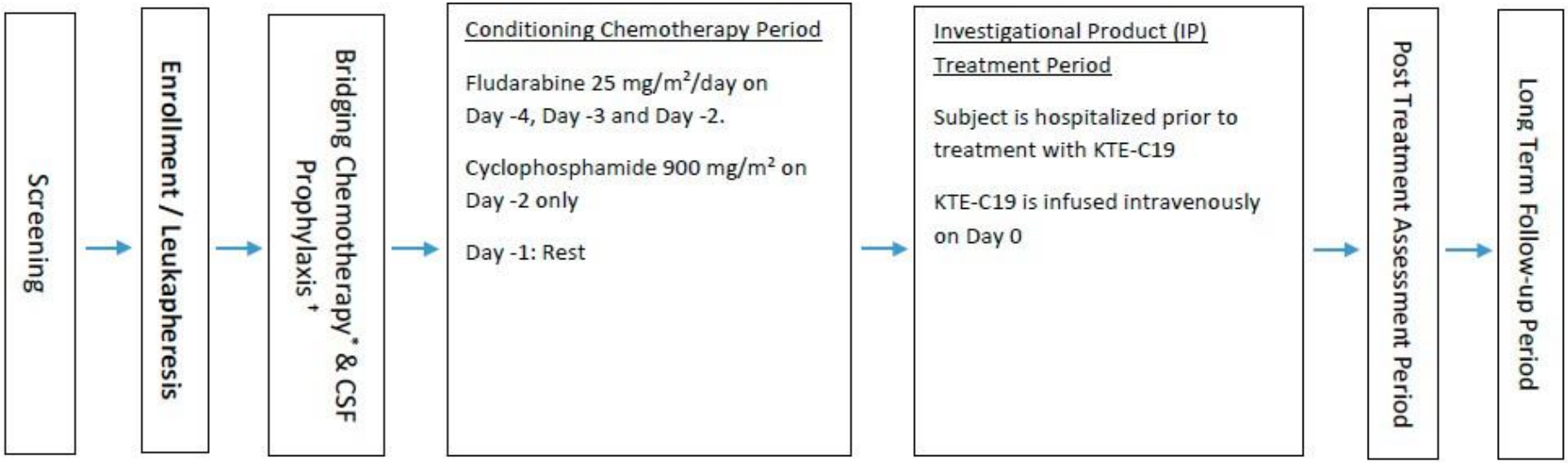
BRIEF REPORT

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.



Study Schema



* Bridging Chemotherapy

Subjects with high disease burden at screening [M3 marrow (>25% leukemic blasts) or ≥ 1000 blasts/mm³ in the peripheral circulation] should receive bridging chemotherapy for high burden disease. Other subjects may receive non-high burden disease bridging chemotherapy per investigator discretion, prior to initiation of conditioning chemotherapy and KTE-C19 infusion. For a detailed list of allowed bridging chemotherapy regimens refer to Table 14 in Section 6.3.2. Chemotherapy doses are recommended and can be adjusted per local or institutional guidelines. If given, bridging chemotherapy must be administered after leukapheresis and completed at least 7 days prior to conditioning chemotherapy.

† CSF Prophylaxis Prior to KTE-C19 Treatment:

Day -14 to Day -7: A mandatory CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines will be administered (e.g., methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, or dexamethasone 4 mg or equivalent steroid dose). Additional intrathecal chemotherapy may be given per institutional guidelines if clinically indicated, but is not required and should be avoided for at least 8 weeks after KTE-C19 infusion if possible.

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.*

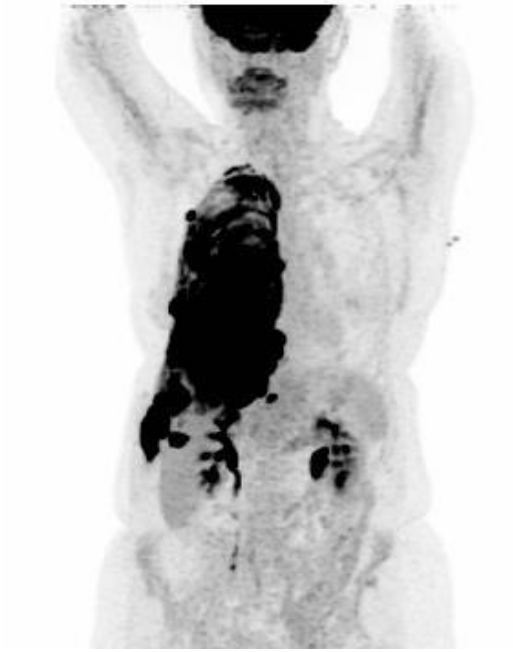
CAR-T-cell targets for the treatment of haematological malignancies

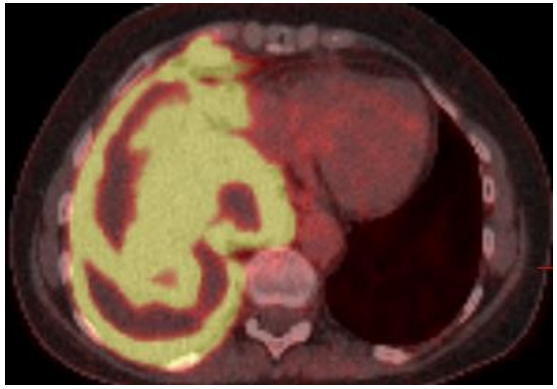
Target	CAR structure	Malignancy	Institution	Reference
CD22	CD3ζ and CD28	FL, NHL, DLBCL, B-ALL	NCI	NCT02315612 (REF. 34)
CD20	CD3ζ or CD3ζ and 4-1BB	CD20-positive malignancies	PLA General Hospital	NCT01735604 (REF. 47)
ROR1	CD3ζ and 4-1BB	CLL, SLL	MD Anderson	NCT02194374 (REF. 36)
Igκ	CD3ζ and CD28	CLL, low-grade B-cell malignancies	Baylor	NCT00881920 (REF. 37)
CD30	CD3ζ and CD28	HL, NHL	Baylor	NCT01316146 (REF. 56)
CD123	CD3ζ and CD28	AML	City of Hope	NCT02159495 (REF. 41)
CD33	CD3ζ and 4-1BB	AML	PLA General Hospital	NCT01864902 (REF. 40)
LeY	CD3ζ and CD28	AML	Peter Mac	NCT01716364 (REF. 42)
BCMA	CD3ζ and 4-1BB	MM	NCI	NCT02215967 (REF. 38)
CD138	CD3ζ and 4-1BB	MM	PLA General Hospital	NCT01886976 (REF. 39)

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

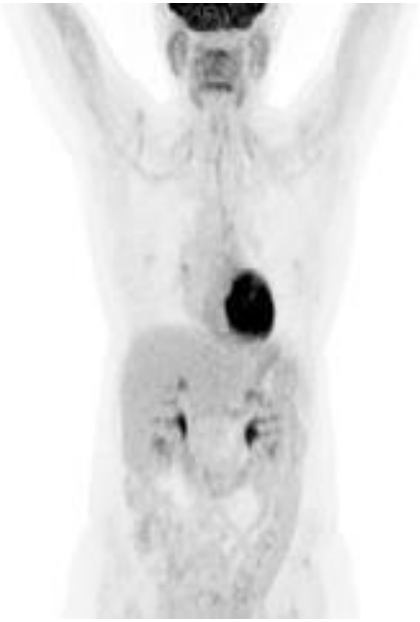
Response in Patient with Refractory DLBCL

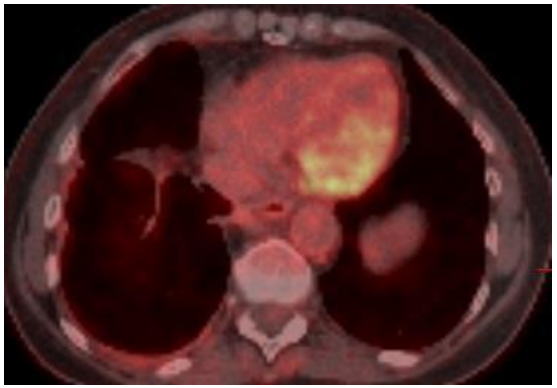
Before treatment



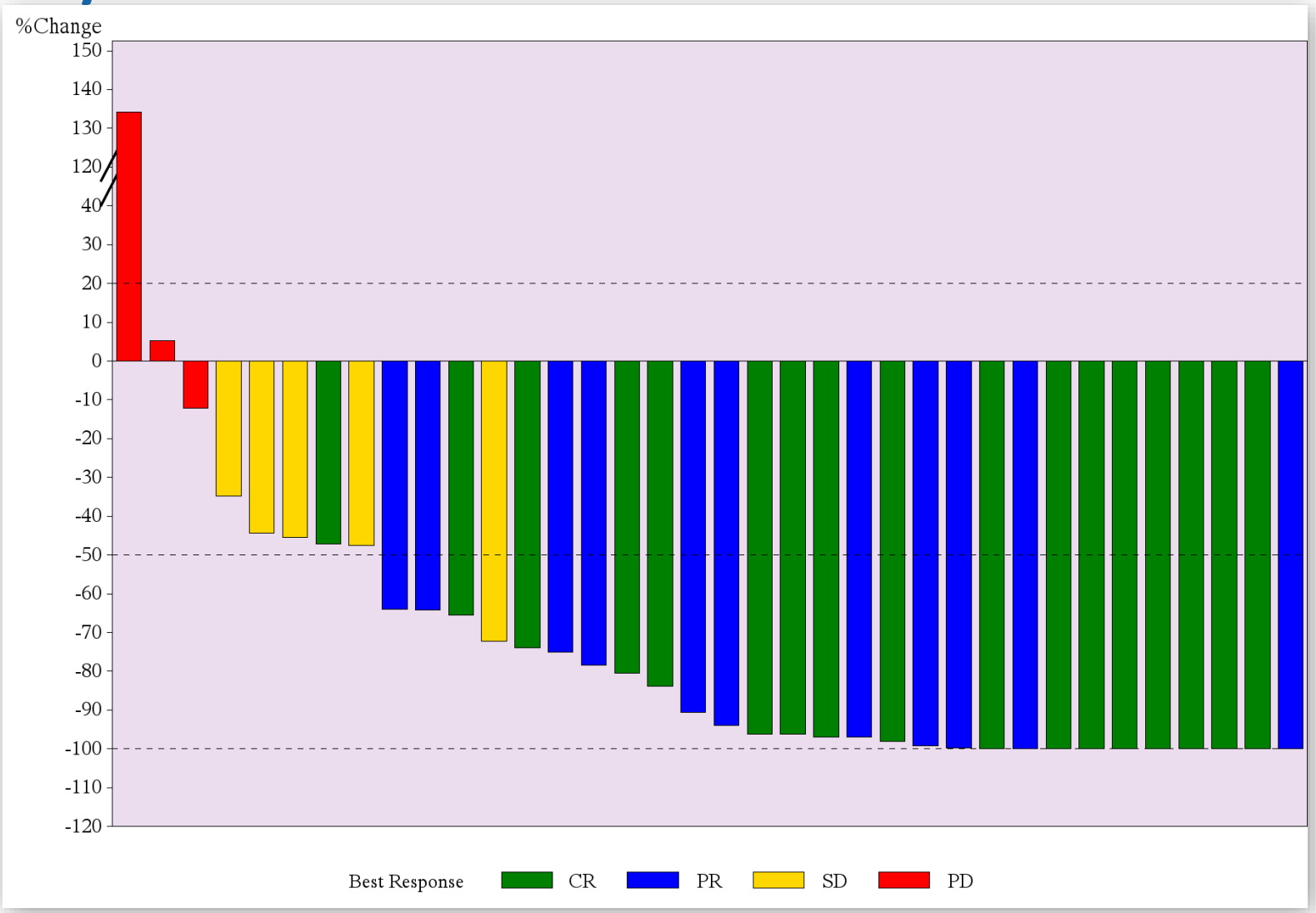


6 months after treatment





Depth of Best Response in NCI B Cell Lymphoma Study



NOVARTIS	Kite Pharma
Two projects in phase I and one in Phase II. Autologous T-Cell. (In the Top 3 Biggest Pharma companies worldwide) Market cap € 215Bn	One Candidate in Phase II, one in Phase I and one at a preclinical stage. In collaboration with Alpine Immune Science, Amgen (at a preclinical stage). IPO €127M - Market Cap €1.95Bn
cellectis	**JUNO THERAPEUTICS**
Registration for Clinical Trial, plus several project at preclinical stage. Collaboration with Servier & Pfizer ***With Allogeneic T-Cell (UCART) .*** Market cap €1.07Bn	Two candidates in Phase II, and Four in phase I stage. Collaboration with Opus Bio (phase I) and Pre-clinical: Editas Medicine, Fate Therapeutics, MabVax Therapeutics. Signed a €950M upfront deal with Celgene, raised €535M. Market cap €4.92Bn

STARTING YOUR PATIENTS ON

KYMRIAH™
(tisagenlecleucel) Suspension for IV infusion

The first FDA-approved CAR-T cell therapy for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

This guide will walk you through how to start your appropriate patients on KYMRIAH™ (tisagenlecleucel), so that you can begin coordinating care with a KYMRIAH Treatment Center.

IMPORTANT SAFETY INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab *[see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.1)]*.**
- **Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed *[see Warnings and Precautions (5.2)]*.**
- **KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS *[see Warnings and Precautions (5.3)]*.**

Please see additional Important Safety Information throughout. Please see full Prescribing Information for KYMRIAH, including Boxed WARNING, and Medication Guide.

		TRIAL	AREA OF RESEARCH	PRE-IND	PHASE 1	PHASE 2/3
Chimeric Antigen Receptor	axicabtagene ciloleucel	ZUMA 1	DLBCL, PMBCL & TFL			
	KTE-C19 (WAVE-1)	ZUMA 2	MCL			
		ZUMA 3 & 4	Adult & Pediatric ALL			
	KTE-C19 (WAVE-2)	ZUMA-5	Indolent NHL			
		ZUMA-6	DLBCL (PD-L1 mAb)			
		ZUMA-7	DLBCL (2nd line)			
		ZUMA-8	CLL			
	Human anti-CD19 (2nd Gen)	NCI	Heme Malignances			
	Humanized anti-CD19 Control CAR (3rd Gen)		Heme Malignances			
	KITE-585 (anti-BCMA)		MM			
	KITE-796 (anti-CLL-1 Control CAR)		AML			
T Cell Receptor	MAGE A3/A6	NCI	Solid Tumor			
	KITE-718 (MAGE A3/A6)		Solid Tumor			
	MAGE A3	NCI	Solid Tumor			
	HPV-16 E6 & E7	NCI	Cervical and HNC			
	KITE-439 (HPV-16 E7)		Cervical and HNC			
	KRAS	NCI	Solid Tumor			
	SSX-2	NCI	Solid Tumor			
	Neoantigens	NCI	Solid Tumor			

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 21% Any		12% Severe 58% Any		31% Severe 84% Any	

Study Group/ Reference	Signaling Domains Targeted	Lymphodepleting Agent(s)	Population	Response Rate	CRS Rate	Neurologic Toxicity Rate
Acute Lymphoblastic Leukemia (ALL)						
Penn/CHOP Maude et al[4]	CD3ζ, 4-1BB[a]	Varied	N = 30 pediatric and adult patients	CR: 90%	Total: 100% 27% severe	Total: 43% Encephalopathy, aphasia, seizures (1 patient)
MSKCC Davila et al[1]	CD3ζ, CD28	Cyclophosphamide	N = 16 adults	CR: 88%	43% severe	Grade 3/4: 25% Encephalopathy, seizures
NCI Lee et al[3]	CD3ζ, CD28	Fludarabine/ cyclophosphamide	N = 21 pediatric and adult patients	CR: 67% in intent-to-treat population	Total: 76% 28% severe	Total: 29% Hallucinations, dysphasia, encephalopathy
FHCRC Turtle et al[7]	CD3ζ, 4-1BB[a]	Cyclophosphamide and fludarabine/ cyclophosphamide	N = 29 adults	CR: 93%	Total: 83% 23% severe	Severe neurotoxicity: 50% TRM: 1 patient
Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin Lymphoma (NHL)						
NCI Kochenderfer et al[2]	CD3ζ, CD28	Fludarabine/ cyclophosphamide	N = 15 (NHL/CLL)	CR: 53% PR: 27%	27% severe	Total: 40% Encephalopathy, aphasia, right facial paralysis, myoclonus, ataxia
Penn Porter et al[6]	CD3ζ, 4-1BB[a]	Varied	N = 14 (CLL)	CR: 29% PR: 29%	Total: 64% 36% severe	Total: 43% Grade 4: 1 patient
MSKCC Turtle et al[39]	CD3ζ, CD28	3 Patients: no treatment 5 Patients: cyclophosphamide	N = 8 (CLL)	No PR/CR	Fever: 8 patients TRM: 1 patient	NR
Baylor Savoldo et al[11]	CD3ζ, CD28	None	N = 8 (NHL)	No PR/CR	NR	NR

Study Title	Conditions	Sponsor/Collaborators
Study of CART-138/BCMA Therapy for R/R Multiple Myeloma	Multiple Myeloma	The First Affiliated Hospital of Soochow University
Dose Escalation Study of JNJ-64007957, a Humanized BCMA CD3 DuoBody® Antibody, in Participants With Relapsed or Refractory Multiple Myeloma	Hematological Malignancies	Janssen Research & Development, LLC
BCMA Chimeric Antigen Receptor Expressing T Cells in Multiple Myeloma	Multiple Myeloma	The Second Affiliated Hospital of Henan University of Traditional Chinese Medicine; Xinqiao Hospital of Chongqing
LCAR-B38M-02 Cells in Treating Relapsed/Refractory (R/R) Multiple Myeloma	Refractory or Relapsed Multiple Myeloma	Nanjing Legend Biotech Co.
BCMA Targeted CAR T Cells for the Treatment of Multiple Myeloma	Multiple Myeloma	Memorial Sloan Kettering Cancer Center; Juno Therapeutics, Inc.
A Clinical Research of BCMA-Targeted CAR-T in B Cell Malignancies	Leukemia; Lymphoma; Multiple Myeloma	Southwest Hospital, China
Study of bb2121 in Multiple Myeloma	Multiple Myeloma	bluebird bio
CART-BCMA Cells for Multiple Myeloma	Multiple Myeloma	University of Pennsylvania
Study of T Cells Targeting B-Cell Maturation Antigen for Previously Treated Multiple Myeloma	Myeloma, Plasma-Cell; Myeloma-Multiple	National Cancer Institute (NCI); National Institutes of Health Clinical Center (CC)
Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, Immunogenicity and Clinical Activity of GSK2857916	Multiple Myeloma	GlaxoSmithKline

CAR T Cell Myeloma

Antigen	Trial Site, Company	Accrual	Identifier/Reference	Comments
BCMA	National Cancer Institute	Completed (26 patients)	NCT02215967[42,43]	First-in-human, CD28 domain, Cy/Flu conditioning; 13 of 16 (81%) ORR at highest dose
	University of Pennsylvania, Novartis	Completed (24 patients' data reported)	NCT02546167[44]	4-1BB domain; 6 of 10 (60%) ORR at high dose with Cy conditioning
	Multisite phase I, Bluebird	Ongoing (21 patients' data reported)	NCT02658929[45]	bb2121 construct, 4-1BB domain, Cy/Flu; 17 of 18 (94%) ORR at higher doses
	Multisite phase II, Bluebird	Ongoing	NCT03361748	bb2121 registration study, 94 patients
	Multisite phase I, Bluebird	Ongoing	NCT03274219	bb21217 product (same as bb2121 but enriched for memory T cells)
	Multisite phase I/II, Nanjing Legend	Ongoing (19 patients' data reported)	NCT03090659[46]	Binds two BCMA epitopes; Cy conditioning; less-treated population; 19 of 19 (100%) ORR
	Memorial Sloan Kettering/Juno	Ongoing (6 patients' data reported)	NCT03070327[47]	2 of 2 responded at higher dose with Cy/Flu; includes cohort with lenalidomide
	Fred Hutchinson, Juno	Ongoing	NCT03338972	Defined CD4/CD8 ratio in final CAR T product
	Multisite phase I/II, Juno	Ongoing	NCT03430011	JCARH125 construct, Flu/Cy
	Multisite phase I, Poseida	Ongoing	NCT03288493	Transposon-based construct[48]
	Multisite phase I, Kite	Ongoing	NCT03318861	KITE-585 construct, Flu/Cy
	Multiple hospital sites in China	Ongoing	NCT03322735 NCT03093168 NCT03380039 NCT02954445 NCT03302403	Small phase I/pilot studies
	Multisite phase I/II, Autolus Limited	Ongoing	NCT03287804	Novel CAR expressing APRIL to target BCMA and TACI
	Virginia Cancer Specialists, Cartesian Therapeutics	Ongoing	NCT03448978	Product contains $CD8^+$ cells only
CD19	University of Pennsylvania, Novartis	Completed (10 patients)	NCT02135406[49,50]	CD19 CAR T + salvage autoSCT. Targeting CD19+ myeloma precursor cells.
	Soochow University, China	Ongoing (10 patients reported)	NCT03196414[51]	CD19 CAR T + BCMA CAR T
			NCT03455972	Includes pilot of upfront CAR T cells + auto-SCT for high-risk MM
	General Hospital of PLA, China	Completed (5 patients)	NCT01886976	4 of 5 with stable disease for 3–7 months; no reported GI toxicity
	Soochow University, China	Ongoing	NCT03196414	Combination of CD138 CAR T + BCMA CAR T cells
Kappa LC	Baylor University	Completed (7 patients with MM)	NCT00881920[52]	No objective responses
CD38	Multisite phase I, Sorrento Therapeutics	Ongoing	NCT03464916	To open in 2018
	Shenzhen Geno-Immune Medical Institute, China	Ongoing	NCT03271632	Pilot study testing CAR T cells against multiple antigens
	NA	Preclinical	NA[53,54]	Affinity optimization to limit binding of CAR to CD38 on nonplasma cells
SLAMF7/CS1	NA	Preclinical	NA[55-57]	Concern for fratricide; can overcome with gene editing to knock out SLAMF7 in CAR T cells

*Current as of March 2018.

Abbreviations: AutoSCT, autologous stem cell transplantation; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; Cy, cyclophosphamide; Flu, fludarabine; GI, gastrointestinal; LC, light chain; MM, multiple myeloma; NA, not available; ORR, overall response rate.

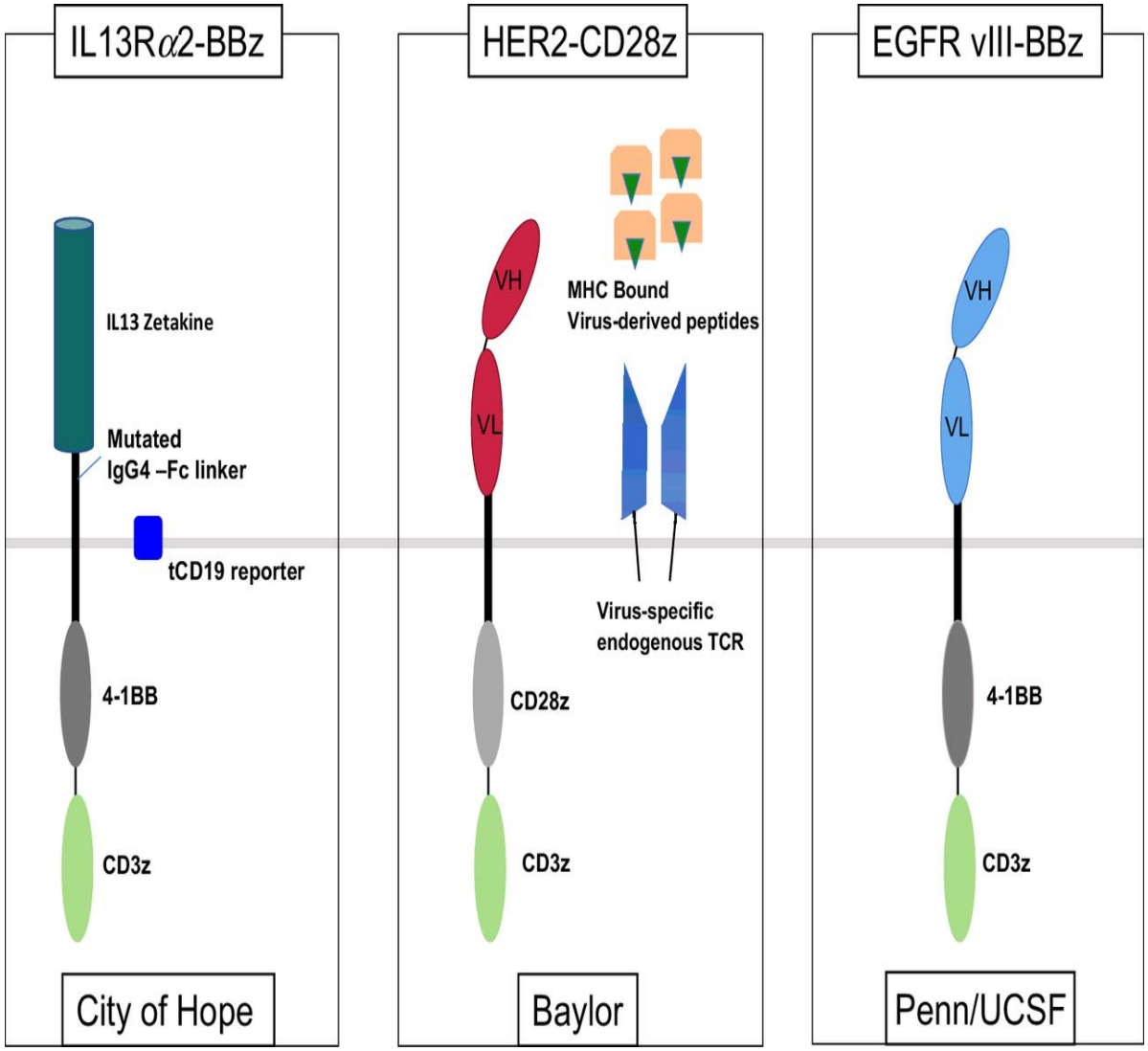
Preclinical CAR T cells work in AML

Author	Antigen Target	Construct	In vitro effects	In vivo effects
Kenderian et al[5]	CD33	Humanized scFv of my96 with either IgG4 or CD8 hinge	Robust cytotoxicity against cell lines and primary AML samples along with extensive degranulation and cytokine production	Decreases disease burden and prolongs survival in xenografts with MOLM14 and primary CD33+ AML patient samples
Rafiq et al[6]	CD33	Variable light and heavy chains of humanized M-195 antibody, CD28 and zeta signaling domain with the IL-12 gene	Significant production of IFN-γ, IL-2 and IL-12, as well as significant cytotoxicity	Reduction in systemic disease burden and improved OS in MOLM13 and patient derived xenografts
O'Hear et al[7]	CD33	CD8 leader sequence with anti-CD33 single chain variable fragment[8] and 4-1BB along with CD3ζ	Cytoxicity against AML cell lines as well as primary patient samples	Dramatic decrease in disease burden and extended median survival in a MOLM13 murine model
Gill et al[9]	CD123	Cloned mouse antihuman CD123 scFv (clone 32716 or clone 26292) along with 4-1BB and CD3ζ	Cytotoxicty against MOLM14 and primary patient samples with high IFN-γ, MIP1α, MIP1β, IL2, GSCF	Long-term survival with decreased disease burden in MOLM14 and primary patient xenografts. Establishment of memory CART123 when rechallenged
Mardiros et al[10]	CD123	Clone 327 16 or clone 26292 of CD123 scFv with human IgG4, CD28, CD3ζ	Cytotoxicity against LCL, KG-1a and primary patient samples with high levels of TNF-α and IFN-γ	Improved survival with decreased disease burden in KG-1a xenografts
Tettamani et al[11], Pizzitola et al[12]	CD123	Anti-CD123 CIK CART with scFv CD123 from mAb7G3 CD28OX40ζ[17]	Cell kill against THP-1 and primary AML blasts[16]	Decreases ability to engraft cells and decreased disease burden in primary patient xenografts[17]
Magnani et al[13]	CD123	Anti-CD123 CIK CART with CD28/ OX40/TCRζ	Specific killing, TNF-α and IFN-γ, proliferation on co-culture with THP-1 and primary patient samples	Decreased disease burden and improved OS in KG-1 NSG mice
Cartellieri et al[21]	CD123 and CD33	Universal CAR (UniCAR), not available	Cytotoxicity against cell lines and patient samples with production of IFN-γ, G-CSF, IL3	Inhibit tumor engraftment in vivo, maintain cytotoxic potential long term
Zhou et al[34]	CD123 and EBV	Not available	Cytolysis of MOLM13 and THP-1 cell lines	Not available
Lynn et al[14]	FRβ	m909 scFv, remainder of construct not available	Cytolytic activity against THP1 with significant IFN-γ release	Improvement in disease burden with subcutaneous and IV inoculation of THP-1 in NOD mice
Kenderian et al[14]	CLL1/ CLEC12A	CLEC12A, 4-1BB, CD3ζ	Modest efficacy against cell lines and patient samples. Significant cytotoxicty in cells engineered to overexpress CLEC12A	Increase in survival of patient derived xenografts treated with cytarabine and CLEC12A-CART
Chien et al[17]	FLT3	scFv from well characterized anti-human FLT3 antibody with 4-1BB and CD3ζ	Proliferate in presence of MOLM13 and MOLM14	Inhibit leukemia progression in MOLM13 or MOLM14 engrafted NSG mice
Ploch et al[18]	B7H6	CART expressing NKp30, remainder of construct not available	B7H6-dependent, potent cytolytic activity and IFN-γ release when co-cultured with leukemia cell lines and primary patient samples	Reduction in tumor burden in animals engrafted with K562

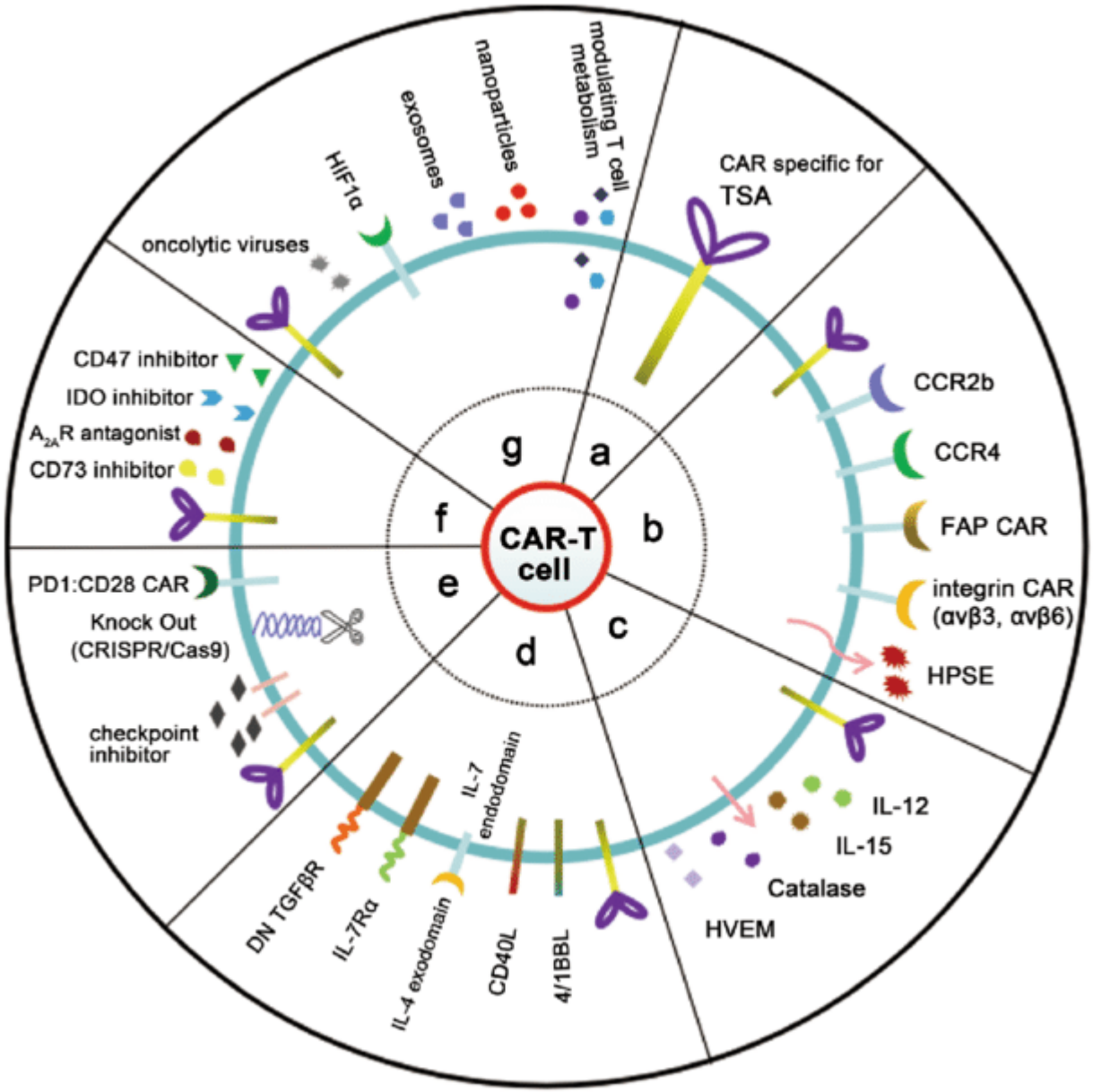
CAR T Cell AML

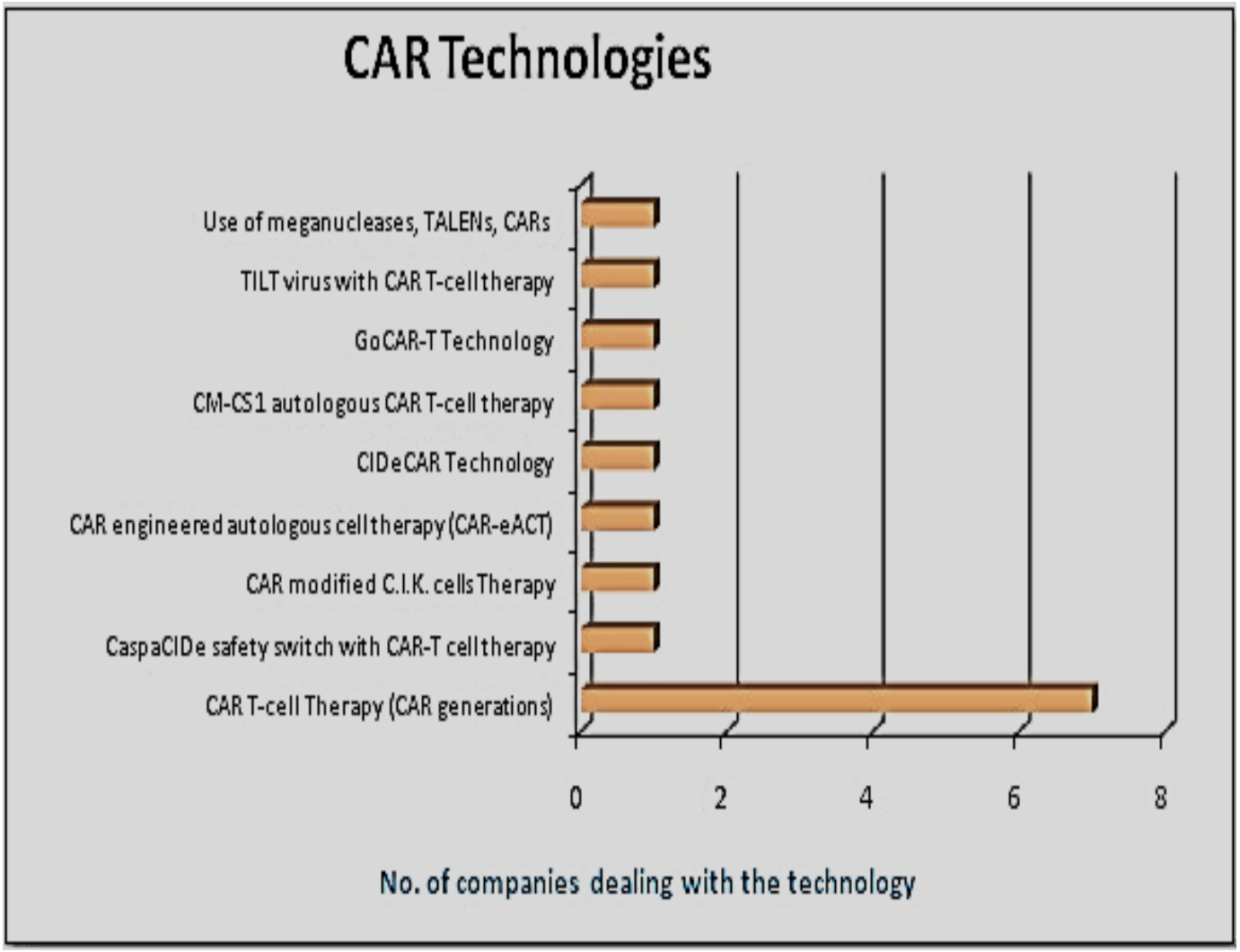
Author	Antigen Target	Construct	In vitro effects	In vivo effects	Stage of Development
Wang et al[20,21]	CD33	Autologous, unavailable	Cytotoxicity against K562, cytolytic against HL60 and primary patient samples	Unavailable	Case report, phase I, II
Guzman et al[33]	CD123	UCAR123, not available	Effective elimination of AML cell lines	Complete eradication of disease in patient-derived xenografts	Phase I
Nikiforow et al[22]	NKG2D	Not available	Not available	Not available	Phase I
Peinert et al[19]	LeY	Not available	Cytolytic activity and IFN-gamma production when co-cultured with AML cell lines and primary patient samples	Not available	Phase I

CAR T cells in glioblastoma

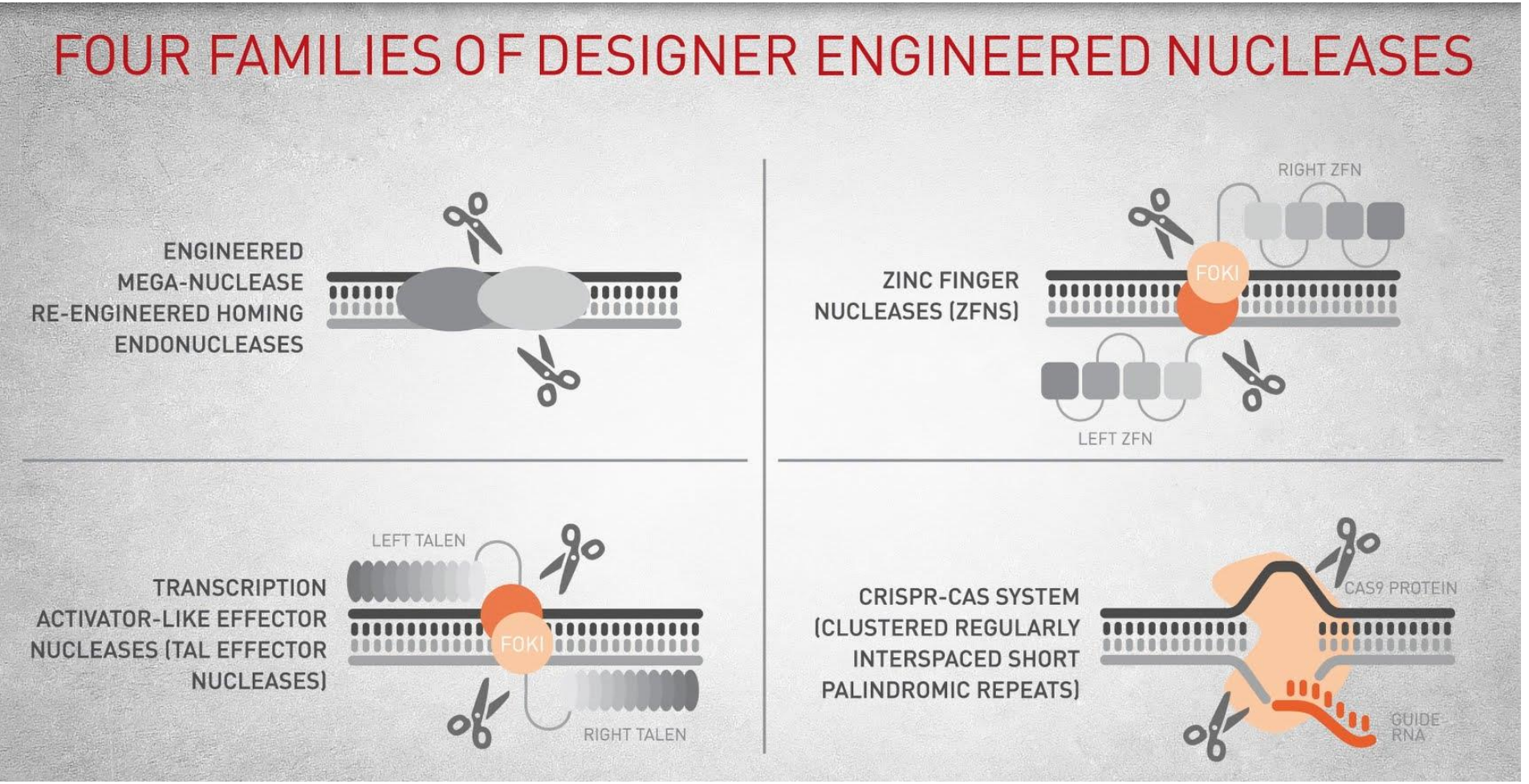


Approaches to improve CAR T Cell outome

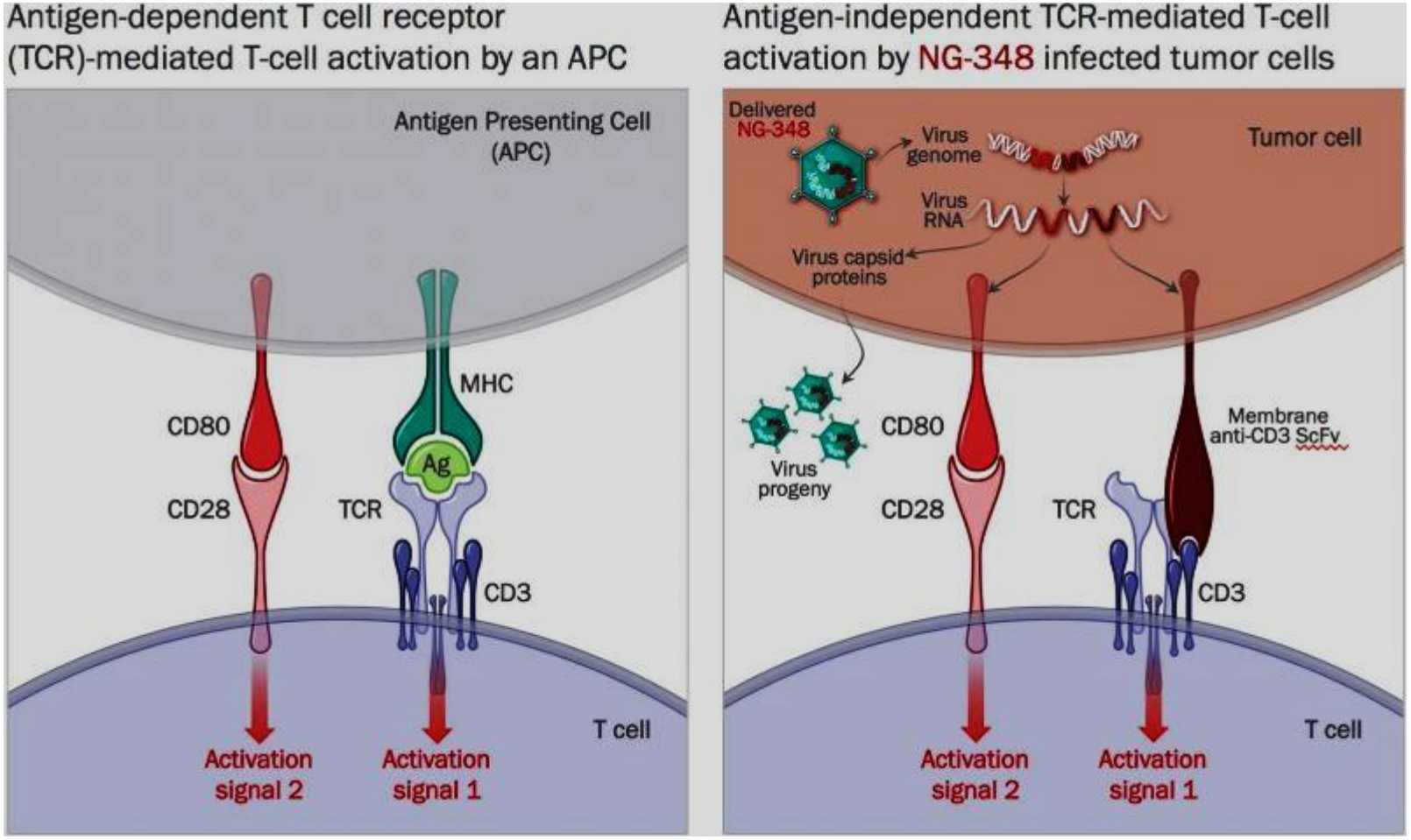



CAR Technologies
Use of meganucleases, TALENs, CARs
TILT virus with CAR T-cell therapy
GoCAR-T Technology
CM-CS1 autologous CAR T-cell therapy
CIDeCAR Technology
CAR engineered autologous cell therapy (CAR-eACT)
CAR modified C.I.K. cells Therapy
CaspaCIDe safety switch with CAR-T cell therapy
CAR T-cell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

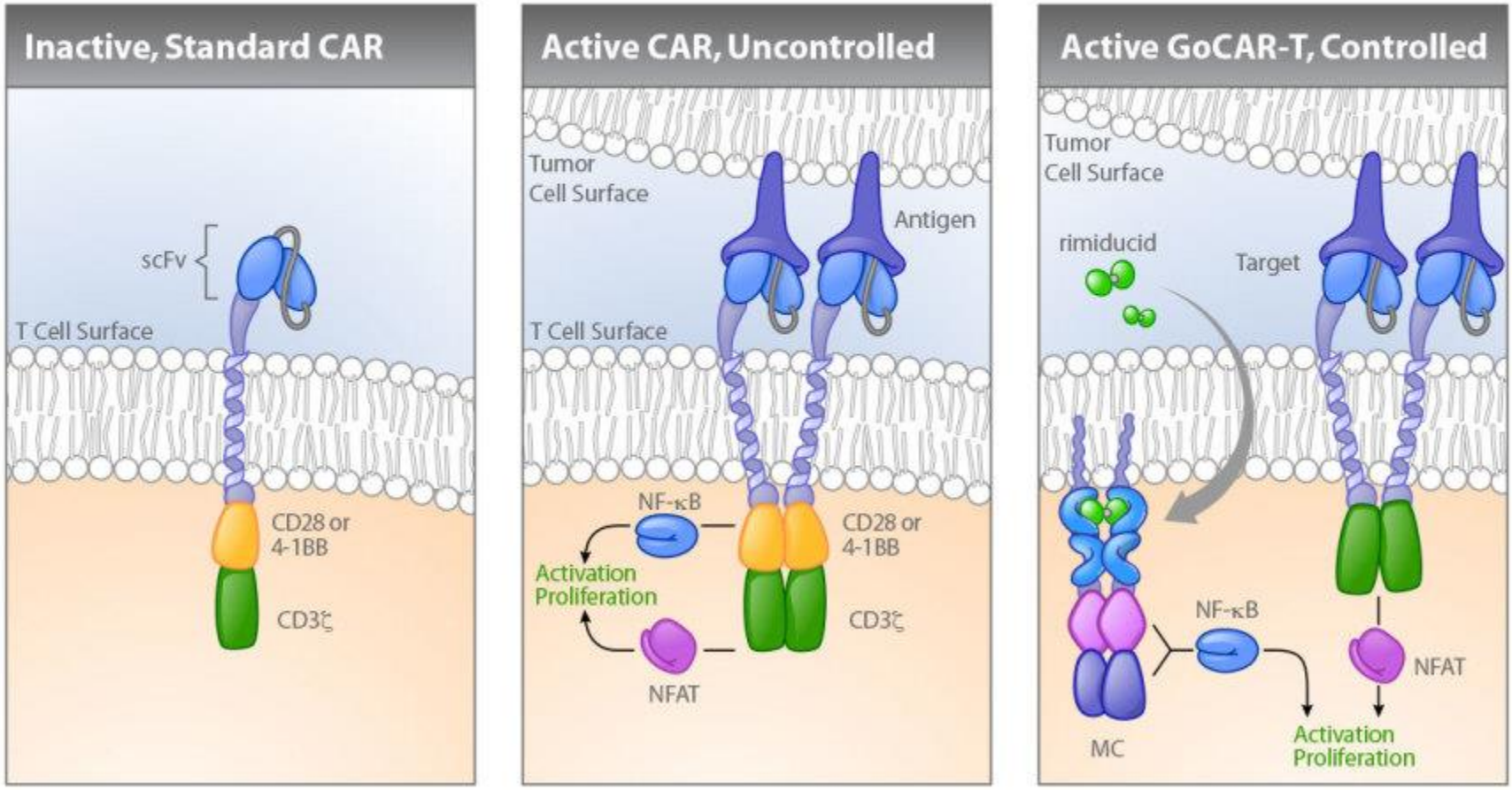
Gene editing for CAR T cells



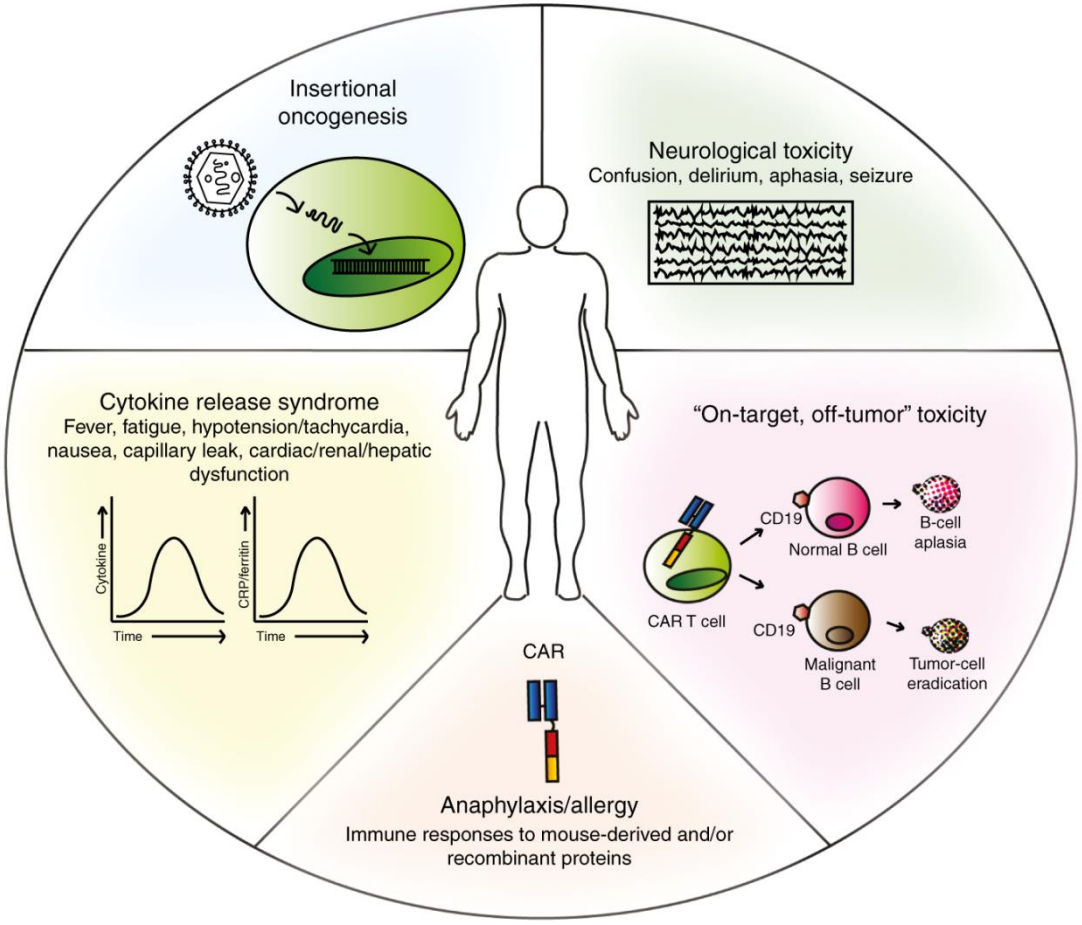
TILT oncolytic virus technology



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

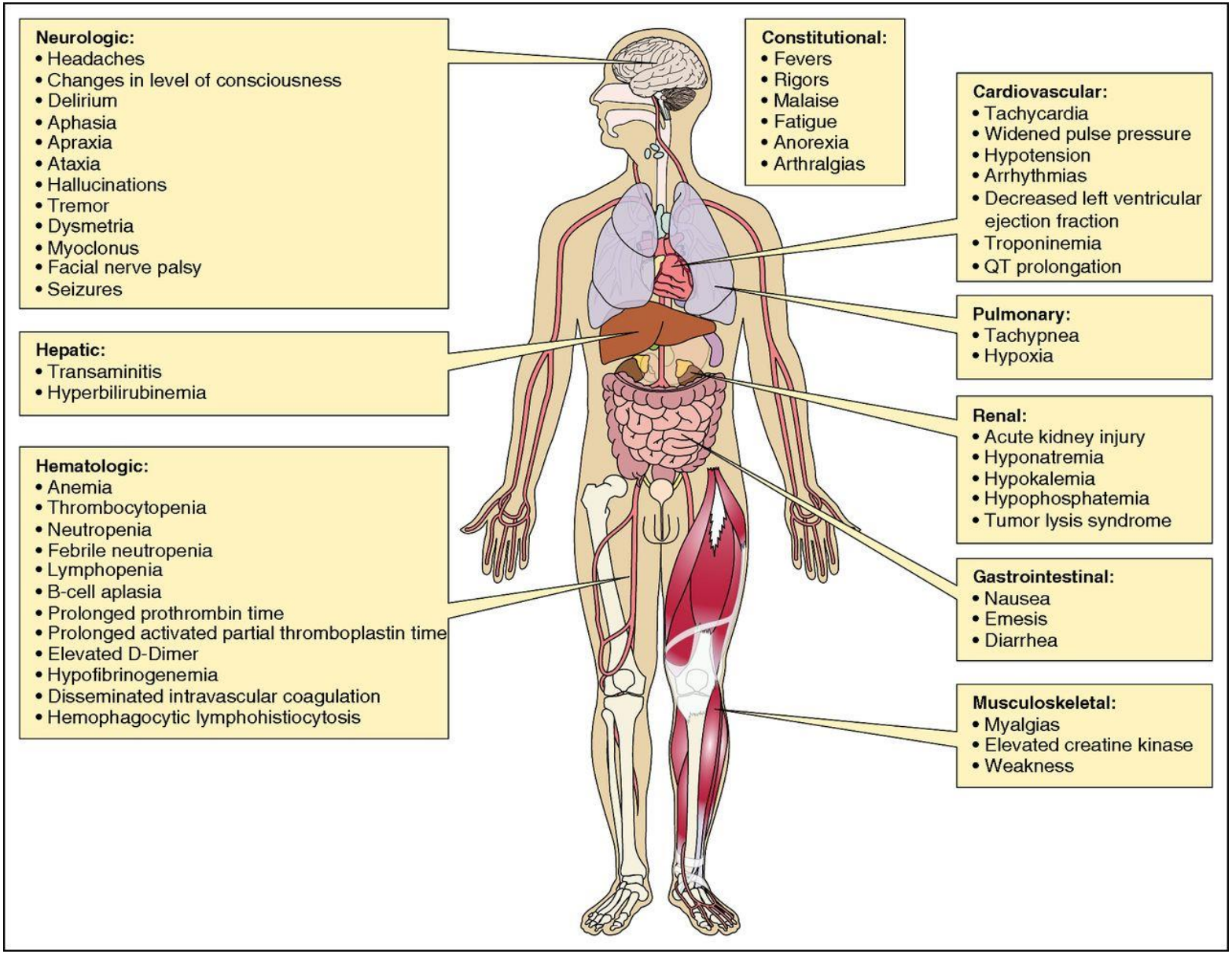


Toxicities



Tumor lysis syndrome

Macrophage activating syndrome

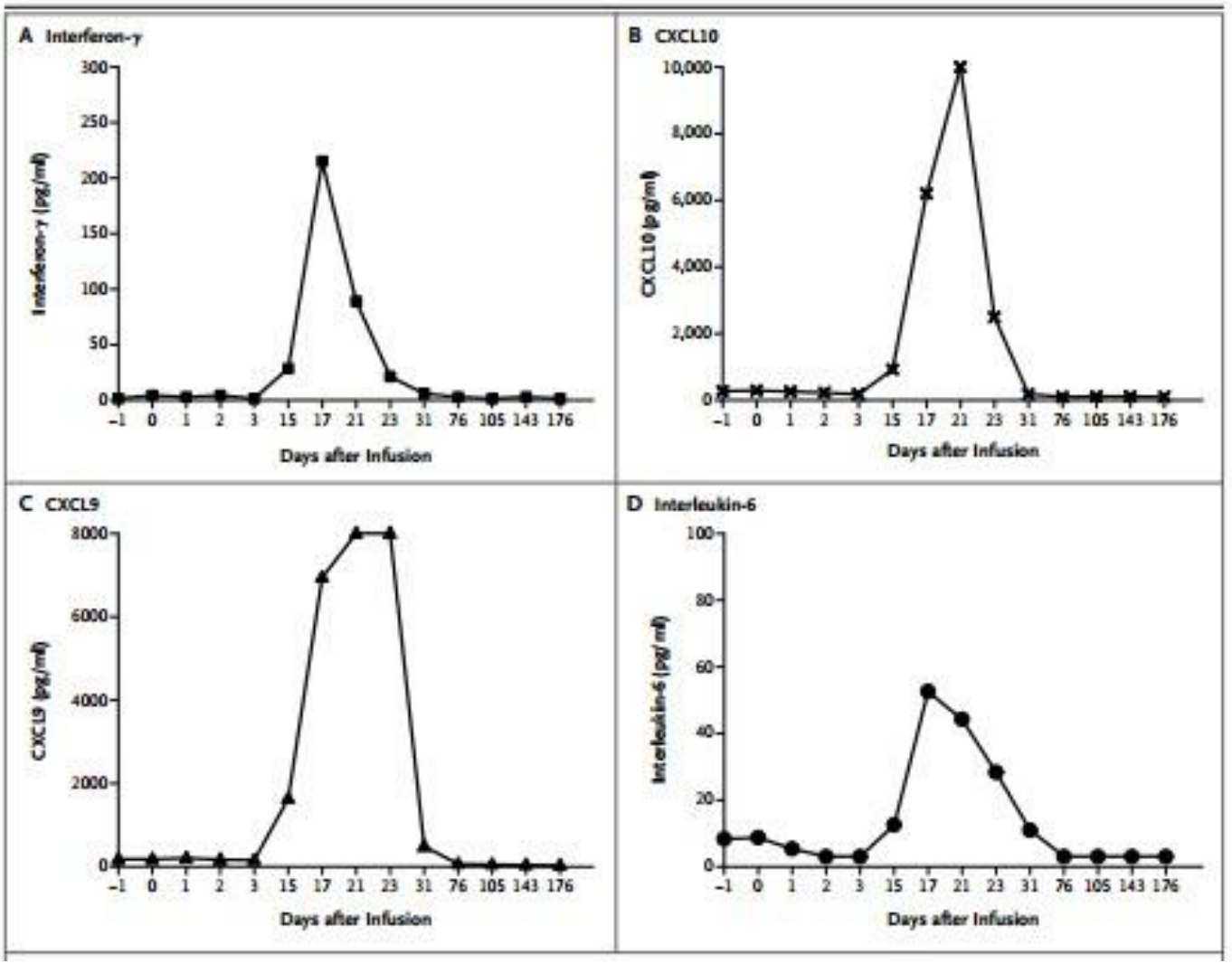

Neurologic:
• Headaches
• Changes in level of consciousness
• Delirium
• Aphasia
• Apraxia
• Ataxia
• Hallucinations
• Tremor
• Dysmetria
• Myoclonus
• Facial nerve palsy
• Seizures
Hepatic:
• Transaminitis
• Hyperbilirubinemia
Hematologic:
• Anemia
• Thrombocytopenia
• Neutropenia
• Febrile neutropenia
• Lymphopenia
• B-cell aplasia
• Prolonged prothrombin time
• Prolonged activated partial thromboplastin time
• Elevated D-Dimer
• Hypofibrinogenemia
• Disseminated intravascular coagulation
• Hemophagocytic lymphohistiocytosis
Constitutional:
• Fevers
• Rigors
• Malaise
• Fatigue
• Anorexia
• Arthralgias
Cardiovascular:
• Tachycardia
• Widened pulse pressure
• Hypotension
• Arrhythmias
• Decreased left ventricular ejection fraction
• Troponinemia
• QT prolongation
Pulmonary:
• Tachypnea
• Hypoxia
Renal:
• Acute kidney injury
• Hyponatremia
• Hypokalemia
• Hypophosphatemia
• Tumor lysis syndrome
Gastrointestinal:
• Nausea
• Emesis
• Diarrhea
Musculoskeletal:
• Myalgias
• Elevated creatine kinase
• Weakness

Symptoms of CRS

- condition resulting from the release of cytokines from cells targeted by antibodies, immune effector cells recruited to the tumor area, and subject's immune cells activated.

Organ system	Symptoms
Constitutional	Fever ± rigors, malaise, fatigue, anorexia, myalgias, arthalgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia ± bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dymetria, altered gait, seizures

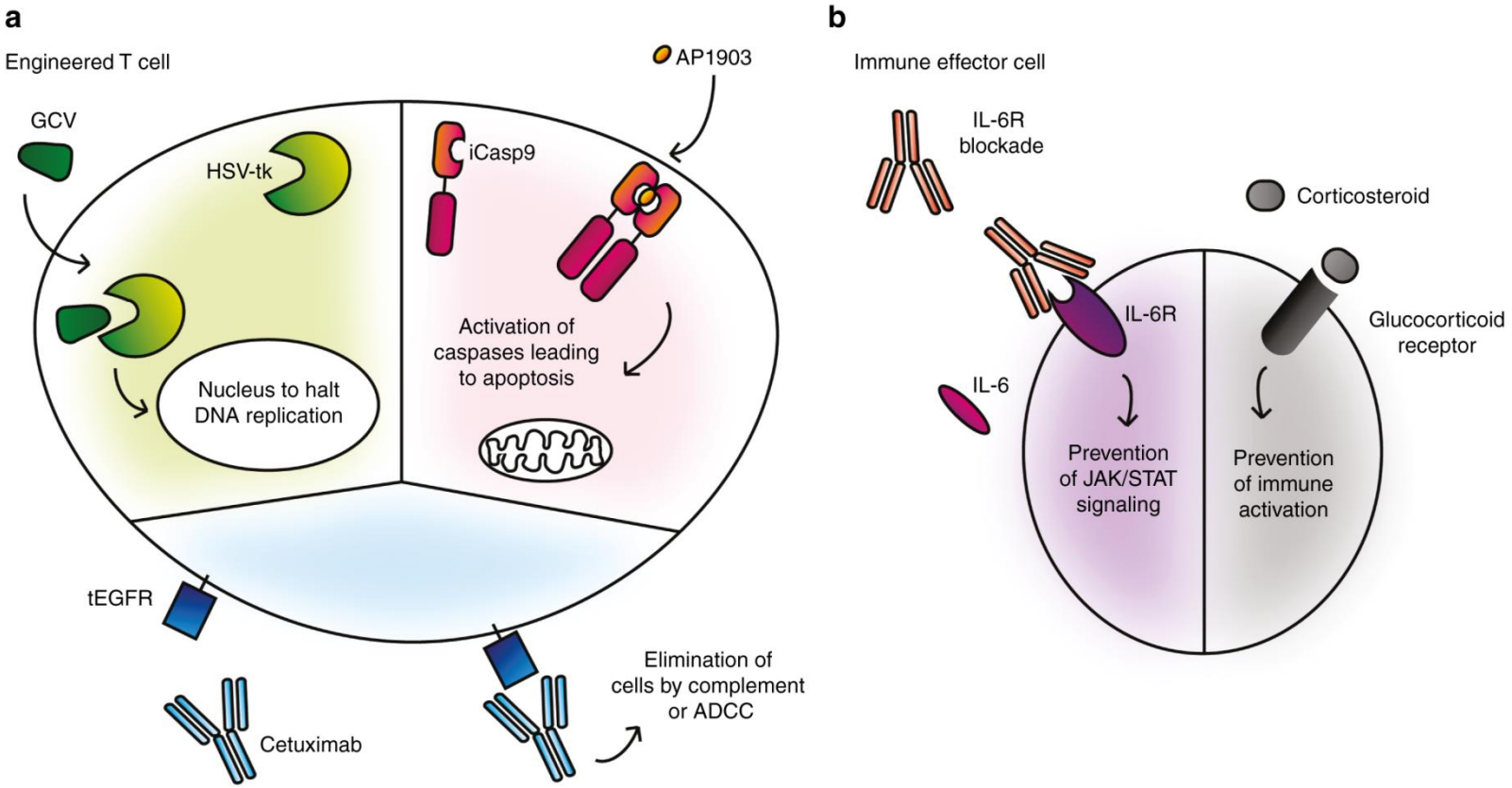
Serum and Bone Marrow Cytokines before and after Chimeric Antigen Receptor T-Cell Infusion.



Neurotoxicity Pathophysiology

- Exact etiology remains unclear
- No clear evidence of expression of CD19 in CNS
  - CD19 expression in archival tissue from non-lymphoma patients, in multiple brain regions by qPCR and immunohistochemistry and found no CD19 expression as a potential cause of neurotoxicity (Kochenderfer 2014)
- Possibility of CNS occult disease in a subset of DLBCL patients with tumor disseminated beyond the lymph nodes and spleen (Wilson 2005)
  - None of the patients in this study had a history of or evidence of CNS disease. Pre-treatment of steroids still results in neurotoxicity
- MRI-no findings, CSF-CAR T, EEG-non focal
- Observed in other CD19 targeted T cell therapy such as blinatumomab

Decreasing the toxicity in CAR modified T cell cancer therapy



Moving Forward with CAR-T Cells

Determinants of successful ACT: CAR-T cells

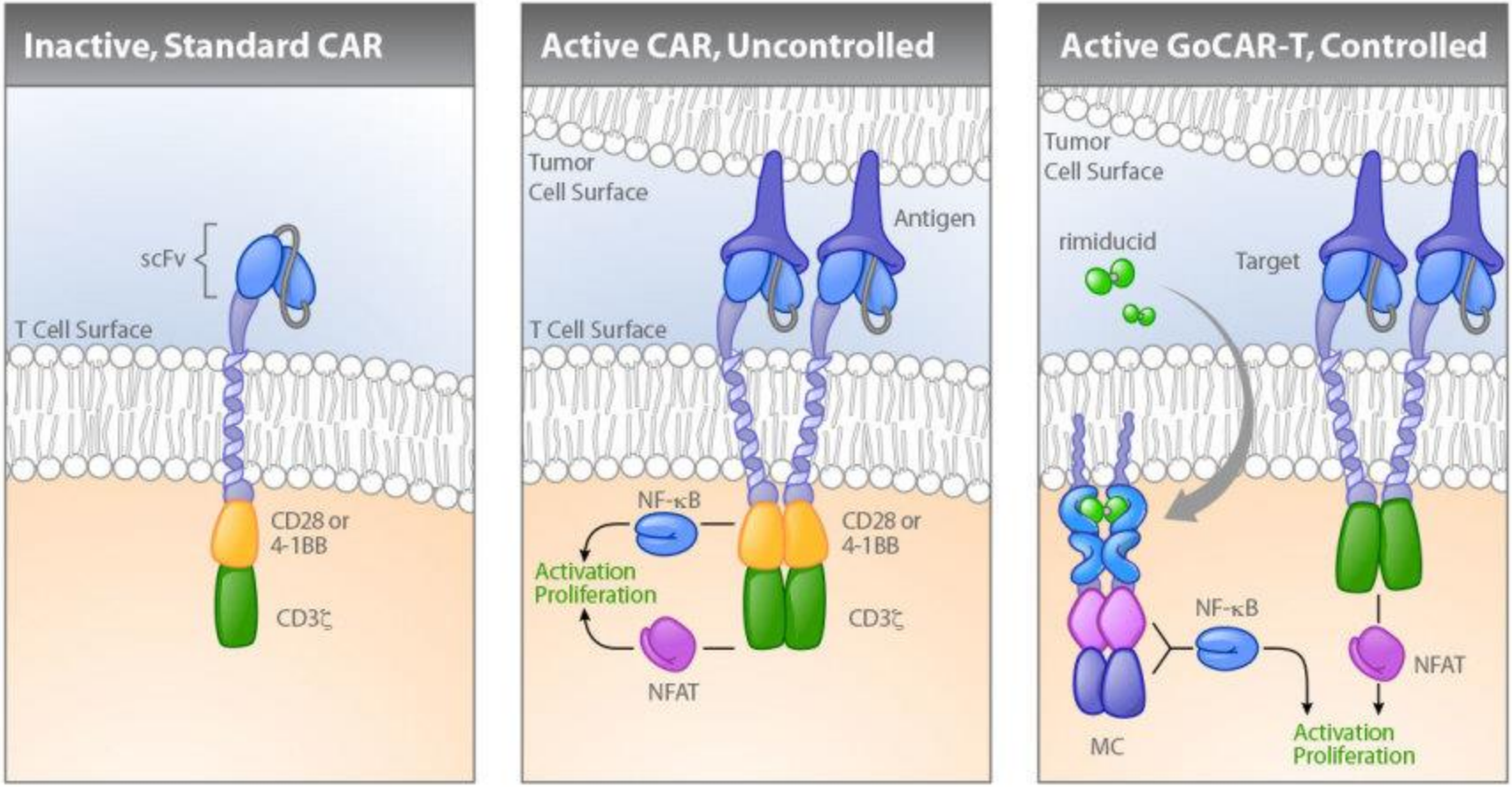
- **Tumor target**
  - Target antigen is critical determinant for efficacy & safety
  - Ideal target uniquely express on tumor cells or on cells which are not essential for survival

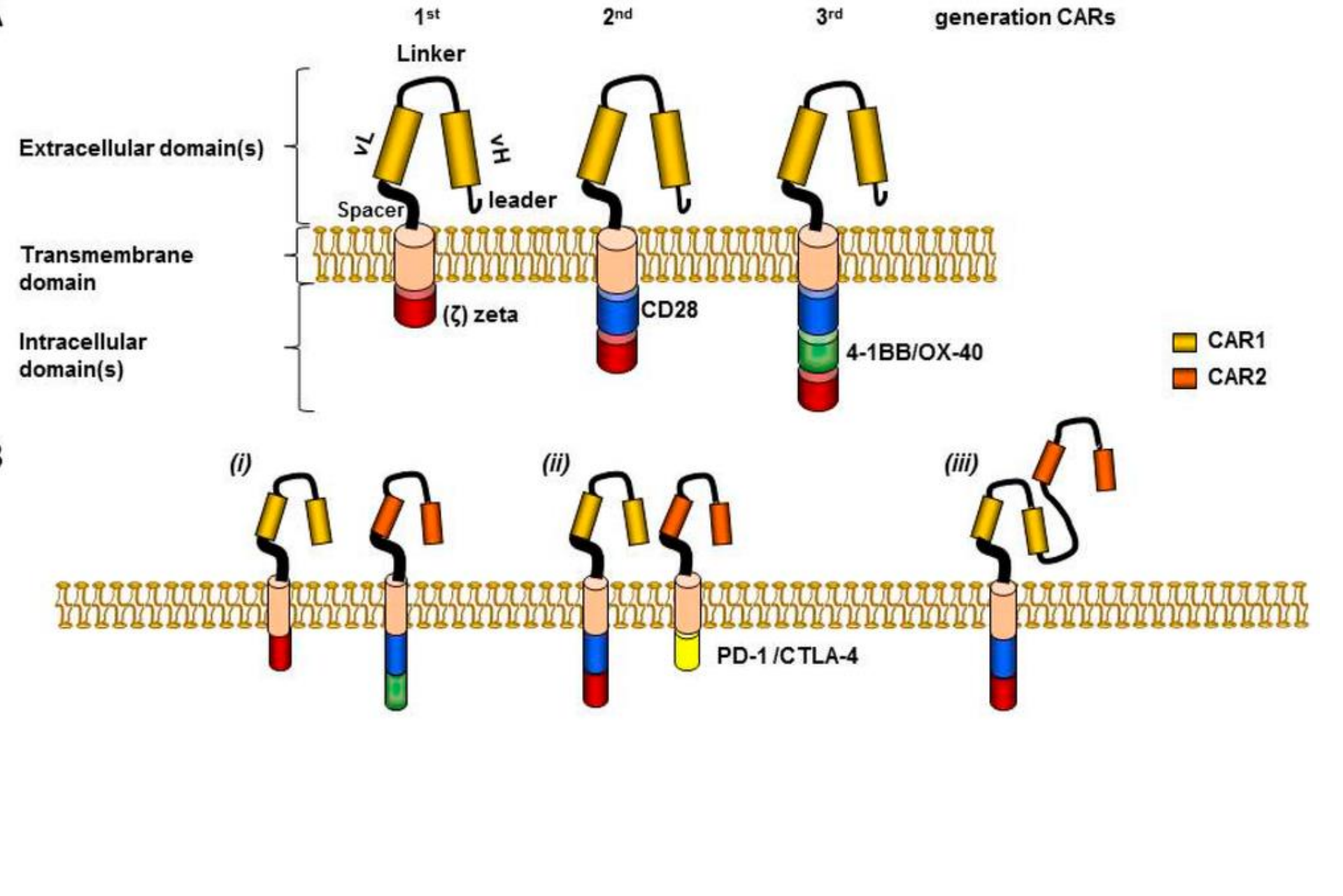
- **Efficacy & Long-term persistence**
  - Subtypes of CD4+T cells (Th1, Th2, Th17, Th9 cells),
  - CD8+T cells
    - naïve, central memory; long-term
    - effector; active but short lived

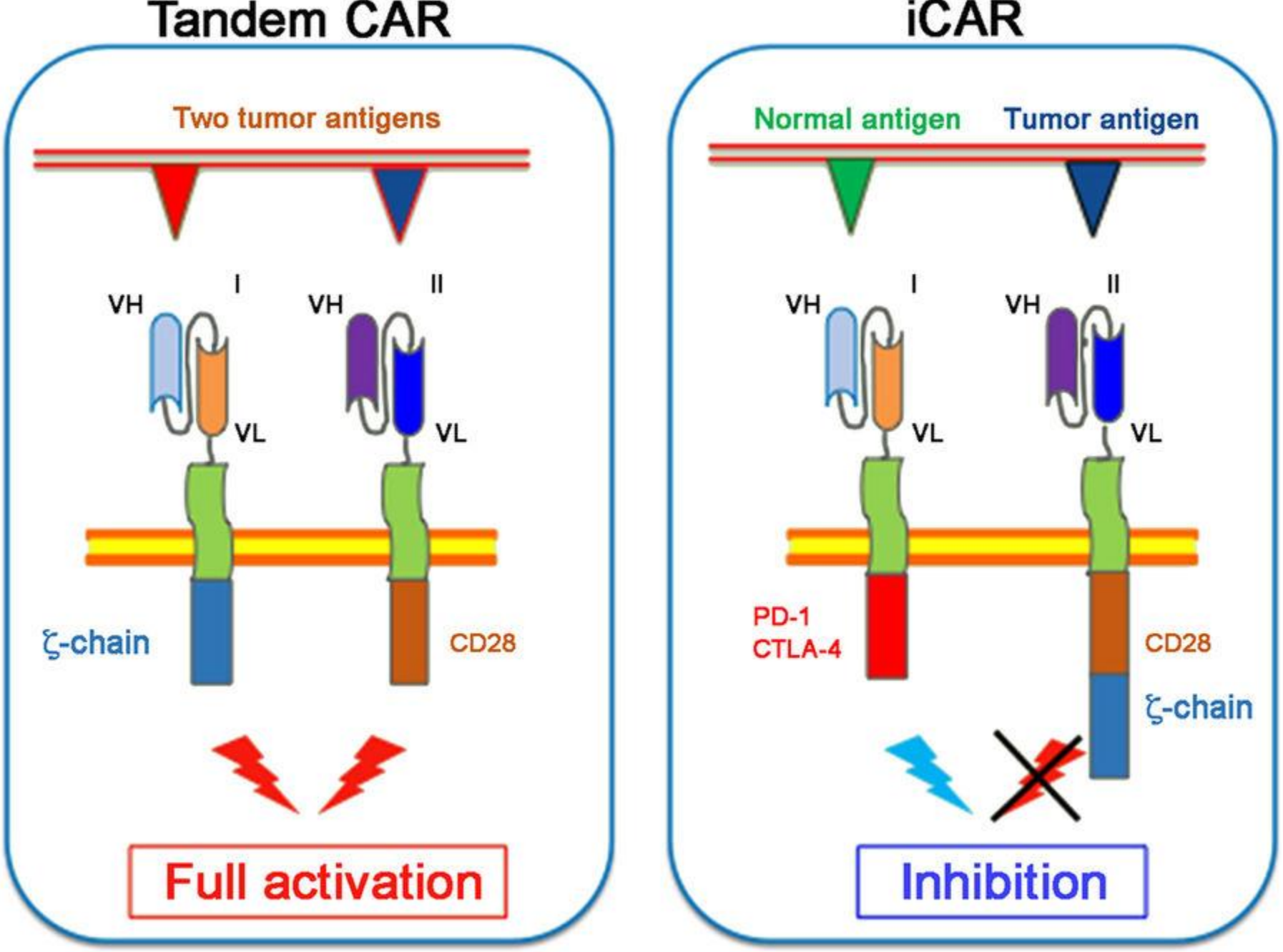
- **Trafficking of CAR T cells to tumor**
  - Expression of addressins
  - Route of CAR-T cell infusion
    - Intra-tumoral/intravenous
  - Optimal co-stimulation of T cells

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

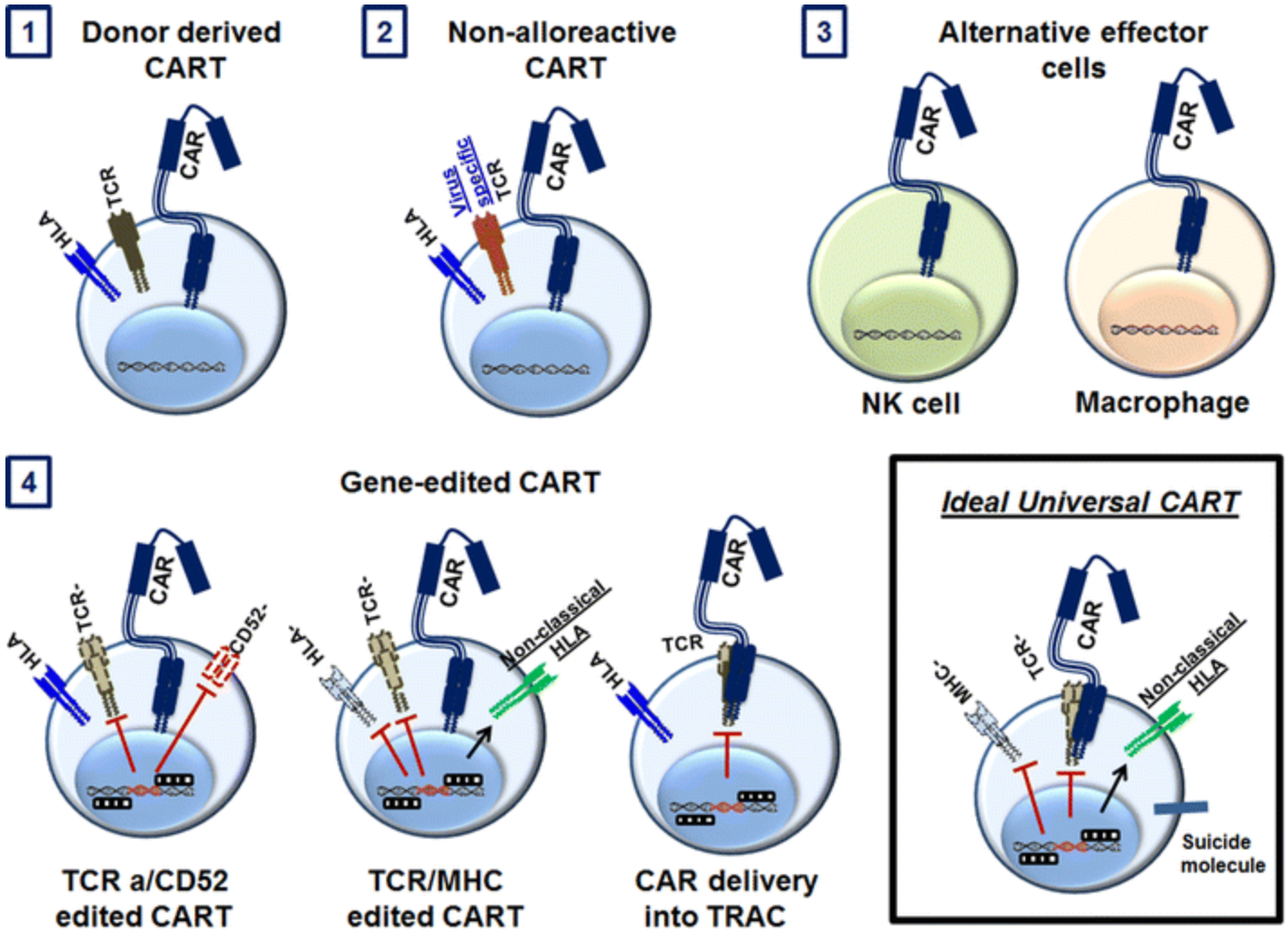
Conventional CAR-T Technology *vs.* GoCAR-T

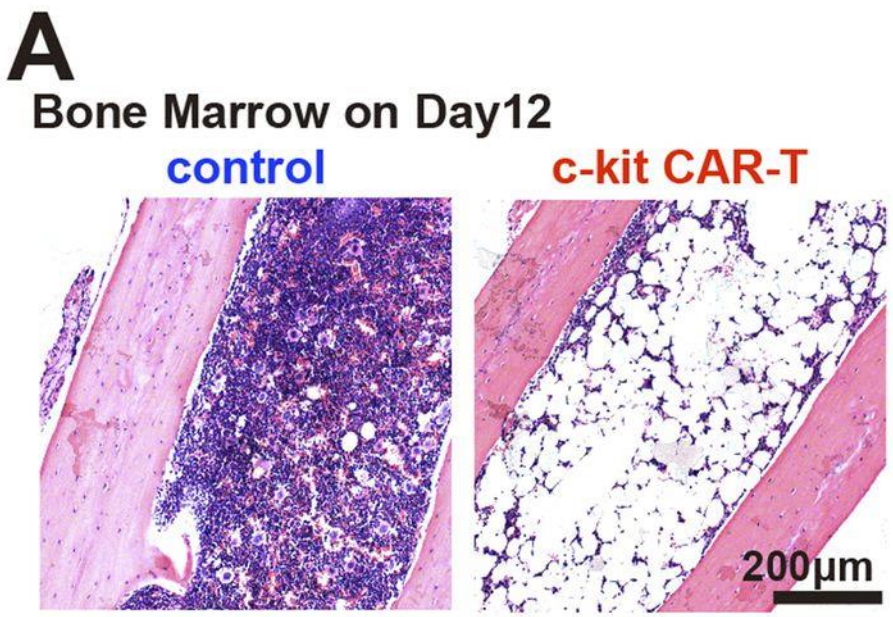


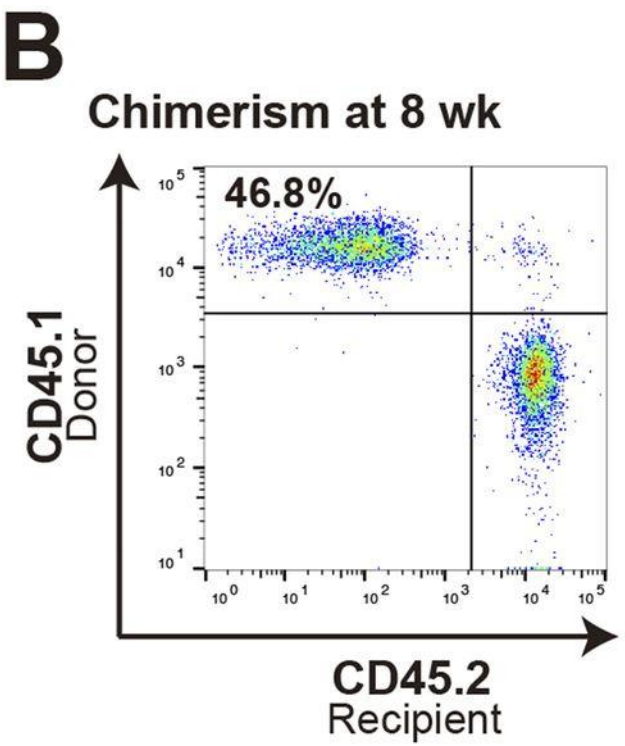

1st
2nd
3rd
generation CARs
Linker
Extracellular domain(s)
VL
VH
leader
Spacer
Transmembrane domain
(ζ) zeta
CD28
4-1BB/OX-40
Intracellular domain(s)
CAR1
CAR2
(i)
(ii)
(iii)
PD-1 /CTLA-4


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

Next-Generation Chimeric Antigen Receptor T-Cell Therapy: Going off the Shelf







Yasuyuki Arai et al. Blood 2017;130:4446

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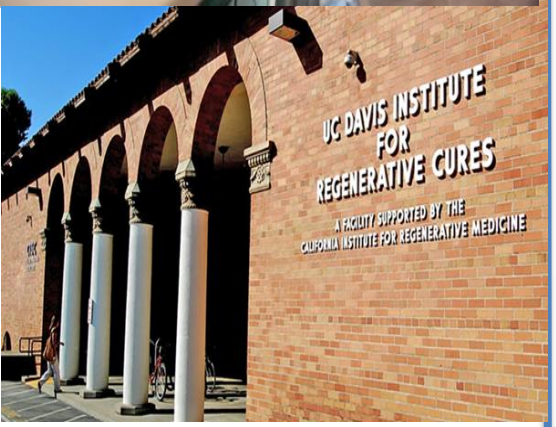


University of California Davis Health, Sacramento, CA

Alpha Stem Cell Clinic

Mehrdad Abedi, MD

Professor of Medicine,
Bone Marrow Transplantation Unit

ASCC Program Director

UCDAVIS HEALTH SYSTEM


Cypress Building
Laboratory
&
Pharmacy


21


1215
INFUSION

City of Hope

Alpha Clinic

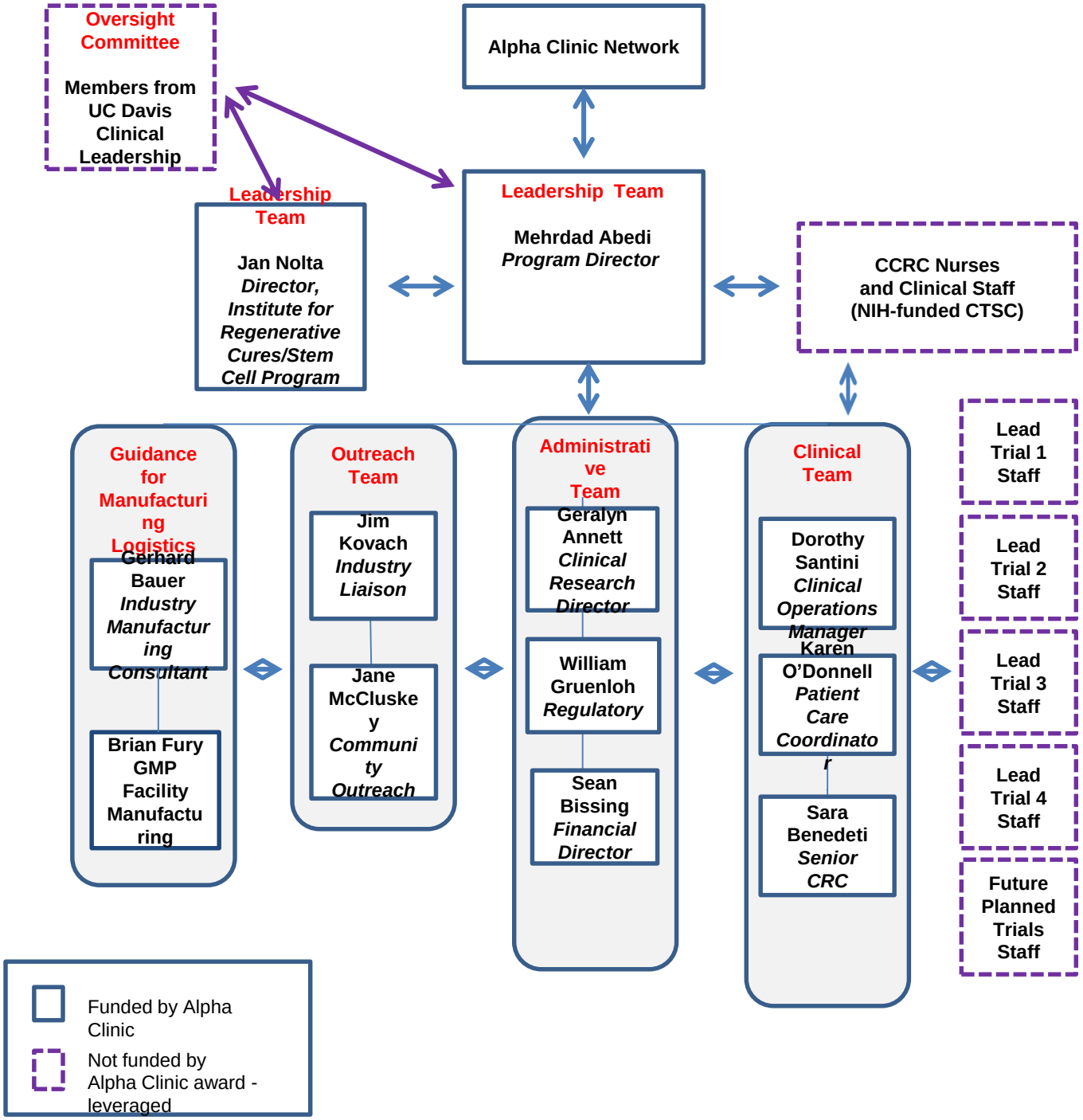
UCLA UCI
Alpha Stem Cell Clinic

UC San Diego Health

UC DAVIS
HEALTH

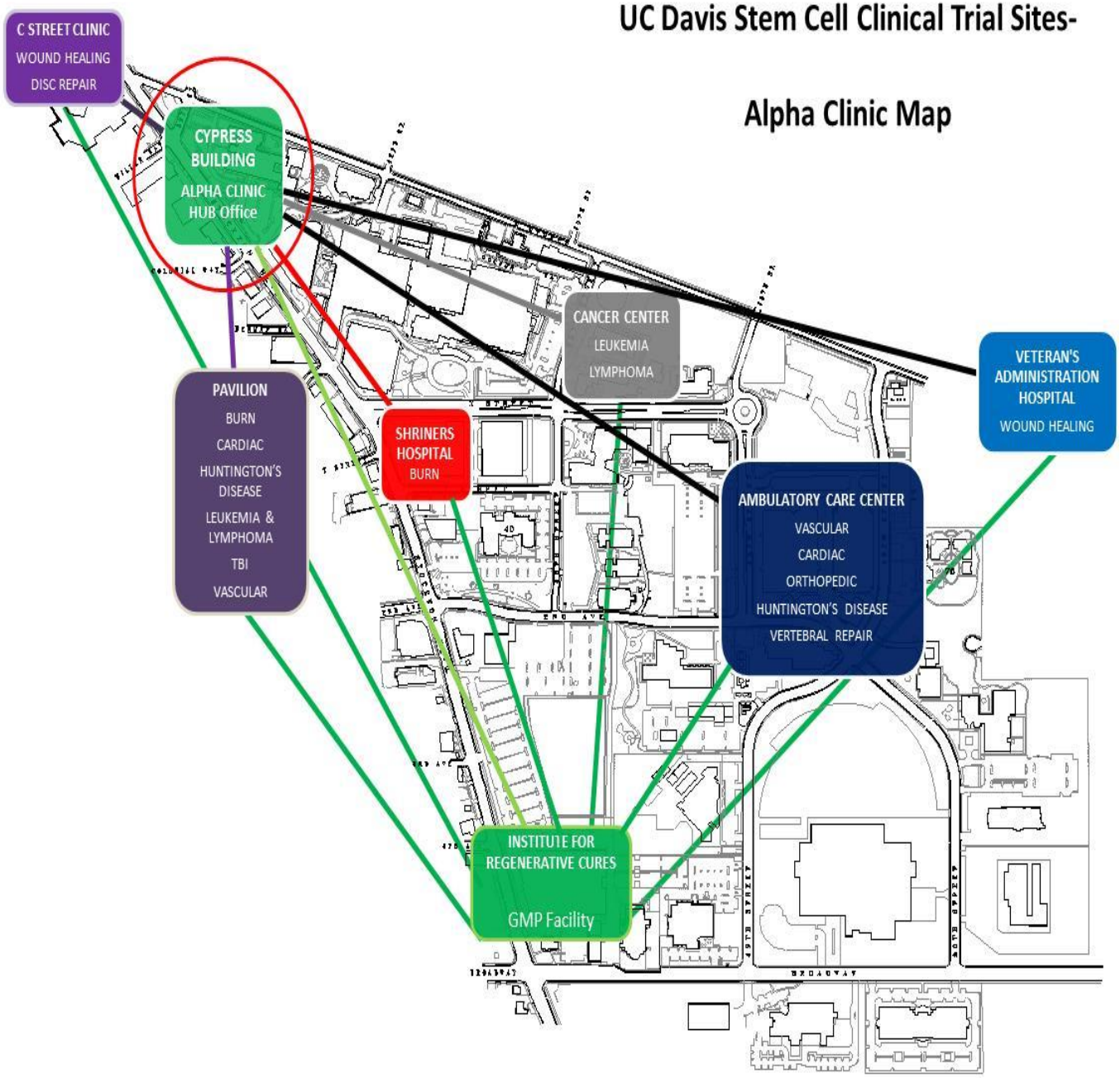
UCSF

*UC Davis and UC San Francisco Alpha Clinic websites coming soon.


Oversight Committee
Members from UC Davis Clinical Leadership
Alpha Clinic Network
Leadership Team
Jan Nolta
Director, Institute for Regenerative Cures/Stem Cell Program
Leadership Team
Mehrdad Abedi
Program Director
CCRC Nurses and Clinical Staff (NIH-funded CTSC)
Guidance for Manufacturing Logistics
Gerhard Bauer
Industry Manufacturing Consultant
Brian Fury
GMP Facility Manufacturing
Outreach Team
Jim Kovach
Industry Liaison
Jane McCluskey
Community Outreach
Administrative Team
Geralyn Annett
Clinical Research Director
William Gruenloh
Regulatory
Sean Bissing
Financial Director
Clinical Team
Dorothy Santini
Clinical Operations Manager
Karen O'Donnell
Patient Care Coordinator
Sara Benedeti
Senior CRC
Lead Trial 1 Staff
Lead Trial 2 Staff
Lead Trial 3 Staff
Lead Trial 4 Staff
Future Planned Trials Staff
Funded by Alpha Clinic
Not funded by Alpha Clinic award - leveraged

UC Davis Stem Cell Clinical Trial Sites-

Alpha Clinic Map



UC Davis Pipeline Clinical Trials Active:

ClinicalTrials.gov	Protocol Title	Disease	Sponsor	PI	Status
NCT02838316	Autologous Muscle Derived Cells for Gastro-Intestinal Repair (AMDC-GIR) for Tongue Dysphagia	Tongue Dysphagia	UCD Cook Myosite	Peter Belafsky, MD,	9 enrolled 11 screened
NCT01736059	Clinical Trial of Autologous Intravitreal Bone-marrow CD34+ Stem Cells for Retinopathy	Retinopathy	UCD	Susanna Park, MD,	9 enrolled 13 screened
NCT03406780	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Safety and Efficacy of Intravenous Delivery of Allogeneic Cardiosphere-Delivered Cells in Subjects with Duchenne Muscular Dystrophy (HOPE-2)	DMD	Capricor	Craig McDonald, MD	6 enrolled 8 screened
NCT02578641	A Phase III Trial Evaluating Chemotherapy and Immunotherapy for Advanced Nasopharyngeal Carcinoma (NPC) Patients	Nasopharyngeal Carcinoma	TESSA	Mehrdad Abedi, MD	1 enrolled 2 screened
NCT03301597	Phase 2 open-label, multi-center, randomized, controlled, dose-finding study of safety and efficacy of NLA101 to reduce the rate of infections associated with CIN in adult subjects with AML	Neutropenia	CIRM Nohla	Mehrdad Abedi, MD	3 enrolled 6 screened
NCT02797470	Gene Therapy in Treating Patients with Human Immunodeficiency Virus-Related Lymphoma Receiving Stem Cell Transplant	HIV-NHL	CIRM	Mehrdad Abedi, MD	3 enrolled 12 screened
NCT03363945	Cellular Immunotherapy in Recipients of	Kidney	Medeor	Junichiro	Open for

UC Davis Pipeline Clinical Trials in Process:

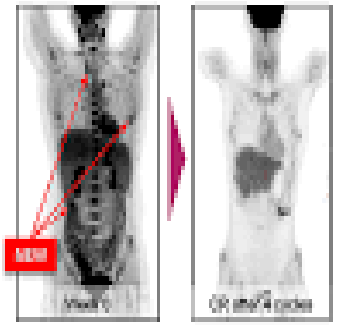
ClinicalTrials.gov	Protocol Title	Disease	Sponsor	PI	Status
NCT03379493	Study of ET190L1-ARTEMIS™ T Cells in Relapsed and Refractory CD19+ Non-Hodgkin's Lymphoma	NHL	Eureka	Mehrdad Abedi, MD	Budget and IRB In Review
NCT03394365	ATA129 for Solid Organ Transplant Subjects With EBV-PTLD After Failure of Rituximab or Rituximab and Chemotherapy (ALLELE) ATA129-EBV-302	EBV-PTLD	Atara Bio.	Mehrdad Abedi, MD	SRC approved
NCT03451916	Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study, Designed to Determine the Efficacy, Safety, and Tolerability of Intramuscular Administration of Allogeneic PLX-PAD Cells for the Treatment of Muscle Injury Following Arthroplasty for Hip Fracture	Muscle Injury/Hip Fracture	Pluristem	Mark Lee, MD	Budget and IRB In Review
NCT03420183	A Phase 1b-2 Study of the ROR1-Targeting Monoclonal Antibody, Cirmtuzumab, and the Bruton Tyrosine Kinase Inhibitor, Ibrutinib, in Patients with B-Cell Lymphoid Malignancies	B-Cell Leukemia	CIRM UCSD	Joe Tuscano, MD	SRC Review 6/7/18
NCT03139370	A Study Evaluating the Safety and Efficacy of MAGE-A3/A6 T Cell Receptor Engineered T Cells (KITE-718) in HLA-DPB1*04:01 Positive Subjects with Advanced Cancers	Advanced Cancer	Kite	Mehrdad Abedi, MD	Budget and IRB In Process
NCT03400917	Phase II Trial of Autologous Dendritic Cells Loaded with Autologous Tumor Associated Antigens (AV-GBM-1) as an Adjunctive Therapy Following Primary Surgery Plus Concurrent Chemoradiation in Patients With Newly Diagnosed Glioblastoma	GBM	AIVITA Biomedical	Robert O'Donnell, MD, PhD	SRC Pending
NCT03005106	A Phase III Open-label, Controlled, Randomized, Multicenter Study Evaluating the Efficacy and Safety of StrataGraft Skin Tissue in Promoting Autologous Skin Tissue Regeneration of Complex Skin Defects Due to Thermal Burns That Contain Intact Dermal Elements and for Which Excision and Autografts Are Clinically Indicated	Burns	Mallinckrodt Pharma.	Tina Palmieri, MD	CDA In Process

A Multicentre, Randomized, Open-Label, Phase III Clinical Trial Of Gemcitabine And Carboplatin Followed By Epstein-Barr Virus-Specific Autologous Cytotoxic T Lymphocytes Versus Gemcitabine And Carboplatin As First Line Treatment For Advanced Nasopharyngeal Carcinoma(NPC) Patients

Arm	Intervention/treatment
Experimental: Arm A 4 cycles of combination IV Gemcitabine (1000 mg/m2) and IV carboplatin (AUC2) on Days 1, 8, 15 every 28 days, followed sequentially by T-cell immunotherapy (2 cycles) of autologous EBV specific Cytotoxic T Lymphocytes every 2 weeks, followed by EBV-specific CTL immunotherapy (4 cycles) every 8 weeks after 6 weeks from the second cycle.	Biological: autologous EBV specific Cytotoxic T Lymphocytes The CTL line will be prepared by co-cultivation of the irradiated EBV-LCL with patient PBMC. A proportion of peripheral blood will be used to generate EBV specific CTLs. Drug: combination IV gemcitabine and IV carboplatin (AUC2) 4 cycles for Arm A and 6 cycles for Arm B
Active Comparator: Arm B 6 cycles of combination IV gemcitabine (1000 mg/m2) and IV carboplatin (AUC2) on Days 1, 8, 15 every 28 days.	Drug: combination IV gemcitabine and IV carboplatin (AUC2) 4 cycles for Arm A and 6 cycles for Arm B

Potential to Transform Treatment of RR EBV+PTLD

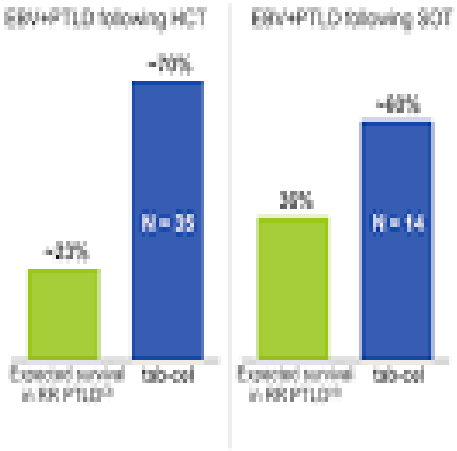
Patient with Rituximab Refractory EBV+PTLD Following HCT[1]



Progression following treatment with rituximab (3 cycles)

Complete response (CR) following treatment with tab-cel

One Year Survival from Phase 2 Clinical Studies Conducted at MSK[2]



Expected survival after rituximab failure in EBV+PTLD following HCT is 16-66 days[3]

MSK: Memorial Sloan Kettering Cancer Center

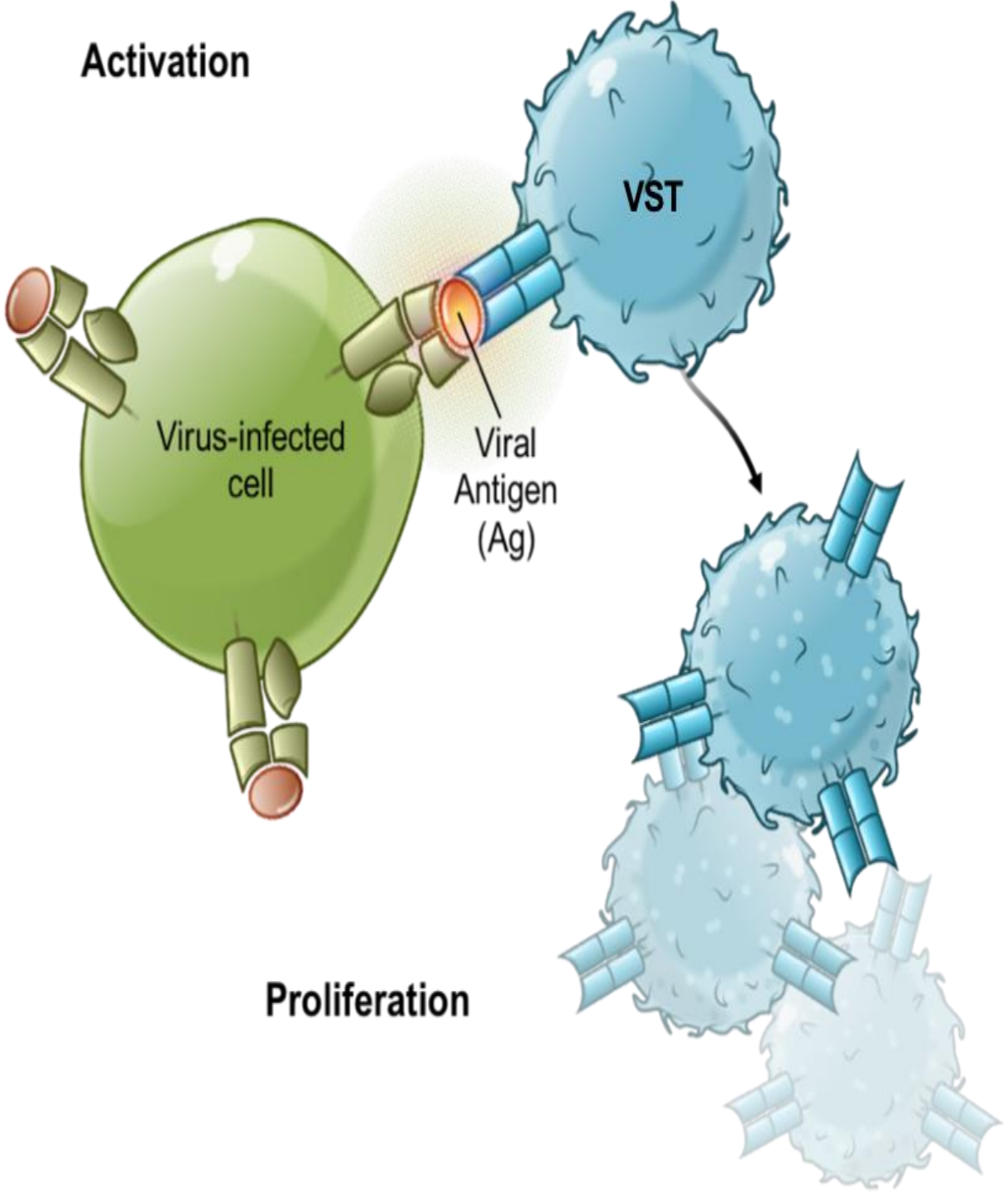
(1) 30 year old woman with Hodgkin lymphoma. Radiographic results from Phase 2 clinical study; patient provided for illustrative purposes only to show how the clinical presentation above may correlate to the clinical presentation of a patient.

(2) Non-treatment related serious adverse events (SAEs): 11 possibly related serious adverse events (SAEs) among 119 patients. As of August related toxicities, as CRS (cytokine release syndrome) and three possibly related graft vs. host disease (GVHD). Safety data on file.

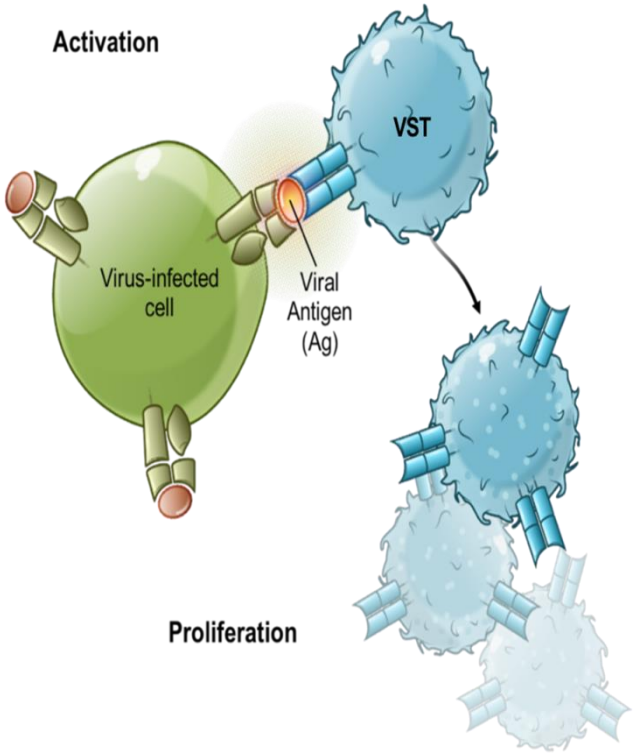
(3) Kaplan-Meier estimated 1 year survival based on analysis of Ofran Y.S., et al. Bone Marrow Transplantation 2008 Aug;42(3):191-4.

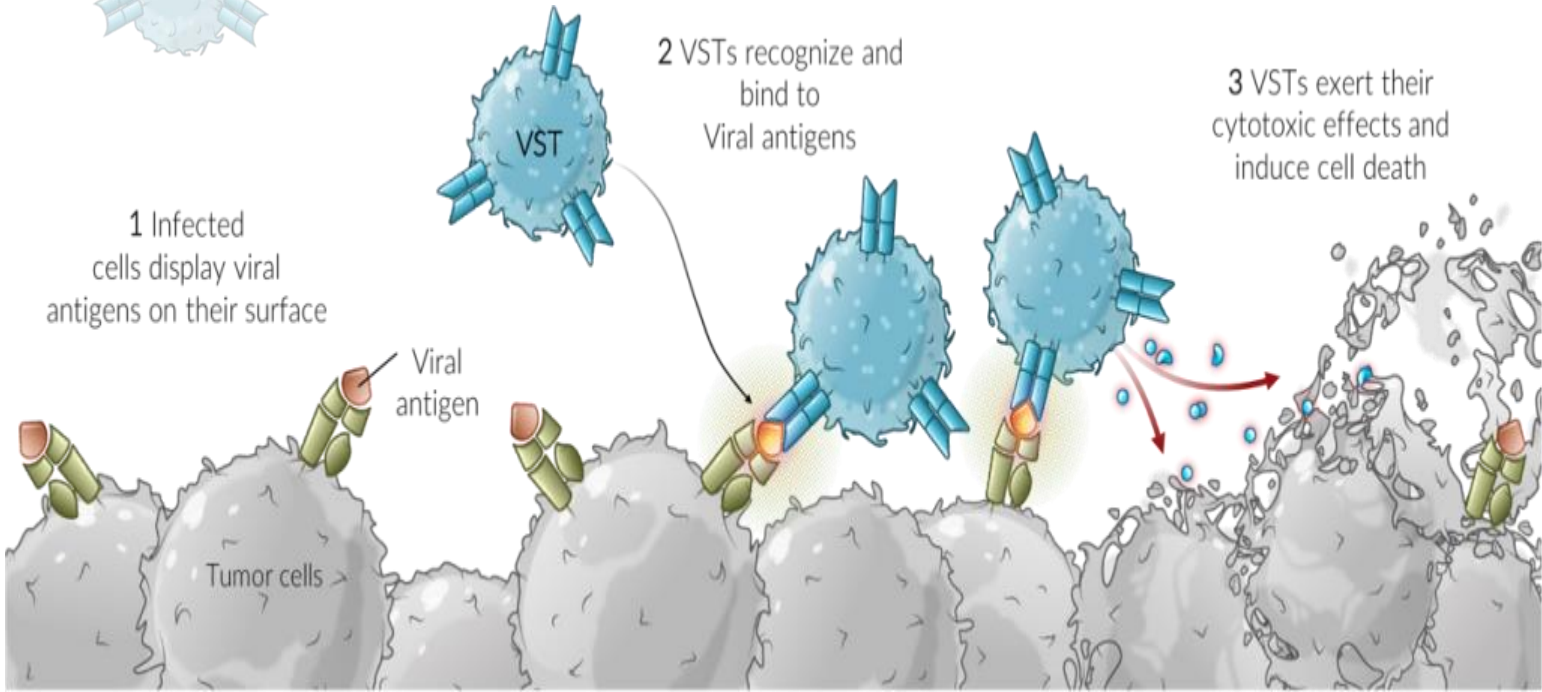
(4) 30% at 1yr and 0% at 2yrs in patients with high-risk PTLD treated with rituximab without chemotherapy. Oertwein S., et al. Ann Hematol. 2007 Aug;86(8):593-601.

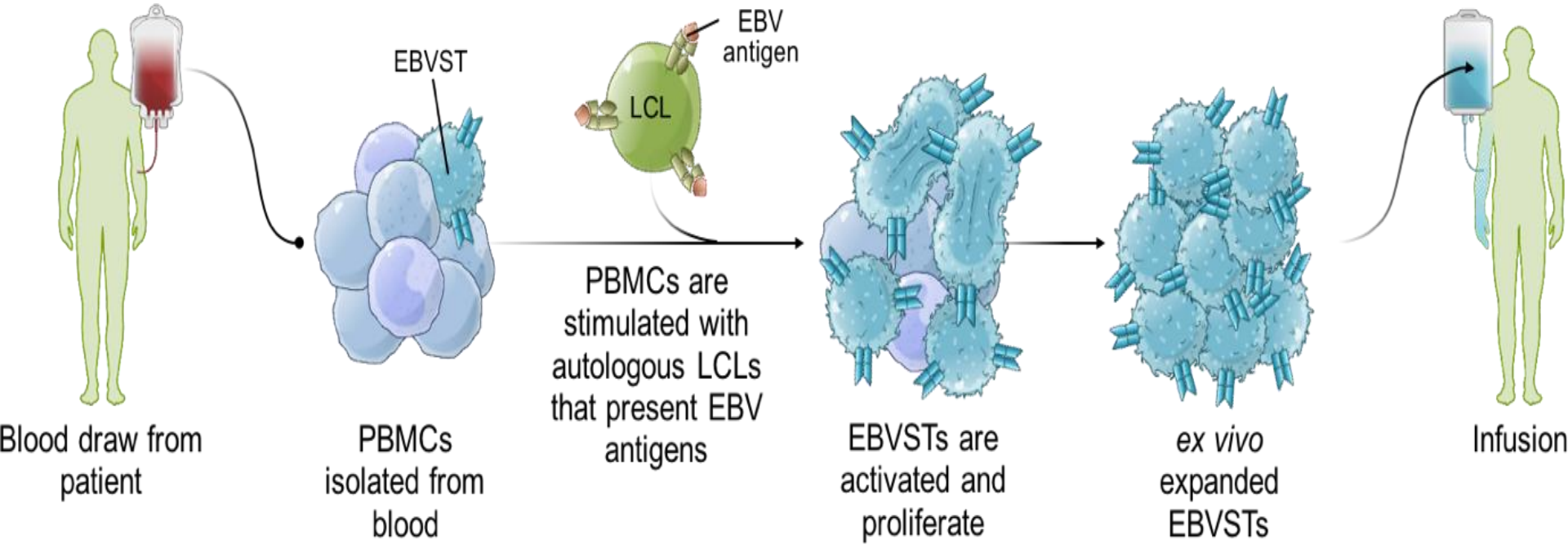
ATARA BIO

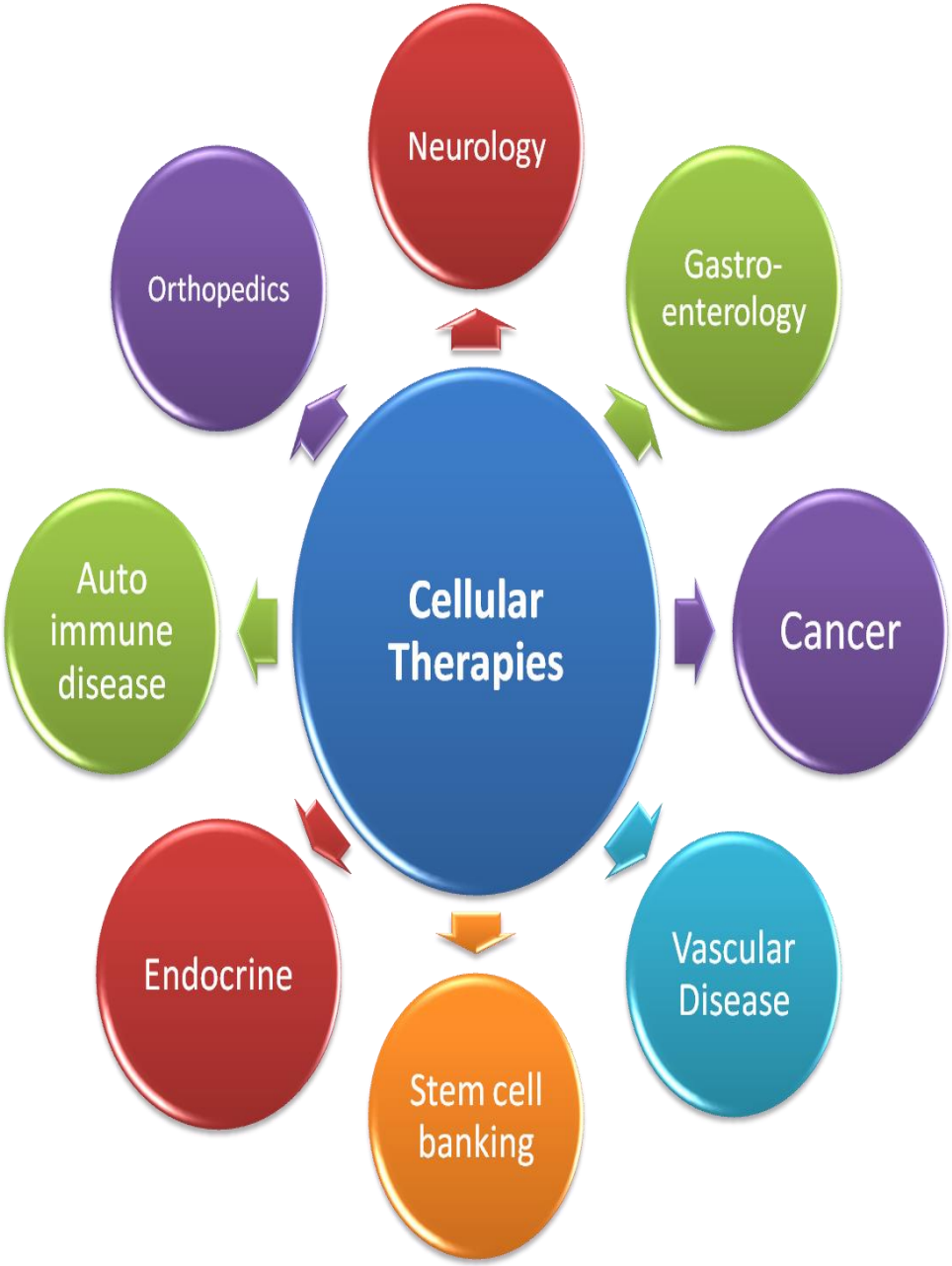

Activation
VST
Virus-infected cell
Viral Antigen (Ag)
Proliferation

Anti EBV T cells






EBVST
EBV antigen
LCL
Blood draw from patient
PBMCs isolated from blood
PBMCs are stimulated with autologous LCLs that present EBV antigens
EBVSTs are activated and proliferate
ex vivo expanded EBVSTs
Infusion


Neurology
Gastro-enterology
Cancer
Vascular Disease
Stem cell banking
Endocrine
Auto immune disease
Orthopedics
Cellular Therapies

AGGRESSIVE DEVELOPMENT

How Aggie Square stands to boost the local economy