Chimeric Antigen Receptor T Cell Therapy

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Alliance Spring Group Meeting - May 13, 2016

Presentation Objectives

- Scientific overview of chimeric antigen receptor (CAR) T cell therapy
- CART Mechanism of action
- Overview of CART clinical trials
- CART patient eligibility considerations

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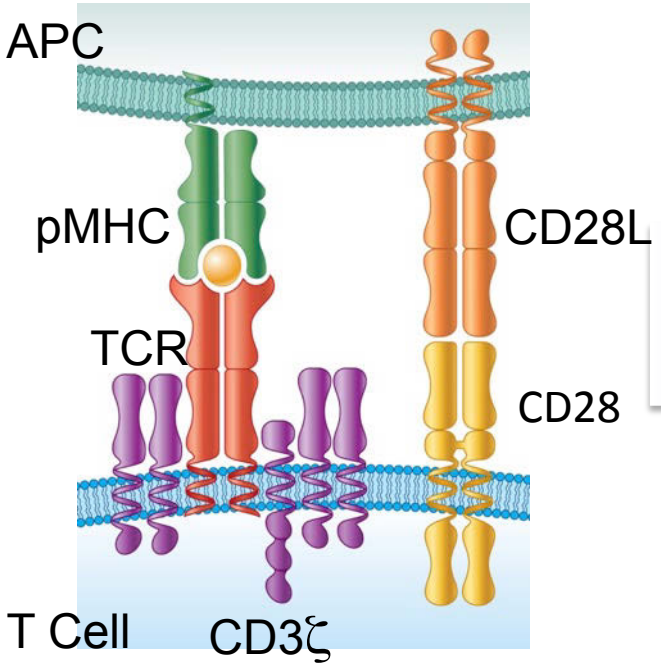
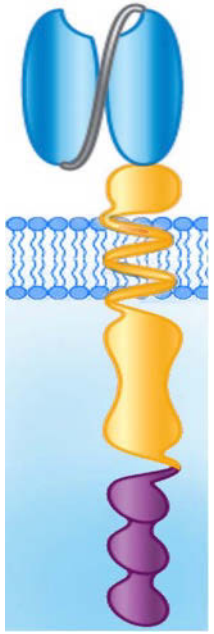
CAR Design: Critical Elements of T Cell Activation and Function in a Single Molecule

CAR T cells are genetically altered to express CAR on the cell surface.

T Cell Receptor



Chimeric Antigen Receptor



scFv: recognize tumor surface proteins

Costimulatory Signal 2: CD28 or 4-1BB or OX40

Essential Signal 1: CD3ζ

Activation Independent of MHC
Limited to cell surface proteins

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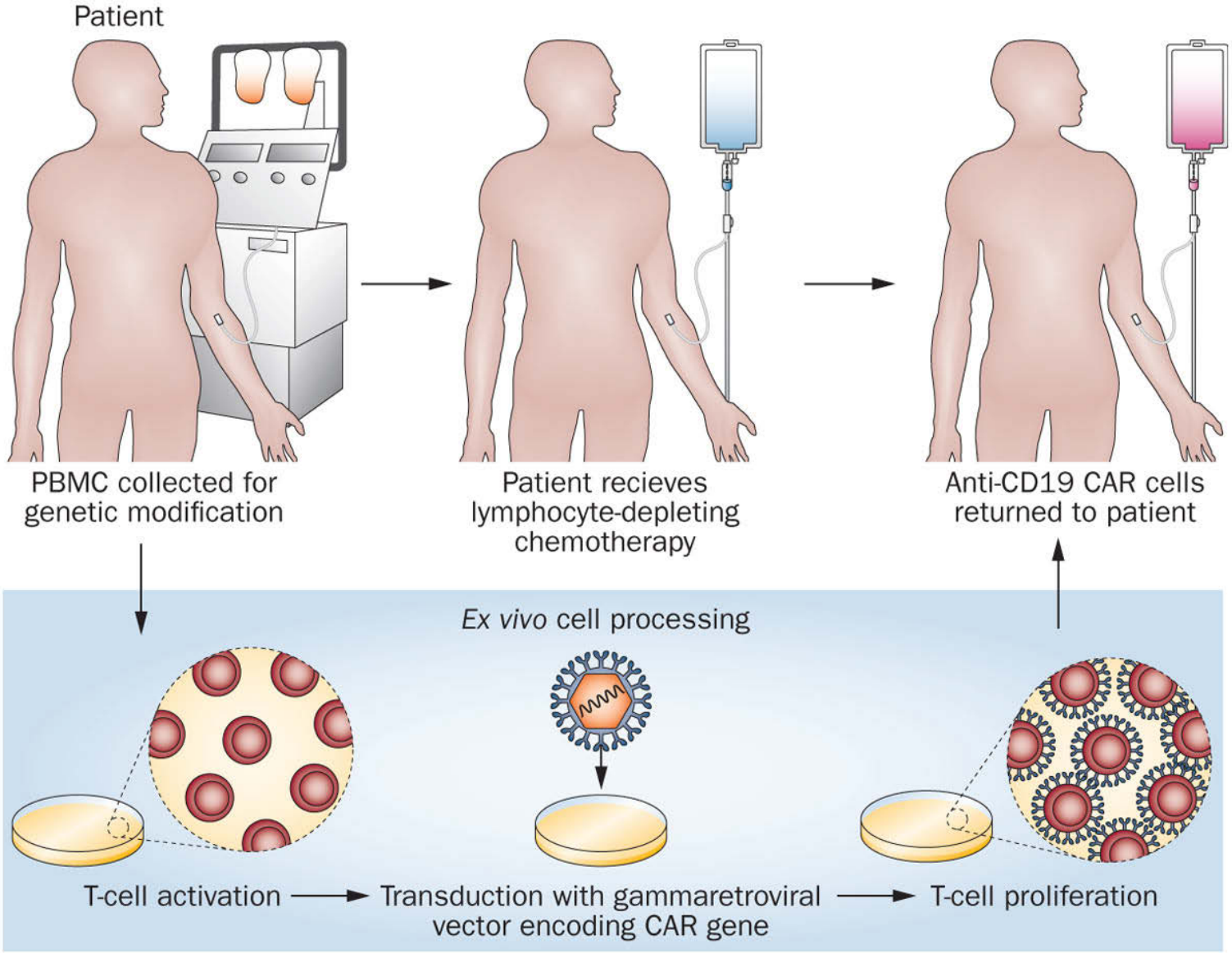
Schema of CAR T manufacturing and administration



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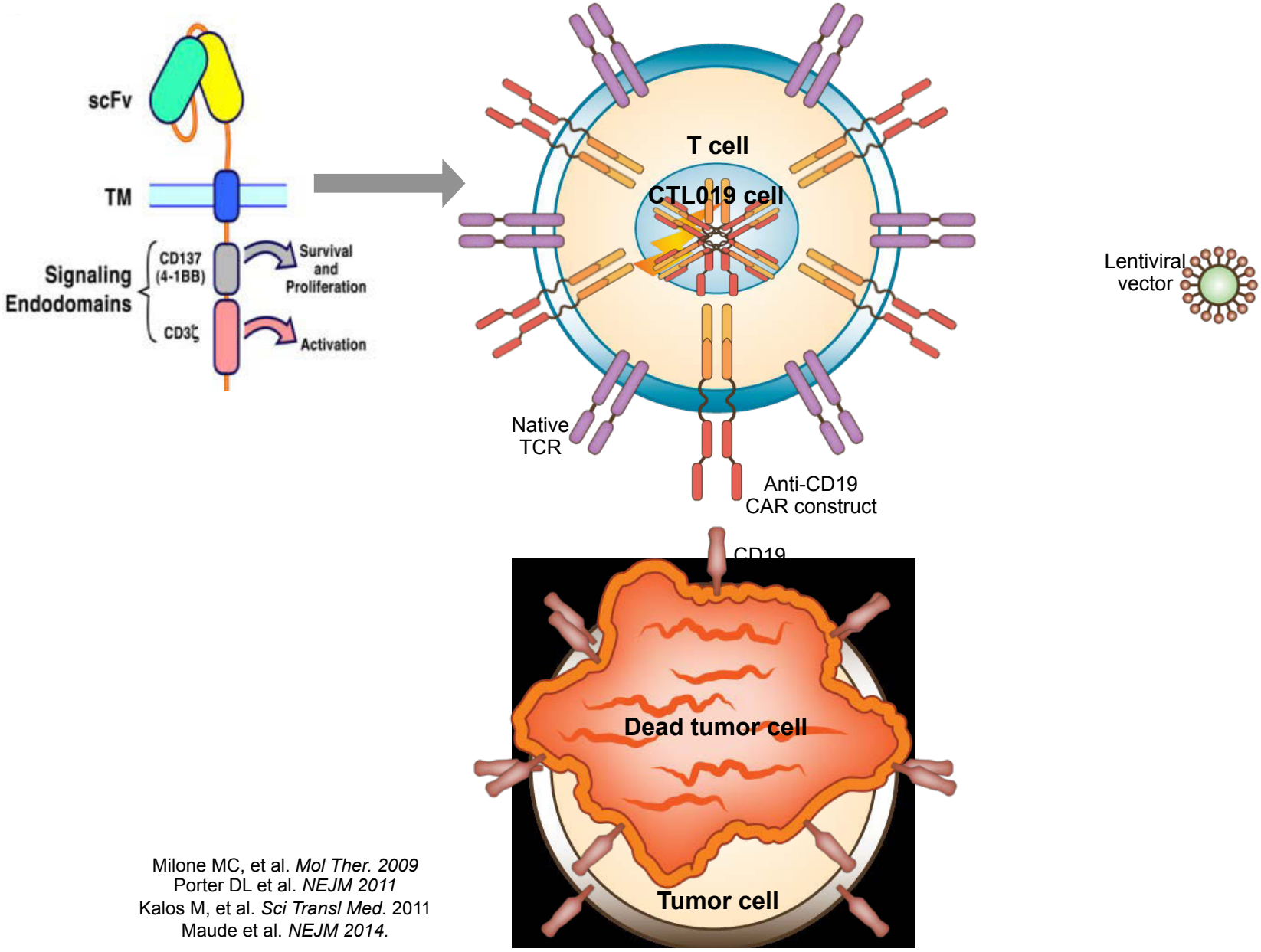
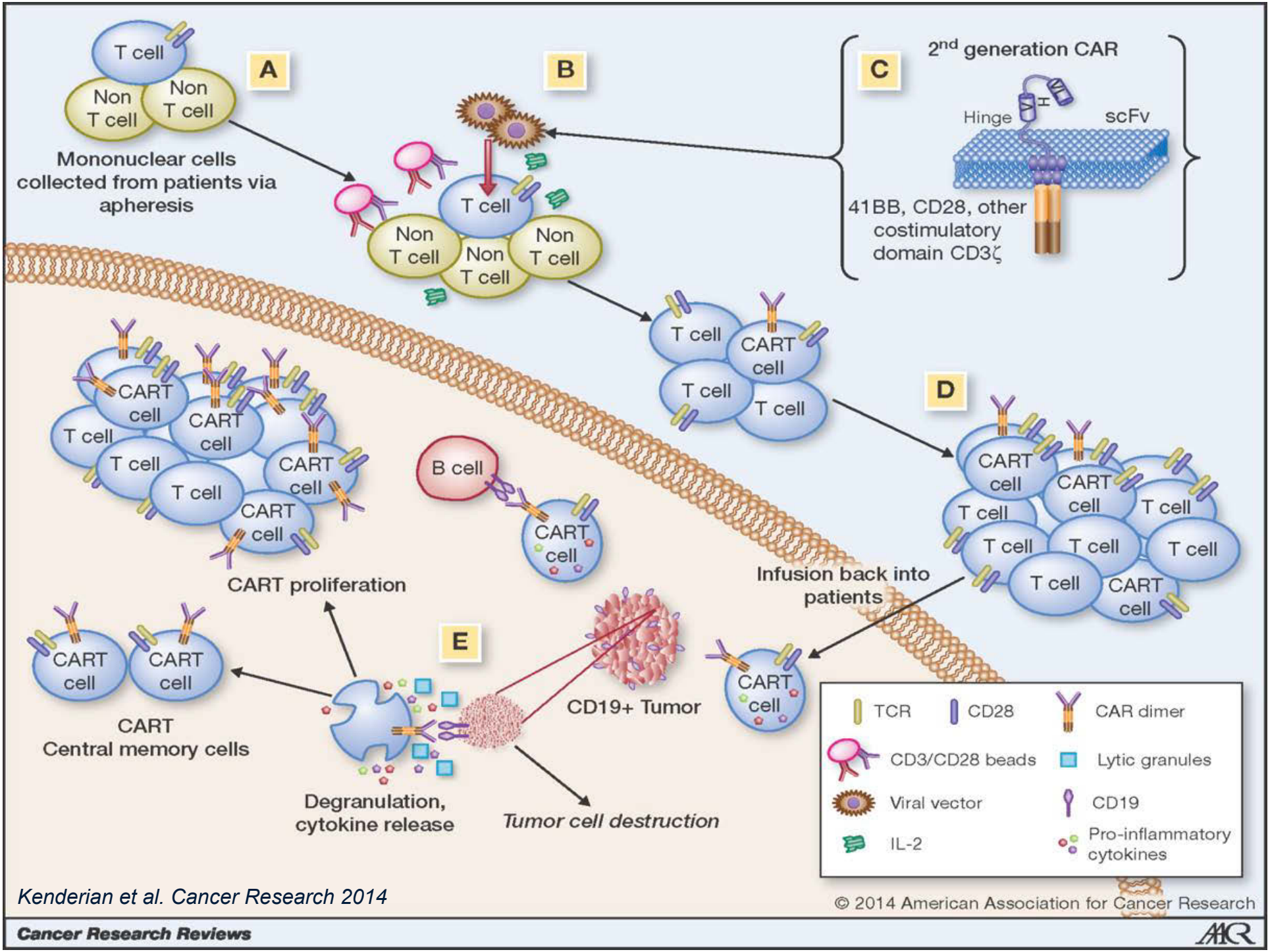
Kochenderfer, J. N. & Rosenberg, S. A. (2013) Treating B-cell cancer with T cells expressing anti-CD19 chimeric antigen receptors. *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.46

Chimeric Antigen Receptor T cells (CARTs)

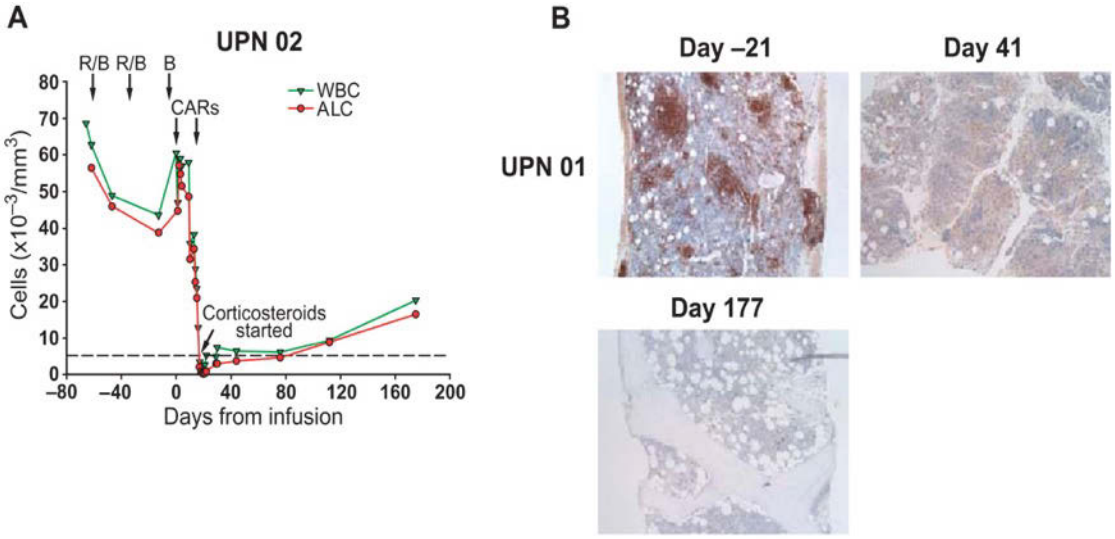


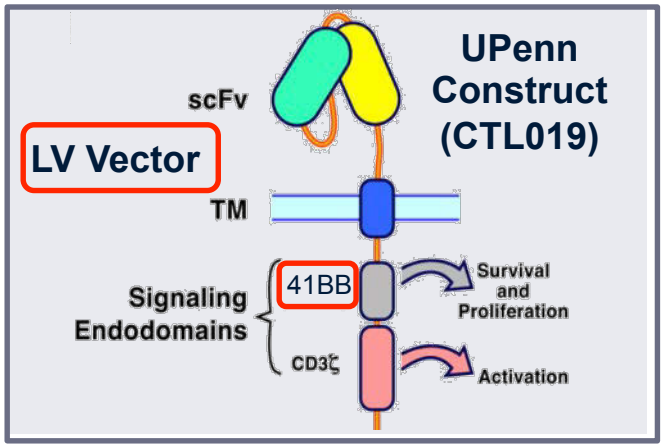
Milone MC, et al. *Mol Ther. 2009*
Porter DL et al. *NEJM 2011*
Kalos M, et al. *Sci Transl Med.* 2011
Maude et al. *NEJM 2014.*



Kenderian et al. Cancer Research 2014

First Successful Report of CART19 in CLL (UPenn Trial)





Results from this report

- ✓ 3 patients R/R CLL
- ✓ 2 → sustained CR, 1 →PR
- ✓ Eradicated bulky disease
- ✓ T cells persisted
- ✓ Memory phenotype
- ✓ Potent (1 cell killed 1000 tumor cells)
- ✓ Cytokine release syndrome
- ✓ Tumor lysis syndrome

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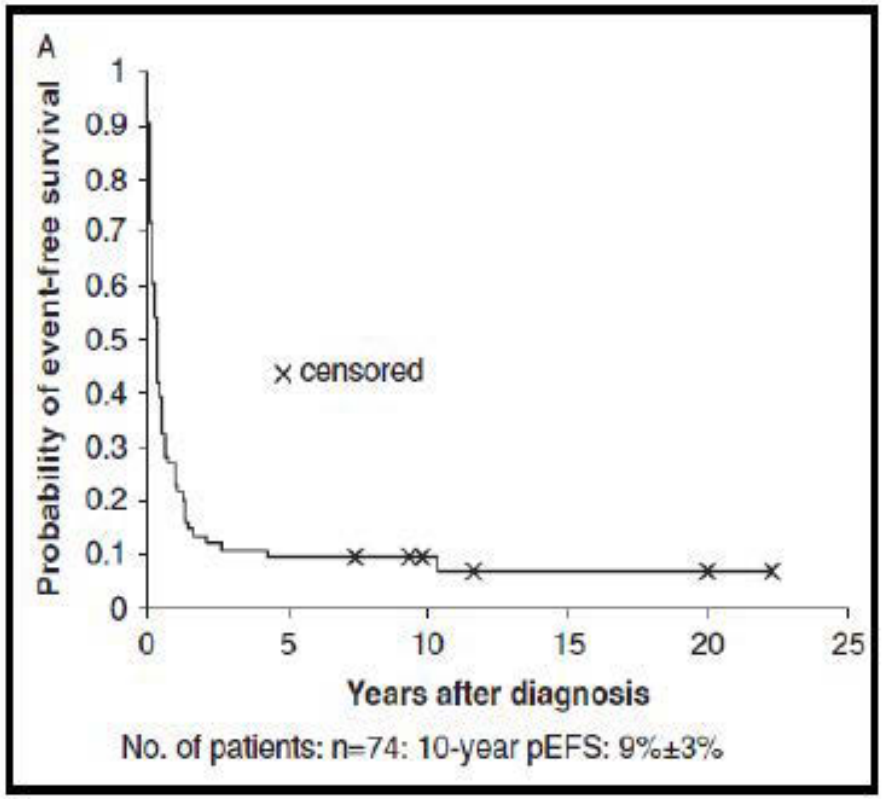
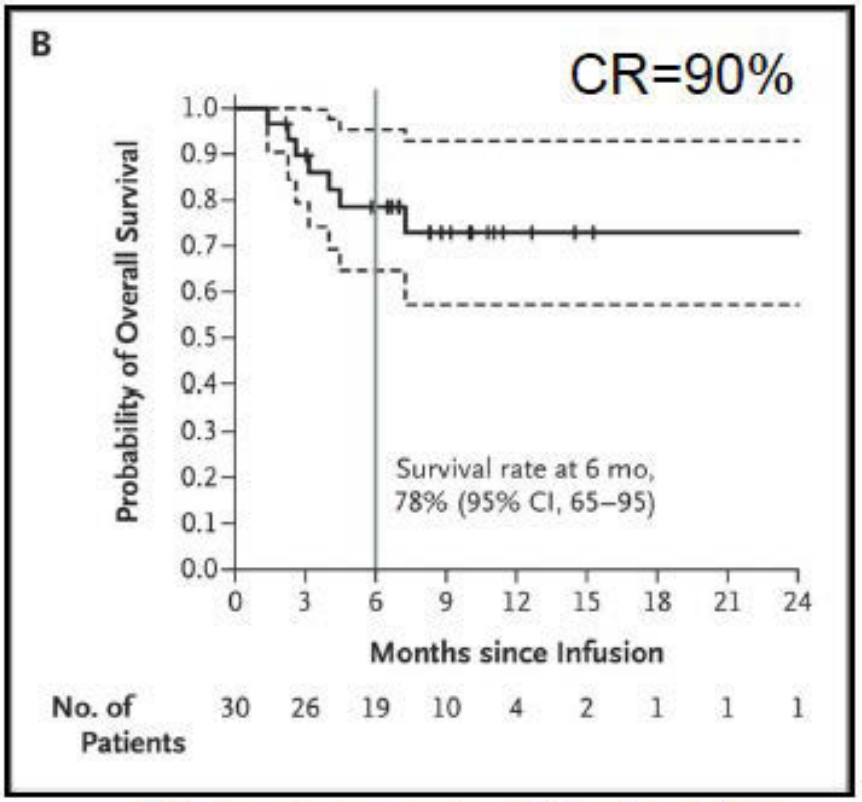
Kalos et al, Sci Transl Med 2011
Porter et al, NEJM 2011

High Response Rates in ALL



Historic outcomes of patients with relapsed/refractory acute lymphoblastic leukemia



Outcomes of patients with relapsed/refractory acute lymphoblastic leukemia treated with **CART19**

Grupp et al, ASH Abstract #380
Maude et al, NEJM 2014

High Response Rates in ALL

	University of Pennsylvania[31]	Memorial Sloan Kettering Cancer Center[28]	National Institutes of Health[30]
Target antigen	CD19	CD190	CD190
CAR generation	2nd	2nd	2nd
Vector	Lentivirus	Retrovirus	Retrovirus
Costimulatory domain	4-1BB	CD28	CD28
Duration of culture	8-12 days		11 days
No. of ALL patients	30	16	20
Conditioning regimen	Individualized, mainly fludarabine based.	Cyclophosphamide 3 g/m^2 day 2	Fludarabine 25 mg/m^2 days 4, 3, 2 Cyclophosphamide 900 mg/m^2 day 2
Median follow-up	7 months	NR	10 months
Overall survival	78%	NR	51.6%
No. of patients undergoing allo-HSCT	3	7	10
Response **Morphologic CR** **MRD negative CR**	90% 73%	88% 75%	70% 60%
Duration of CAR T-cell persistence	11 months	3 months	68 days

Cancer Immunotherapy Breakthrough of the Year 2013

2013 Breakthrough

- Cancer Immunotherapy

The Runners-Up

- CRISPR
- CLARITY
- Human Stem Cells from Cloning
- Mini-Organs
- Cosmic Particle Accelerators Identified
- Perovskite Solar Cells
- Why We Sleep
- Our Microbes, Our Health
- In Vaccine Design, Looks Do Matter

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Critical Components of CART as a Drug

- CAR construct
- CAR delivery system
- CART phenotype and function
- CART persistence

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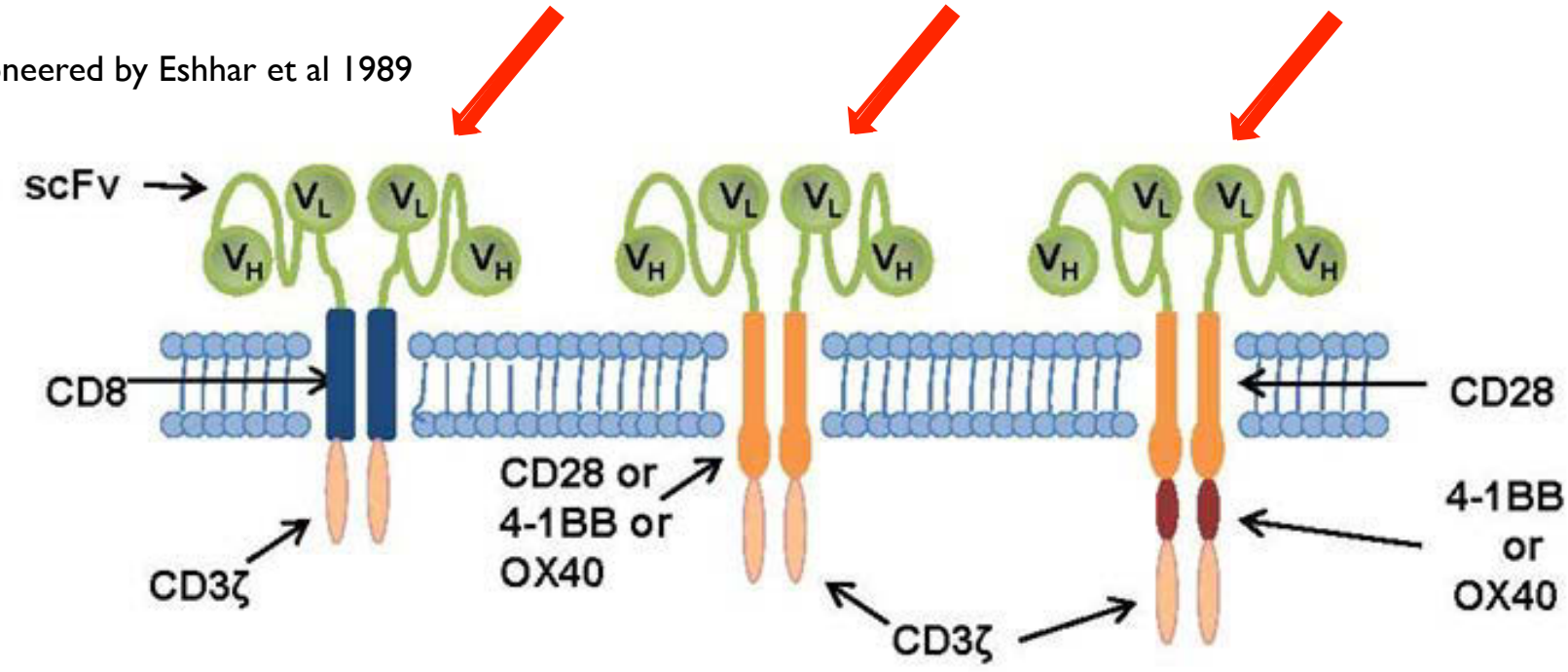
CAR Construct: What generation is your CAR?

Pioneered by Eshhar et al 1989



First-Generation CAR
scFv-CD3ζ

Second-Generation CAR
scFv-CD28-CD3ζ

Third-Generation CAR
scFv-CD28-4-1BB-CD3ζ
scFv-CD28-OX40-CD3ζ

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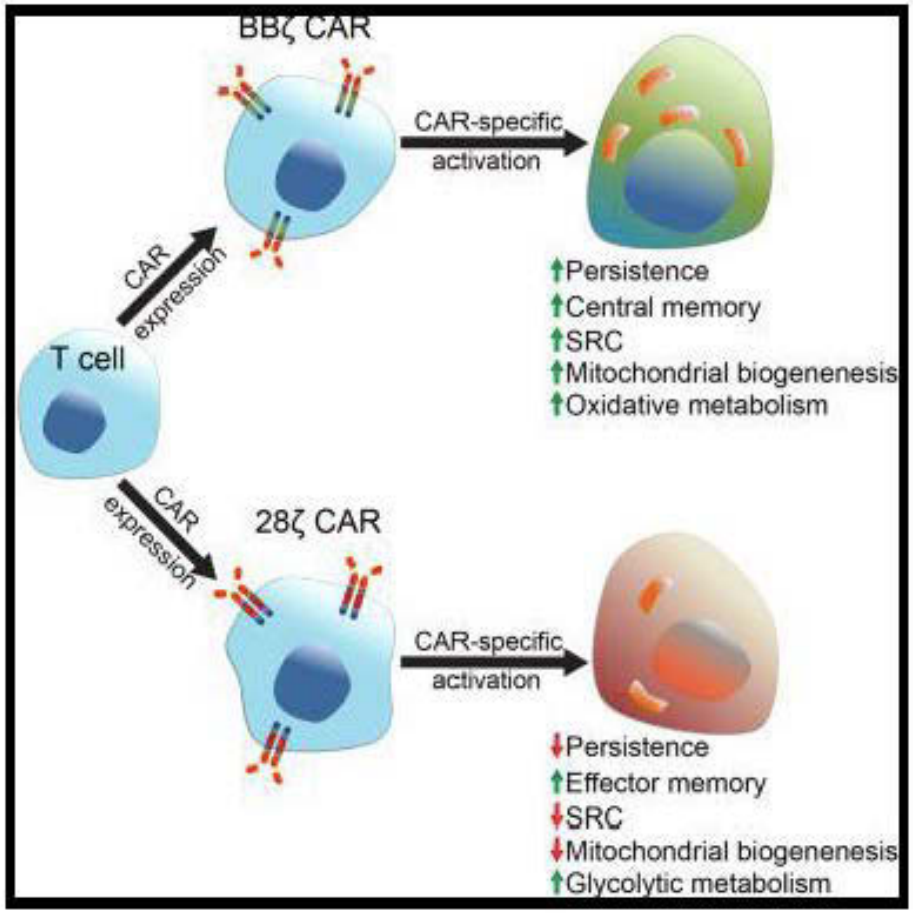
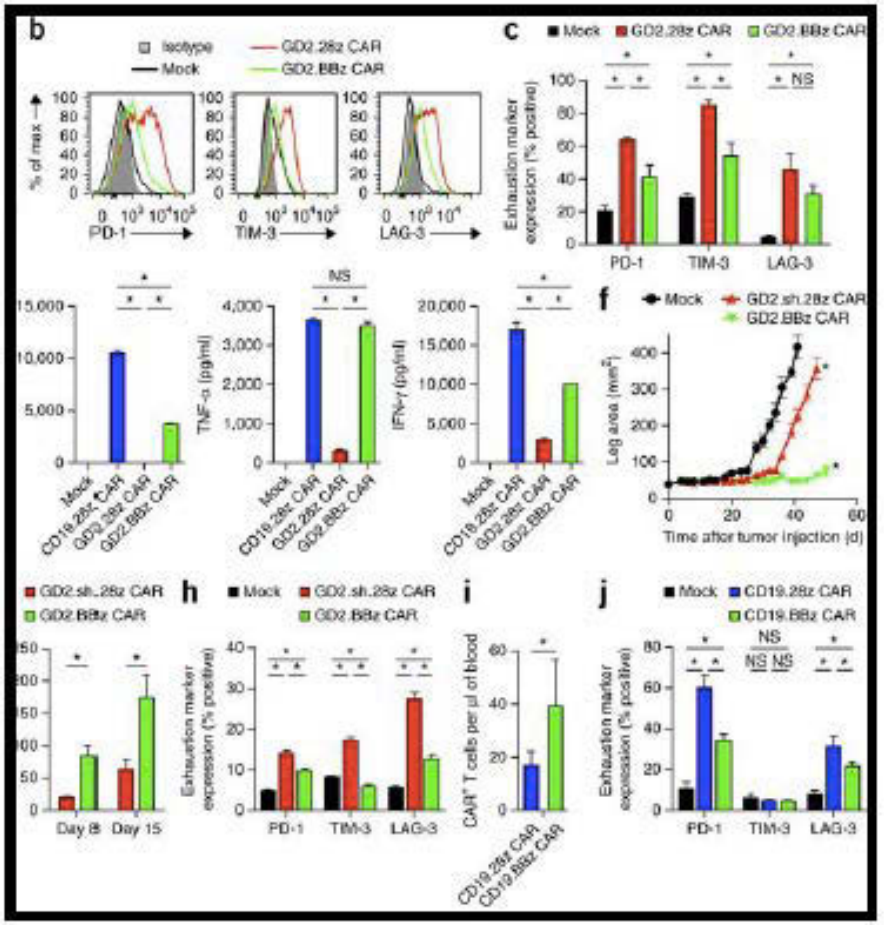
CAR Construct: CD28 vs 41BB



Kalawekar et al. Immunity 2016



Long et al. Nature Medicine 2015

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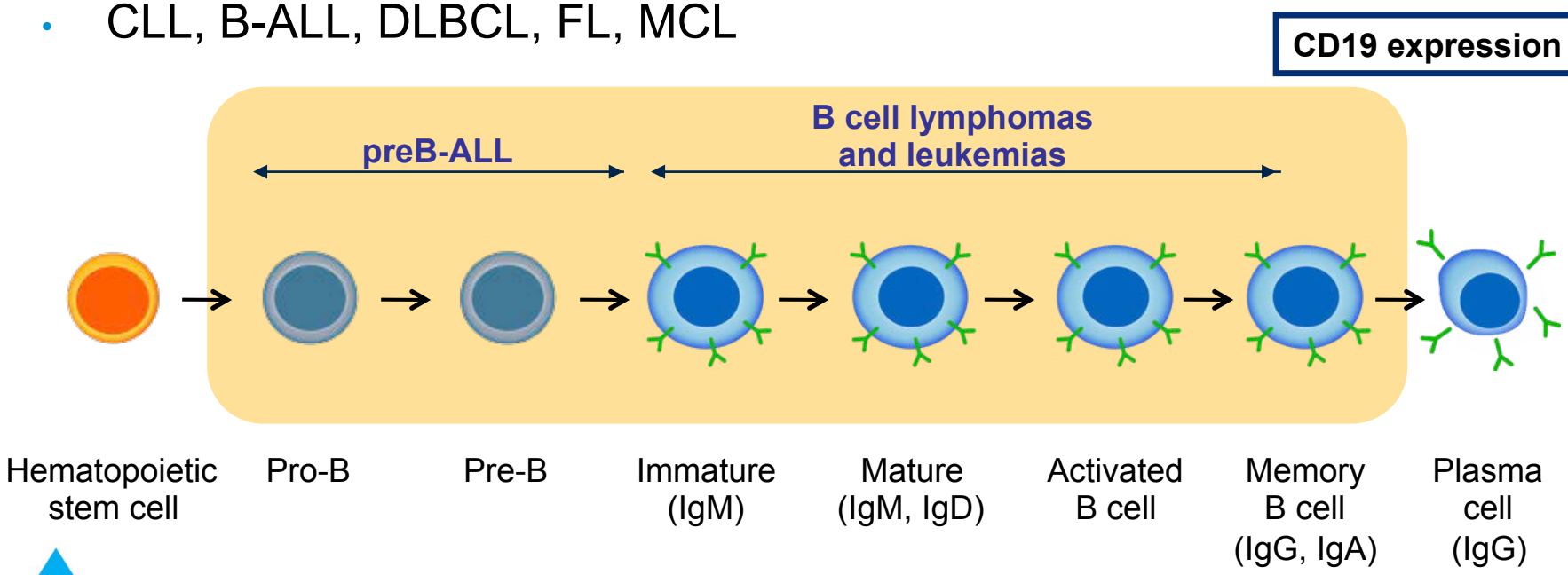
CAR Construct: Antigen Selection

- CD19 expression is generally restricted to B cells and B cell precursors[1]
  - CD19 is not expressed on hematopoietic stem cells or other tissue
- CD19 is expressed by most B-cell malignancies
  - CLL, B-ALL, DLBCL, FL, MCL



ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Image adapted from Janeway CA, Travers P, Walport M, et al. *Immunobiology*. 5th ed. New York, NY: Garland Science; 2001:221-293; Scheuermann RH, et al. *Leuk Lymphoma*. 1995;18:385-397; and Feldman M, Marini JC. Cell cooperation in the antibody response. In: Roitt I, Brostoff J, Male D, eds. *Immunology*. 6th ed. Maryland Heights, Missouri: Mosby;2001:131-146.

CAR Construct: Antigen Selection

- On target, off-tumor toxicity
  - High binding affinity results in recognition of low antigen expression in normal tissue
  - Ex. Liver injury with anti-carbonic anhydrase IX CART
  - Ex. Pulmonary toxicity with anti-Her2 CART
  - Can be fatal

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Morgan RA et al. Mol Ther 2010; 18(4):843-851.
Lamers CH. JCO 2006;24(13):e20-e22.

CAR Construct: Delivery System

Viral System

- Lentivirus, retrovirus
- Most commonly used in trials to date
- Permanent genetic modification
- Costly

Non-Viral System

- Transposon/Transposase
  - Permanent genetic modification
  - Less expensive for manufacturing
- RNA transfection
  - Temporary genetic expression
  - Strategy for limiting toxicity

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CAR T Phenotype & Function

- Optimize T cell population
  - CD4 to CD8 proportion
  - Central vs effector vs stem memory T cells
- Activated vs exhausted state
  - Duration of culture
  - Cytokines

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CAR T Persistence *in vivo*: Clinical Relevance

CD19 positive relapses (4/30 patients, 13.3%)
Poor expansion - CTL019 cells are lost

CD19 negative relapses (3/30 patients, 10%)
Good expansion and persistence of CTL019

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Grupp et al, ASH Abstract #380
Maude et al, NEJM 2014

CAR T Persistence *in vivo*: Conditioning Chemotherapy

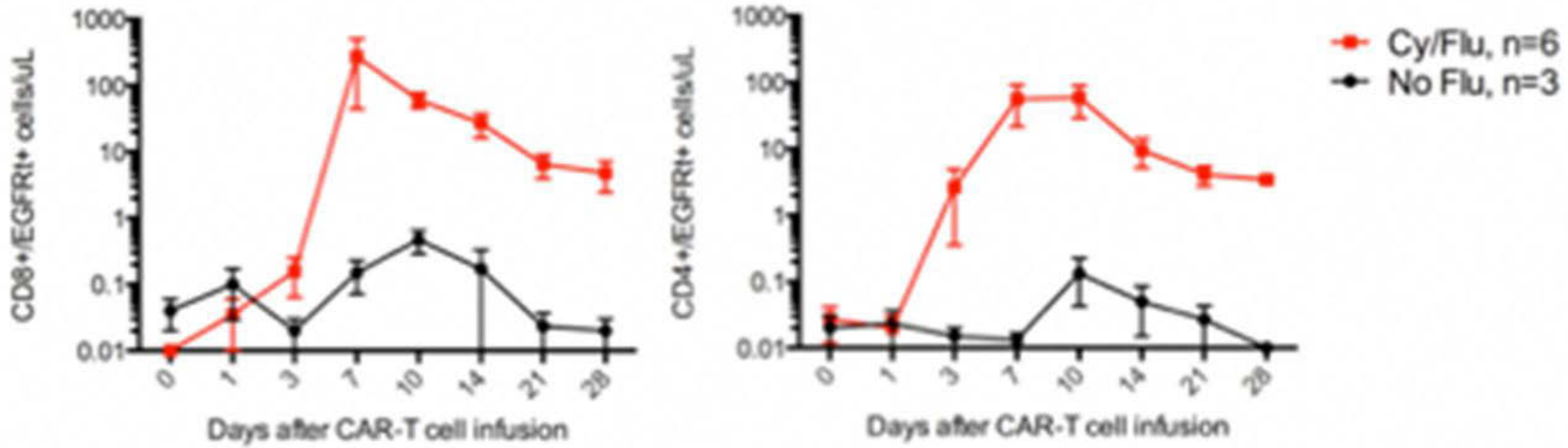

Figure 1. CD4 and CD8 CAR-T cell persistence in NHL patients following infusion of 2×10^7 cells/kg after conditioning with (n=6) or without (n=3) Fludarabine.

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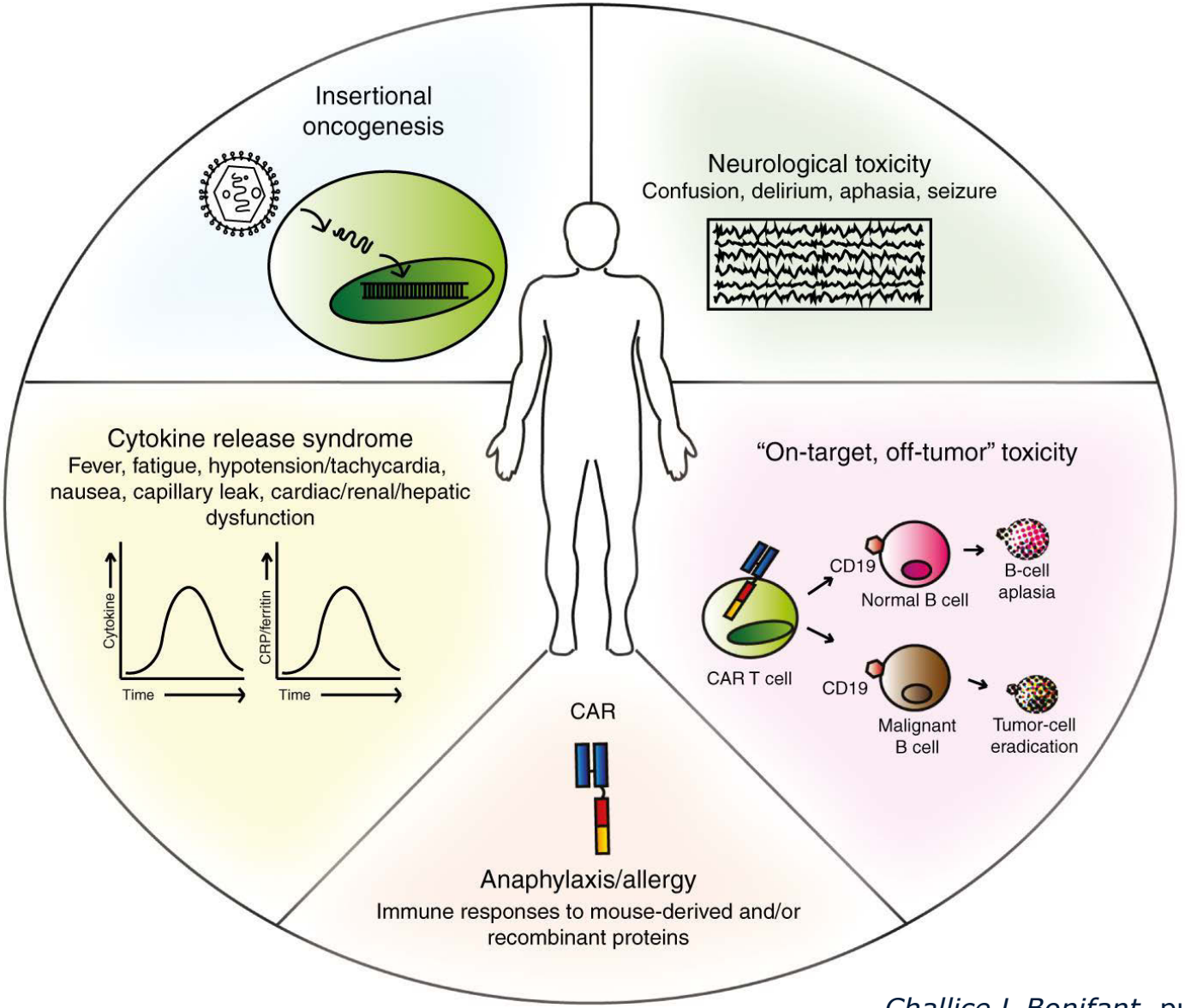
Cameron J Turtle et al. Blood 2015;126:184

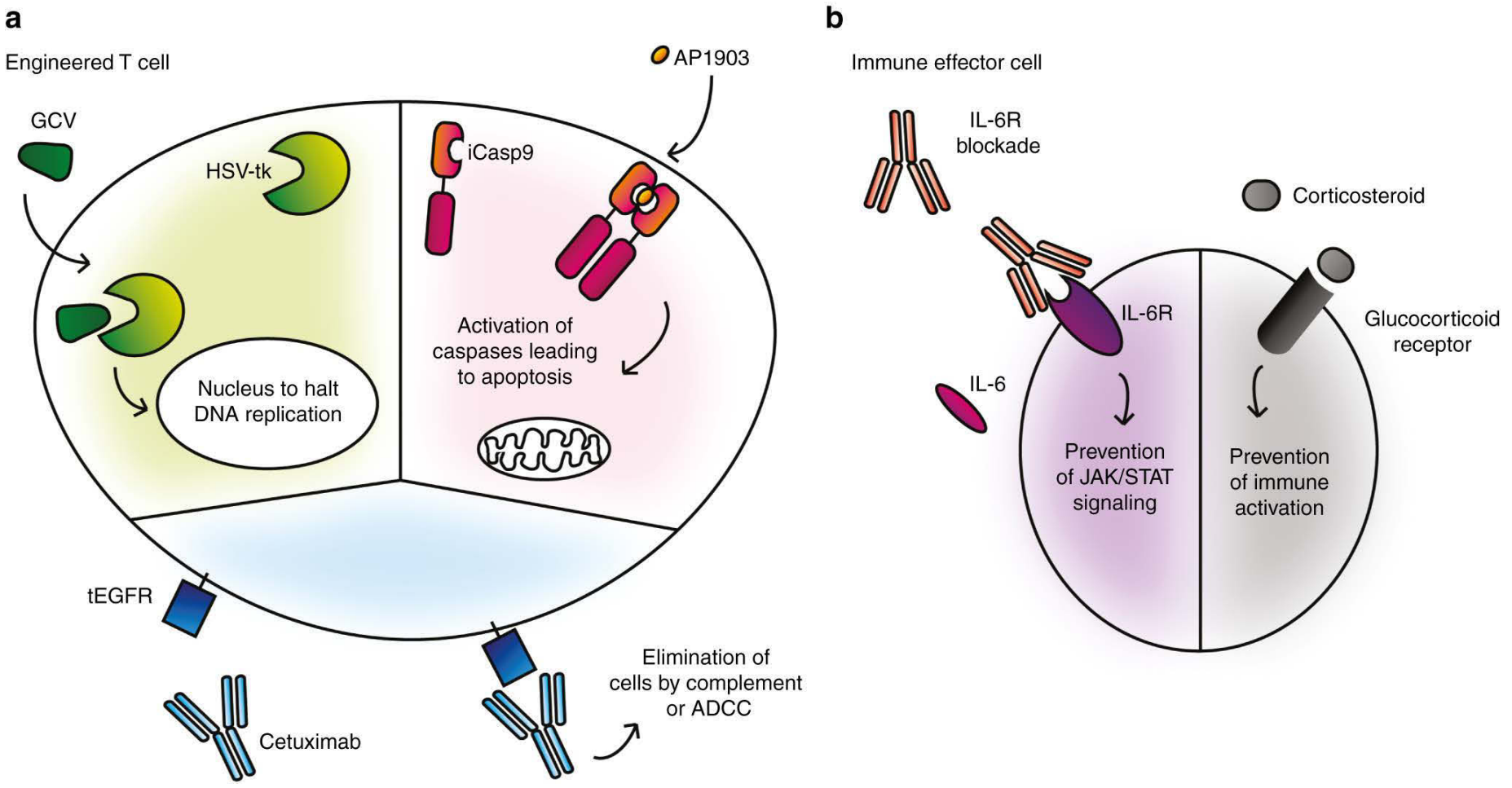
CAR T Toxicities



ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Challice L Bonifant, published online 20 April 2016. doi:10.1038/mto.2016.11

Strategies to Manage CAR Toxicities



ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Challice L Bonifant, published online 20 April 2016. doi:10.1038/mto.2016.11

ONGOING CLINICAL TRIALS

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CART Programs at Academic Centers

Center	Target	Condition	Construct	Results
Penn	CD19 CAR	ALL	BBz, LV	90% CR
NIH	CD19 CAR	ALL	28z, RV	70% CR(ITT)
MSKCC	CD19 CAR	ALL	28z, RV	88% CR
NIH	CD19 CAR	Lymphoma	28z, RV	85% aggressive lymphomas, 100% indolent lymphomas
Seattle	CD19 CAR	ALL	BBz, LV	83% CR
Penn	CD19 CAR	Lymphoma	BBz, LV	50% CR aggressive lymphoma, 100% indolent
Penn	CD19 CAR	CLL	BBz, LV	25% CR rate
MDACC	CD19 CAR	CLL/ALL/NHL	28z, SB	23% CR rate
NIH	CD22 CAR	ALL	BBz, LV	8 patients treated
NIH	BCMA CAR	Myeloma	28z, RV	6 patients treated

Kenderian et al. BBMT in press.

Reference	Antigen	Gene-transfer vector used	Endomains	Cell culture	Cell dose	Conditioning regimen	Cytokine support	No. of patients	Responses to CAR T-cells	Persistence
Kershaw 2006 (111)	o-folate receptor	Gammaretrovirus	FcRγ	10ng/mL OKT3+600 IU/mL IL-2; 21–56 d	3×10^9-1.69×10^{11} T-cells (1–3 infusions)	None	IL-2 9(720000 IU/ kg) was given i.v. every 12h in cohort 1	14 patients with ovarian cancer	14 PD	4–21 d
Park 2007 (71)	CD171	Electroporation	CD3ζ	30ng/mL OKT3+50U/mL IL-2 + irradiated PBMC/ lymphoblastoid cell line feeders; 14 d (1–3 infusions)	$1\times10^8/m^2$ -$1.1\times10^9/m^2$	Salvage chemotherapy	None	6 children with neuroblastoma	1 PR, 5 PD	Short (1–7 d) in patients with bulky disease, but significantly longer (42 d) in a patient with a limited disease burden
Lamers 2013 (108)	CAIX	Gammaretrovirus	FcRγ	10ng/mL OKT3+100 IU/mL IL-2; approximately 21 d	0.2×10^9-2.1×10^9 CAR T-cells (5 infusions)	None	5×10^5 U/m^2 twice daily administered for 20 d	12 patients with metastatic renal cell carcinoma	12 NR	Up to 3–5 wk
Louis 2011 (20)	GD2	Gammaretrovirus	CD3ζ	OKT3+100 or 50U/mL IL-2 + irradiated PBMC/ lymphoblastoid or PBMC; 12–18 d and 36–54 d	$2\times10^7/m^2$ -1×10^8 CAR T-cells/m^2	None	None	19 patients with neuroblastoma	8 NED, 3 CR, 1 PR, 1 SD, 4 PD, 2 tumor necrosis	≥6 wk
Morgan 2010 (107)	HER2	Gammaretrovirus	CD137-CD28-CD3ζ	50ng/mL OKT3+300 IU/mL IL-2 (a rapid expansion) procedure: 6000 IU/mL + 50ng/mL OKT3 + irradiated PBMC feeders; 24 d	10^{10} T-cells	60mg/kg cyclophos phamide ×2 and flurodarabine 25mg/m^2 ×5	None	1 patients with colorectal cancer	Died of cytokine release syndrome	Died 5 d after treatment
Brown 2015* (70)	IL13Rα2	Electroporation	CD3ζ	30ng/mL OKT3+50U/mL IL-2; approximately 63 d	9.6×10^8 - 15.35×10^8 CD8+ T (11–17 infusions)	None	None	13 enrolled, 3 treated (glioblastoma)	3 PD	Up to 184 d
Katz 2015† (106)	CEA	Gammaretrovirus	CD28-CD3ζ	50ng/mL OKT3+3000U/ mL IL-2; 17–25 d	Cohort 1: 10.1×10^9 CAR T; Cohort 2:30×10^9 CAR T (3 infusion)	None	Cohort 1: none; Cohort 2: 75 000U/ kg/day	6 patients with denocarcinoma liver metastases	5 PD, 1 SD	Approximately 1 wk
Ahmed 2015 (12)	HER2	Gammaretrovirus	CD28-CD3ζ	OKT3 or CD3/CD28 beads + 100U/mL IL-2; 12–21 d	$1\times10^4/m^2$ -1×10^8 CAR T-cells/m^2 (1–9 infusions)	None	None	19 patients with sarcoma	4 SD	Up to 18 mo

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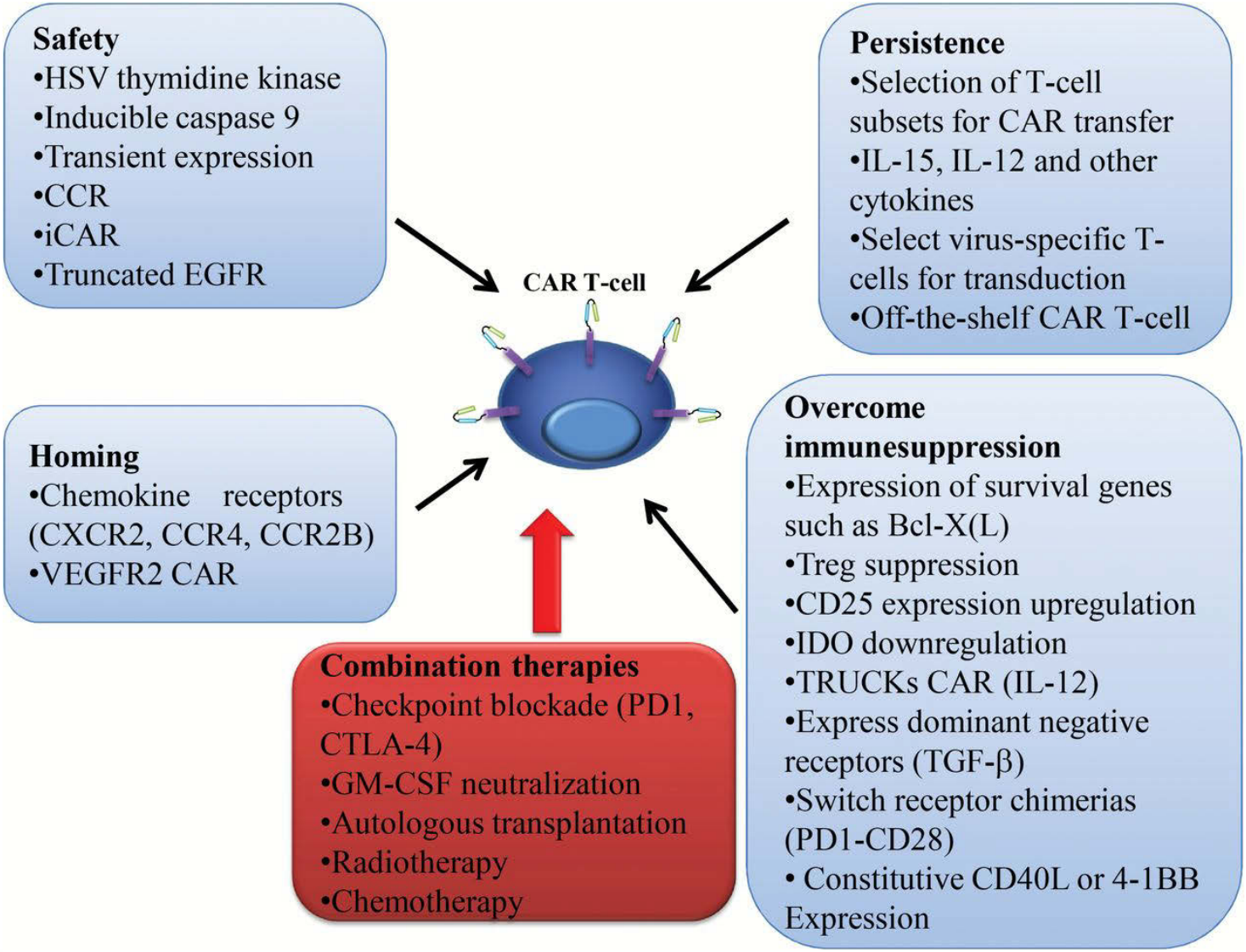
CART Research Directions



Hanren Dai et al. JNCI J Natl Cancer Inst 2016;108:djv439

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CAR T-CELL DEALS

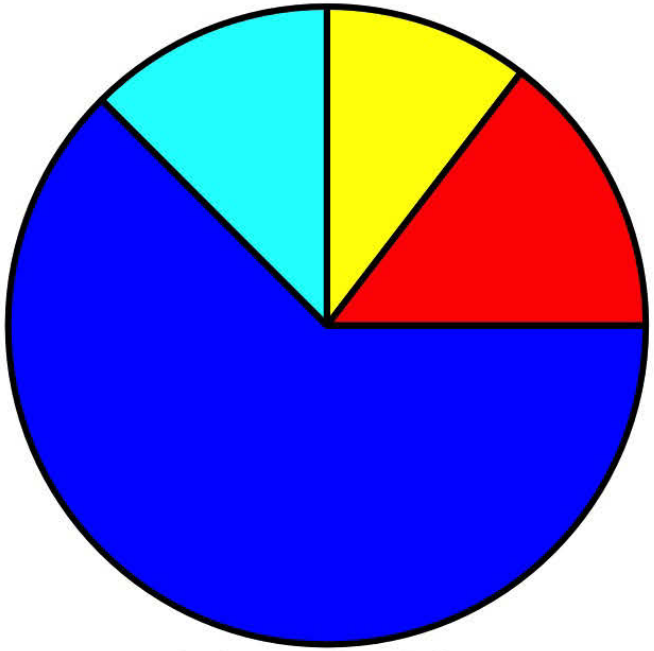
Institution/Company	Date	Partner	Terms
University of Pennsylvania	August 2012	Novartis	Undisclosed
Celgene	March 2013	Bluebird Bio, Baylor College of Medicine	Unspecified upfront payment plus up to $225 million per product in option fees and milestone payments
Cellectis	June 2014	Pfizer	$80 million upfront plus up to $185 million per product and royalties
Cellectis	January 2015	Ohio State University	Undisclosed
Kite Pharma	January 2015	Amgen	$60 million upfront and up to $525 million per product in milestone payments, plus royalties on sales and IP licensing
Md Anderson	January 2015	Ziopharm, Intrexon	$100 million in stock and $15–20 million/year for 3 years

CAR T-CELL BIOTECH IPOs

Company	Date	Value
Kite Pharma	June 2014	$134.1 million
Bellicum	December 2014	$160 million
Juno	December 2014	$264.6 million
Cellectis	March 2015	$228 million

The CAR T Cell Race. The Scientist April 2015.

CART Clinical Trials



Total=48

- Pharma Phase I
- Pharma Phase I/II, II
- Academic Centers Phase I/II, II
- Academic Centers Phase I

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Clinicaltrials.gov

CART Clinical Trials

Hematologic Malignancies

- Lymphomas, ALL (n=34)
- Myeloma (n=3)
- AML (n=2)

Solid tumors (n=10)

- Types
  - GBM
  - Neuroblastoma
  - Pancreas cancer
  - Sarcoma
  - NSCLC
  - Triple negative breast cancer
- Antigens
  - EGFRvIII, PSCA, GD2, Her2, ROR1, CD171

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Patient Eligibility Considerations

- Adequate blood cell count for leukapheresis
- Relative disease stability
  - CART manufacturing generally 2 – 4 weeks
  - Disease not progressing rapidly through manufacturing period
- Patient ability to tolerate CAR T toxicities
  - Good major organ functions
    - heart, lung, kidney, liver
  - Neurologic considerations
    - Seizure risk, CVA, CNS disease

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Conclusion

- Questions from Audience
- Answers from Presenter

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