Immunotherapy on the Horizon: Adoptive Cell Therapy

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Conflicts of Interest

- Advisory Board – Prometheus
- Speakers Bureau – BMS, Merck
- Research Support (to institution) – BMS, Merck, Prometheus

- I will be addressing non-FDA-approved uses of treatments.

T-cells

- Lymphocytes matured in the thymus
- Majority are αβT-cells
  - Rearrangement of alpha and beta chains of T-cell receptors (TCR)
  - Various subtypes (not limited to)
    - Cytotoxic T-cells (CD8)
    - Helper T-cells (CD4)
    - Memory T-cells
    - Suppressor T-cells

(Janeway, Immunobiology, 2005)

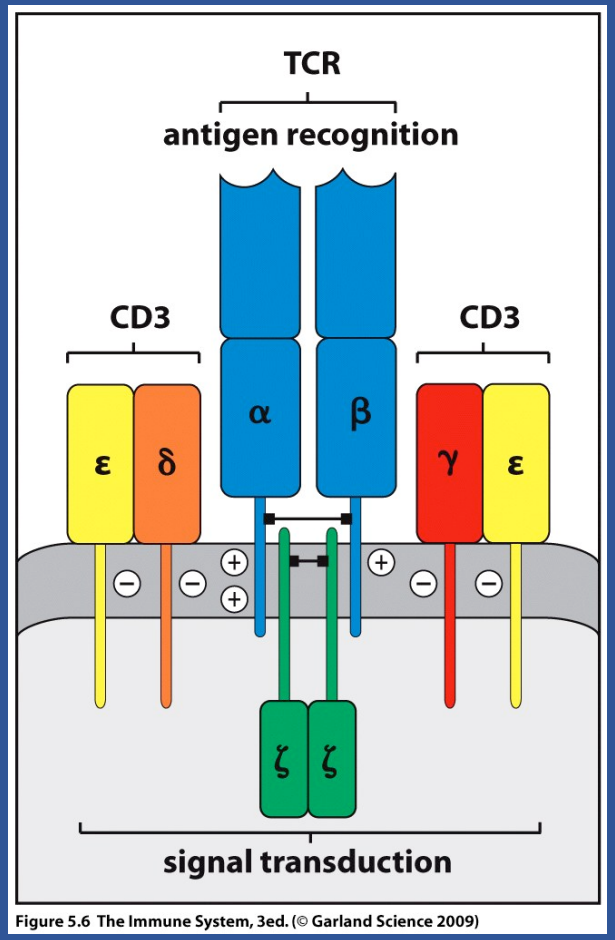
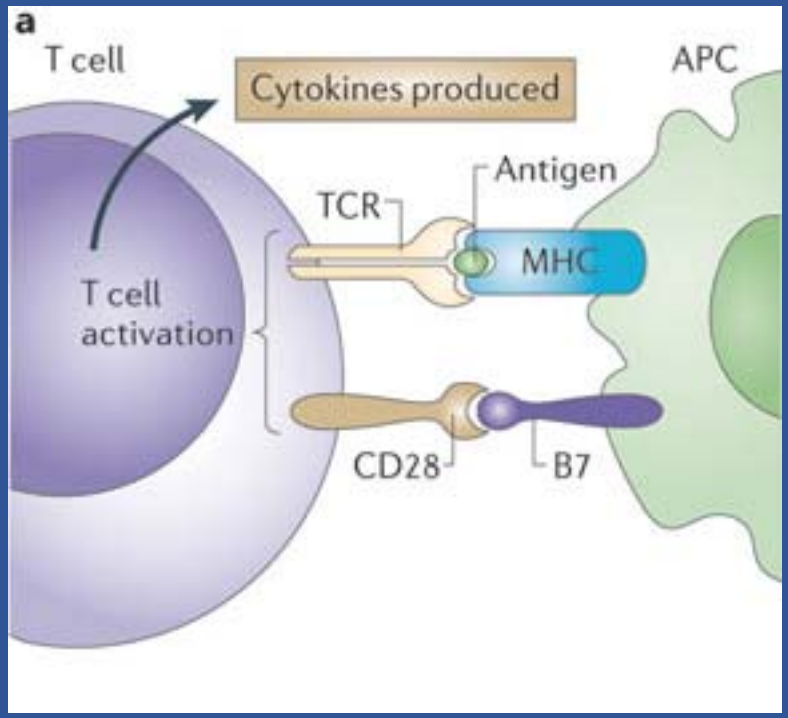


Figure 5.6 The Immune System, 3ed. (© Garland Science 2009)

T-cell Activation

- T-cell activation requires two signals
  - Signal One: Engagement of TCR with a specific antigen presented on a major histocompatibility complex (MHC)
  - Signal Two: Engagement of a costimulatory receptor to costimulatory molecule

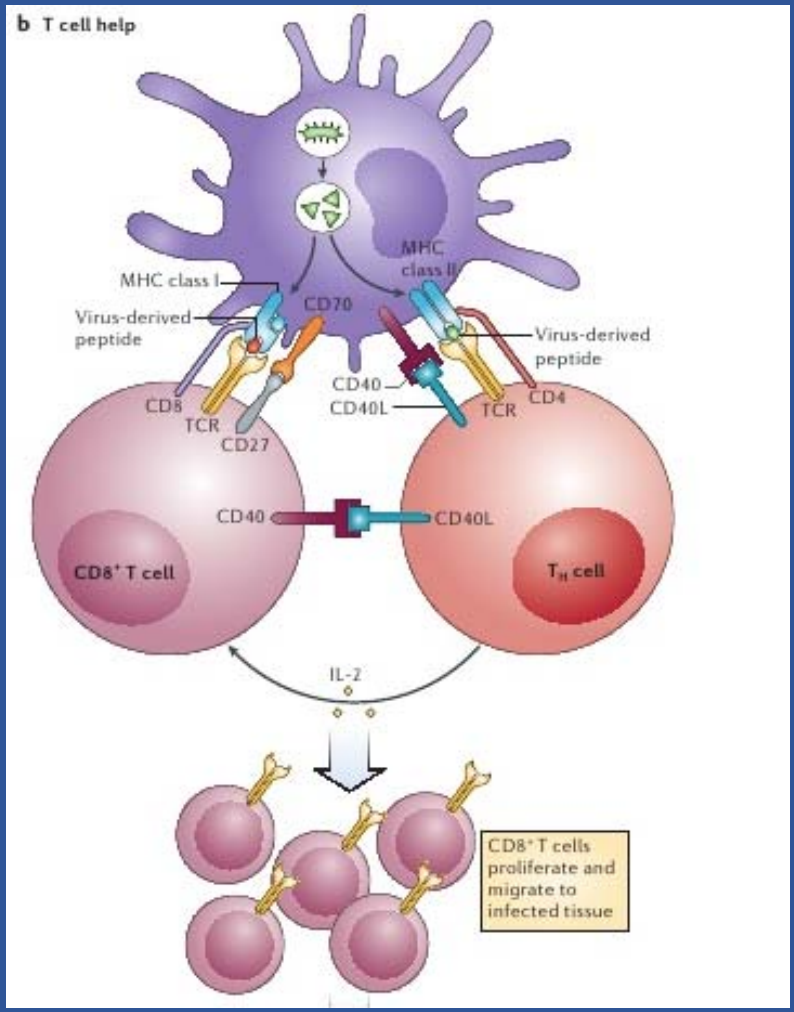
(Janeway, Immunobiology, 2005; Sharma et al., Nat Rev Cancer, 2011)



T-cell Activation

- CD4 T-cell activation
  - IL-2 production and proliferation
  - Production of various other cytokine profiles
    - Th1: Enhances killing efficiency (including CD8 T cells)
    - Th2: Stimulates B-cell function

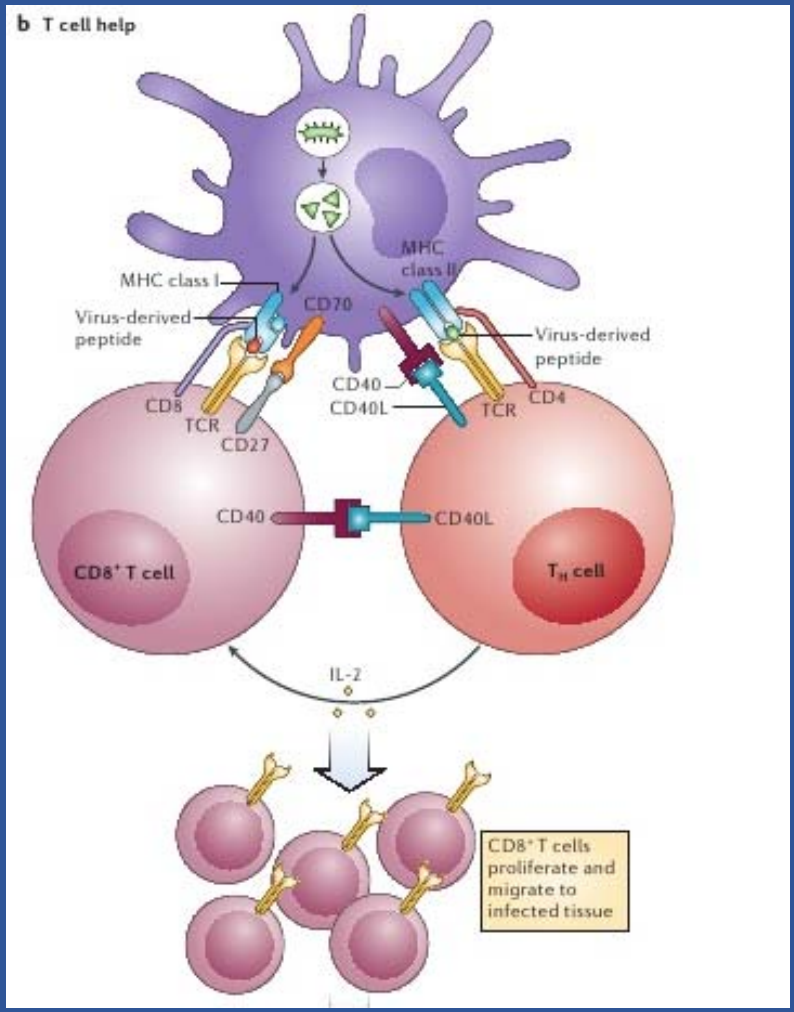
(Janeway, Immunobiology, 2005; Swain et al., Nat Rev Immunology, 2012)



T-cell Activation

- CD8 T-cell activation
  - Proliferation with IL-2 receptor signaling
  - Migrates throughout body to engage cells presenting the specific antigen on MHC class I

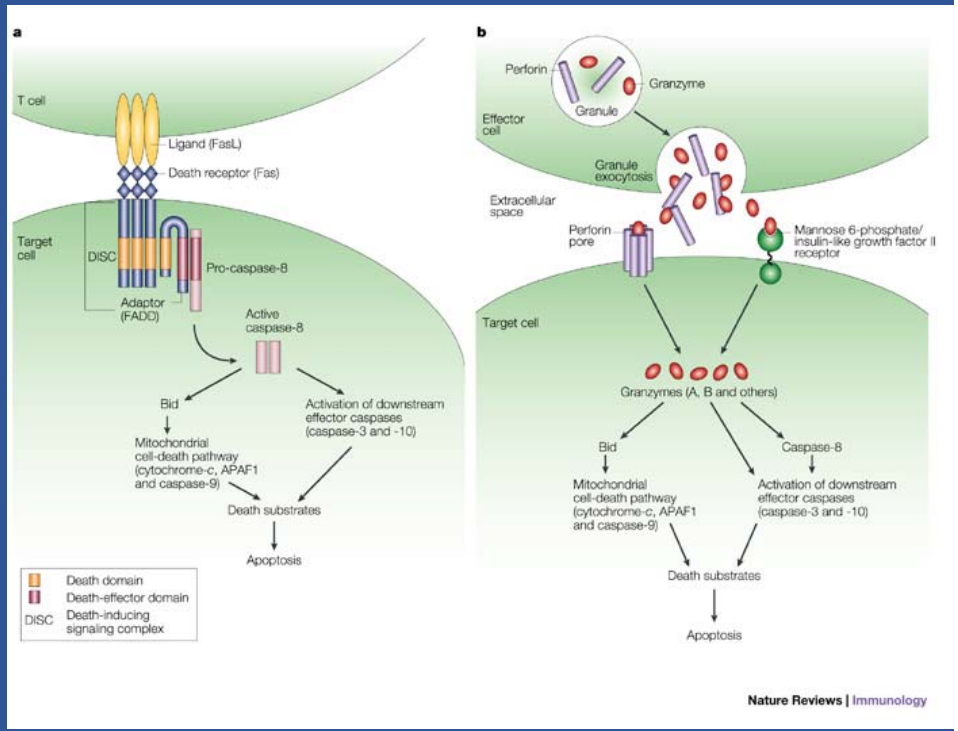
(Janeway, Immunobiology, 2005; Swain et al., Nat Rev Immunology, 2012)



Cytotoxic T-cell Function

- Cytotoxic T cells engage cells with an antigen presented by MHC I
  - Release cytotoxins that induce apoptosis
    - Perforin
    - Granzymes
    - Granulysin
  - Express FAS ligand, which binds to FAS and leads to apoptosis

(Janeway, Immunobiology, 2005; Van den Brink and Burakoff, Nat Rev Immunology, 2002)



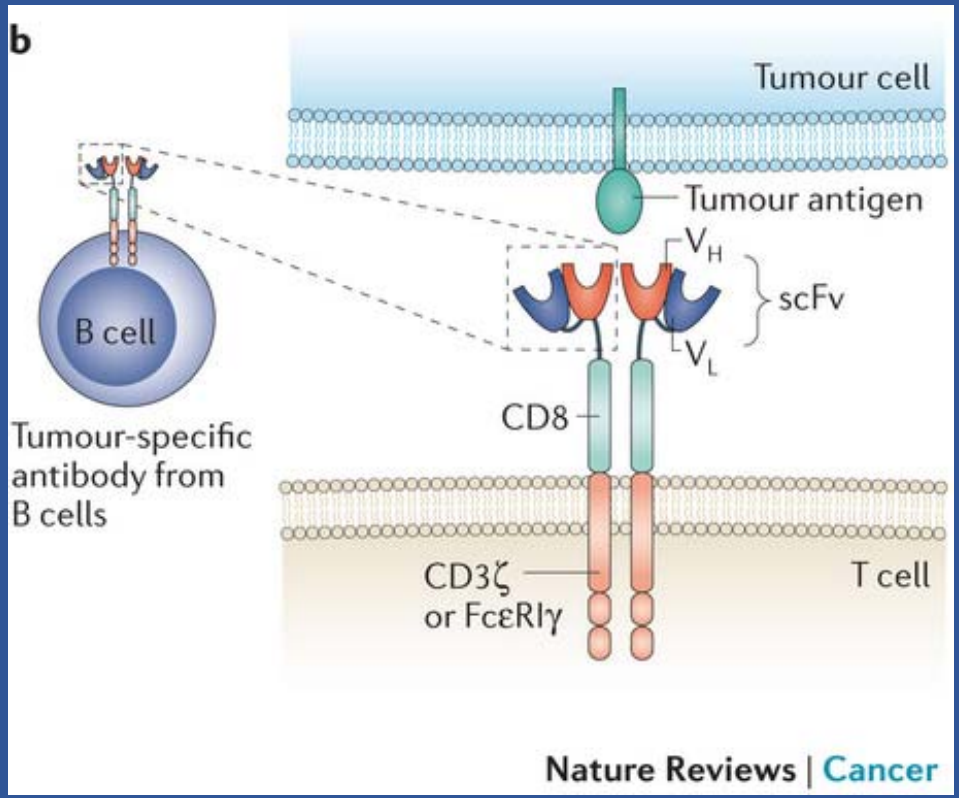
Summary

- T-cell receptors recognize specific antigens presented on an MHC
- T-cell activation requires signaling from TCR and costimulatory receptor.
- CD4 T-cell activation results in IL-2 production, proliferation, and release of cytokines that mediate various cell functions (including cellular cytotoxicity)
- CD8 T-cell activation and IL-2 exposure results in proliferation and migration throughout the body as cytotoxic T-cells
- Cytotoxic T-cells induce apoptosis on cells presenting specific antigens presented on MHC Class I

Chimeric Antigen Receptors

- Engineered receptors composed of parts from different sources
  - Single chain variable fragments (scFv) from monoclonal antibodies
  - CD3-zeta transmembrane and intracellular domains
- Initiate T-cell activation upon binding to specific cell-surface antigens
- Allows targeting by T-cells in an MHC independent manner

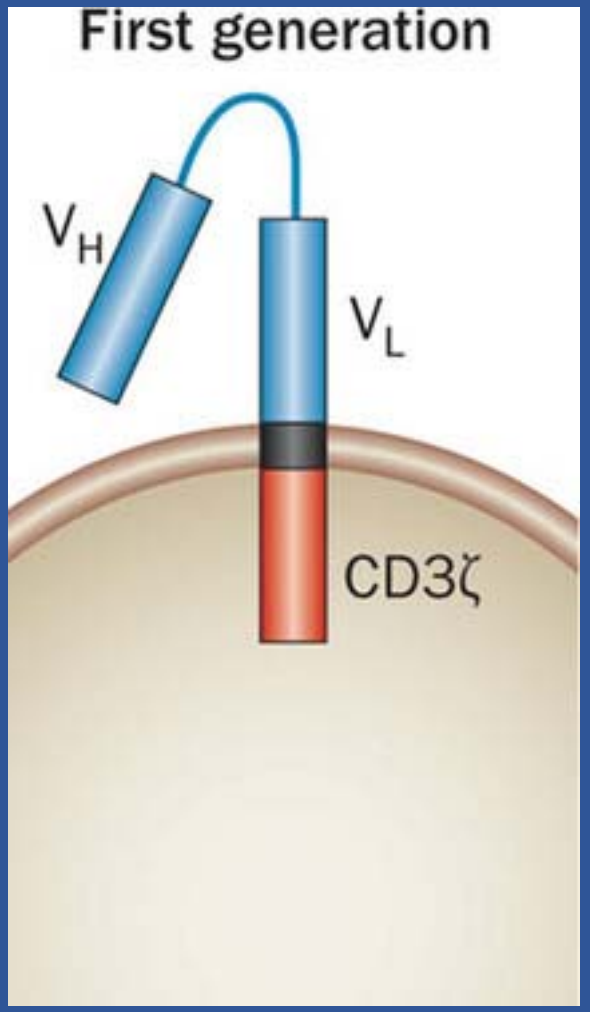
(Kershaw et al., Nat Rev Cancer, 2013)



Chimeric Antigen Receptors

- First-generation CARs first described in 1989
  - scFv
  - CD3-zeta signaling chain
- Poor expansion and low anti-tumor efficacy
- Evidence of persistence of tumor-specific CAR T-cells.
- No transformational events reported

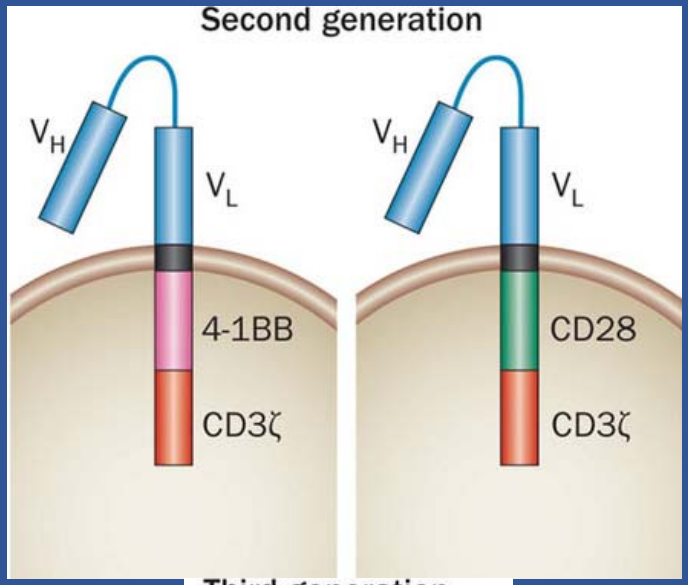
(Savoldo et al., J Clin Invest, 2011; Crystal et al, Nat Rev Clin Onc, 2014)

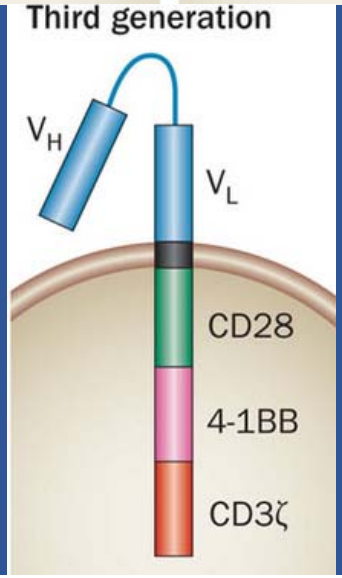


Chimeric Antigen Receptors

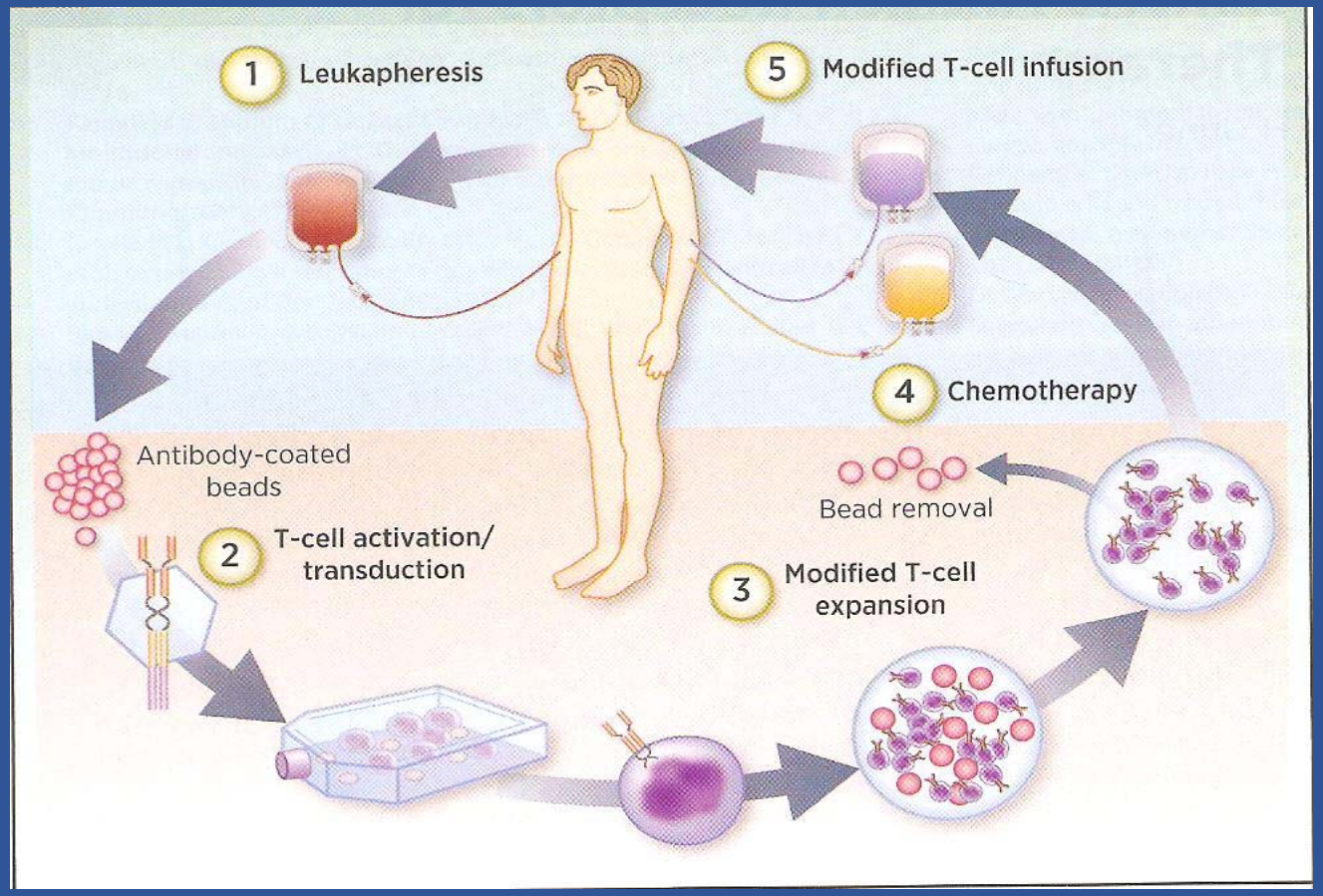
- Second-generation CARs
  - Addition of costimulatory signaling domain
    - CD28
    - 4-1BB
    - OX40
  - Enhanced persistence and proliferation
- Third-generation CARs
  - Addition of two costimulatory domains

(Savoldo et al., J Clin Invest, 2011)





Adoptive T-cell Transfer

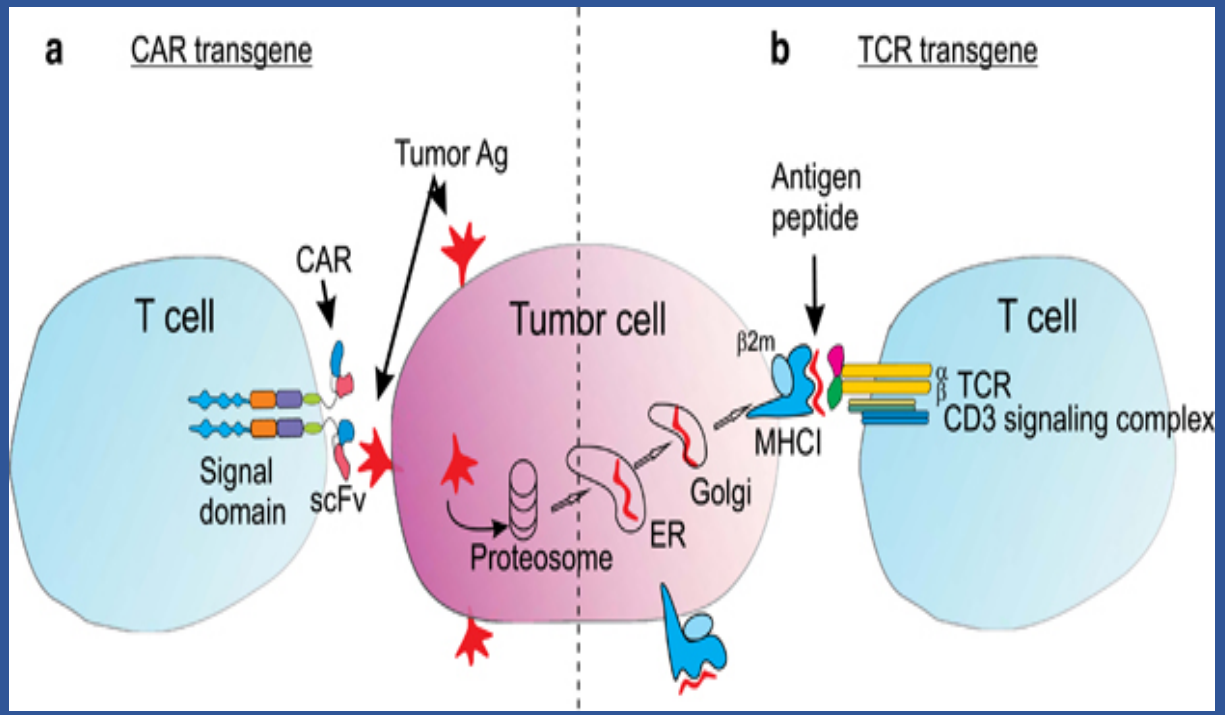


Clin Cancer Res 22:1875-84, 2016

Summary

- CARs are engineered to combine scFv from monoclonal antibodies to TCR signaling domains.
- CARs induce T-cell activation upon binding to cell-surface antigens in an MHC independent manner.
- The addition of costimulatory signaling domains to CARs enhance persistence, expansion, and anti-tumor activity.
- There has been no reported transformational events following adoptive transfer of CAR T-cells

CAR T-cells / Genetically Engineered T-cells



Clinical & Translational Immunology (2014) **3**, e16; doi:10.1038/cti.2014.7
Published online 16 May 2014

Adoptive Cell Therapy

Chimeric Antigen Receptors (CAR)

- Engineered fusion proteins constructed from antigen recognition, signaling, and costimulatory domains that can be expressed in cytotoxic T cells with the purpose of reprogramming the T cells to specifically target tumor cells.

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Genetically Engineered T-cells

- Genetically modified to express a T cell receptor (TCR) to redirect them toward tumor associated antigens (TAA).

Background – Engineered T-cells

- The TCR is a heterodimer formed by the pairing of an alpha chain and a beta chain.
- The receptor interacts with an antigenic peptide presented by a major histocompatibility complex (MHC) molecule, (HLA in humans), on the surface of a target cell for T cell-mediated cytolysis via induction of apoptosis in the target cell.
- This is mediated by perforins and FasL that induce apoptosis of target cells.
- The TCR is associated with the CD3 complex (gamma, delta, epsilon and zeta chains) and upon TCR recognition of an HLA/peptide complex the CD3 chains that mediate signal transduction in the T cell.
- T cells equipped with a novel TCR can in theory target any protein antigen, including mutated intracellular antigens, often found in tumor cells, as they are processed and presented on the cell surface by HLA molecules.
- However, as the HLA is 'polymorphic', T cells with a novel TCR can only be used in a subset of patients.
- HLA-A2 is the most predominant HLA class I, present in ~50% of Caucasians. Consequently, most TCR gene transfer studies have focused on TCRs recognizing HLA-A2/peptide complexes.

Background – CAR T-cells

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- To date, CAR T-cells have been reported to target a number of antigens on tumor cells including CD33, CD19, CA-IX, CD20, Her2/neu, GD2, PSMA, PSCA, mesothelin, CD171, VEGF-R2, MUC-16 and folate receptor-α.

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- The ScFv portion of the CAR molecule is generally derived from a mouse mAb. This may evoke immune responses and potential clearance of CAR-engineered T cells.

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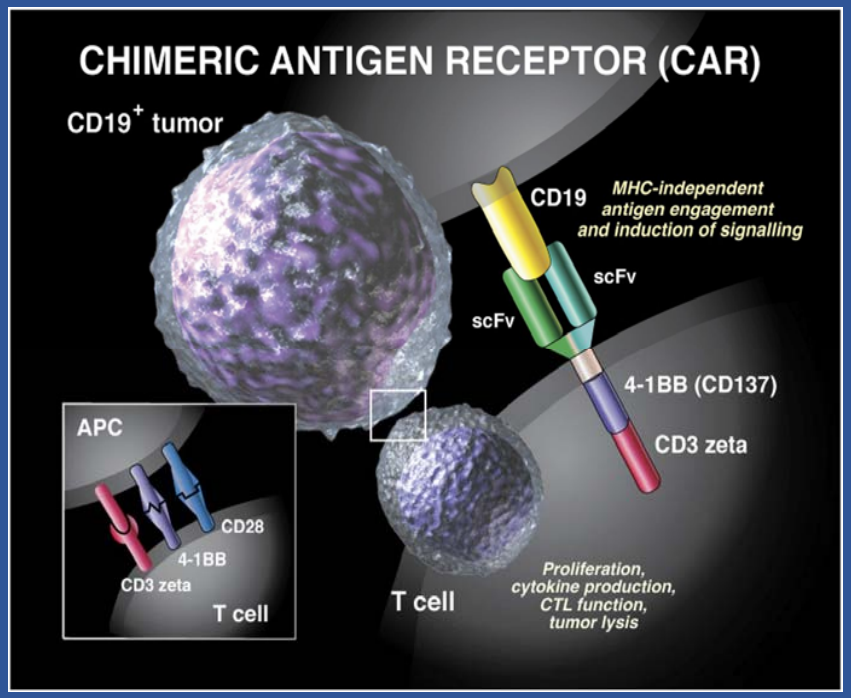
- The ScFv portion of the CAR molecule is generally derived from a mouse mAb. This may evoke immune responses and potential clearance of CAR-T cells.
- To avoid this possibility, fully human CARs can be constructed.

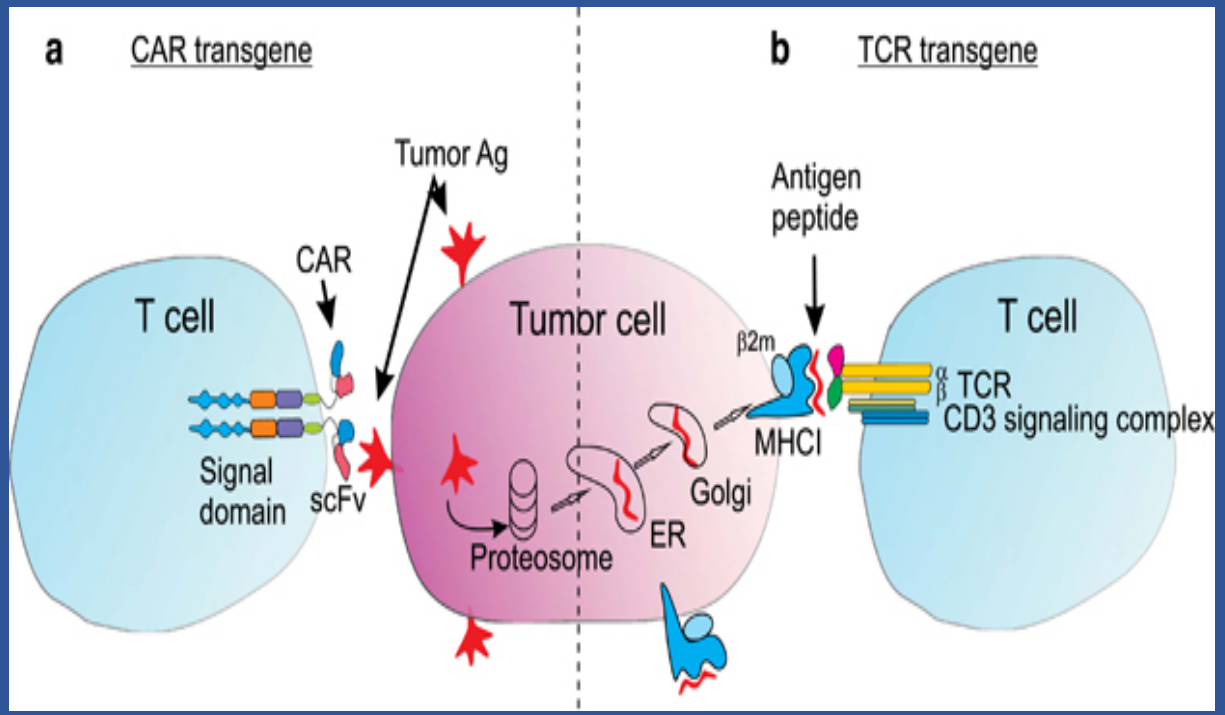
CAR T-cell



a CAR mainly consists of a single chain variable fragment (scFv), an extracellular hinge and spacer element, a transmembrane domain and an internal signaling domain such as CD3ζ.

Kite Pharma 2015

CAR T-cells / Genetically Engineered T-cells



Clinical & Translational Immunology (2014) **3**, e16; doi:10.1038/cti.2014.7
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CD19-targeted CAR T-cells

Home / November 18, 2010; Blood: 116 (20)

Brief report

Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19

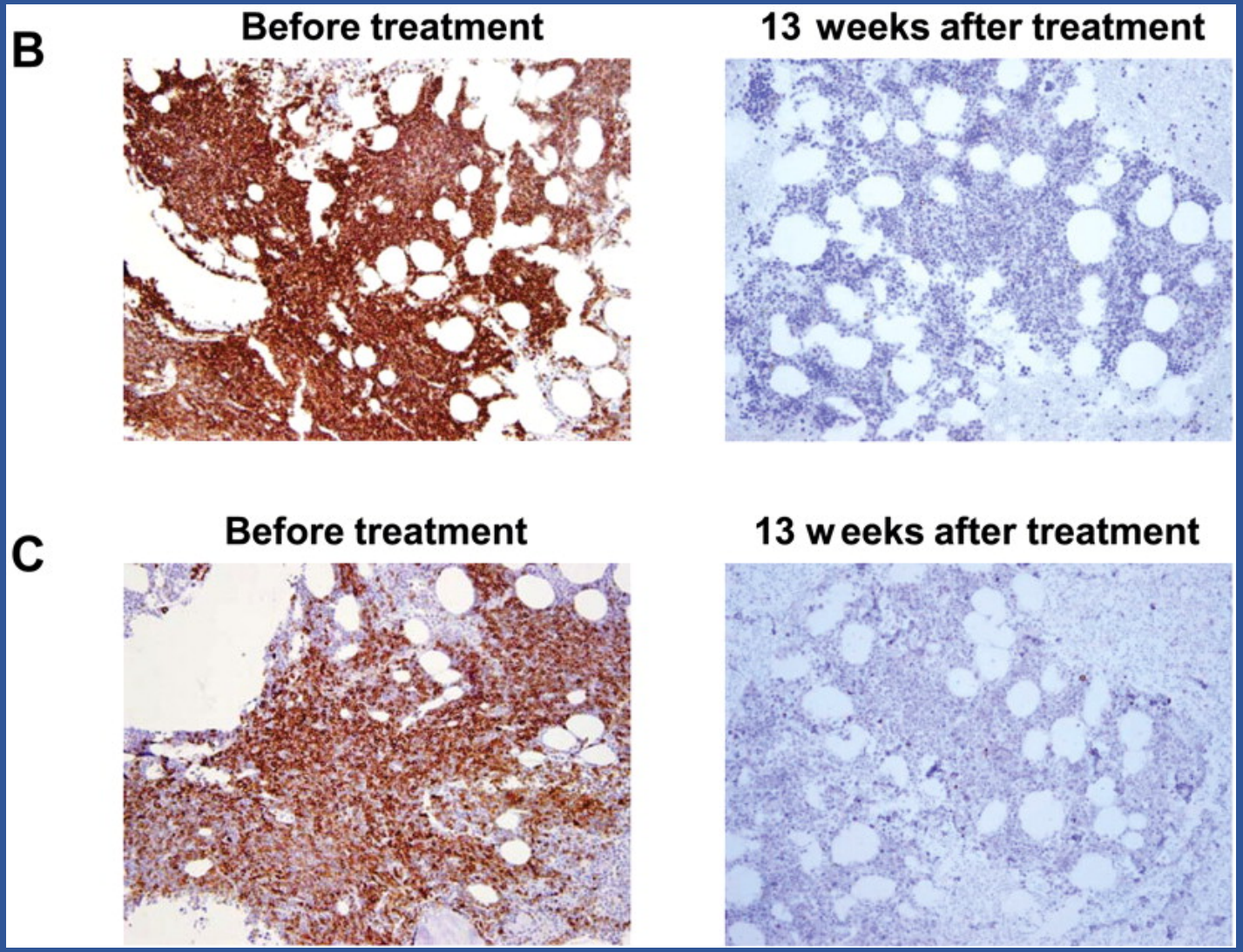
James N. Kochenderfer[1], Wyndham H. Wilson[2], John E. Janik[2], Mark E. Dudley[1], Maryalice Stetler-Stevenson[3], Steven A. Feldman[1], Irina Maric[4], Mark Raffeld[3], Debbie-Ann N. Nathan[1], Brock J. Lanier[1], Richard A. Morgan[1], and Steven A. Rosenberg[1]

Home / March 22, 2012; Blood: 119 (12)

B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor–transduced T cells

James N. Kochenderfer[1], Mark E. Dudley[2], Steven A. Feldman[2], Wyndham H. Wilson[3], David E. Spaner[4], Irina Maric[5], Maryalice Stetler-Stevenson[6], Giao Q. Phan[2], Marybeth S. Hughes[2], Richard M. Sherry[2], James C. Yang[2], Udai S. Kammula[2], Laura Devillier[2], Robert Carpenter[1], Debbie-Ann N. Nathan[2], Richard A. Morgan[2], Carolyn Laurencot[2], and Steven A. Rosenberg[2]

Did anti-CD19 CAR T cells infusion induce a clinical response?



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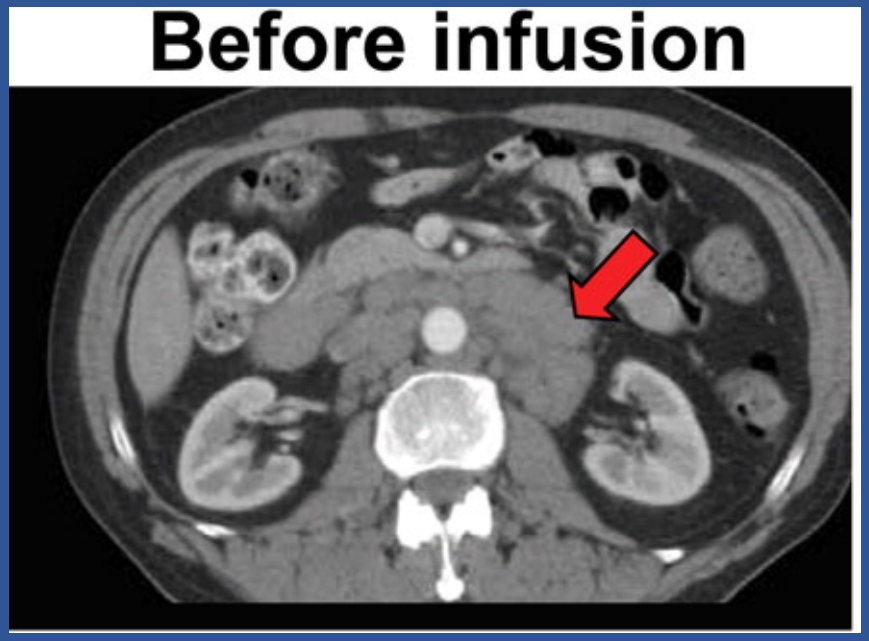
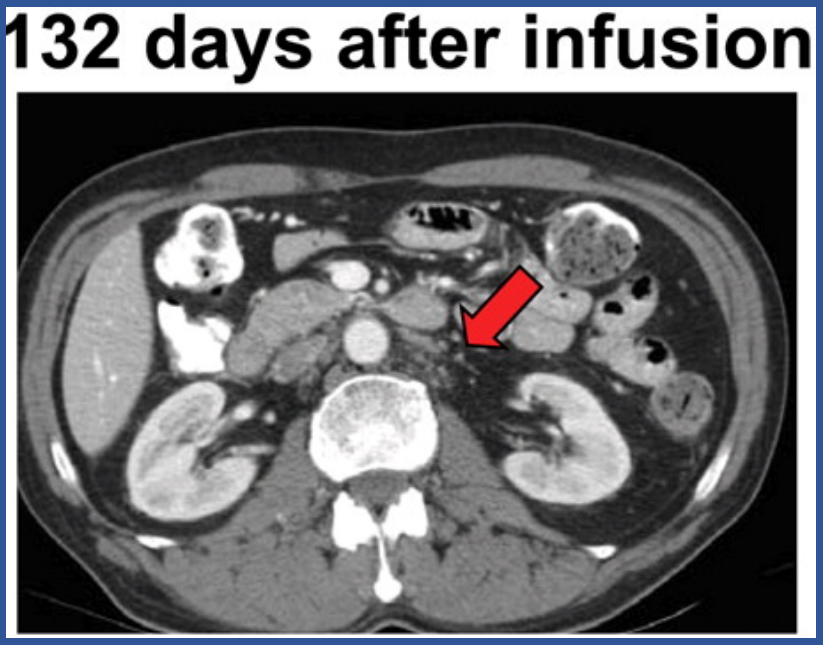
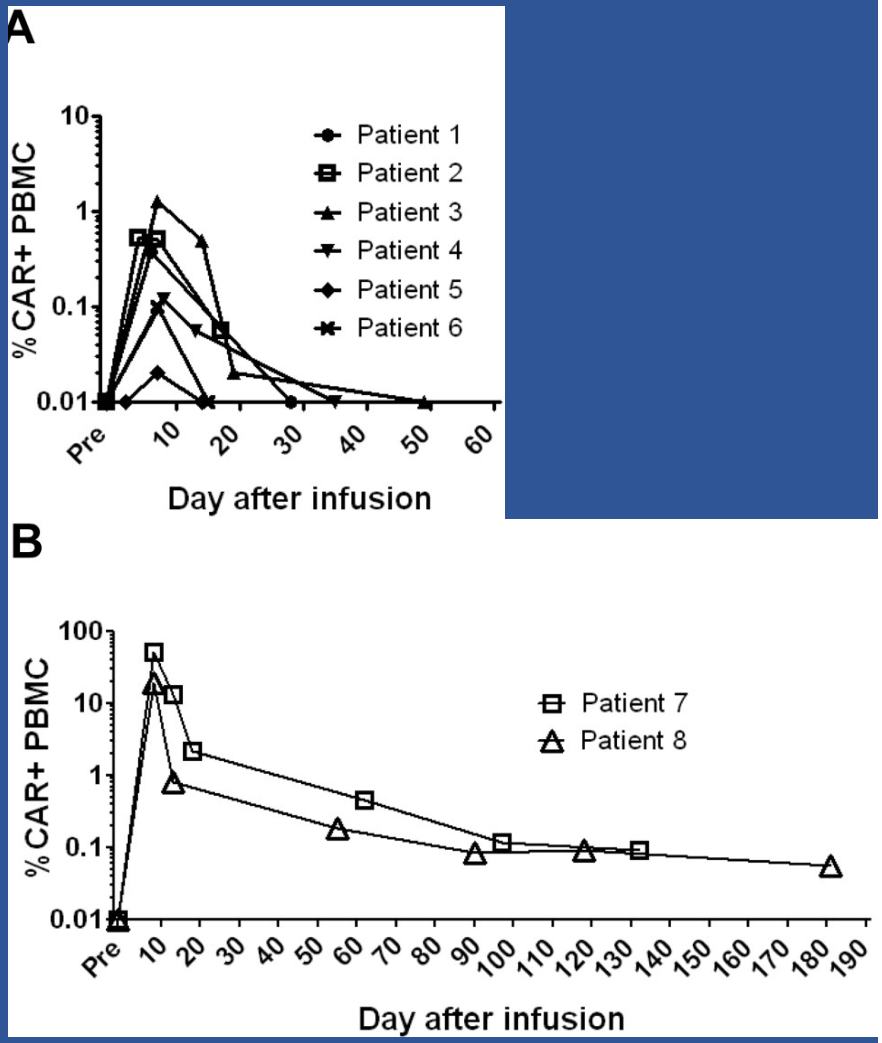




Did anti-CD19 CAR T cells persist after infusion?

- qPCR for anti-CD19 CAR
- Peak levels of anti-CD19 CAR T cells in peripheral blood occurred at ~Day 10 at various levels.
- Patient 7 and 8 demonstrated persistent anti-CD19 CAR T cells in peripheral blood.

(Kochenderfer et al., Blood, 2012)



CD19-targeted CAR T-cells

- Toxicities generally peaked at day 8.
  - B-cell depletion
  - Fevers
  - Hypotension
  - Fatigue
  - Renal Failure
  - Obtundation

(Kochenderfer et al., Blood, 2012)

Patient	Toxicities*†
1‡	Fatigue, herpes zoster with secondary otitis externa 6 months after treatment
2	*Escherichia coli* bacteremia, died with influenza pneumonia, dyspnea, hypoxemia, nonbacterial thrombotic endocarditis, cerebral infarction, elevated liver enzymes
3	Hypotension, acute renal failure, hypoxemia, hyperbilirubinemia, capillary leak syndrome
4	Diarrhea, fatigue
5	Fever, fatigue, hypotension
6	Hypotension, capillary leak syndrome, hypoalbuminemia
7	Obtundation, acute renal failure, hyperbilirubinemia, capillary leak syndrome, anorexia, elevated liver enzymes, electrolyte abnormalities
8	Hypotension, obtundation, acute renal failure, capillary leak syndrome, headache, pleural effusion, electrolyte abnormalities

CD19-targeted CAR T-cells in CLL

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.

T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia

Michael Kalos[1,2,*], Bruce L. Levine[1,2,*], David L. Porter[1,3], Sharyn Katz[4], Stephan A. Grupp[5,6], Adam Bagg[1,2], and Carl H. June[1,2,†]

CD19-targeted CAR T-cells

Home / November 3, 2011; Blood: 118 (18)

Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias

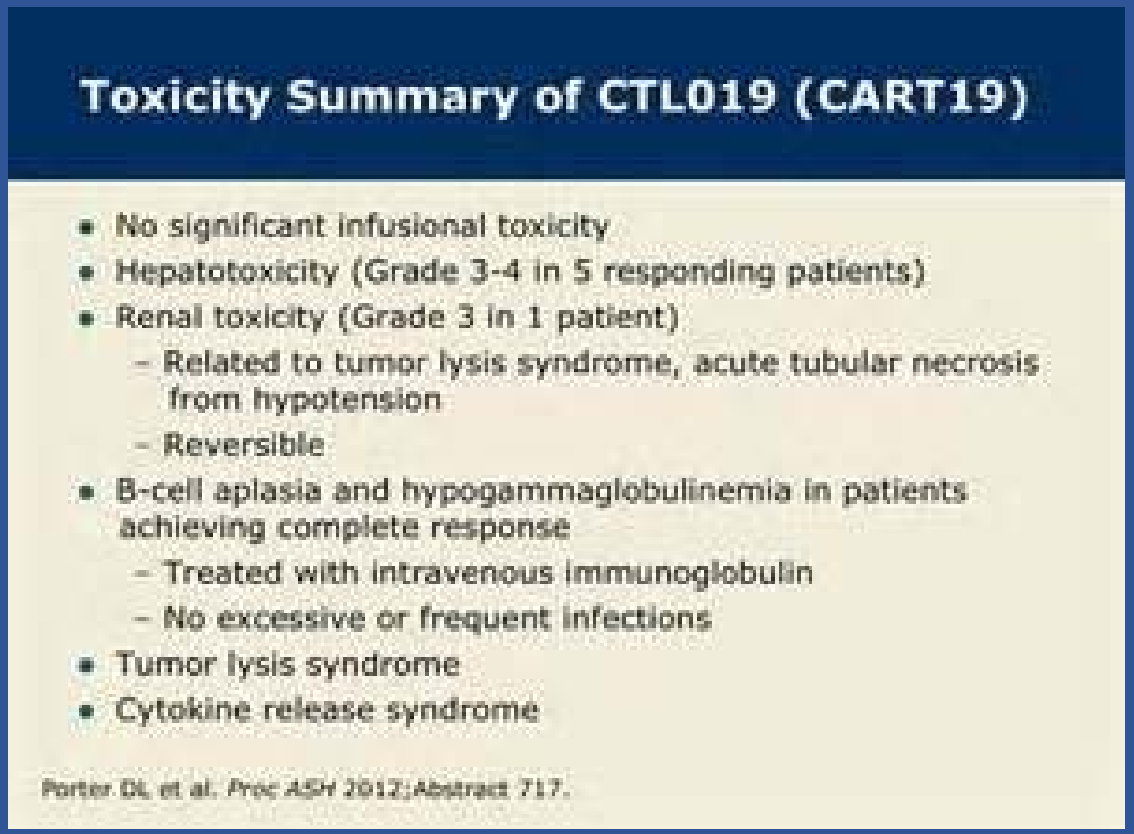
Renier J. Brentjens[13,*], Isabelle Rivière[14,*], Jae H. Park[1,2], Marco L. Davila[1,2], Xiuyan Wang[24], Jolanta Stefanski[24], Clare Taylor[24], Raymond Yeh[1,2], Shirley Bartido[2,3], Oriana Borquez-Ojeda[24], Malgorzata Olszewska[24], Yvette Bernal[1], Hollie Pegram[1,2], Mark Przybylowski[24], Daniel Hollyman[24], Yelena Usachenko[1,2], Domenick Pirraglia[24], James Hosey[24], Elmer Santos[3,5], Elizabeth Halton[1], Peter Maslak[1], David Scheinberg[13], Joseph Jurcic[1], Mark Heaney[1], Glenn Heller[6], Mark Frattini[1], and Michel Sadelain[13]

Table 4. Currently recruiting CAR T-cell therapy trials by antigen

Center	Disease	Patient population	Co-stimulation	Gene transfer	Notes	Clinicaltrials.gov identifier
CD19						
MSKCC	CLL	>18 years old	*CD28*	RV	Dose-escalation	NCT00466531
BCM	B-cell malignancy	Any	*CD28*	RV	With ipilimumab	NCT00586391
BCM	B-cell malignancy	Any	*CD28*	RV	Dose escalation	NCT00608270
BCM	B-cell malignancy	Any	*CD28*	RV	After AlloHCT, viral co-specificity	NCT00840853
NCI	B-cell malignancy	18–68	*CD28*	RV	With IL2	NCT00924326
MDACC	B-cell lymphoma	18–65			With or without IL2	NCT00968760
MSKCC	B-ALL	>18 years old	*CD28*	RV		NCT01044069
NCI	B-cell malignancy	18–75	*CD28*	RV	Active GVHD not allowed	NCT01087294
MSKCC	CLL	>18 years old	*CD28*	RV	Upfront therapy	NCT01416974
MSKCC	B-ALL	<19 years old	*CD28*	RV	After AlloHCT, viral co-specificity	NCT01430390
Manchester, UK	B-cell malignancy	>18 years old	*None*			NCT01493453
MDACC	B-cell malignancy	1–65			After AlloHCT	NCT01497184
NCI	B-cell malignancy	1–30 years old	*CD28*	RV		NCT01593696
CHOP	$CD19^+$ leukemia and lymphoma	1–24 years old	*4-1BB*	LV		NCT01623495
Seattle Children's	$CD19^+$ ALL	Age 1–26			$EGFR^+$ construct (may allow deletion)	NCT01683279
Penn	CLL/SLL	>18 years	*4-1BB*	LV	2 dose level comparison	NCT01747486
MSKCC	Aggressive B-NHL, relapsed/refractory	18–70	*CD28*	RV	After autologous SCT	NCT 01840566
BCM	B-cell malignancy	Up to 75 years old	$CD28^{+/-}$ *4-1BB*	RV		NCT01853531
MSKCC	B-ALL	<26 years old	*CD28*	RV		NCT01860937
Beijing	B-cell malignancy	5–90 years old	*4-1BB*			NCT01864889
FHCRC	B-cell malignancy	>18 years		LV		NCT01865617
Penn	B-cell NHL	>18 years old	*4-1BB*	LV		NCT02030834
Seattle Children's	B-ALL		*4-1BB*	LV	$EGFR^+$ construct (may allow deletion)	NCT02028455
Penn	B-ALL	>18 years old	*4-1BB*	LV		NCT02030847
BCM	B-cell malignancy		*CD28*	RV	After AlloHCT	NCT02050347
Beijing	Mantle cell lymphoma	50–80				NCT02081937
Sweden	B-cell malignancy	>18 years old	*CD28 and 4-1BB*	RV		NCT02132624
Japan	B cell NHL	20–70	*CD28*	RV		NCT02134262

(Gill and June, Immunol Rev, 2015)

Toxicity of CAR T-cells targeting CD19



Cytokine Release Syndrome

CTL019 (CART19)-Associated Cytokine Release Syndrome (CRS)

- All responding patients developed a CRS at time of T-cell expansion
  - High fevers, nausea, hypotension, hypoxia, etc
- Associated with high levels of:
  - IL-6 (6-400x)
  - IFN-gamma (89-1,000)
  - IL-2R (5-25)
  - No significant increase in TNF-alpha, IL-2
- Immediately reversed with steroids (n = 1), steroids/etanercept/tocilizumab (n = 1), tocilizumab (n = 2)

Porter DL et al. *Proc ASH* 2012;Abstract 717.

Summary

- CAR T-cells targeting CD19 have the potential to induce remissions in otherwise refractory/relapsed CD19 positive B-cell malignant diseases.
- Differences in CAR design, preconditioning, and infusion protocol may affect efficacy of treatment.
- Lymphodepleting chemotherapy appears to be important and may be contributing to the responses to CAR T-cell therapy.
- Cytokine release syndrome is common in patients following infusion of CAR T cells.
- Tocilizumab (anti-IL-6 mAb) may be effective for treating cytokine release syndrome.
- Corticosteroids may be effective in treating cytokine release syndrome but may cause ablation of CAR T cells.

CAR T-cell Targets for hematological malignancies

Table 2 | **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)

Does not include CD19 targets. AML, acute myeloid leukaemia; B-ALL, B-cell acute lymphoblastic leukaemia; Baylor, Baylor College of Medicine (USA); BCMA, B-cell maturation antigen; City of Hope, City of Hope National Medical Center (USA); CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; LeY, Lewis Y antigen; MM, multiple myeloma; MD Anderson, MD Anderson Cancer Center (USA); NCI, National Cancer Institute; NHL, non-Hodgkin lymphoma; Peter Mac, Peter MacCallum Cancer Centre (Australia); PLA General Hospital, People's Liberation Army General Hospital (China); ROR1, inactive tyrosine-protein kinase transmembrane receptor ROR1; SLL, small lymphocytic lymphoma.

(Jackson et al, Nat Rev Clin Onc, 2016)

Table 3 | **CAR targets for the treatment of solid malignancies**

Target	CAR structure	Malignancy	Institution	Reference
PSMA	CD3ζ and CD28	Prostate cancer	MSKCC	NCT01140373 (REF. 76)
			Roger Williams	NCT00664196 (REF. 78)
Mesothelin	CD3 and 4-1BB	Malignant pleural mesothelioma	UPenn	NCT01355965 (REF. 81)
		Pancreatic cancer	UPenn	NCT02465983 (REF. 156)
		Metastatic pancreatic (ductal) adenocarcinoma, epithelial ovarian cancer and malignant epithelial pleural mesothelioma	UPenn	NCT02159716 (REF. 84)
	CD3ζ and CD28	Mesothelioma and malignant pleural disease	MSKCC	NCT02414269 (REF. 85)
	CD3ζ, CD28 and 4-1BB	Mesothelioma, pancreatic and ovarian cancer	NCI	NCT01583686 (REF. 86)
FAP	CD3ζ and CD28	Mesothelioma	University of Zurich (Switzerland)	NCT01722149 (REF. 90)
EGFRvIII	CD3ζ and 4-1BB	Glioma	UPenn	NCT02209376 (REF. 95)
	CD3ζ, CD28 and 4-1BB	Glioma	NCI	NCT01454596 (REF. 97)
EGFR	Unknown	Malignant glioma	Renji Hospital (China)	NCT02331693 (REF. 98)
CEA	CD3ζ and CD28	Liver metastases	Roger Williams	NCT02146466 (REF. 100)
	Unknown	Lung, colorectal, gastric, breast andpancreatic cancer	Southwest Hospital (China)	NCT02349724 (REF. 103)
CD171	CD3ζ and 4-1BB or CD3ζ, CD28 and 4-1BB	Neuroblastoma	Seattle Children's	NCT02311621 (REF. 106)
GD2	CD3ζ, OX40, CD28	Neuroblastoma, osteosarcoma and melanoma	NCI	NCT02107963 (REF. 112)
		Neuroblastoma	Baylor	NCT01822652 (REF. 114)
	CD3ζ, Ox40, CD28, virus specific	Sarcoma	Baylor	NCT01953900 (REF. 115)
Glypican-3	CD3ζ, CD28 and 4-1BB	Advanced-stage hepatocellular carcinoma	Renji Hospital (China)	NCT02395250 (REF. 117)
HER2	CD3ζ and CD28 virus specific	Sarcoma	Baylor	NCT00902044 (REF. 122)
	CD3ζ and CD28	Glioblastoma	Baylor	NCT02442297 (REF. 126)
		Glioblastoma multiforme	Baylor	NCT01109095 (REF. 127)
IL-13	RαCD3ζ and 4-1BB	Glioma	City of Hope	NCT02208362 (REF. 131)

Baylor, Baylor College of Medicine (USA); CEA, carcinoembrionic antigen; City of Hope, City of Hope National Medical Center (USA); EGFRVII, epidermal growth factor receptor variant III; FAP, prolyl endopeptidase FAP/fibroblast activation protein alpha; MSKCC, Memorial Sloan Kettering Cancer Center (USA); NCI, National Cancer Institute (USA); PSMA, prostate-specific membrane antigen; Roger Williams, Roger Williams Medical Center (USA); Seattle Children's, Seattle Children's Hospital (USA); UPenn, University of Pennsylvania (USA).

(Jackson et al, Nat Rev Clin Onc, 2016)

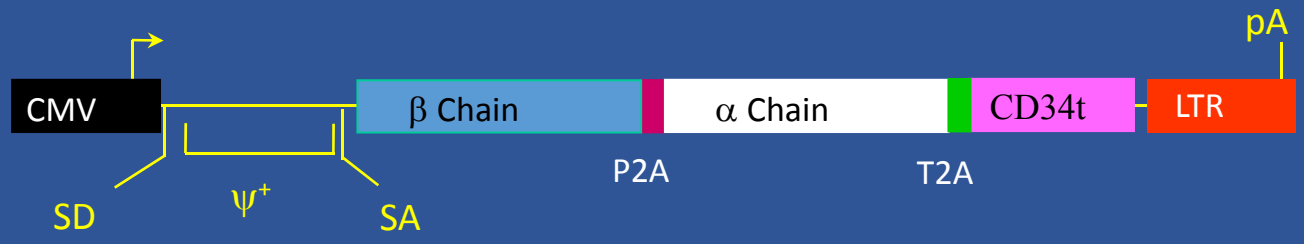
Engineered T-cell Targets/Trials

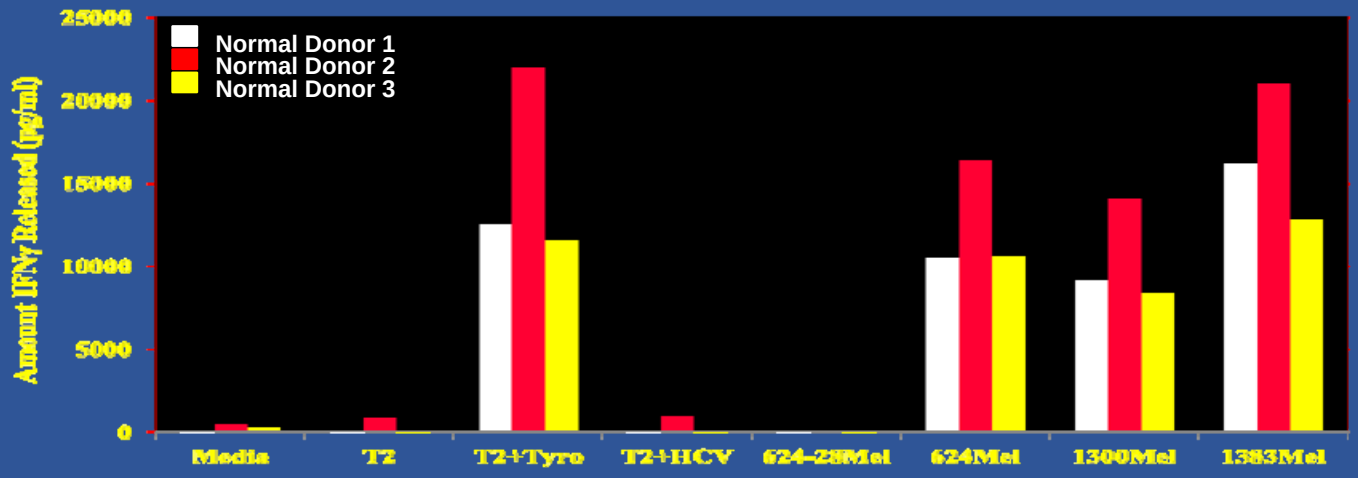
- Tyrosinase – melanoma (LUMC)
- HPV-16 E6 – cervical CA, HNSCC, anal CA, vulvar CA, vaginal CA
- NY-ESO-1 – numerous cancer
- MART-1 – melanoma
- MDM-2
- gp100 – melanoma
- p53
- CEA – colorectal CA
- MAGE-A3
- MAGE-C2
- TARP – breast CA, prostate CA
- WT1 – Wilms' tumor

Selected Engineered T-cell Trials

Trial no.	Status	Phase	Treatment	Pre-conditioning	Diagnosis	Sponsor
NCT01567891	Recruiting	I/II	MAGE HLA-A1 or NY-ESO-1 HLA-A2 TCR	No	Ovarian cancer	U-Penn
NCT01350401	Recruiting	I/II	MAGE HLA-A1 or NY-ESO-1 HLA-A2 TCR	Yes	Melanoma	U-Penn
NCT00704938	Terminated	II	p53 HLA-A2 TCR + IL-2	Yes	Kidney, melanoma, non-specific metastatic cancer	NCI
NCT00706992	Ongoing but not recruiting	II	MART-1 HLA-A2 TCR + peptide vaccine + IL-2	No	Melanoma	NCI
NCT00612222[a]	Terminated	II	MART-1 HLA-A2 TCR + peptide vaccine + IL-2	Yes	Melanoma	NCI
NCT00610311[a]	Terminated	II	gp100 HLA-A2 TCR + ALVAC vaccine + IL-2	Yes	Melanoma	NCI
NCT00923390	Recruiting	I/II	2G-1 (non-HLA restricted) TCR + IL-2	Yes	Metastatic renal cancer	NCI
NCT00910650	Recruiting	II	MART-1 HLA-A2 TCR + IL-2 + DC vaccine	Yes	Advanced melanoma	UCLA

Retroviral Vectors for the Transfer of T Cell Receptor Genes to PBL-Derived T Cells





Clinical Trial Design

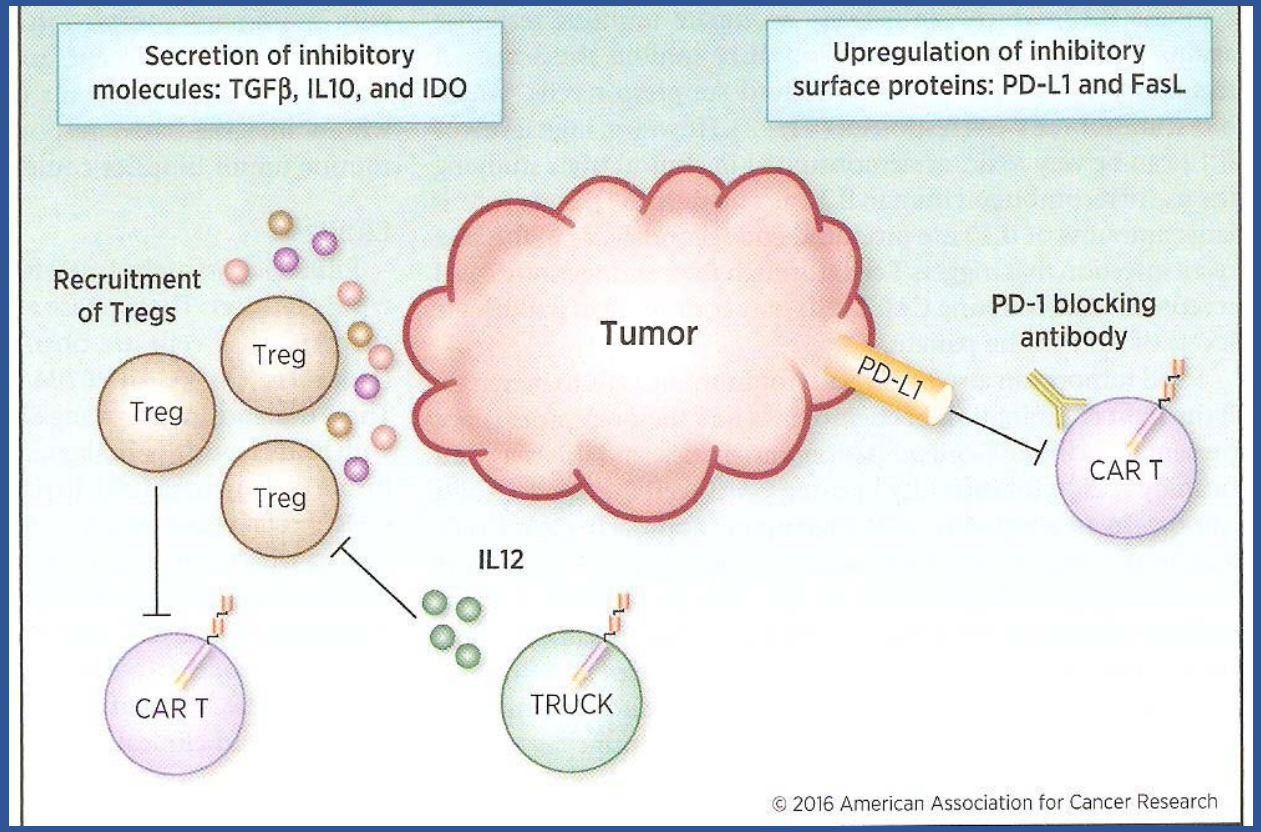
- HLA screening trial
- Phase I clinical trial design
  - Patients T cells are engineered with viral vectors encoding a TCR that targets tyrosinase on melanoma cells
  - 3+3 design
    - Dose 1: 7.5 x 10^6 TCR transduced T cells per kg
    - Dose 2: 25 x 10^6 TCR transduced T cells per kg
    - Dose 3: 75 x 10^6 TCR transduced T cells per kg
  - 3 dose levels = 12 patients
  - Patients are pretreated with nonmyeloablative chemotherapy
  - Following cell infusion, patients receive low dose IL-2 for a week
- Patient Monitoring
  - Blood is drawn at regular intervals to monitor for the presence of the infused T cells.
  - Patients will be followed radiologically for evidence of tumor regression/progression.

Screening and Phase I Clinical Trial

Summary of Patients

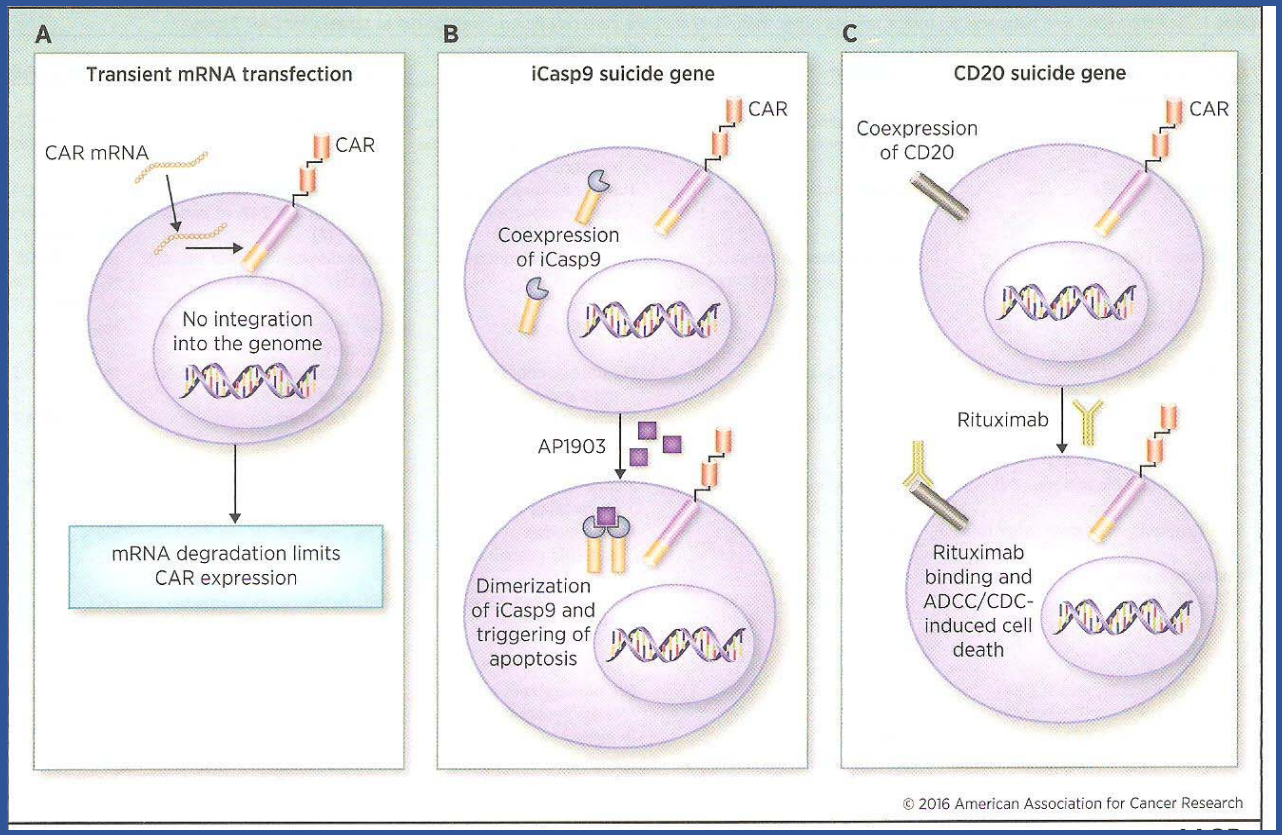
- 55 stage IV melanoma patients screened for HLA-A2 status
- 28 (50.9%) HLA-A2 positive, eligible for further screening.
- 7 signed the consent and proceeded to full screening

Influences on CAR T-cell Activity



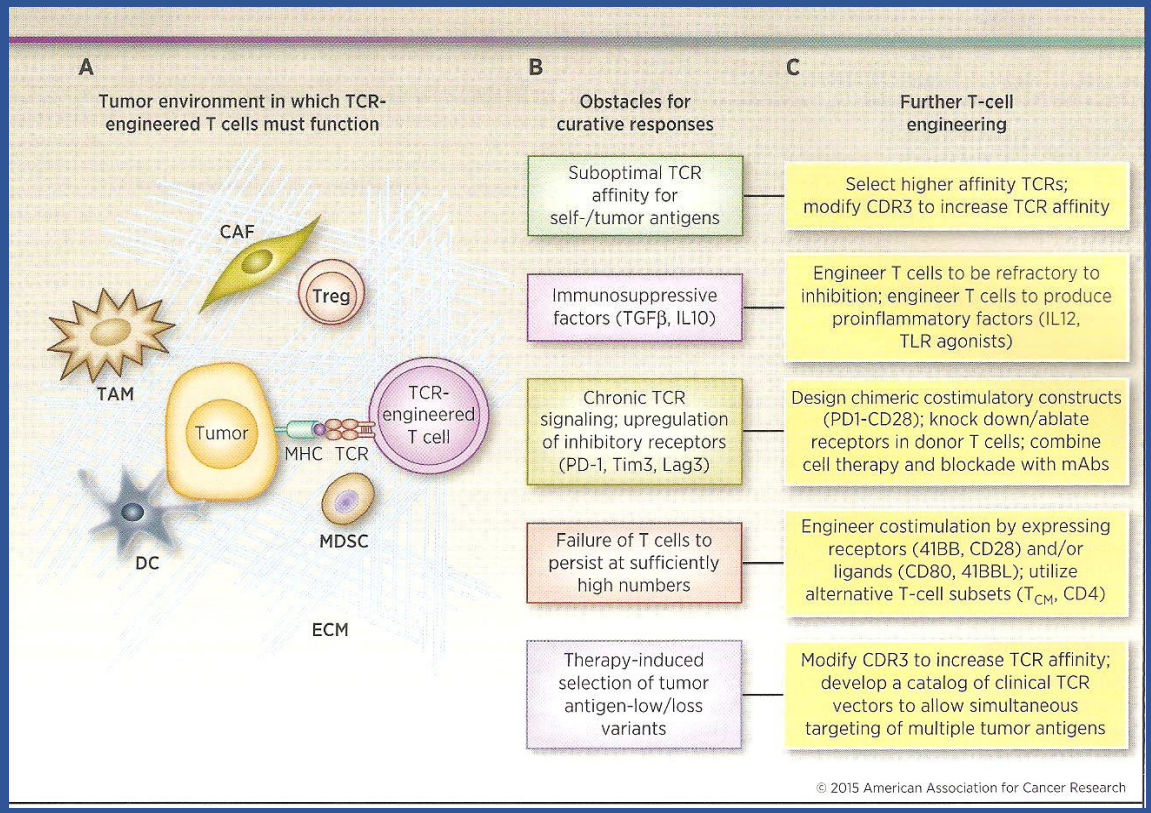
Clin Cancer Res 22:1875-84, 2016

Strategies to Regulate CAR T-cell Persistence



Clin Cancer Res 22:1875-84, 2016

Enhanced Engineering for Improved Targeting



Clin Cancer Res 21:5191-7, 2015

Conclusions

- Adoptive T-cell therapy is a promising approach for the treatment of a number of malignancies.
- CAR T-cell and genetically engineered T-cell strategies each have their advantages and disadvantages.
- Management of the Cytokine Release Syndrome is key with CD19 CAR therapy.
- Strategies to regulate CAR T-cell and engineered T-cell persistence is an active area of investigation.