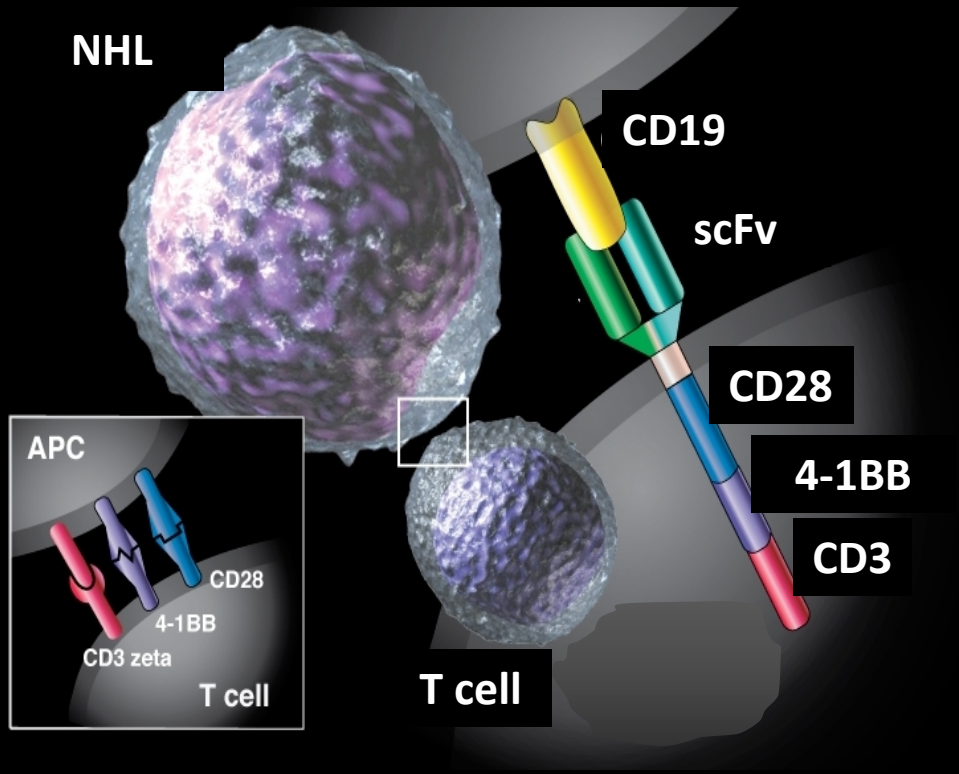
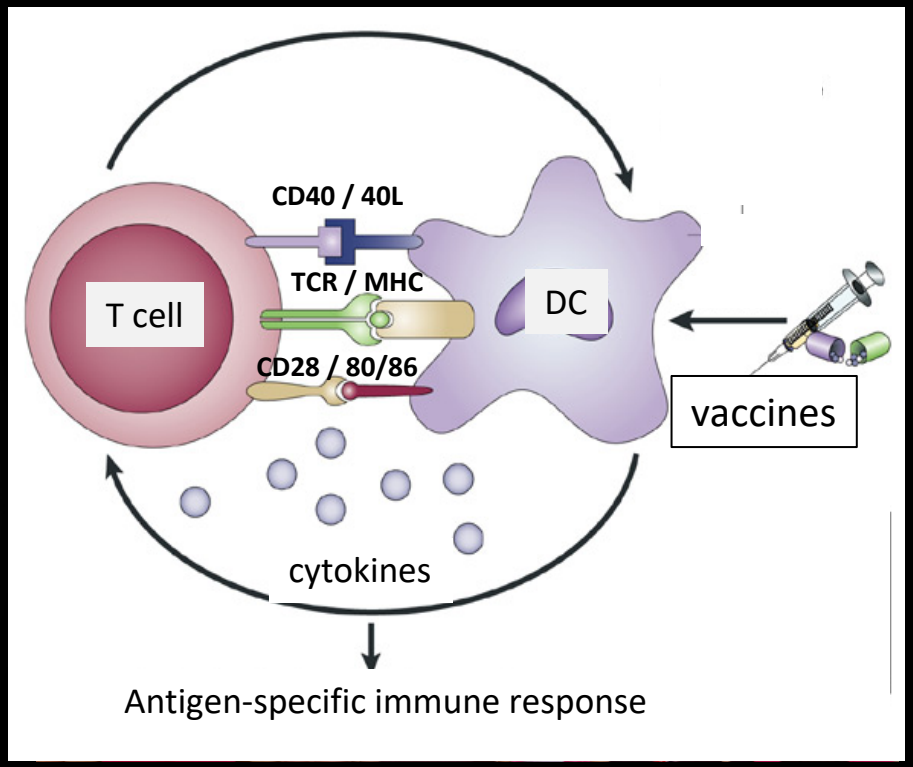
T cell Therapies for Cancer





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Disclosures

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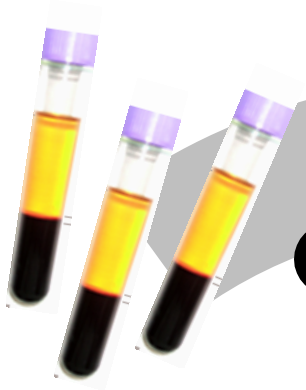
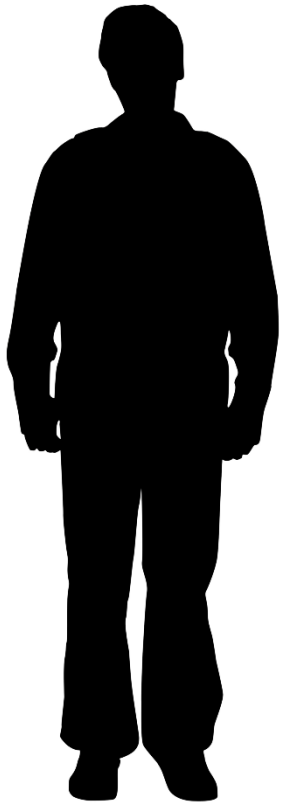
Co-Founder: Mana Therapeutics and Catamaran Bio

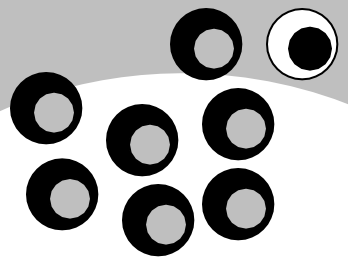
Board of Directors: Cabaletta Bio

Stock/ownership: Repertoire Immune Medicines and Neximmune Therapeutics

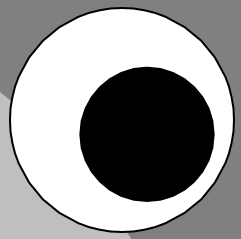
Blood drawn contains different kinds of killer cells called “T cells”



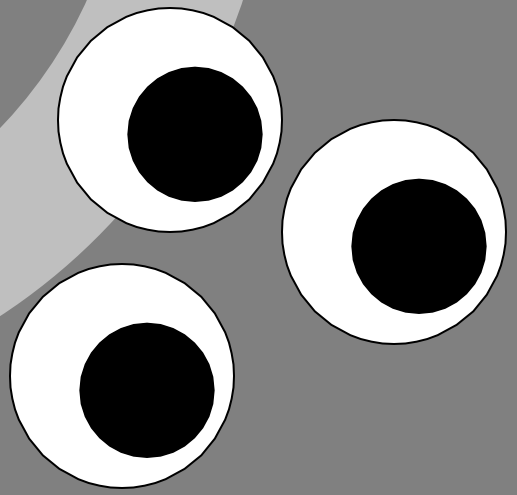


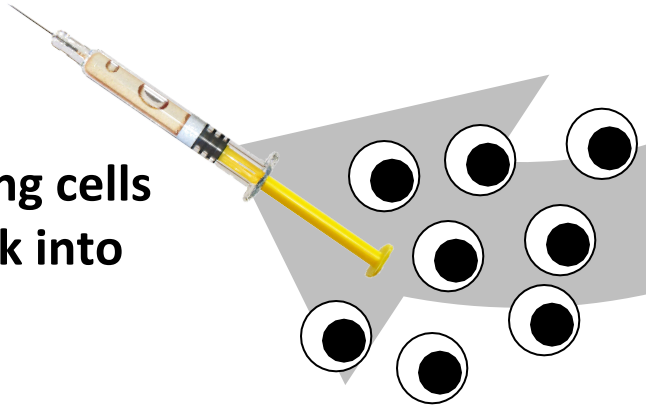


Some T cells have the potential to recognize and kill cancer



These cancer-killing T cells are enriched or modified in the lab



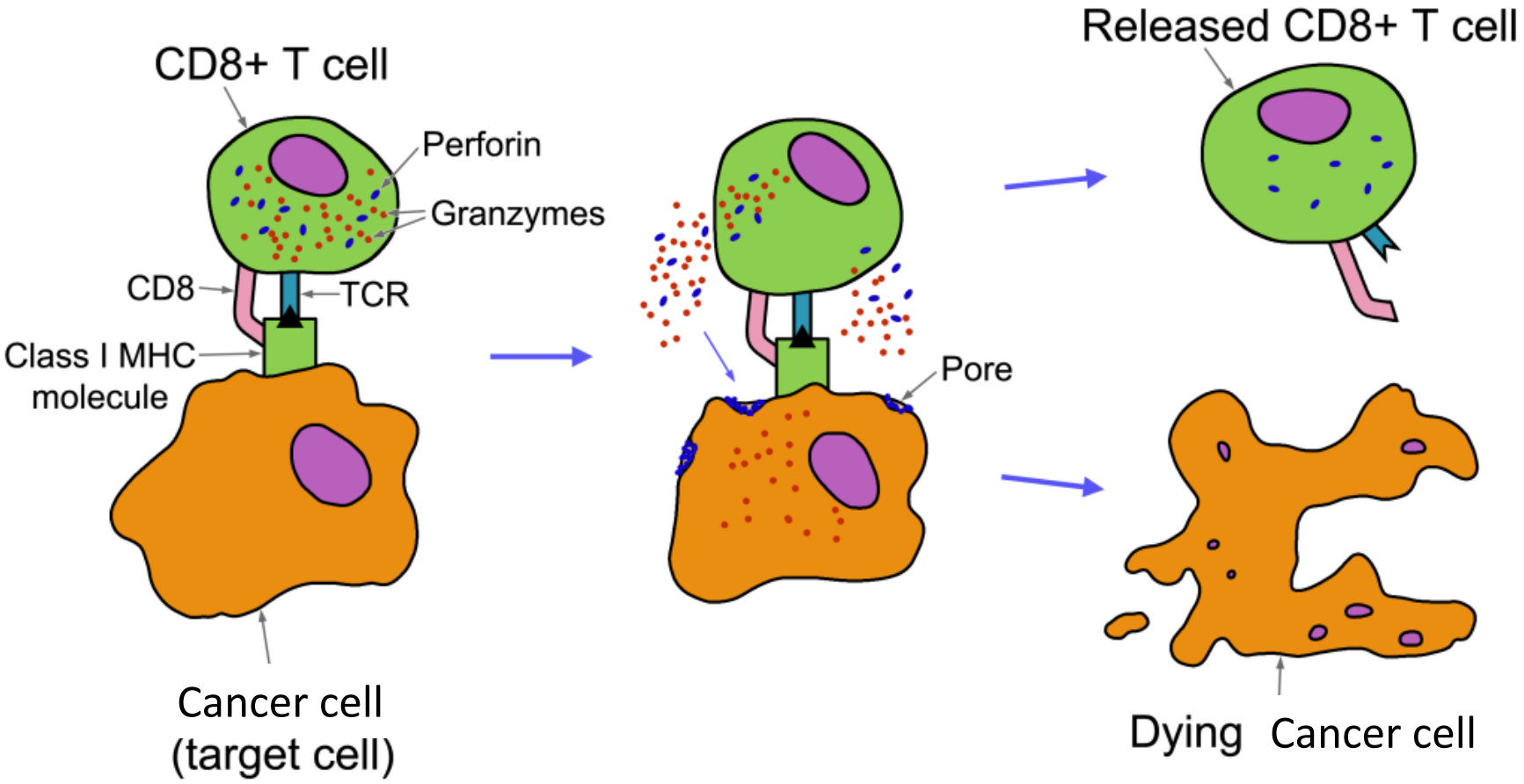


Cancer-killing cells infused back into patient

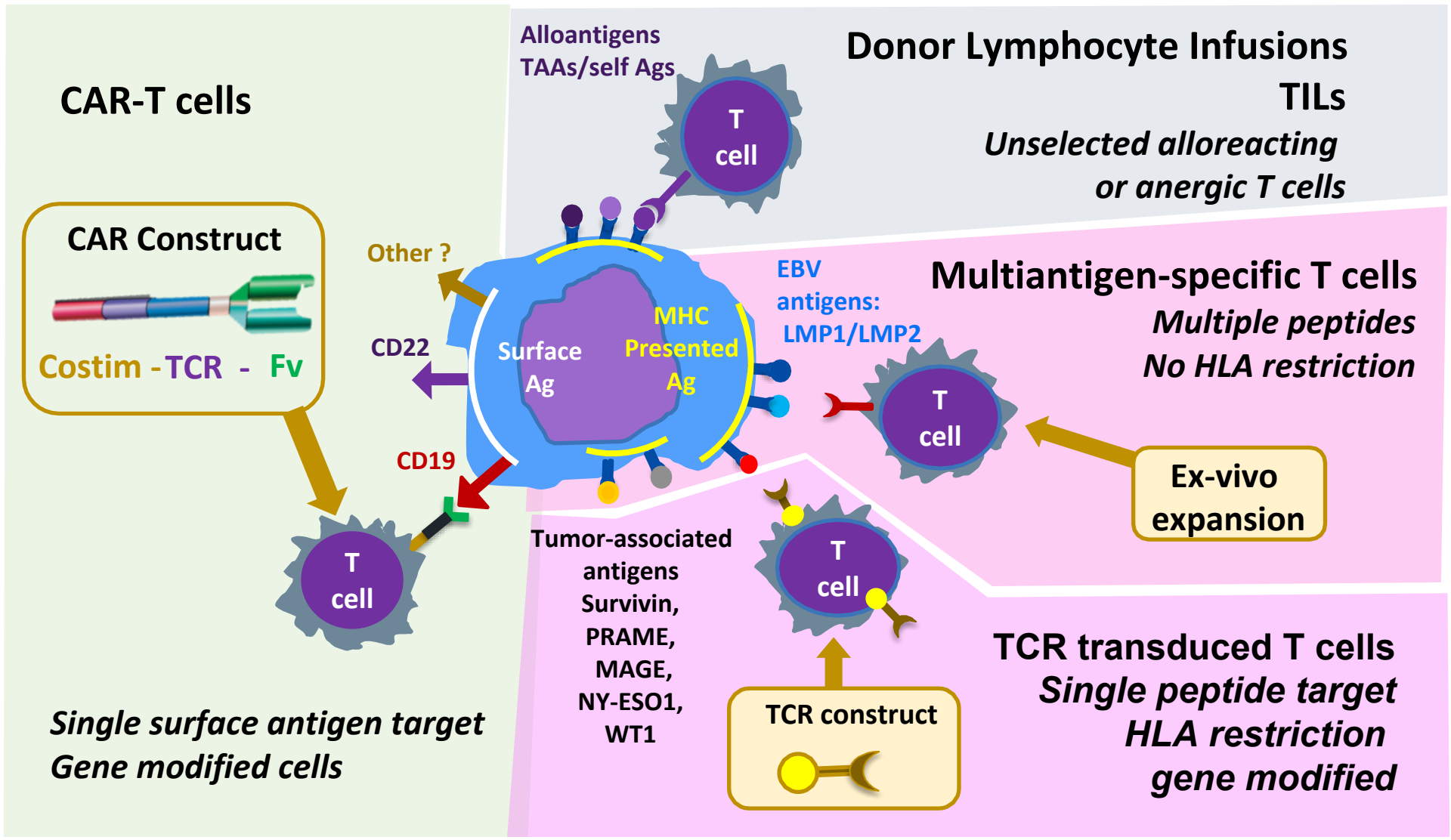
Advantages of T-cell therapies

- sequentially kill a multiplicity of target cells
- recruit additional components of the immune system
- migrate through microvascular walls, extravasate and penetrate the core of solid tumors (e.g. EBV lymphomas)

T cell mediated killing of its target cell



Antigen Targets and T cell effectors

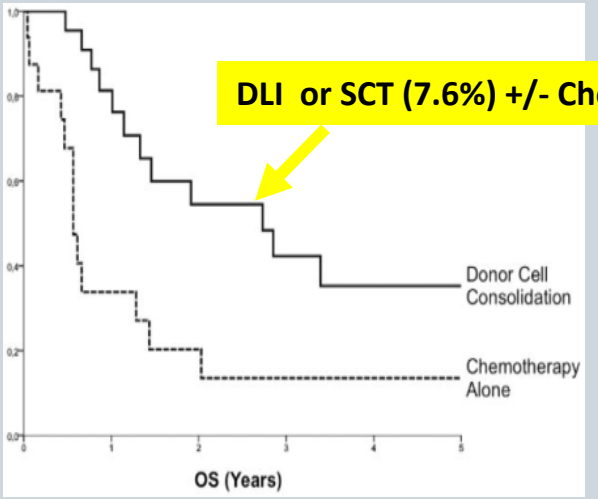


1. DLI and TILs

DLI FOR POST SCT RELAPSE MOST EFFECTIVE WITH CHEMOTHERAPY

Prolonged survival after DLI / 2nd SCT

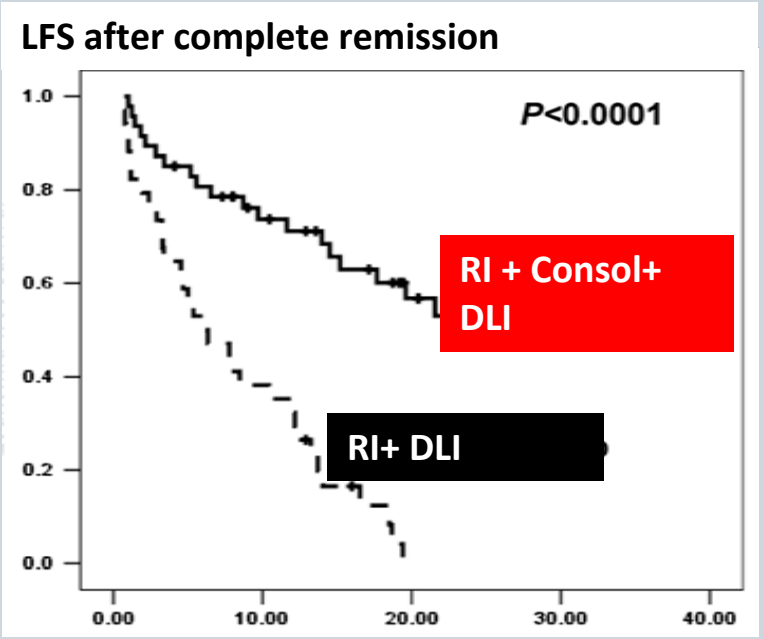
2815 RIC allo SCT (1999-2008)
263 relapse CR after relapse 32%



Schmid et al: Biol Blood Marrow Transplant. 2014 ; 20: 4–13

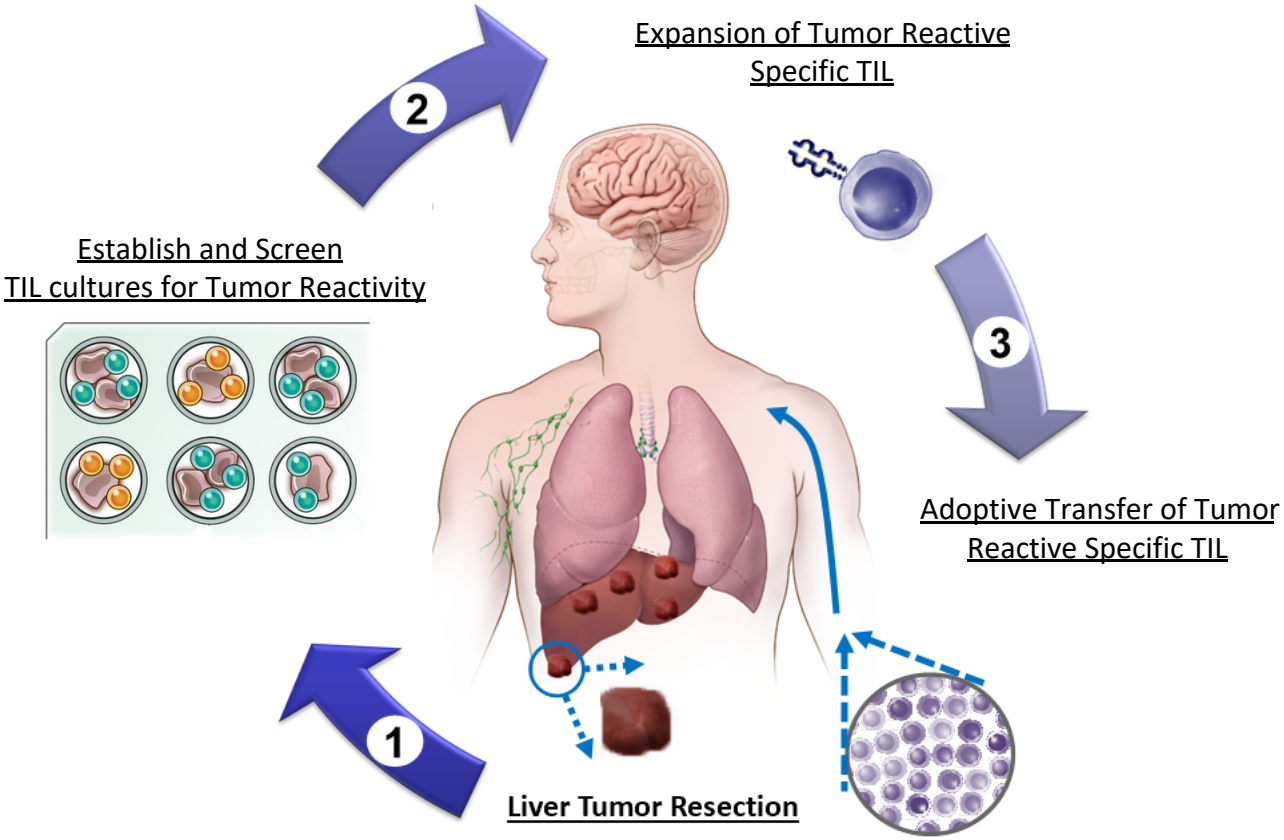
Best results for DLI after CR induction

LFS after complete remission



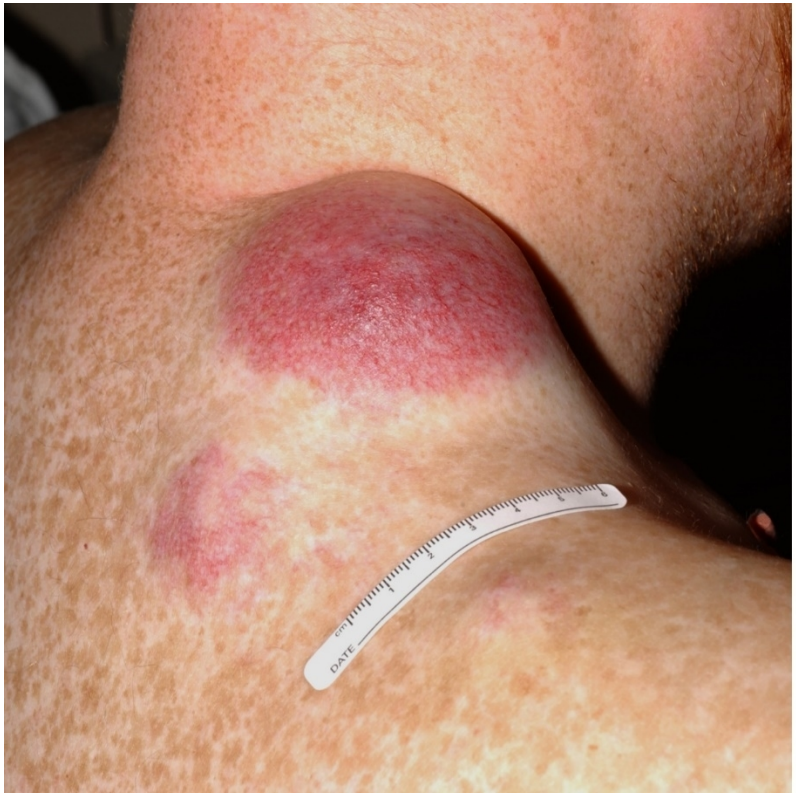
Yan et al. Journal of Hematology & Oncology (2016) 9:87

Adoptive Immunotherapy for Metastatic Melanoma

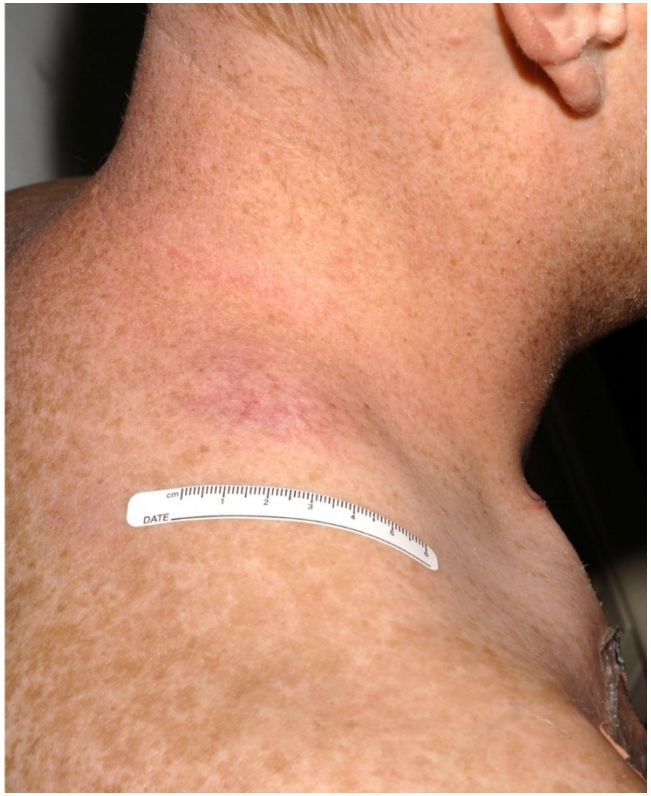


Rapid Tumor Response after TIL Transfer Therapy: Cutaneous Melanoma

Pre



12 days

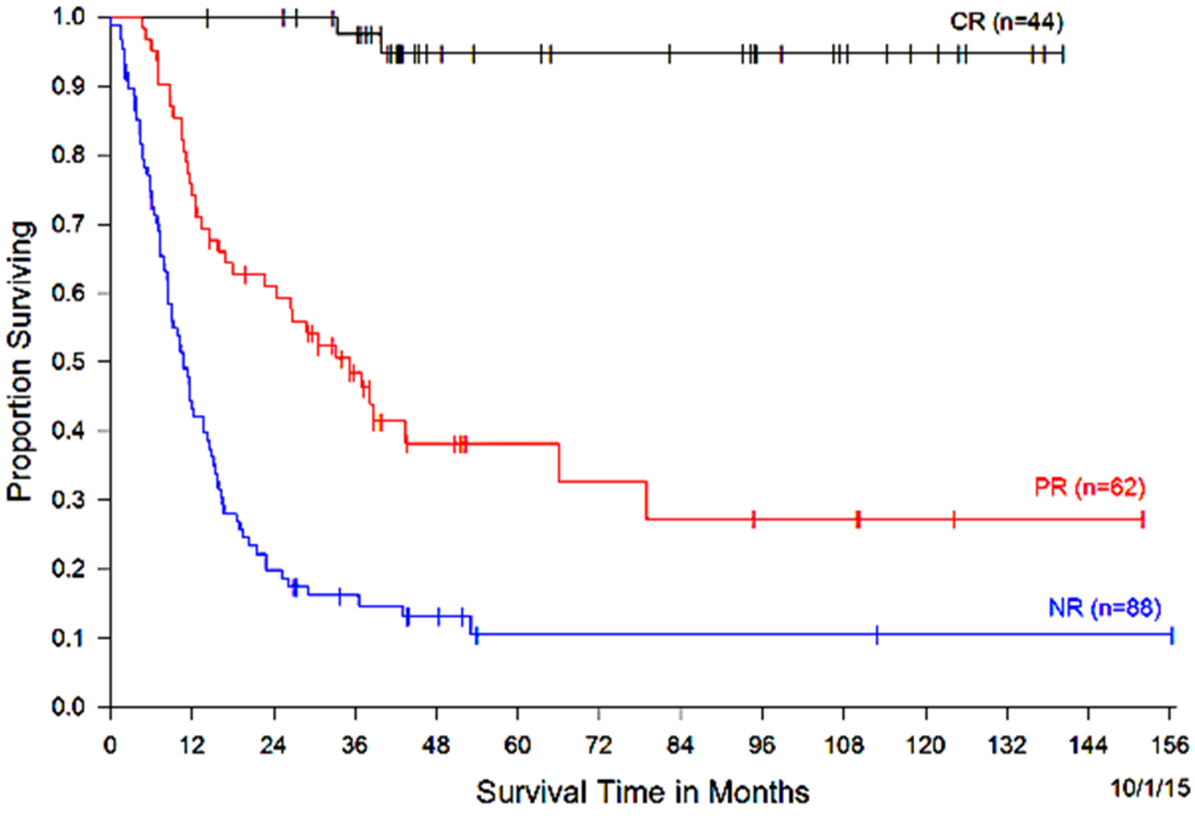


Adoptive TIL Transfer Therapy for Metastatic Cutaneous Melanoma: Surgery Branch/NIH

n	PR (%)	CR (%)	ORR (%)
194	62 (32%)	44 (23%)	106 (55%)

- *J Clin Oncol.* 2005 Apr 1;23(10):2346-57
- *J Clin Oncol.* 2008 Nov 10;26(32):5233-9
- *J Clin Oncol.* 2016 Jul 10;34(20):2389-97

Survival of Metastatic Melanoma Patients After TIL Therapy



Adoptive TIL Transfer for Additional Metastatic Solid Tumors

Cervical Cancer

3/9 responses (1 CR) - NCI

Cholangiocarcinoma

Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer.

Tran et al., *Science*. 2014 May 9;344(6184):641-5.

Colorectal Cancer

T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer.

Tran et al., *N Engl J Med*. 2016 Dec 8;375(23):2255-2262.

TIL ADVANTAGES

- Evidence of efficacy
  - Documented PR and CR rates with long durations
  - Patients with prior immunotherapy
  - Patients with brain metastases
  - Patients with advanced, high bulk disease
- One treatment
  - No ancillary therapies needed after TIL and IL-2
- TIL can now be successfully prepared from > 90% of melanoma patients (NCI, Moffitt)
- Response rates reproduced at multiple sites and in multiple countries
- Opportunity for combination with checkpoint inhibitors

TIL CHALLENGES

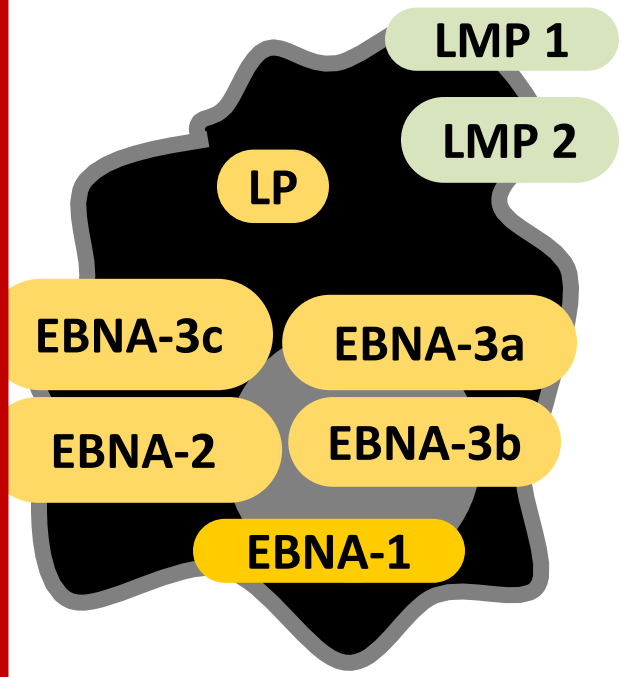
- Requires GMP manufacturing facility
- Special skills required for manufacture
- Production is expensive (labor, cytokines, plasticware)
- Length of time from tumor resection to treatment
  - Some patients may progress in the interim
- Preconditioning with cy/flu required → TOXICITY
- High dose IL-2 used
  - Inpatient treatment to monitor toxicities
  - Centers need to be comfortable administering high dose IL-2
  - IL-2 is expensive

JCI Insight. 2018 Oct 4; 3(19): e122467.

Optimizing Antigen-specific T cells

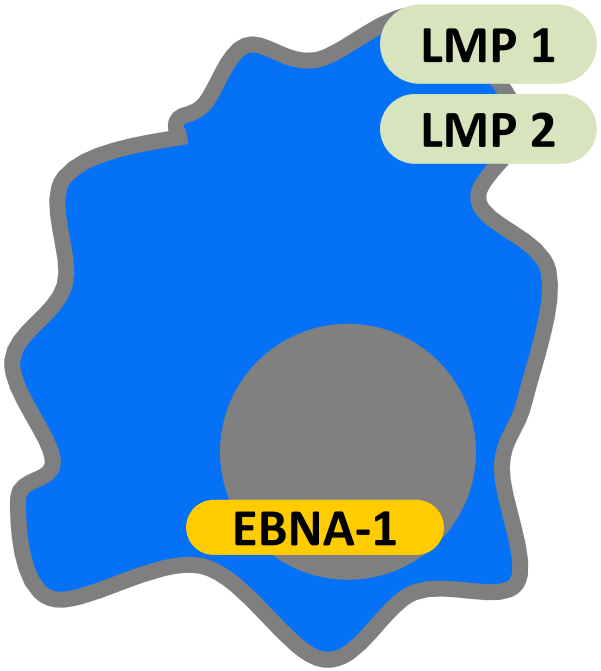
2. Targeting EBV+ Lymphomas

Types of EBV Latency



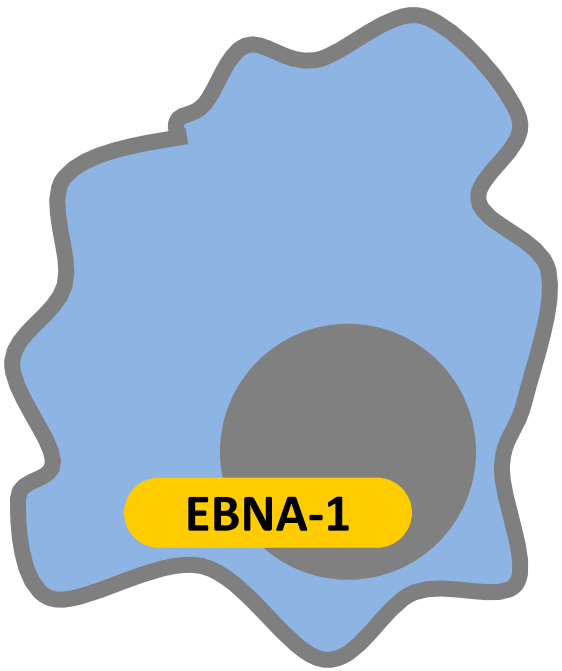
Type 3

Post transplant lymphoproliferative Disease
Lymphoblastoid cell lines



Type 2

NHL and HL
Nasopharyngeal carcinoma



Type 1

Burkitt's lymphoma

EBV-specific T cells for PTLD

- Use of EBV-CTL post HSCT is highly successful *(Rooney and Heslop, Blood 2010 / Doubrovina and O'Reilly, Blood 2012)*

  155 patients

  6.5% GVHD

  ≈91% success (durable)

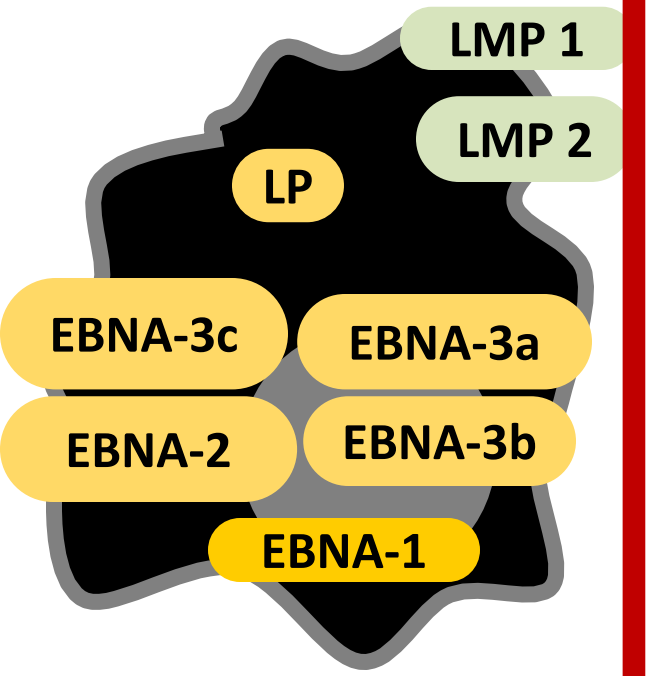
  14 failures -1 death from PTLD

  1.2% CRS ***Heslop and Bollard, Blood 2016***

Rationale of Immunotherapy for Lymphoma ….Beyond PTLD

- Significant failure rate of therapy for advanced stage or recurrent disease
- Long-term side effects of chemotherapy and radiation
- EBV antigens expressed by 20-40% of lymphomas are potential targets for T cell immunotherapy

Types of EBV Latency



Type 3

Post transplant lymphoproliferative Disease
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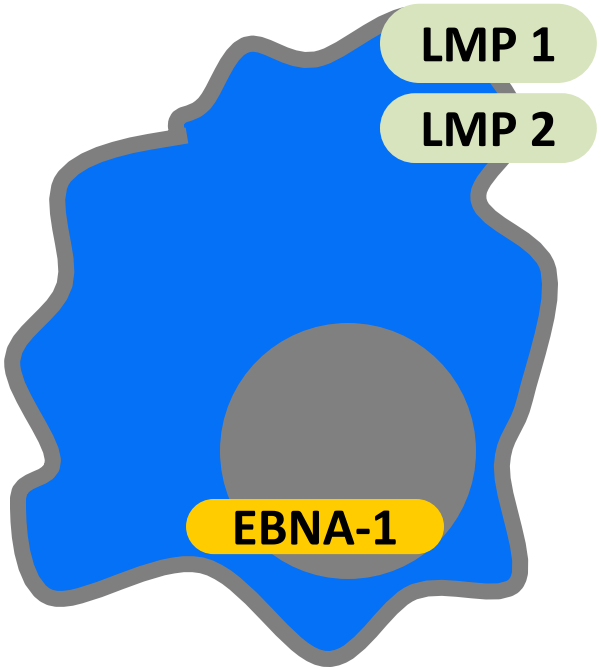
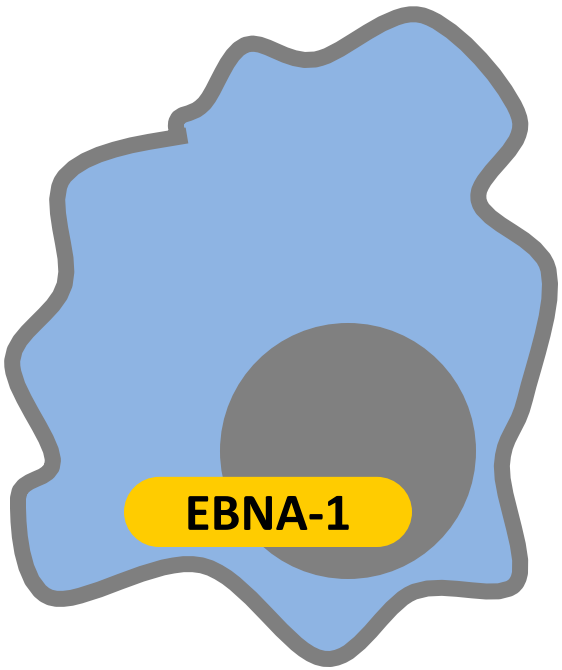


Type 2

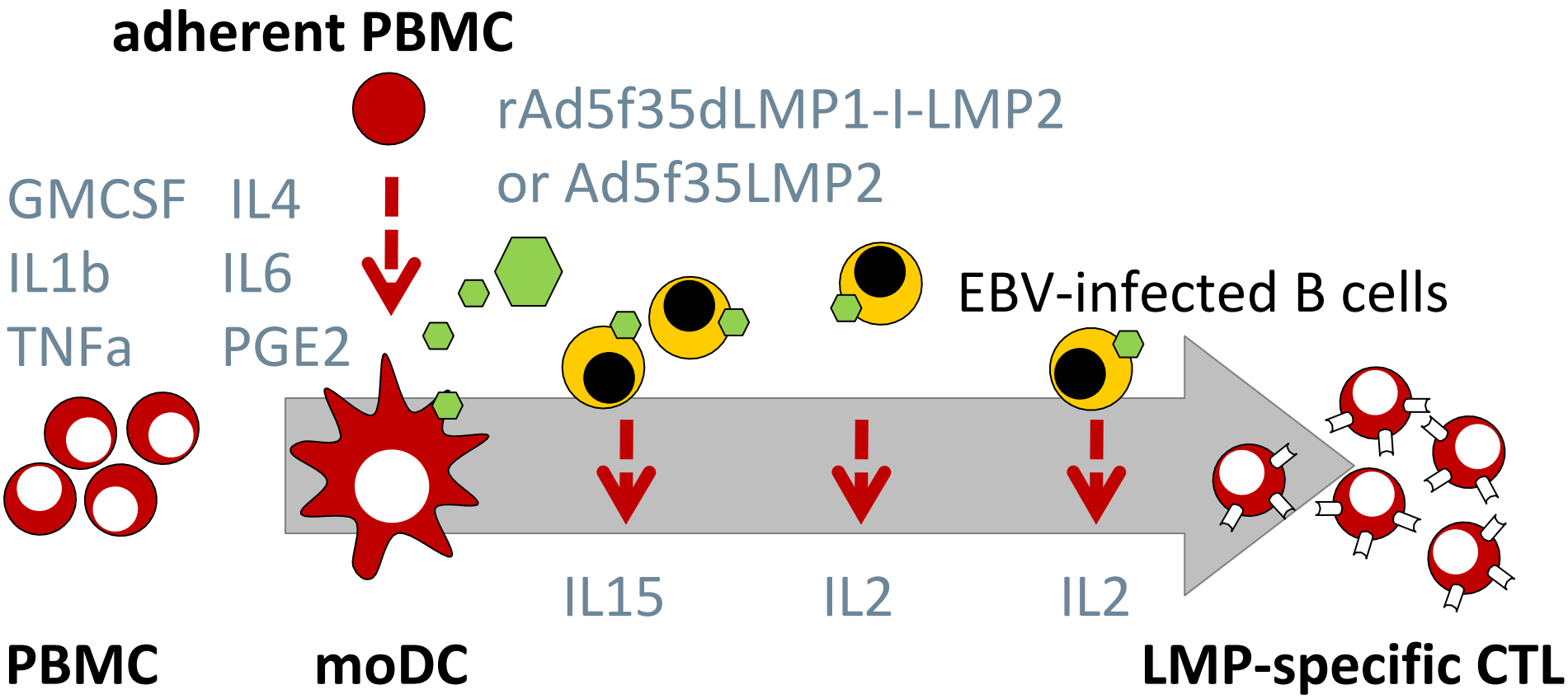
NHL and HL
NPC



Type 1

Burkitt's lymphoma

Making LMP1 and LMP2 Immunodominant Antigens

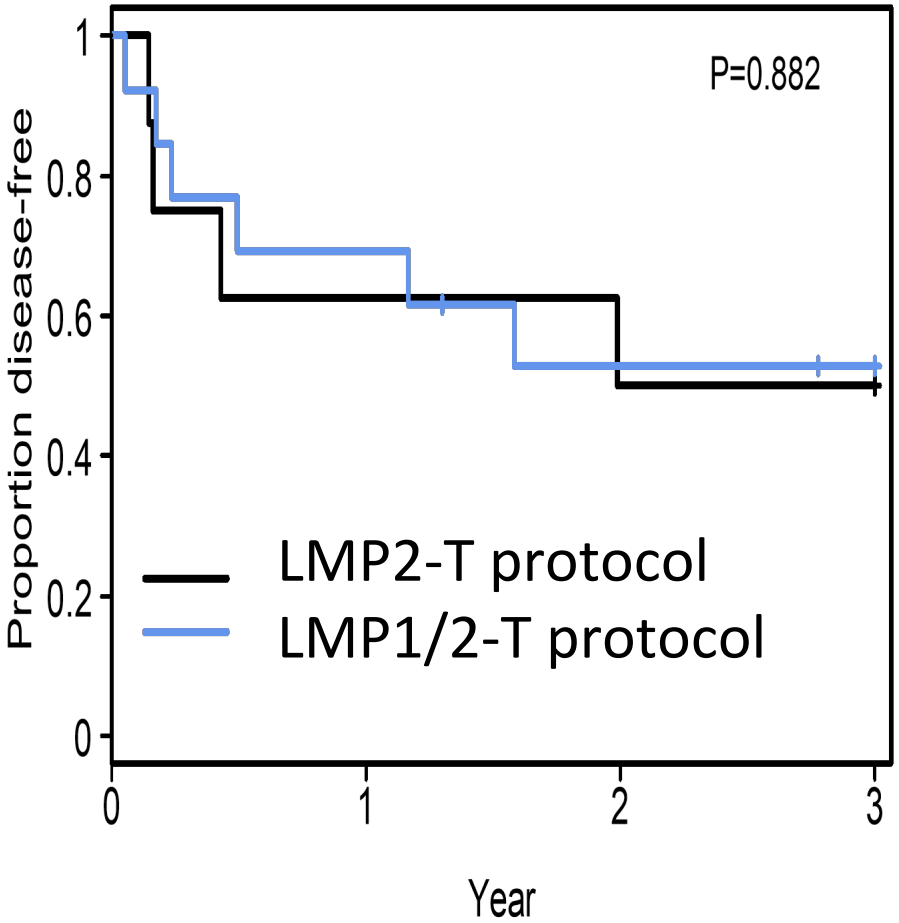


Bollard et al, JIT 2004

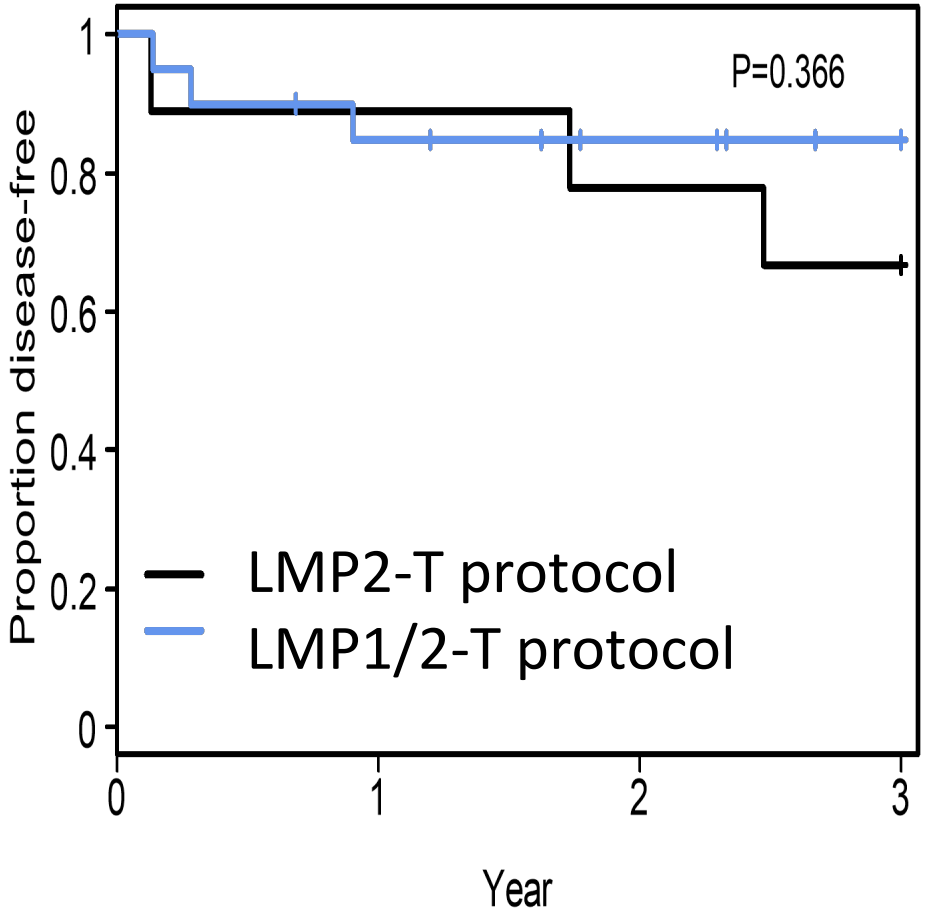
Straathof et al J Immunol 2005

Clinical Responses Post LMP T cells in Patients with Active Disease and Adjuvant Rx

12/21 CR - 50% Disease Free Survival at 2 Years



27/28 CR as Adjuvant Therapy 90% DFS at 2 years



Bollard et al, JCO 2014

Conclusions – LMP1/2 T Cells

- No toxicity
- Accumulation of LMP-T at disease sites
- Anti-tumor effects seen (13/21 patients PR/CR)

(*Bollard et al, JCO 2014*)

Next….

→ LMP T cells post allo BMT (*McLaughlin et al, Blood 2018*)

→ TGFβ resistant LMP-T (*Bollard et al, JCO 2018*)

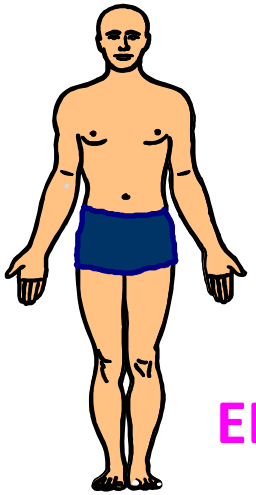
Antigen specific T cells

3: Making T cells “Off the Shelf”

Making T cell Therapies "Off the Shelf"

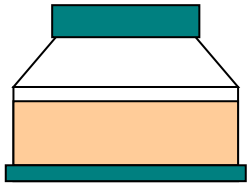
Utilizing a third party EBV/LMP T cell bank can bypass the need for an available donor, and eliminates the wait for T cell production.

Blood donor



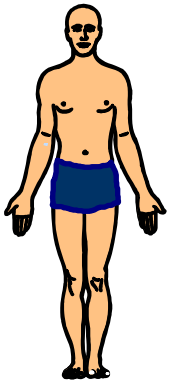
A1, A24; B8, 18; DR1, 15

EBV/LMP-T cells

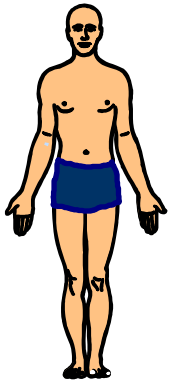


EBV activity –B8, DR15

Patients



A2, 3; **B8**, 35; DR3, 8



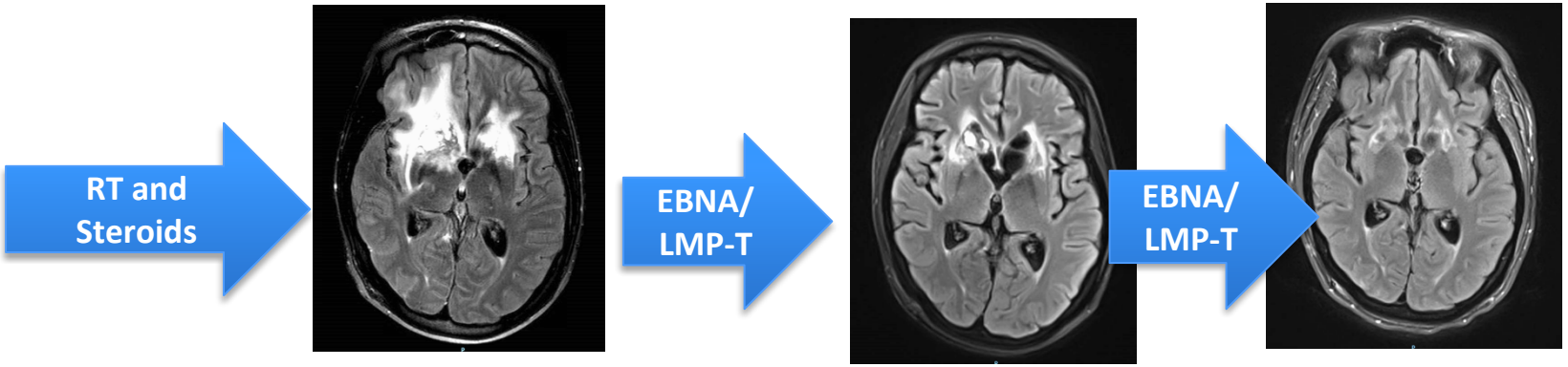
A1, 11; B7, 8; DR3, 15

Third-Party EBV-directed T cells Support Safety

Study	Target	n	SAEs	Clinical Results
Haque, 2007	EBV post SOT / BMT	33	None	14 patients achieved CR, 3 PR (52%)
Barker, 2010; Doubrovina, 2012	EBV	5	None	4 patients achieved CR (3-5 VST doses)
Uhlin, 2010	EBV	1	None	CR (2 VST doses)
Leen, 2013	CMV, EBV, Adv	50	8 cases GvHD after VST (2 *de novo*)	74% CR/PR (69% for EBV n=9)
Tzannou, 2017	EBV, BKV, CMV, Ad, HHV6	38	2 cases *denovo* GVHD (grade I)	92% CR/PR (100% for EBV n=2).
Prockop, JCI, 2020	EBV post SOT/BMT	46	None	65% CR/PR (BMT) 54% CR/PR (SOT)

CNS Disease Successfully Treated with 3rd party EBV-directed T cells

87% CR/PR after SOT or BMT (MSKCC, BCM, CNMC)

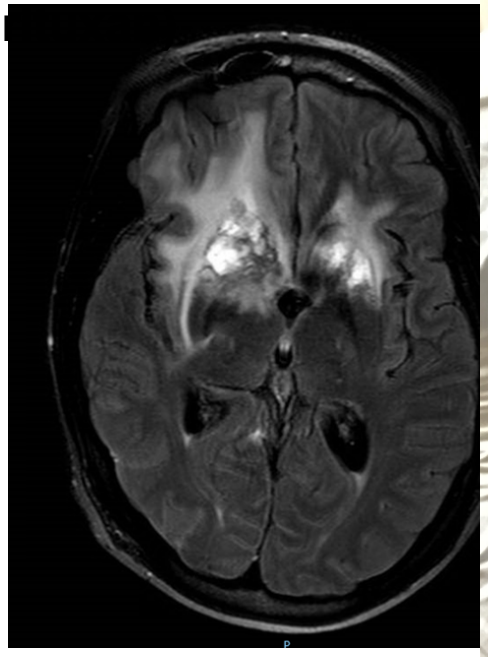


Prockop et al, JCI 2020
Bollard et al, ASHI 2017 Keller et al, ESID 2017

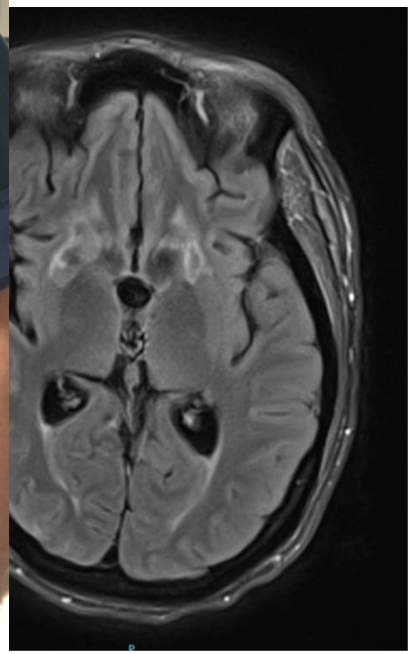
Pakakasama S et al, Transplantation. 2004

Third party erapy

Pre-VST therapy (following steroids,XI



months post ST dose 2



Mike Keller, unpublishe

4. Antigen specific T cells - Targeting tumor associated antigens (TAA)

Targeting TAAs in Heme Malignancies– The Shortlist

Goswami et al, Leukemia 2014 *Rooney et al, Imm Rev 2014*	AML	CML	ALL	CLL	HL	NHL
WT1	+	+	+			
Proteinase 3	+	+				
PRAME	+	+	+		+	+
RHAMM	+	+	+	+		
Aurora A Kinase	+	+	+			
MAGE	+	+		+	+	+
MPP11				+		
HAGE	+	+				
BCR/ABL	+	+		+		
NY ESO 1		+				+
BMI-1		+		+		
Telomerase	+	+	+	+		
Fibromodulin				+		
Syntaxin				+		
SSX					+	+
Survivin	+	+	+	+	+	+

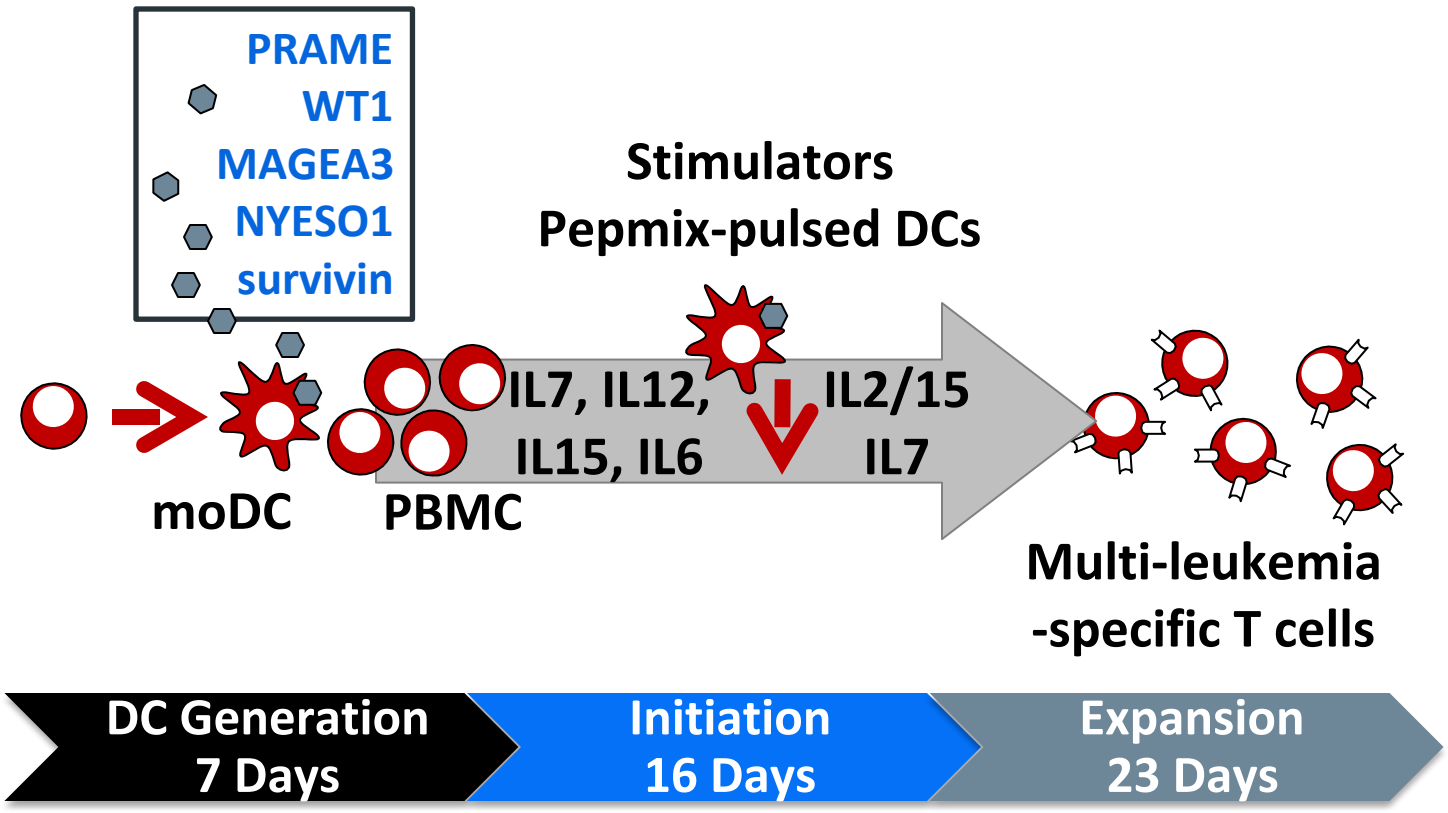
Use of Donor-derived WT-1 specific T cells for Acute Leukemia

- 11 patients infused with HLA-A*0201-restricted WT1-specific donor-derived CD8+ T cell clones.
- No attributed toxicities/GVHD.
- 2 clinical responses
- 3 patients at high risk for relapse remain in CR.
- CTLs generated in the presence of IL-21 remained detectable long-term

Studies using WT1 specific T cells generated using overlapping peptides ongoing at MSKCC
(Koehne and O'Reilly)

Chapuis and Greenberg Sci Trans Med 2013

Clinical Use of Multi TAA T cells for Cancer



Weber et al, CCR 2013, ***Weber et al, Leukemia 2013****, Gerdemann et al, Mol Ther 2012*

TAA-T for AML after Allogeneic SCT – Phase I study

TAA: WT1 NyESO PRAME Survivin Dose escalation 5 x 10^6 → 1x 10^7 → 2 x 10^7 /m^2

27 enrolled

20 treated

13 HIGH RISK for relapse ADJUVANT

- 3 CR2/3
- 3 FLT3-ITD
- 3 MDS tAML
- 2 MLL-r
- 1 Ph+
- 1 DNMT3a

- 8 CCR
- 4 Relapsed

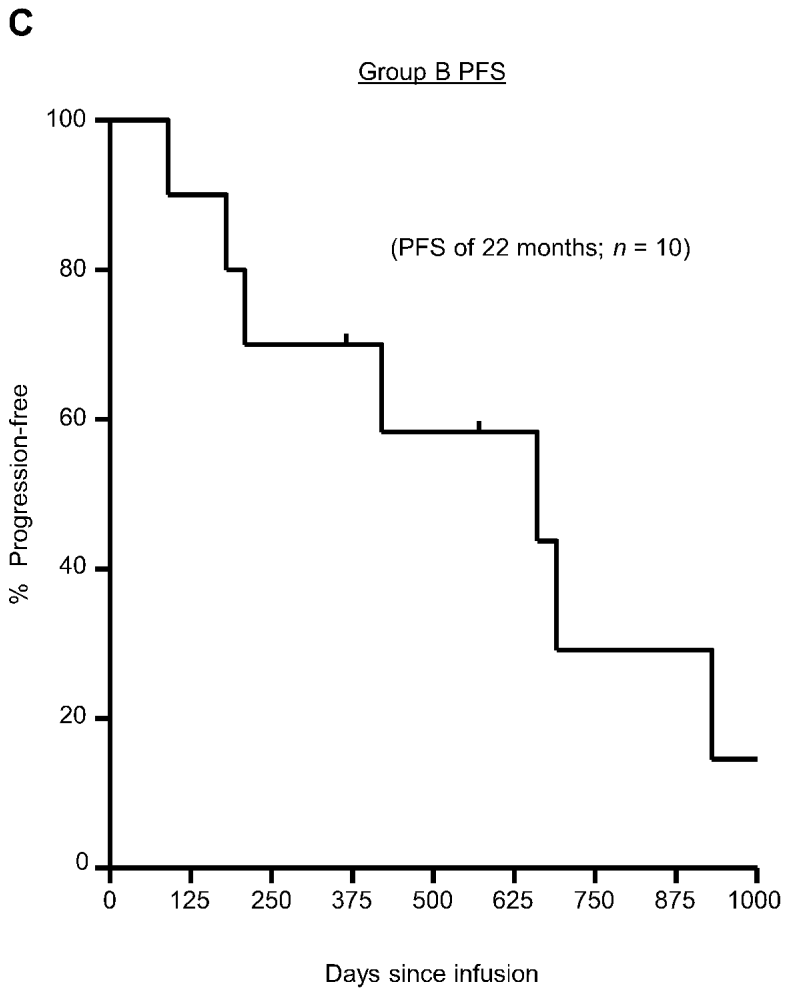
7 RELAPSE /ACTIVE DISEASE POST SCT >d30

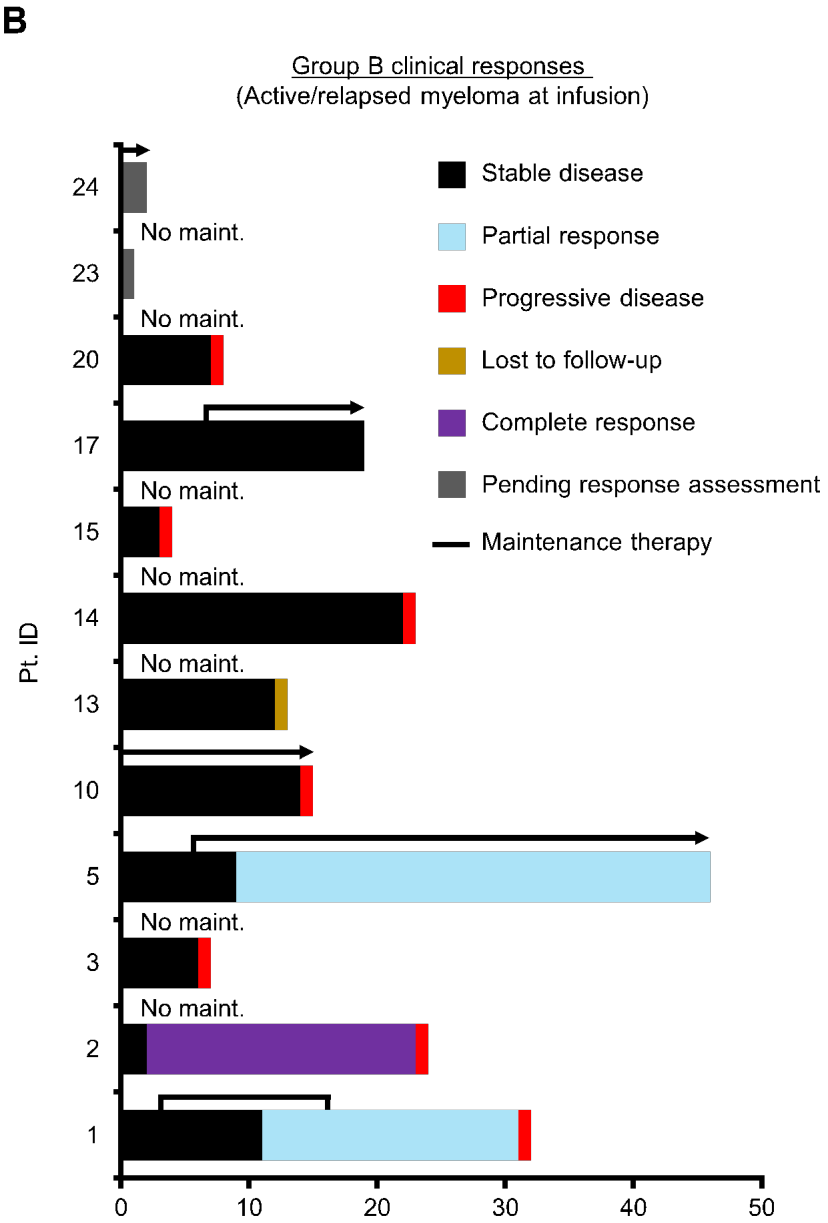
- 5 30-70% blasts in BM
- 2 extramedullary relapse

- 1 CR
- 1 PR
- 4 NR
- 1 NE

Lulla et al , TCT meeting 2019 and Blood 2020

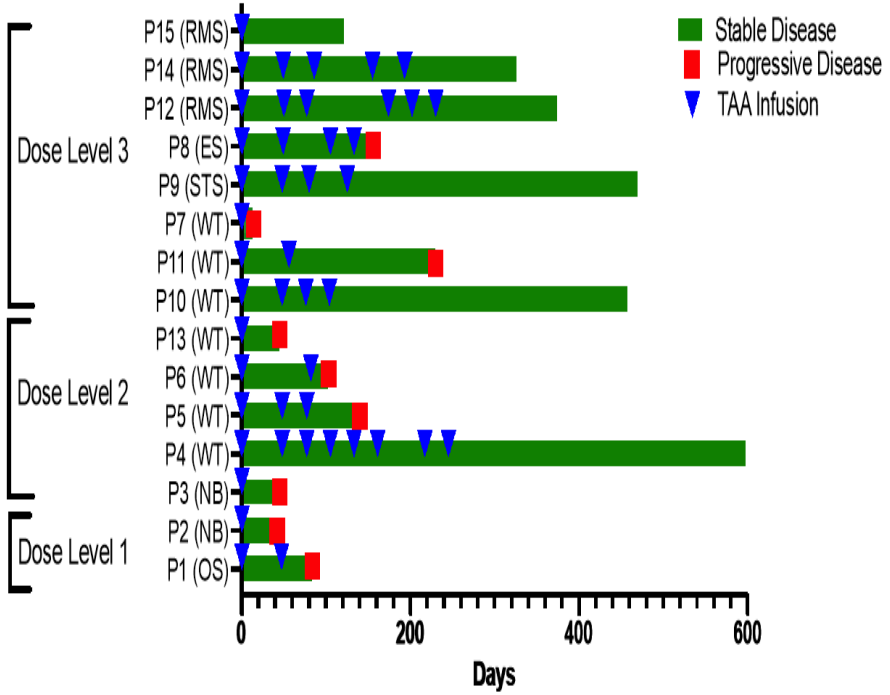
Use of TAA-T cells in Myeloma

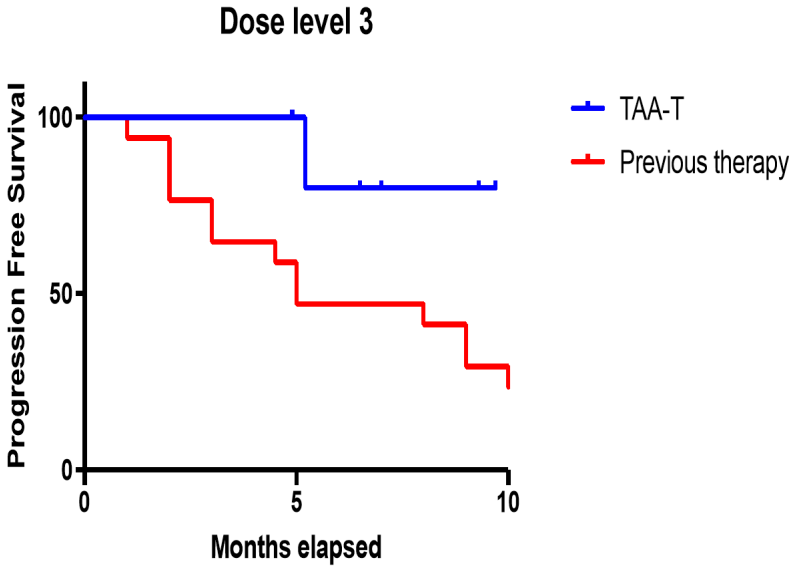




Lulla et al, STM 2020

Prolonged Disease Stabilization in Patients with Solid Tumors post TAA-T





No SAEs attributable to Rx

No CRS

Hont et al JCO 2019

Summary- Use of TAA-T as Treatment for Relapsed Cancers

- TAA-T cells can be generated from healthy donors for clinical use (> 90% success rate)
- TAA-T cells are safe for patients with relapsed hematopoietic malignancies (lymphoma, AML, myeloma) after chemotherapy/autologous BMT and post allo HSCT
- Early evidence of efficacy?

5. abTCR transduced T cells

HIGH AFFINITY WT1 TCR TRANSDUCED T CELLS TO PREVENT POST SCT RELAPSE

12 AML HLA A2 (10 proven WT1 +) RISK: 6 adverse, 4 intermediate, 2 favorable

At transplant 8 CR 4 detectable disease

Days between SCT and T cell infusion 47-175 median 100d

1-4 infusions of WT1 high affinity TCR transfected into donor EBV specific CD8+ T cells

Study group
12 AML
100% RFA at 44 mo

P = 0.002

Comparative untreated group
88 AML
54% RFS

Long-term persistence of functional WT1 TCR T cells

Chapuis et al 2019 Nature Medicine 25: 1106

Published clinical TCR-T therapy for solid tumors and Myeloma.

Target	Disease	Vector	Pretreatment	#patients	Response
MART-1	Melanoma	Retrovirus	Chemotherapy	20	30% objective antitumor response
Gp100	Melanoma	Retrovirus	Chemotherapy	16	19% objective antitumor response
CEA	Colorectal	Retrovirus	Chemotherapy	3	1 objective response
NY-ESO-1	Melanoma/ sarcoma	Retrovirus	Chemotherapy	17	2 CR; 1 PR
NY-ESO-1	MM	Lentivirus	Chemotherapy	20	80% maintained remissions post ASCT
MAGE A3	Melanoma Sarcoma Esophageal	Retrovirus	Chemo/RT/Surgery	9	4 PR (4-12+mths), 1 CR (15+mths)
MAGE-A3	Melanoma /MM	Lentivirus	CY	2	2 died of cardiac toxicities (titin)
MAGE-A4	Esophageal	Retrovirus	Surgery; radiotherapy; chemotherapy	10	7/10 tumor progression

Zhao L, Cao YJ. Engineered T Cell Therapy for Cancer in the Clinic. *Front Immunol*. 2019;10:2250. Published 2019 Oct 11. doi:10.3389/fimmu.2019.02250

Cancer Regression and Neurological Toxicity Following Anti-MAGE-A3 TCR Gene Therapy

Richard A. Morgan, Nachimuthu Chinnasamy,* Daniel Abate-Daga,* Alena Gros,* Paul F. Robbins,* Zhili Zheng,* Mark E. Dudley,* Steven A. Feldman,* James C. Yang,* Richard M. Sherry,* Giao Q. Phan,* Marybeth S. Hughes,* Udai S. Kammula,* Akemi D. Miller,* Crystal J. Hessman,* Ashley A. Stewart,* Nicholas P. Restifo,* Martha M. Quezado,† Meghna Alimchandani,† Avi Z. Rosenberg,† Avindra Nath,‡ Tongguang Wang,‡ Bibiana Bielekova,‡ Simone C. Wuest,‡ Nirmala Akula,§ Francis J. McMahon,§ Susanne Wilde,‖ Barbara Mosetter,‖ Dolores J. Schendel,‖¶ Carolyn M. Laurencot,* and Steven A. Rosenberg**

Case Report of a Fatal Serious Adverse Event Upon Administration of T Cells Transduced With a MART-1-specific T-cell Receptor

Joost H van den Berg[1,2], Raquel Gomez-Eerland[1], Bart van de Wiel[3], Lenie Hulshoff[4], Daan van den Broek[5], Adriaan Bins[6], Hanno L Tan[7], Jane V Harper[8], Namir J Hassan[8], Bent K Jakobsen[8], Annelies Jorritsma[1], Christian U Blank[1,6], Ton NM Schumacher[1] and John BAG Haanen[1,6]

Plenary Paper

CLINICAL TRIALS AND OBSERVATIONS

Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma

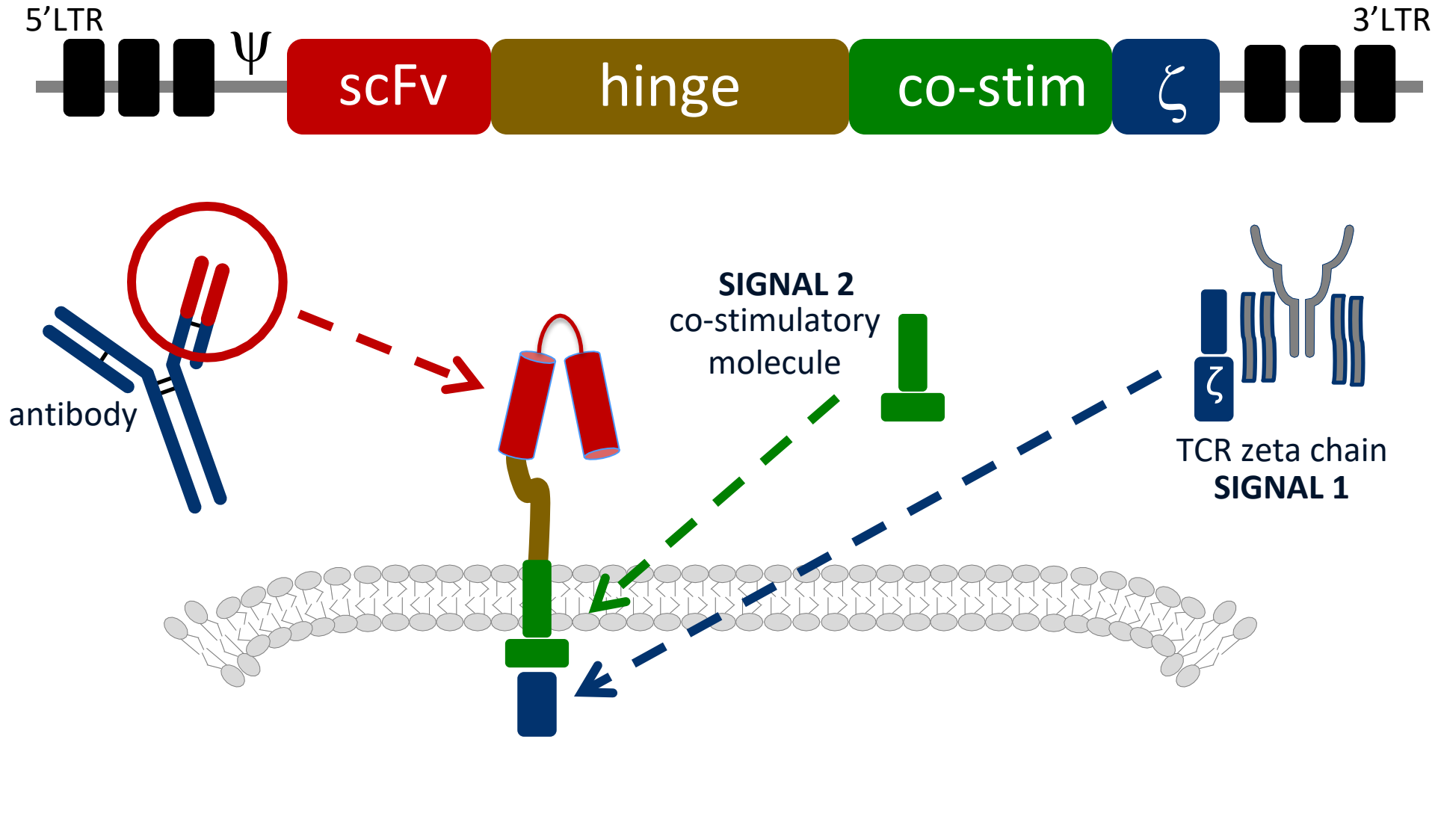
Gerald P. Linette,[1] Edward A. Stadtmauer,[2] Marcela V. Maus,[2] Aaron P. Rapoport,[3] Bruce L. Levine,[2] Lyndsey Emery,[2] Leslie Litzky,[2] Adam Bagg,[2] Beatriz M. Carreno,[1] Patrick J. Cimino,[1] Gwendolyn K. Binder-Scholl,[4] Dominic P. Smethurst,[4] Andrew B. Gerry,[4] Nick J. Pumphrey,[4] Alan D. Bennett,[4] Joanna E. Brewer,[4] Joseph Dukes,[5] Jane Harper,[5] Helen K. Tayton-Martin,[4] Bent K. Jakobsen,[4,5] Namir J. Hassan,[5] Michael Kalos,[2] and Carl H. June[2]

[1]Siteman Cancer Center and Departments of Medicine and Pathology and Immunology, Washington University School of Medicine, St. Louis, MO; [2]Abramson Cancer Center, Department of Medicine, and Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA; [3]The Greenebaum Cancer Center, University of Maryland, Baltimore, MD; [4]Adaptimmune Ltd, Philadelphia and Abingdon, United Kingdom; and [5]Immunocore Ltd, Abingdon, United Kingdom

Chimeric Antigen Receptor (CAR) T cells

4: CD19 CAR T cells

Designing a Chimeric Antigen Receptor



Redirecting the Specificity of T Cells

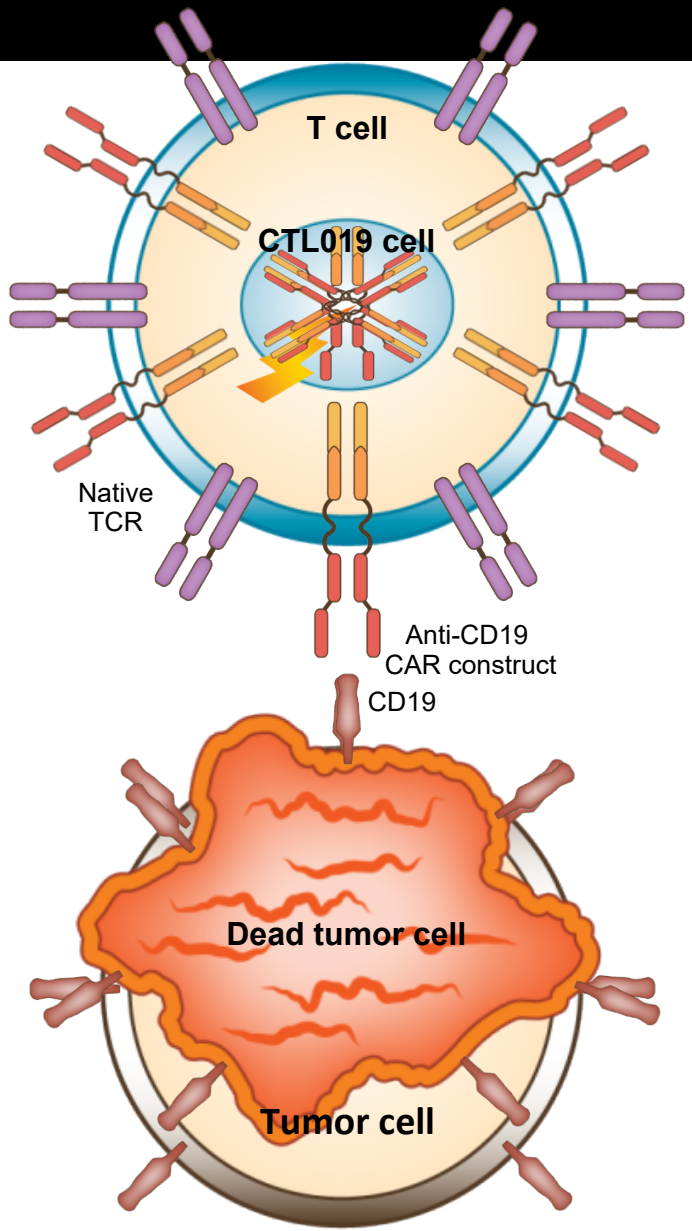
- Different transduction systems to get CARs into T cells:

→Retroviral transduction

→Lentiviral transduction

versus

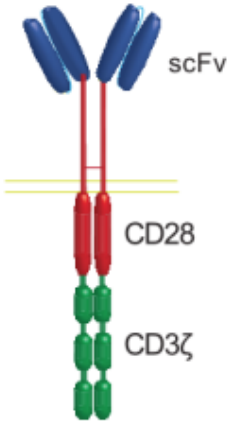
→ non viral transduction (Sleeping Beauty)



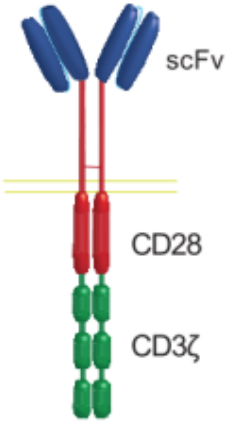
Courtesy of David Porter- U Penn

Original CD19 CARs

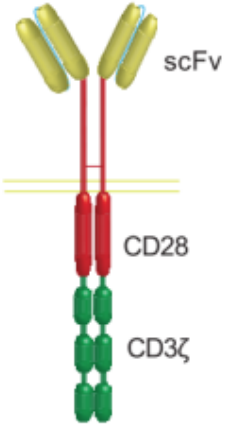
MSKCC
CD28z CAR



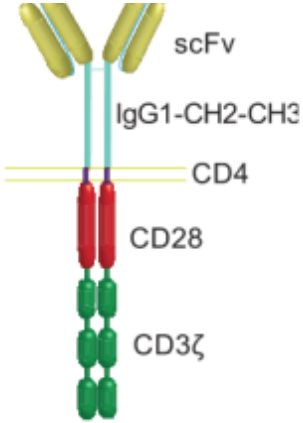
Juno
MSKCC



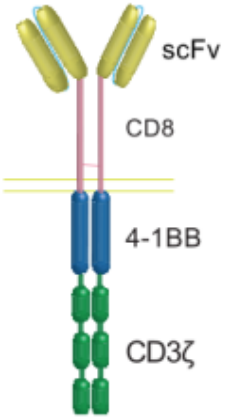
Axicabtagene Ciloleucel
Kite/Gilead (*NCI*)



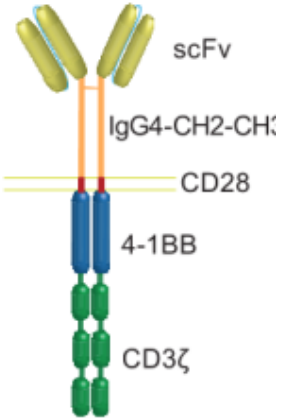
Bluebird Bio
Baylor



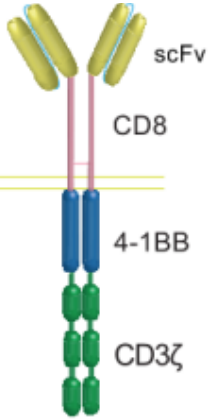
SJRH-4
4-1BB CAR



Lisocabtagene Maraleucel
Juno (*FHCRC*)



Novartis Tisagenlecleucel
CHOP + UPenn



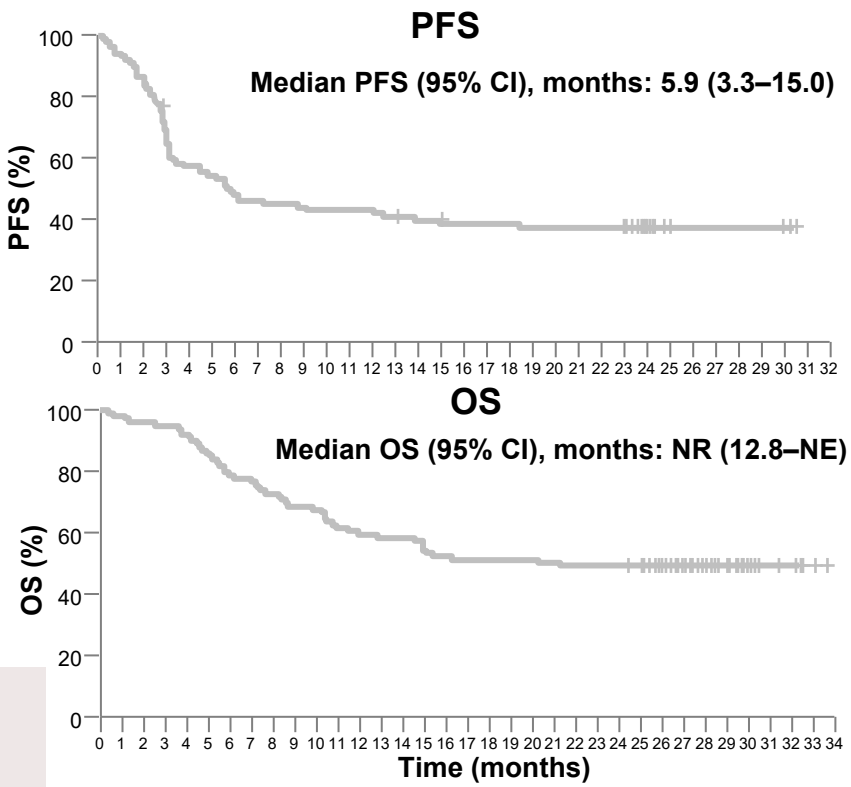
Courtesy of
M Sadelain MSKCC

Three Major anti-CD19 CAR T-cell Products for Aggressive B-cell NHL

	Axicabtagene Ciloleucel (KITE)	Tisagenlecleucel (Novartis)	Lisocabtagene Maraleucel (Juno)
Construct	antiCD19-**CD28**-CD3z	antiCD19-**41BB**-CD3z	antiCD19-**41BB**-CD3z
Vector	Retrovirus	Lentivirus	Lentivirus
T-cell manufacturing	Bulk	Bulk	Defined doses CD4, CD8
Dose	2×10^6/kg (max 2×10^8)	0.6 to 6.0×10^8	DL1: 0.5×10^7 DL2: 1.0×10^8 DL3: 1.5×10^8
Bridging therapy	None allowed in pivotal trial but often used in standard practice	93%	72%
Lymphodepletion	Flu/Cy 500/30 x 3d	Flu/Cy 250/25 x 3d, or Benda	Flu/Cy 300/30 x 3d
Approval status	FDA/EMA approved for DLBCL, high grade B-cell lymphoma, transformed FL, PMBCL	FDA/EMA approved for pediatric B-ALL, DLBCL, high grade B-cell lymphoma, transformed FL	Not yet FDA/EMA approved

Characteristics	Phase 1 and 2 (N = 108)
Median age (range), years	58 (23–76)
Age ≥ 65 years, n (%)	27 (25)
Disease stage III/IV, n (%)	90 (83)
IPI risk score 3 or 4, n (%)	48 (44)
≥ 3 prior therapies, n (%)	76 (70)
Refractory to 2nd- or later-line therapy, n (%)	80 (74)
Best response as PD to last prior therapy, n (%)	70 (65)
Relapse post ASCT, n (%)	25 (23)

2 yr PFS approx 40%



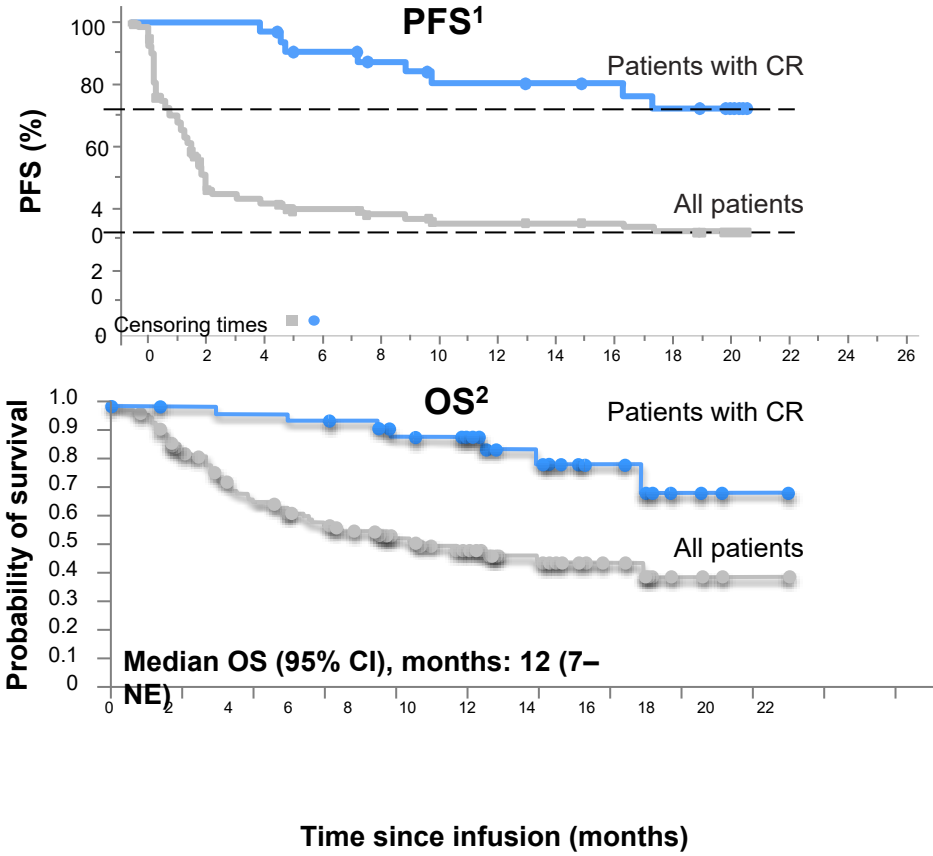
ORR: (n=101): **83%** [74% by IRC]
CR: **58%** [54% by IRC]

Locke FL, et al. Lancet Oncol. 2019;20:31-42.

JULIET: PFS and OS of patients with R/R DLBCL receiving tisagenlecleucel (CD19-CAR.41BB)

Characteristics	Patients (N = 111)
Median age (range), years	56 (22–76)
Double-/triple-hit lymphoma, %	27
Number of prior lines of therapy, %	
2	44
3	31
4–6	21
Refractory to last therapy, %	55
Prior ASCT, %	49

2 yr PFS approx 38% (70% if in CR)



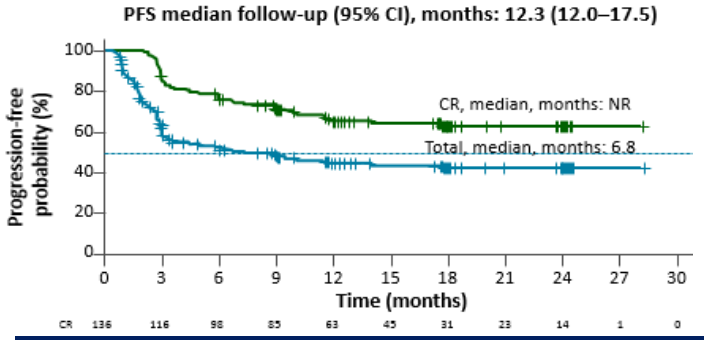
Schuster SJ, et al. N Engl J Med. 2019;380:45-56

ORR: 52%
CRR: 40%

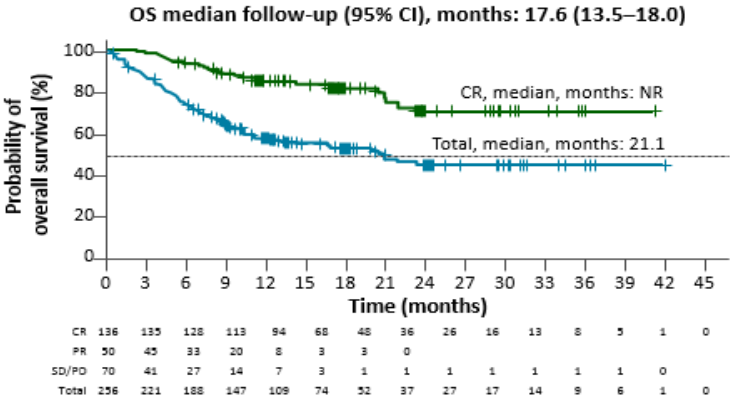
TRANSCEND-NHL-001 trial: liso-cel in multiply R/R aggressive B-NHL (CD19.CAR.41BB - CD4/CD8)

Characteristic	Patients (N = 269)
Age, median (range), years	63 (18–86)
Double- / triple-hit lymphoma, n (%)	36 (13)
CNS involvement, n (%)	7 (3)
Median prior lines, n (range)	3 (1–8)
Chemo-refractory, n (range)	181 (67)
Prior HSCT, n (%)	94 (35)

Best response	Patients (N = 256)
Best ORR, %	73
Best CR, %	53
12-month duration of response, %	55



2 yr PFS approx 45% (70% if in CR)



Abramson JS, et al. The Lancet 2020.

ORR: 73%
CRR: 53%

Notable CAR-T Toxicities

- Cytokine Release Syndrome (CRS)
- Neurological toxicity
  - CAR T-cell associated Encephalopathy Syndrome (CRES)
  - Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)
- Prolonged cytopenias
- B-cell aplasia
- Hypogammaglobulinaemia
- Toxicities are usually manageable and reversible

Toxicity of 3 Major CAR T-cell Products for relapsed/refractory DLBCL

	Axicabtagene Ciloleucel	Tisagenlecleucel	Lisocabtagene Maraleucel
Construct	antiCD19-**CD28**-CD3z	antiCD19-**41BB**-CD3z	antiCD19-**41BB**-CD3z
n	101	111	269
Any CRS Median time to onset	93% 2 days	58% 3 days	42% 5 days
≥ Gr 3 CRS†	11%	23%	**2%**
Any neurotoxicity	**64%**	21%	30%
≥ Gr 3 neurotoxicity	**32%**	12%	10%
Tocilizumab	43%	15%	20%
Steroid use	27%	11%	21%
	Locke, et al. Lancet Onc 2018	Schuster, et al. NEJM 2018	Abramson, et al. Proc ASH 2019

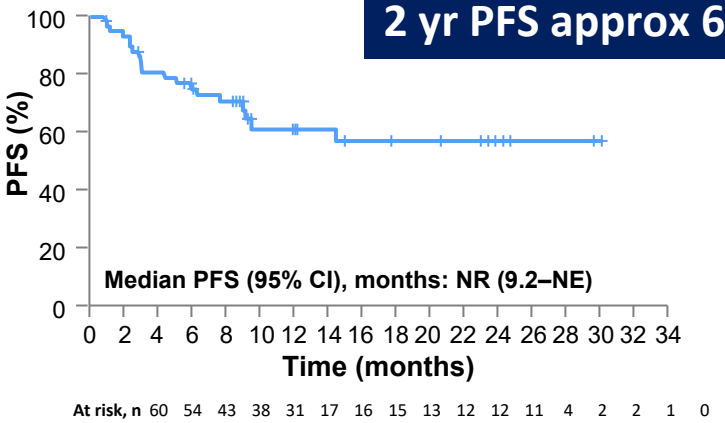
* Caveats in cross trial comparisons: Different eligibility criteria, phase of study, dose levels

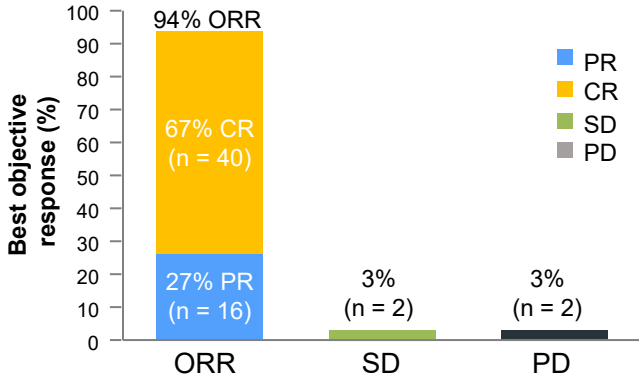
†CRS toxicity grading scales differ across studies. Axi-Cel and Liso-cel used Lee criteria. Tisa-cel used Penn criteria

ZUMA-2: Brexucabtagene autoleucel (KTE-X19) in relapsed/refractory mantle cell lymphoma

Characteristics	n = 68
Age, median (range), years	65 (38-79)
Median no. of prior treatments (range)	3 (1–5)
Prior BTKi, n (%)	68 (100)
BTKi refractory, n (%)	42 (62)
Prior ASCT, n (%)	29 (43)
Ki67 ≥ 30%, n/N (%)	40/49 (82)
Blastoid variant, n (%)	21 (31)

2 yr PFS approx 60%





Toxicity	n = 68
Any-grade CRS, n (%)	62 (91)
Grade 3 or 4 CRS, n (%)	10 (15)
Time to onset, median, days (range)	2 (1–13)
Any-grade neurological toxicity, n (%)	43 (63)
Grade 3 or 4 neurological toxicity, n (%)	21 (31)
Time to onset, median, days (range)	7 (1–32)

- **KTE-X19 approved by FDA.** ASCT, autologous stem cell transplant; BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; CR, complete remission; CRS, cytokine release syndrome; NE, not estimatable; NR, not reached; NT, neurological toxicity; mORR, overall response rate; PD, progressive disease; PR, partial response; PFS, progression-free survival; SD, stable disease.
- Wang M, et al. N Engl J Med. 2020;382:1331-42.

Current Challenges and Opportunities

- Understand and overcome mechanisms of resistance
- Understand sequencing and combining of novel agents pre CAR, at bridging, and post CAR
- Move CAR T-cells earlier in the course of disease
- Expand indications
- Further understand mechanisms of toxicities and develop prophylactic strategies
- Develop new CAR T-cell constructs including off the shelf products

BCMA-CAR T cells for Myeloma

B-cell maturation antigen (BCMA)-directed CAR T cells have shown promising efficacy and safety profiles in various phase I/II clinical trials.

CR rates range from <10- 30%

However, almost all treated patients continue to relapse

A BCMA-directed product for the treatment of multiple myeloma may be approved in 2021

Curr Opin Oncol . 2020 Jul 27.

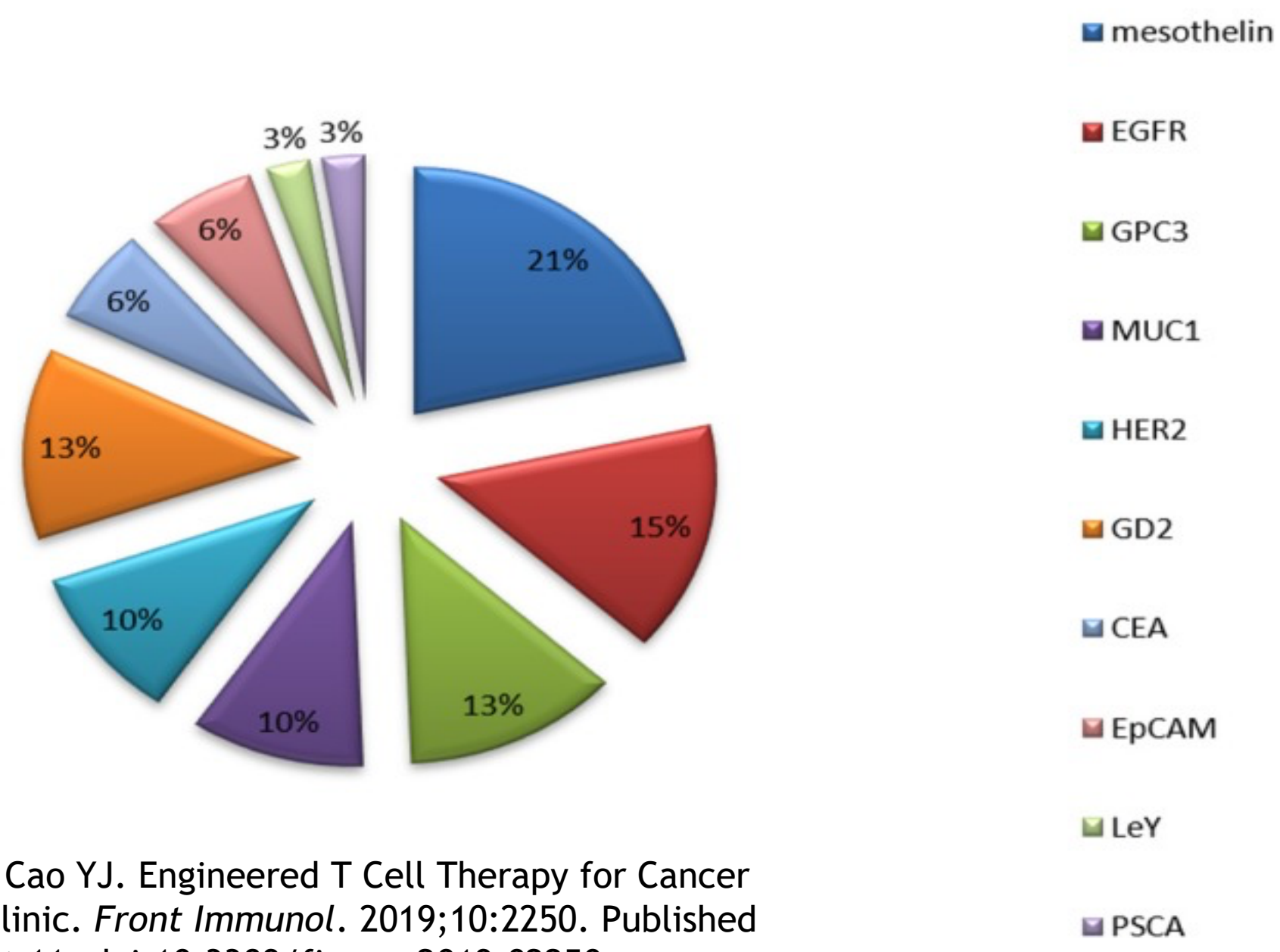
Published Clinical Results: CAR-T Cells in AML

CAR Target	Cytotoxicity	Results
CD123	Long term hematopoiesis High rates of CRS	Potent in vitro activity In vivo studies No clinical trials results
CD33	Lung and GI Hematopoietic toxicity	"potent but transient"
Lewis-Y Antigen	GI Toxicity High rates of CRS	Transient – all pts relapsed
NKG2D	No toxicity	No response

Other Targets Under Investigation:

CD33, CD38, CD56, CD117,CD123,CD34 or Muc1 *

Current clinical target of CAR-T therapy in solid tumor



Zhao L, Cao YJ. Engineered T Cell Therapy for Cancer in the Clinic. *Front Immunol*. 2019;10:2250. Published 2019 Oct 11. doi:10.3389/fimmu.2019.02250

Selected Clinical Trials - CAR T cells Solid Tumors

Trial	Tumor	Target	CAR Design	Phase	Best Response Data
Brown et al[26]	Glioblastoma	IL-13Rα2	CD3ζ	I	*
Louis et al[27]	Neuroblastoma	GD2	CD3ζ	I	CR, 27%; 19 patients**
Park et al[28]	Neuroblastoma	CD171	CD3ζ	I	PD
Feng et al[29]	Non–small cell lung cancer	EGFR	4-1BB/CD3ζ	I	PR, 18%; SD, 45%; 11 patients
Beatty et al[17]	Mesothelioma/pancreatic cancer	Mesothelin	4-1BB/CD3ζ	I	PR, 50%; 2 patients
Junghans et al[30]	Prostate cancer	PSA	CD3ζ	I	PR, 40%; 5 patients
Lamers et al[18,31]	Renal cell carcinoma	CAIX	FcRγ	I	PD
Kershaw et al[32]	Ovarian cancer	Folate receptor α	FcRγ	I	PD
Ahmed et al[33]	Sarcoma	*HER2*	CD28/CD3ζ	I/II	SD, 24%; 17 patients
NCT02209376	Glioblastoma	EGFRIII	4-1BB/CD3ζ	I	N/A
NCT01454596	Malignant glioma	EGFRIII	CD28/CD3ζ	I/II	N/A
	Glioblastoma				
	Brain cancer				
NCT02664363	Glioblastoma	EGFRIII	†	I	N/A
NCT02208362	Glioblastoma	IL-13Rα2	4-1BB/CD3ζ	I	N/A
NCT02311621	Neuroblastoma	CD171	4-1BB/CD3ζ	I	N/A
	Ganglioneuroblastoma		CD28/41BB/CD3ζ		
NCT01822652	Neuroblastoma	GD2	CD28/OX40/CD3ζ	I	N/A
NCT01818323	Head and neck cancer	*ErbB*	CD28/CD3ζ	I	N/A
NCT02547961	Breast cancer	*HER2*	CD28/CD3ζ	I/II	N/A
NCT02349724	Lung cancer	CEA	†	I	N/A
	Colorectal cancer				
	Gastric cancer				
	Breast cancer				
	Pancreatic cancer				
NCT02414269	Malignant pleural disease	Mesothelin	CD28/CD3ζ	I	N/A
	Mesothelioma				
	metastases				
	Lung cancer				
	Breast cancer				
NCT02159716	Pancreatic cancer	Mesothelin	4-1BB/CD3ζ	I	N/A
	Ovarian cancer				
	Mesothelioma				
NCT01583686	Cervical cancer	Mesothelin	†	I/II	N/A
	Pancreatic cancer				
	Ovarian cancer				
	Mesothelioma				
	Lung cancer				
NCT01140373	Prostate cancer	PSMA	CD28/CD3ζ	I	N/A
NCT02498912	Ovarian cancer	Muc-16	CD28/CD3ζ	I	N/A
NCT00902044	Sarcoma	*HER2*	CD28/CD3ζ	I	N/A
NCT02107963	Sarcoma	GD2	OX40/CD28/CD3ζ	I	N/A
	Osteosarcoma				
	Neuroblastoma				
	Melanoma				

*Patients underwent craniotomy before CAR therapy.
**Patients with NED before CAR therapy were not included in denominator of responders.
†Not listed on clinicaltrials.gov.
Abbreviations: CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; CR, complete response; EGFRIII, EGFR variant III; FcR, fragment crystallizable receptor; GD2, disialoganglioside GD2; IL-13Rα2, interleukin-13 receptor α2; MUC-16, mucin 16; N/A, not applicable; NED, no evidence of disease; PD, progressive disease; PR, partial response; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SD, stable disease.

Published in: Oladapo Yeku; Xinghuo Li; Renier J. Brentjens; *American Society of Clinical Oncology Educational Book* 37193-204, 2017.
DOI: 10.1200/EDBK_180328

CAR Therapy in the USA 2014 to present: Summary

Large trials with long follow up confirm ability of CD19-directed CAR T cells to induce CRs

Partnerships with industry and licensure now broaden applicability

But still no major “home run” beyond CD19-CAR

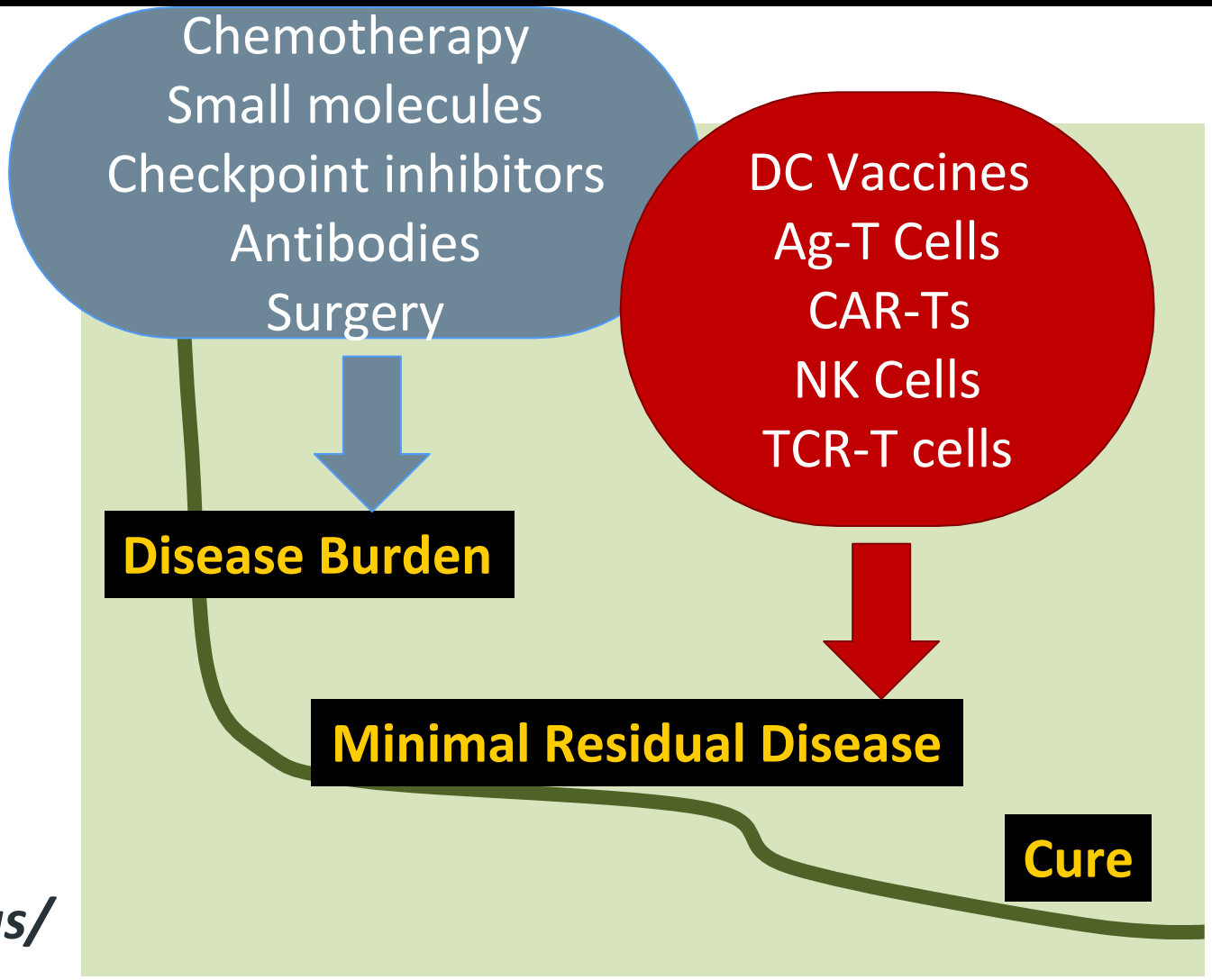
Overall Summary

- CD19 CAR-T cells highly effective in R/R - B cell NHL and Acute lymphoblastic leukemia
- CD19-negative escape is a mechanism of relapse
- Other CAR targets are available (with advantages and disadvantages) - still in early stages of development
- Combinatorial targeting could reduce antigen-negative escape and improvement of T cell based therapies overall?

→ improve outcome with a combination approach (SCT, checkpoint blockade, vaccines, multi tumor antigen specific T cells, oncolytic viruses, nanoparticles, etc etc etc) ?

Cell Therapy for Cancer – The Vision

Potential for Combination Therapies



Sources: Autologous/ Allogeneic

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