Multidisciplinary Approaches to Cancer Symposium

Plenary Session

T Cell Immunotherapy for Treatment of Cancer: CARS and TILS

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City of Hope Comprehensive Cancer

Disclosures

- Grant/Research Support in Mustang Bio.
- Consultant for Allogene Therapeutics.
- Stock/Shareholder in Lixte Biotechnology Holdings, Inc.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of T Cells, and CAR T Cells will be addressed.

Goals

- Review status of immune cell therapy for treatment of cancer: currently approved indications and those in development
- ALL in older adults
- Brain cancer including GBM, her 2+ breast cancer, CNS lymphoma
- prostate cancer
- ovarian cancer
- TIL therapy for pancreatic cancer, melanoma, renal cell
- Head and neck cancer: oncolytic virus to modify antigen expression

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Immune effector cell therapy for treatment of hematologic cancers and solid tumors at City of Hope

- Develop immune cell therapies across the spectrum of adult oncologic diseases: adults and children
- CAR T cells: target antigen that is “unique” to tumor
- TILs: enriched for tumor peptide antigen recognition, melanoma, pancreatic cancer
- NK cells: cord blood derived, lung cancer
- TCR peptide T cell therapy: pancreatic cancer, head and neck
- CAR Macrophages: modifier of tumor microenvironment

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Cellular Therapy for Hematologic Malignancy Developed by City of Hope Laboratory and Translational Scientists

- Lymphoma: Tanya Siddiqi, Elizabeth Budde, Larry Kwak, John Baird, Alex Herrera, Xiuli Wang
- ALL: Xiuli Wang, Ibrahim Aldoss, Lior Goldberg, Larry Kwak
- AML/MDS/ MPD: Elizabeth Budde, Guido Marcucci, Karamjeet Sandhu, Idoroenyi Amanam
- Multiple Myeloma: Myo Htut, Amrita Krishnan, Scott Goldsmith
- Hodgkin disease: Mathew Mei

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Cellular therapy for solid tumors developed by City of Hope laboratory and translational scientists

- Glioblastoma: Christine Brown, Behnam Badie, Jana Portnow, Leo Wang, Lisa Feldman
- Prostate cancer: Saul Priceman, Tanya Dorf
- Ovarian cancer: Saul Priceman, Lorna Rodriguez
- Melanoma: Christine Brown, Toni Ribas (UCLA)
- Lung cancer: Miguel Villalona-Calero, Michael Caligiuri, Jianhua Yu
- Breast Cancer (HER2+): Saul Priceman, Jana Portnow
- Melanoma, renal, head and neck: Sunil Sharma
- Pancreatic cancer: Sunil Sharma, Vincent Chung, Gagandeep Singh, Saul Priceman

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Pharma Cellular Therapy Trials, phase I, first in human for solid tumors

- GI/colon cancer: Marwan Fakih
- Liver cancer: Daneng Li
- Breast Cancer: Joanne Mortimer
- Renal Cell: Sumanta Pal
- Head and Neck: Victoria Villaflor, Ellie Maghami
- Lung: Erminia Massarelli, Miguel Villalona-Calero
- GI (stomach): Afsaneh Barzi
- Sarcoma: Mark Agulnik

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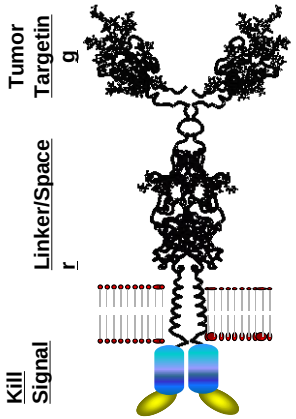
Engineering Anti-Cancer Immunity with Chimeric Antigen Receptors (CARs)

Chimeric Antigen Receptor (CAR)



Tumor Targeting Domain

- scFv or ligand
- MHC-independent target recognition
- Epitope binding, affinity, and specificity

Extracellular Spacer Domain

- Non-signaling
- Determines proximity to target cell, flexibility, and dimerization potential
- Common spacers: IgG-Fc, CD8h, CD28h

Intracellular Signaling Domain

- CD3ζ directed cytolytic killing
- Costimulation improves CAR T cell signaling
- Proliferation, survival, recursive killing
- Costimulatory domain: CD28, 4-1BB, OX40, CD27, ICOS

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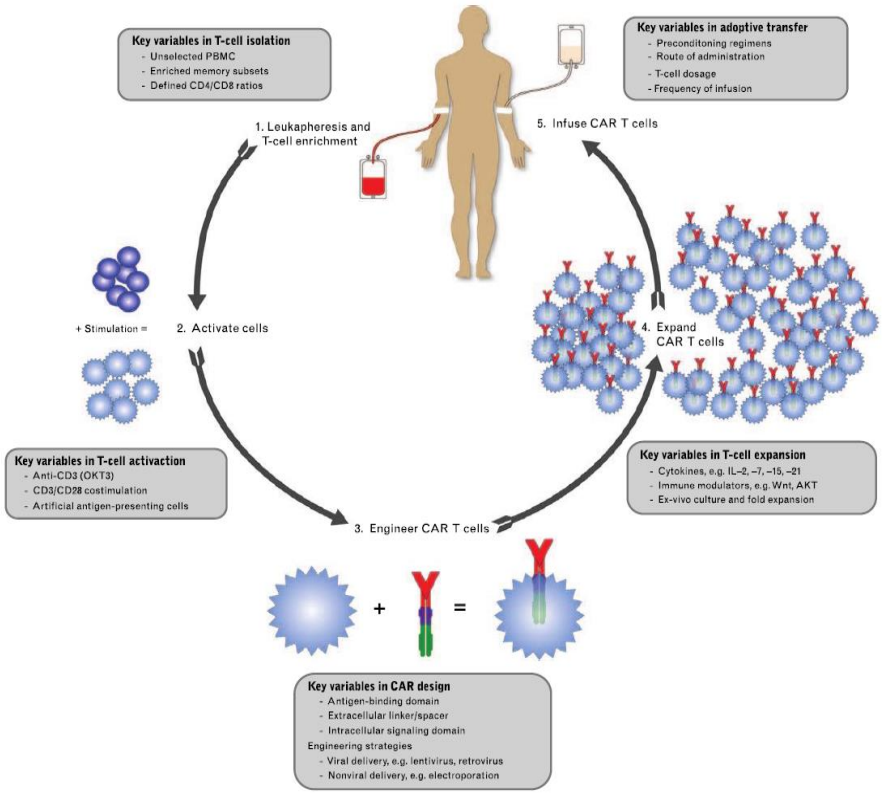
COH T Cell Therapy Program



Priceman, et al. Curr Opin Oncol 2015

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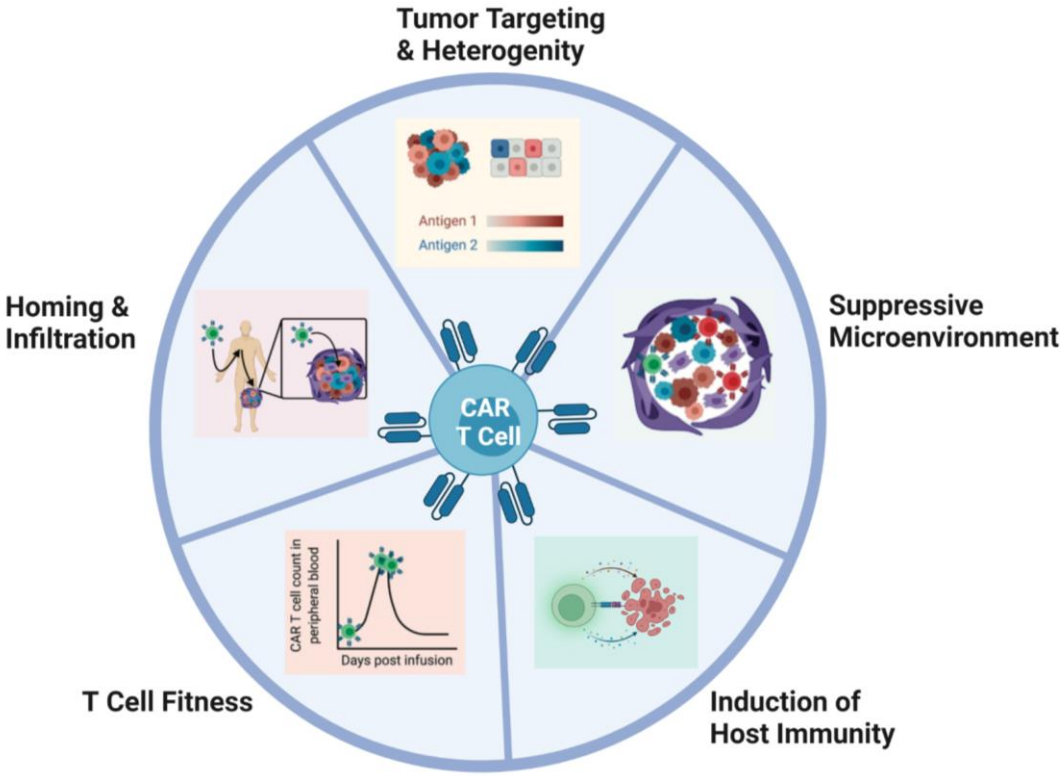

Adapted from Wagner et al. Mol Therapy 2020

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Approved Cell Therapies for Treatment of Cancer

- Relapsed diffuse large B cell lymphoma (CD19)
- Relapsed mantle cell lymphoma (CD 19)
- Relapsed ALL in children and young adults (CD19)
- Relapsed multiple myeloma (BCMA, GPRC5D)
- TIL therapy for melanoma (2024)

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C19 CAR T Cell Therapy for B Cell Lymphoma

- Relapsed large B cell lymphoma
- 40% DFS
- Patients usually achieve DFS after 6 months of remission
- Relapse often with loss of CD19 target antigen
- Now being used earlier in the course of disease
- CAR T cell versus autologous stem cell transplant

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CD19 CAR T Cell Therapy for Pre-B Cell ALL

- High response rate
- Can treat disease in CNS
- Best results in children
- Correlates with CAR T cell persistence, absent B cell reconstitution
- Relapse associated with loss of CD19

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What is the Role for CAR-T Cells in Hematopoietic Cell Transplantation for ALL?

Older adults with ALL have poor prognosis with frontline conventional chemo

Study	No. of Patients	TKI	Median Age (years; range)	CR Rate (%)	IM Rate (%)	OS	Response, EFS, or DFS
Studies including both Ph-positive and Ph-negative ALL							
HyperCVAD[2]	122	NR	≥ 60	84	10	20% at 5 years	NR
MRC UKALL XII/ECOG E2993[3]	100	None	56 (55-65)	73	18	21% at 5 years	5-year EFS, 19%
Modified DFCI[19]	30	Imatinib	58 (51-72)	67	13	52% at 2 years	2-year DFS, 52%
Ph-negative ALL studies							
CALGB 9111[4]	41	None	≥ 60	77	17	17% at 3 years	3-year DFS, 19%
GMALL[6]	268	NA	67 (55-85)	76	18	23% at 5 years	5-year CCR, 32%
EWALL[7]	59	NA	65 (61-83)	76	7	24% at 3 years	3-year DFS, 19%
PETHEMA ALL-96[17]	33	NA	65 (56-77)	58	36	39% at 2 years	2-year DFS, 46%
GRAALL-SA1[34]	60	NA	66 (55-80)	82	8	24% and 35% at 2 years	2-year EFS, 24% and 35%
PETHEMA ALL-OLD07[20]	56	NA	66 (56-79)	74	11	Median, 12.4 months	Median DFS, 8 months

Aldoss et al. J Oncol Pract. 2019;15:67-75.

RIC alloHCT has outcomes in older pts with ALL

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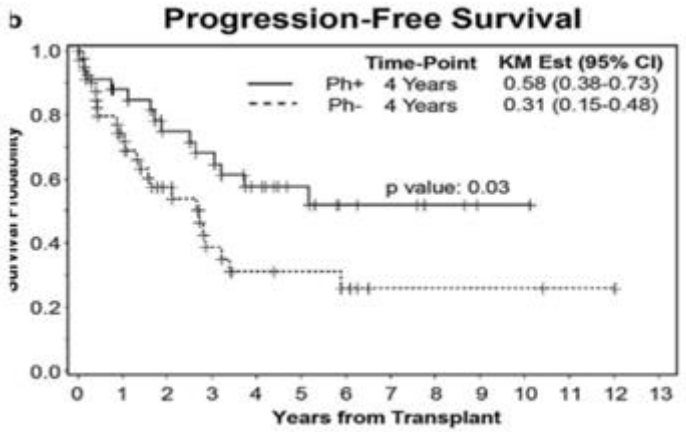

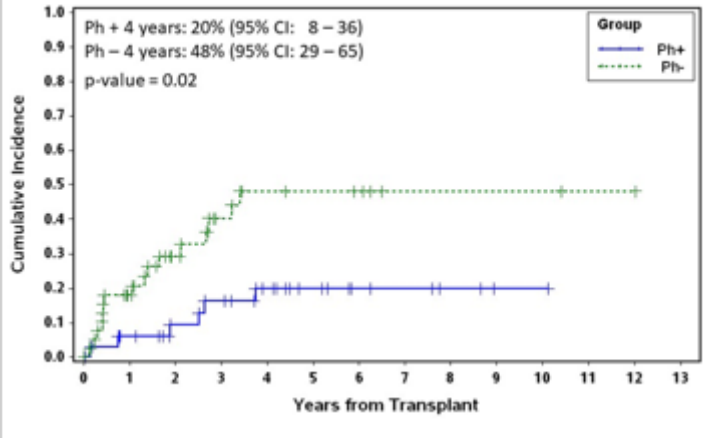

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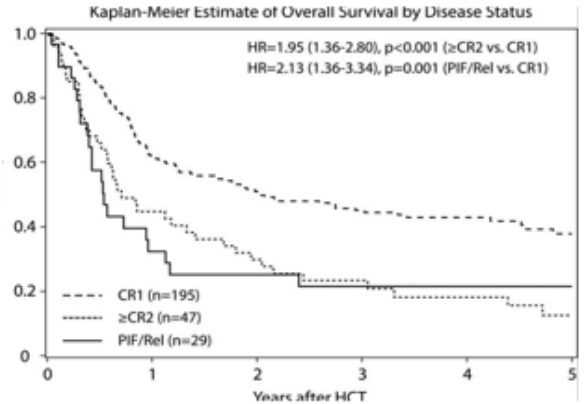
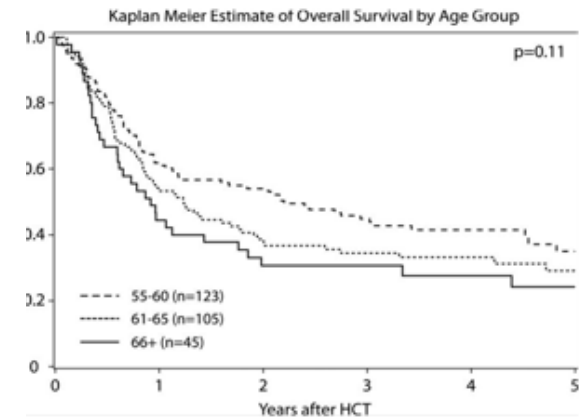
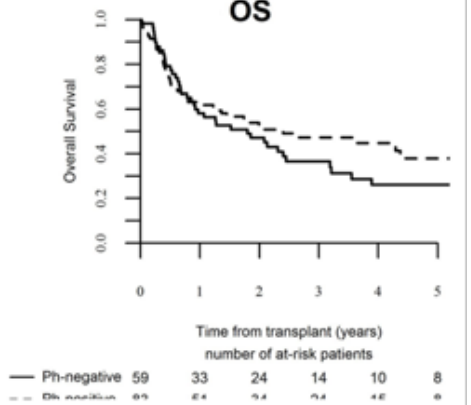
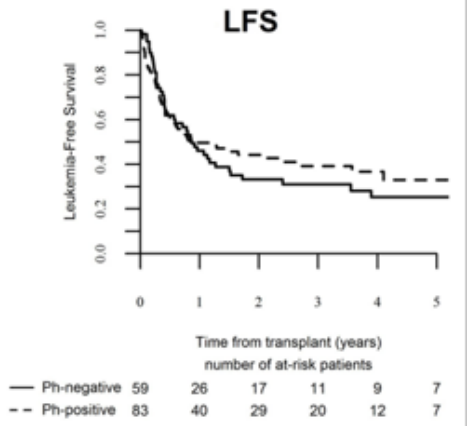




EBMT





Mei M et al. BBMT. 2020; Rosko A et al. Am J Hematol. 2017; Roth-Guepin G et al. Oncotarget. 2017

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CD19CAR T cell therapy activity in r/r ALL

Table 2. Clinical trials with CD19CAR T cell

Study	N	Median age (range), y	Prior allo-HCT (%)	Pre-lympho disease (<5%) in the absence of EMD (%)	Prior blinatumomab (%)	CNS	EMD (%)	CR/CRi% (MRD⁻ %)	Post-CAR allo-HCT in responders, %	Relapse, %	Survival	CD19⁻ relapse, %	No. of pts who underwent leuk but no CAR T	Ref.
U Penn/ CHOP	30	14 (5-60)	18 (60)	6 (20)	3 (10)	CNS-2 = 2	NR	90 (88)	3 (11)	7 (26)	6-mo EFS = 67% 6-mo OS = 78%	3 (43)	NR	22
MSKCC	53	44 (23-74)	19 (36)	21 (48)	13 (25)	None	5 (9)	83 (67)	17 (39)	25 (57)	Median EFS = 6.1 mo Median OS = 12.9 mo	4 (16)	24	14
Novartis multicenter	75	11 (3-23)	46 (61)	NR	NR	CNS-2 = 1 CNS-3 = 1	NR	81 (81)	8 (13)	22 (36)	12-mo EVS = 50% 12-mo OS = 76%	15 (68)	17	17
NCI	21	13 (1-30)	8 (38)	5 (24)	0 (0)	CNS-2 = 2	NR	67 (86)	10 (71)	2 (14)	5-mo LFS = 79% 10-mo OS = 52%	2 (100)	NR	42
Seattle Children's Hospital	45	12 (1-25)	28 (62)	15 (33)	6 (13)	CNS-2 = 7 CNS-3 = 2	NR	93 (100)	11 (28)	18 (45)	12-mo EFS = 51% 12-mo OS = 70%	7 (39)	NR	21
FHCRC	53	39 (20-76)	23 (43)	14 (26)	10 (19)	CNS-2 = 5	18 (34)	85 (85)	18 (40)	22 (49)	For responders, median EFS = 7.6 mo, and median OS= 20 mo =	6 (27)	2	41
Hebei Yanda Lu Daopei Hospital, China	51	11 (3-68) and 24 (2-44)*	NR	9 (18)	NR	4	16 (31)	90 (88)	27 (60)	11 (24)	Relapse = 60% vs 6% for responders who did and did not receive HCT (P = .023)	6 (55)	NR	27

Aldoss et al. Blood. In press. Davila ML et al. Sci Transl Med. 2014;6:224e225. Lee DW et al. Lancet. 2015;385:517-28. Maude SL et al. N Engl J Med. 2014;371:1507-17. Turtle CJ et al. J Clin Invest 2016;126:2123-8.

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City of Hope CAR T Cell Trial for Relapsed ALL

- 40 of 46 patients (87%) achieved CR/CRi
  - 1 (2%) patient progressed
  - 5 (11%) patients were unevaluable for response
    - (infection n=2; cerebral edema n=1; T cells below allowable dose n=1; CD19- EMD progression post LD, n=1).

- When analysis was restricted to ***response-evaluable pts***
  - **CR/CRi rate = 98%**
  - MRD- CR/CRi among evaluable responders= **95%**

- 21 (53%) responders underwent consolidation with alloHCT in CR
  - including 7 as 2nd alloHCT

- Among evaluable pts for response
  - **Older pts** (≥50 yrs); CR/CRi= 100%
  - **Ph-like** (n= 17); CR/CRi= 94%
  - **EMD** at LD (n=14); CR/CRi= 93%

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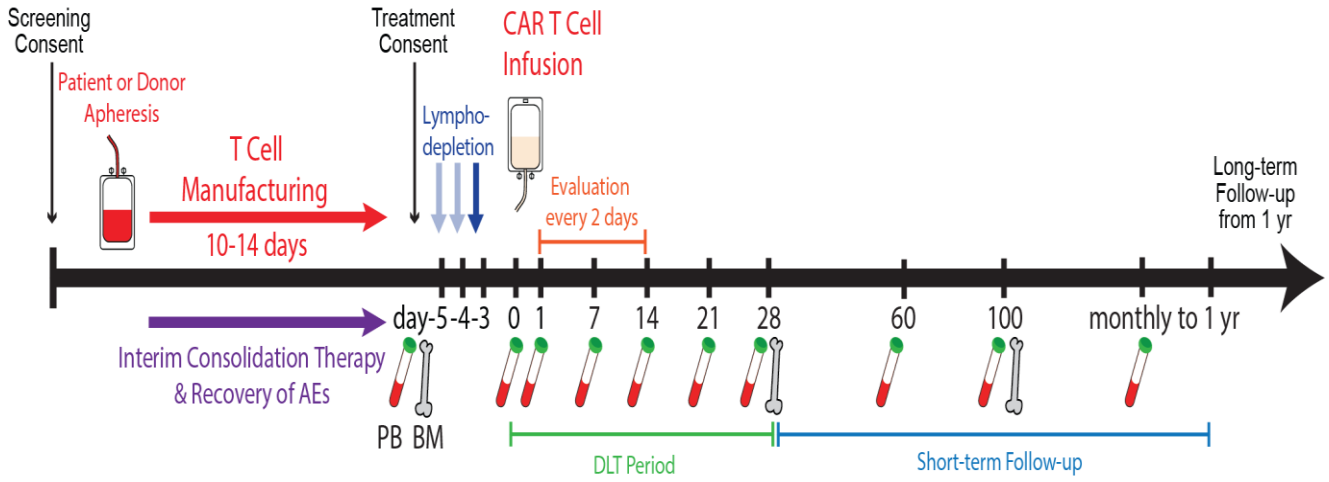
Study Proposal

- We propose to test the application of our CD19 specific CAR T cells as a curative consolidation therapy in older adults with B-cell ALL who are at increased risk of relapse and treatment-related mortality with chemo & transplant



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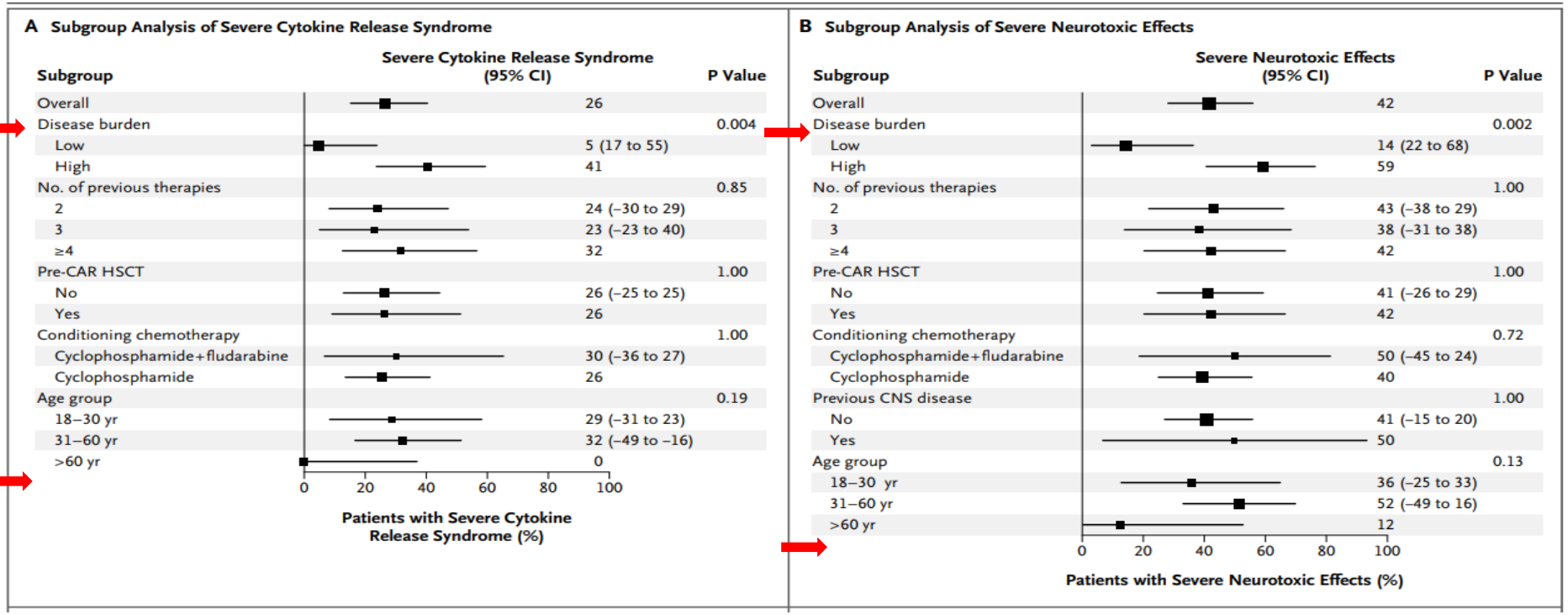
Rationale

- Single infusion of CD19-CAR T cell is likely ***safer*** than repeated cycles of chemo and alloHCT consolidation in older pts
  - CAR will be administered in low disease burden (MRD+/MRD-);
    - less CRS & ICANS



Park J et al. N Engl J Med. 2018; Turtle CJ et al. J Clin Invest. 2016; Gardner RA et al. 2017; Maude SL et al. N Engl J Med. 2014; Lee DW et al. Lancet. 2015

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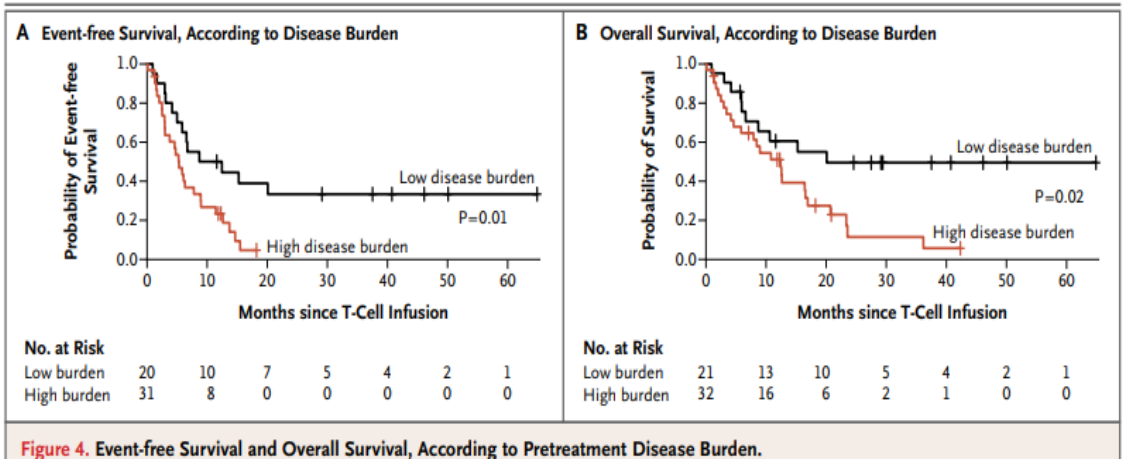

Figure 4. Event-free Survival and Overall Survival, According to Pretreatment Disease Burden.

- Could be ***more effective*** in producing cure
  - Low disease burden at LD correlates with longer RFS post CAR in ALL
  - Early utilization of healthier T cells
    - Less T cells exhaustion

	All patients (n=195)	CNS stratification		
		CNS-negative stratum (n=129)	CNS-positive stratum (n=66)	p value
Disease response at day 28				
Complete response	185 (95%)	121 (94%)	64 (97%)	0·74
No response	7 (4%)	6 (5%)	1 (2%)	..
Not evaluable*	3 (2%)	2 (2%)	1 (2%)	..
Patients with relapse	72/185 (39%)	45/121 (37%)	27/64 (42%)	0·51
CNS status at relapse	..	..	..	0·0066
CNS1	45/72(63%)	33/45 (73%)	12/27 (44%)	..
CNS2	4/72 (6%)	1/45 (2%)	3/27 (12%)	..
CNS3	7/72 (10%)	1/45 (2%)	6/27 (22%)	..
Unknown	16/72 (22%)	10/45 (22%)	6/27 (22%)	..
Follow-up duration, months	37 (21–49)	36 (18–49)	39 (25–49)	0·73

- Possibly CAR T cells are more capable in CNS/EMD prevention/control
  - CAR T cells trafficking & anti-leukemic activity in the CNS & EMD sites

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Park J et al. N Engl J Med. 2018; Leahy AB et al. Lancet Haemtol. 2021

Treatment

- Participants will be enrolled after achieving CR with any frontline therapy
- Undergo T cells collection
  - Then receive interim consolidation per treating physicians
    - Recommendation for low toxicity interim therapies
    - Blinatumomab is an exclusion to avoid target loss
  - At least 4 IT chemo b/w diagnosis & LD
- Once cells are made, participant will receive LD and followed by CD19-CAR T cells
- Monitor for toxicity in the first 28 days
- MRD assessment by ClonoSEQ or MCF q3 months x2 years

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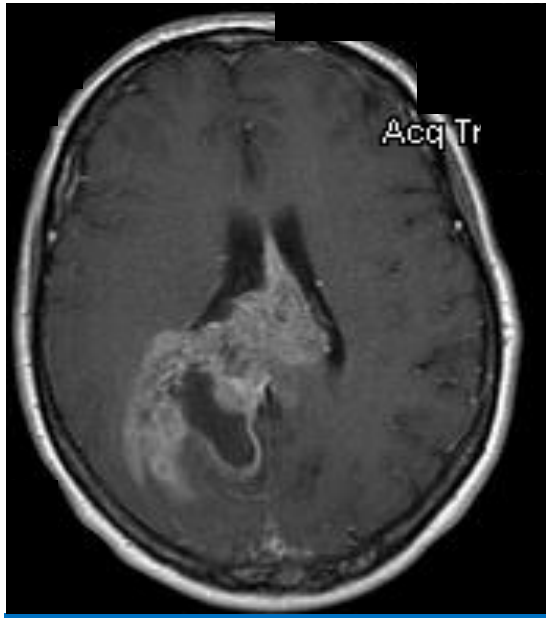
The Unmet Challenge of Glioblastoma

Christine Brown, Behnam Badie, Jana Portnow, Leo Wang, Lisa Feldman



Median Survival
1980: 12 months (BCNU)
2012: 17 months (Temozolomide)
2014: 17 months (Avastin)
2015: 19 months (NovoTTF)*

Recurrent GBM OS 5-8 months

Challenges for GBM Therapy

- Invasiveness
- Heterogeneity
- Immunosuppressive
- Blood-brain barrier limits the penetration of many therapeutics
- Incomplete elimination following standard therapies (surgery, radiation, and chemotherapy) results in inevitable relapse.
- Toxicities can be life-threatening – e.g. CNS inflammation and off-tumor targeting
- Immunotherapies (vaccines, ICB) have not demonstrated a survival benefit in randomized trials.

❖ *Lack of understanding in CNS immunity*
❖ *Low mutational burden*
❖ *Multi-factor immune-suppression*

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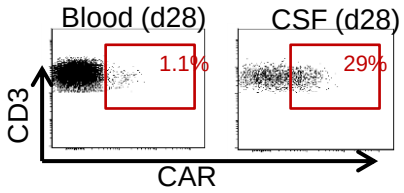
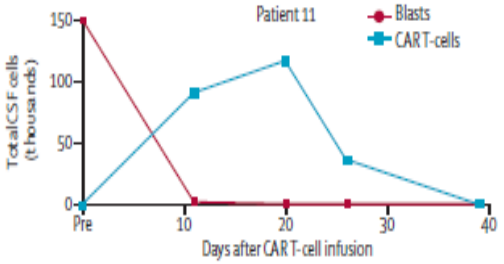
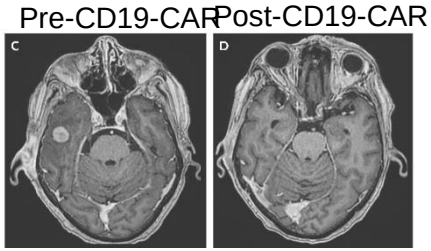
Is There Opportunity for CAR T Cells for Treatment of Brain Tumors?

- CD19-CAR T cells traffic to the CSF and can eliminate CNS leukemia and lymphoma.



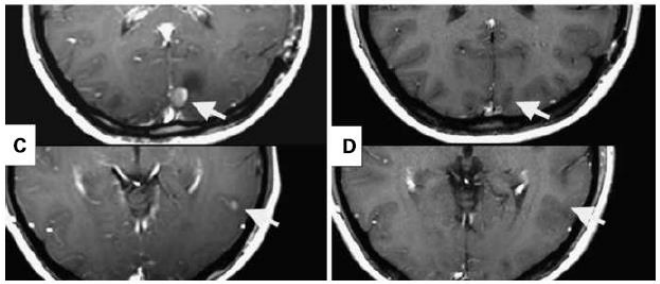


Lee et al. Lancet 2015



Abramson et al. NEJM 2017

- Resolution of melanoma brain metastases following TIL/TCR immunotherapy.



Hong et al CCR 2010

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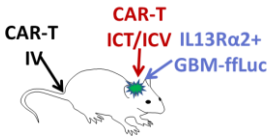
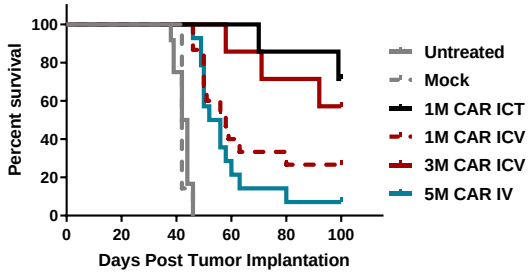
Overview of CAR T Cell Trials for Glioblastoma

Locoregional CAR T Cell Delivery for GBM Therapy



- ICT; intratumoral
- ICV; intraventricular
- IV; intravenous



Brown et al. Mol Therapy 2018; Priceman et al CCR 2018; Donavan et al. Nature Med 2020; Theruvath et al. Nature Med 2020

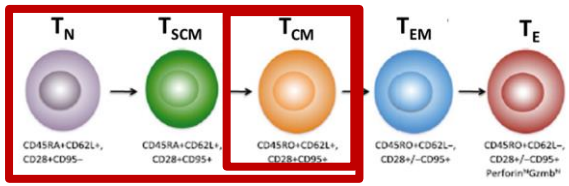
Memory/Naïve-Enriched CAR T Cell Manufacturing Platform

Select **CD62L+ naïve/memory T cells** for CAR-engineering.

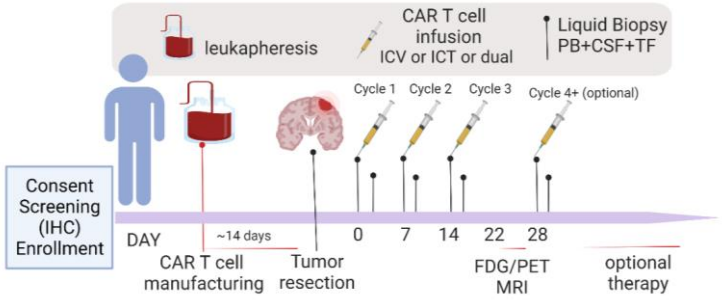
- ❖ Less-differentiated CAR products for greater potency
- ❖ More homogenous product to reduce patient-to-patient variability

Tcm; CD45RA-CD62L+

Tn/mem; CD62L+



Clinical Trial Design:



- Maximal surgical resection or biopsy
- Weekly locoregional delivery:
- No lymphodepletion
- 2-200x10^6 CAR T cells

Patient Population:

- Grade III or IV glioma: ≥75% rGBM
- >4 weeks life expectancy
- Evidence for recurrence/progression

- **No enrollment exclusion for number of recurrences, tumor size, multifocal disease, or prior bevacizumab**

Wang et al. Blood. 2011; Aldoss et al. CCR 2022; Larson Cancer Discov 2022; Arcangeli et al. JCI 2022

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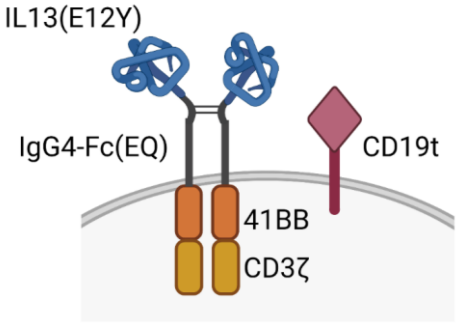
IL13Rα2-CAR T Cell Therapy: Phase I Trial Evaluating (NCT02208362)

IL13-41BBζ CAR



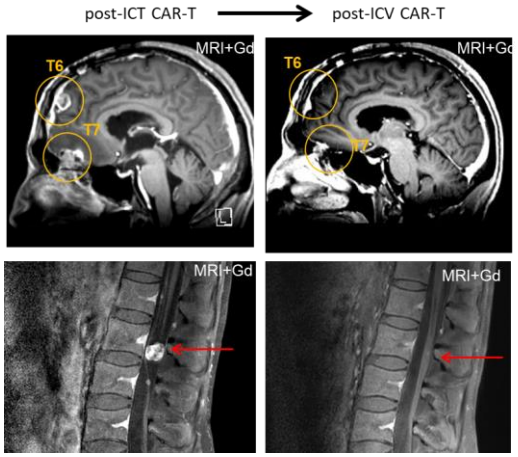
Brown et al. 2018; Starr et al. 2022; Jonnalagadda et al 2012

IL13Rα2

Debinski et al. 1999; Brown et al 2013; Barish et al. 2022

Patient Outcomes:

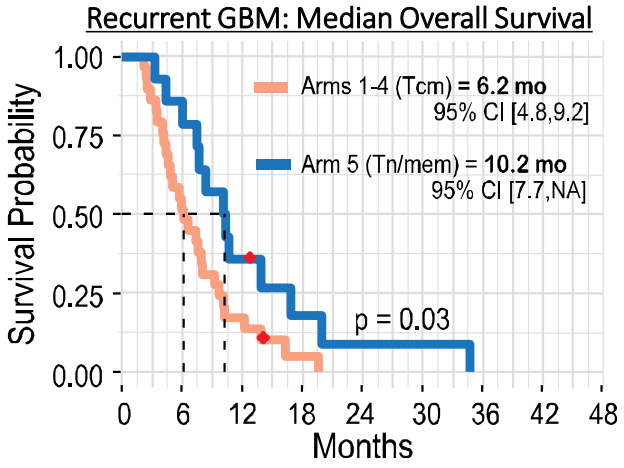
- 50% of patients achieved Stable Disease (SD) or better
- 2 partial response (PR)
- 2 complete response (CR; 1 on SSP)
- Optimized Arm 5 rGBM OS 10.2 mo



Brown et al. NEJM 2016

Trial Summary (2014-2021)

- 58 patients
- 5 Arms study:
  - 3 delivery routes (ICT, ICV, **Dual**)
  - 2 manufacturing processes (Tcm vs **Tn/mem**)
- 2 to 200M CAR+ T cells per infusion
- No dose limiting toxicities (DLTs)
- Most common AEs were fatigue, myalgia, headache and hypertension



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Take Home Lessons

- We have shown feasibility and safety for three CAR T cell therapies targeting GBM-associated antigens **IL13Rα2**, **HER2** and **MMP2/CLTX-receptor**
- Findings expand the repertoire of validated tumor associated antigens for treatment of GBM and other brain tumors
  - Other targets include, **EGFRvIII** (Maus et al 2017; Goff et al. 2019), **B7H3** (Vitanza et al 2023) and **GD2** (Majzner et al. 2022)
- Regional delivery of CAR-T cells is safe, feasible and bioactive
- Encouraging evidence of anti-tumor activity in a subset of patients across three single antigen targeted CAR-T cell trials
- Ongoing trials are evaluating combinations to further enhance therapeutic activity, including combining with lymphodepletion and checkpoint blockade (IPI/NIVO)
- Multi antigen targeting

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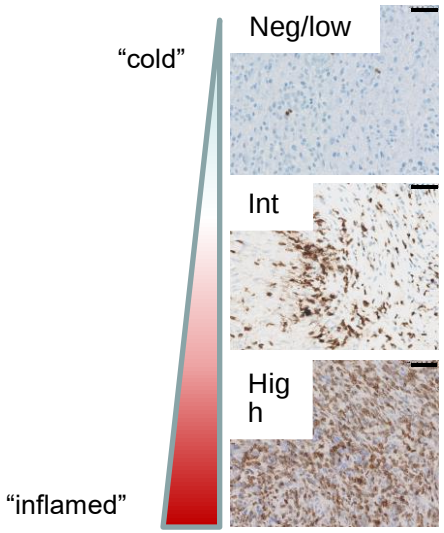
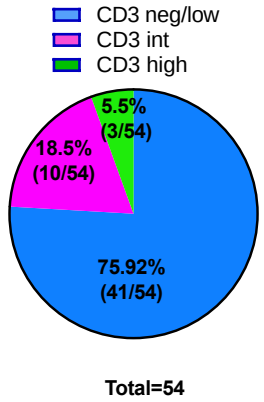
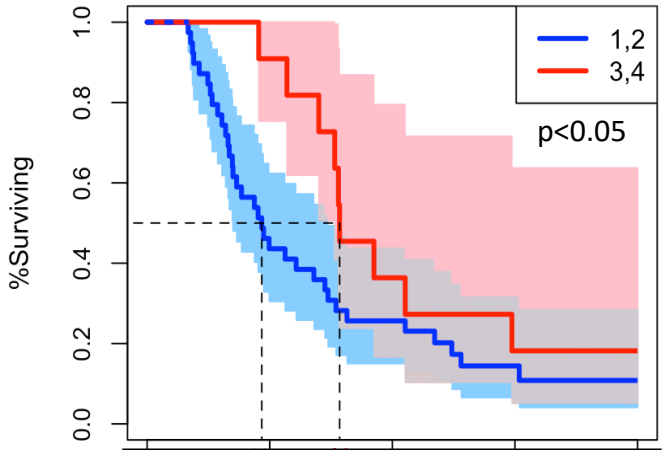
Pretreatment Tumors with High CD3 Infiltrates are More Responsive to CAR T Cell Therapy





Patient Survival by CD3 Score

HIGH/INT CD3 (11/12 GBM) = OS 10.8 mo
LOW/NEG CD3 (34/41 GBM) = OS 6.3 mo



	CD3 high/int	CD3 low/neg
GBM	92%	83%
Age (median)	52	48
IDHmut	9%	20%
MGMTmeth	64%	61%

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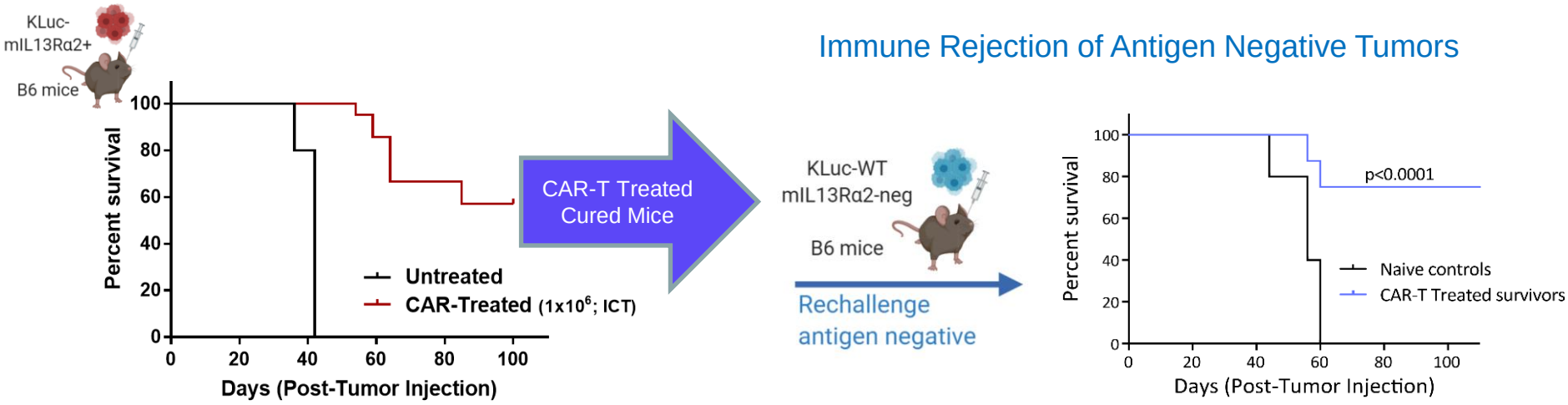
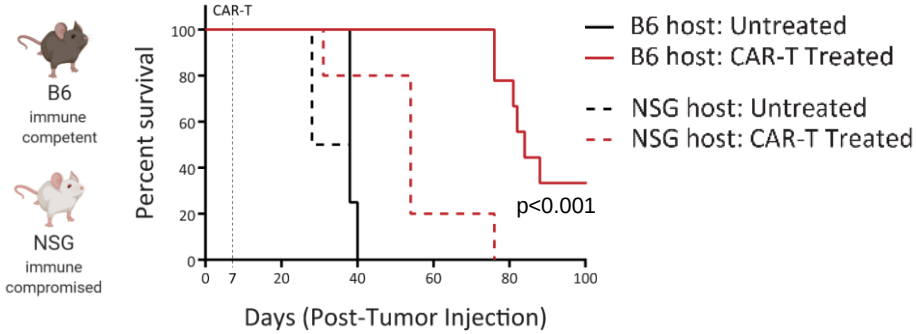
Murine IL13Rα2-CAR T cells Induce Endogenous Antitumor Responses against Antigen Negative GBM



Superior Antitumor in Immunocompetent Mice



Alizadeh et al; Cancer Discovery; 2021

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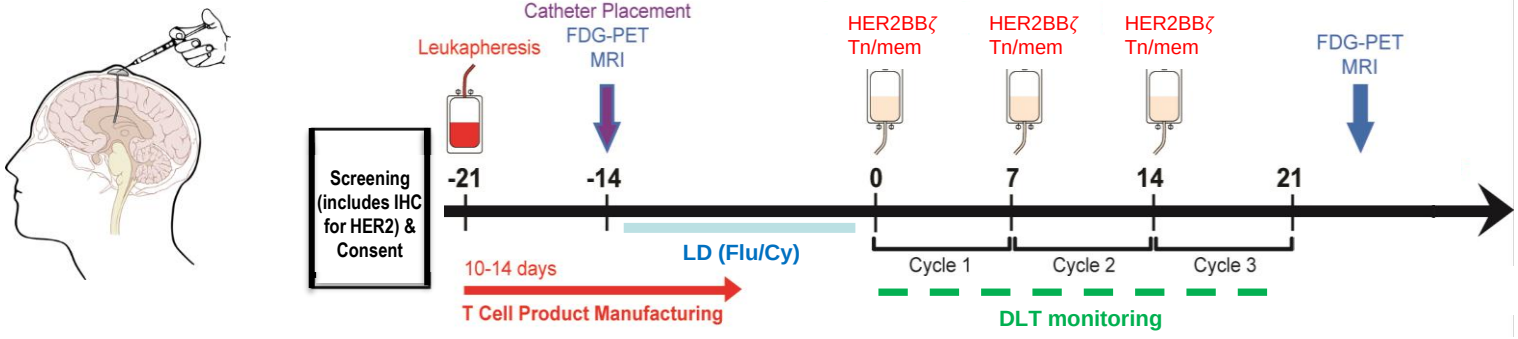
IRB 17237 A Phase 1 Study of CAR-Engineered Stem/Memory T Cells for the Treatment of HER2+ Brain and/or Leptomeningeal Metastases

CLIN2-11574 Principal Investigator: Saul Priceman, Ph.D.

Clinical PI: Jana Portnow, M.D.

- Origin is expression of HER2 in GBM
- Multi antigen targeting to address heterogenicity (CIRM)
- Brain metastasis in women with HER2 breast cancer
- HER2 cells for treatment of systemic breast disease

NCT03696030:
Intraventricular delivery of HER2BBζ T cells for Brain and/or Leptomeningeal Metastases



	Cycle 1	Cycle 2	Cycle 3+
DL3:	$20x10^6$ CAR+	$100x10^6$ CAR+	$100x10^6$ CAR+
DL2:	$10x10^6$ CAR+	$50x10^6$ CAR+	$50x10^6$ CAR+
DL1:	$2x10^6$ CAR+	$10x10^6$ CAR+	$10x10^6$ CAR+

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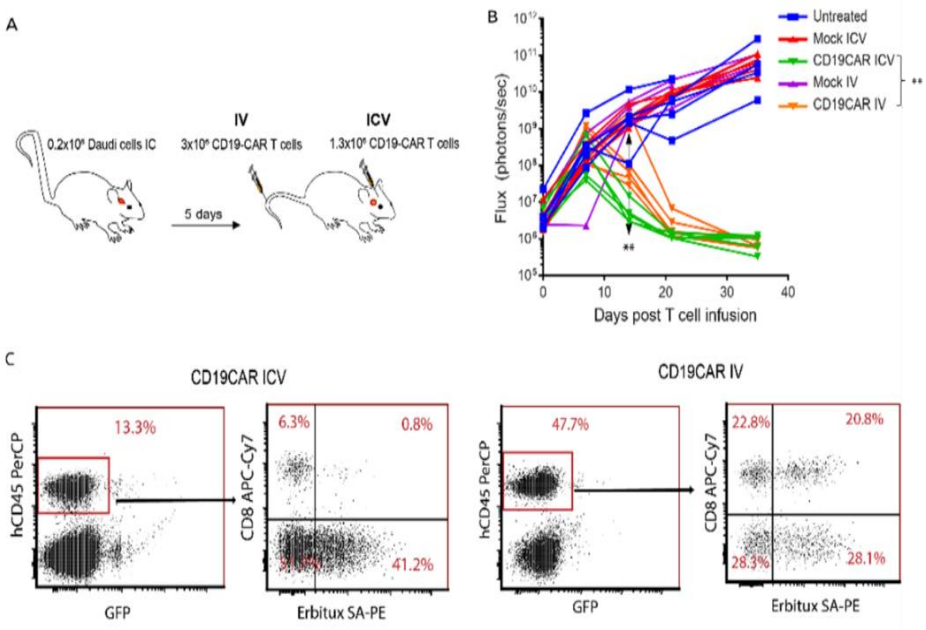
CANCER IMMUNOLOGY RESEARCH | RESEARCH ARTICLE

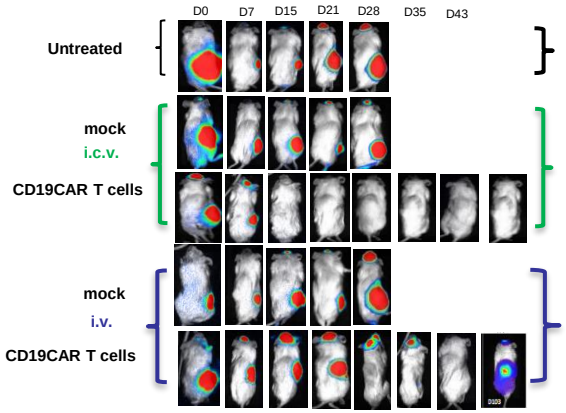
The Cerebroventricular Environment Modifies CAR T Cells for Potent Activity against Both Central Nervous System and Systemic Lymphoma

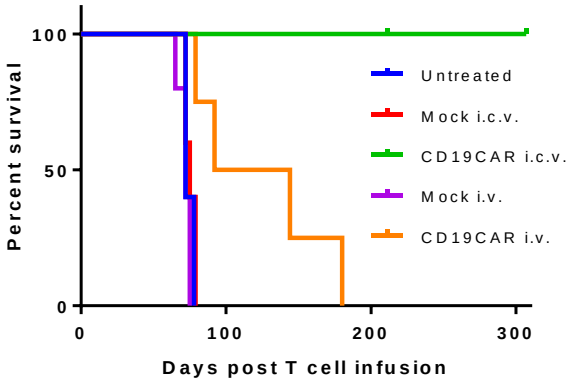
Xiuli Wang[1], Christian Huynh[1], Ryan Urak[1], Lihong Weng[1], Miriam Walter[1], Laura Lim[1], Vibhuti Vyas[1], Wen-Chung Chang[1], Brenda Aguilar[1], Alfonso Brito[1], Aniee Sarkissian[1], N. Achini Bandara[2], Lu Yang[3], Jinhui Wang[4], Xiwei Wu[4], Jianying Zhang[5], Saul J. Priceman[1], Hong Qin[6], Larry W. Kwak[6], Lihua E. Budde[1], Sandra H. Thomas[2], Mary C. Clark[2], Leslie Popplewell[1], Tanya Siddiqi[1], Christine E. Brown[1], and Stephen J. Forman[1]

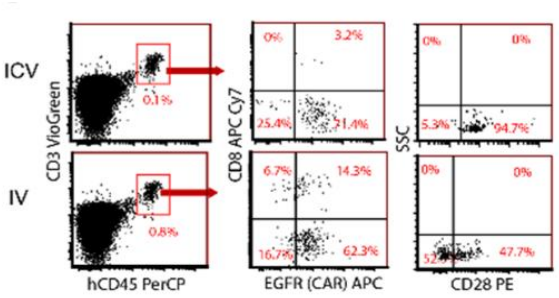


105 days post-CD19-CAR T cell treatment (blood)

ICV-delivered CD19 CAR T cells demonstrate efficacy in controlling both CNS and systemic lymphoma







Wang X et al. DOI: 10.1158/2326-6066.CIR-20-0236

IRB22240 A Phase 1 Study to **Evaluate** Intracerebroventricular (ICV) Administration of CD19-28 CAR T cells in Patients with Primary CNS Lymphoma

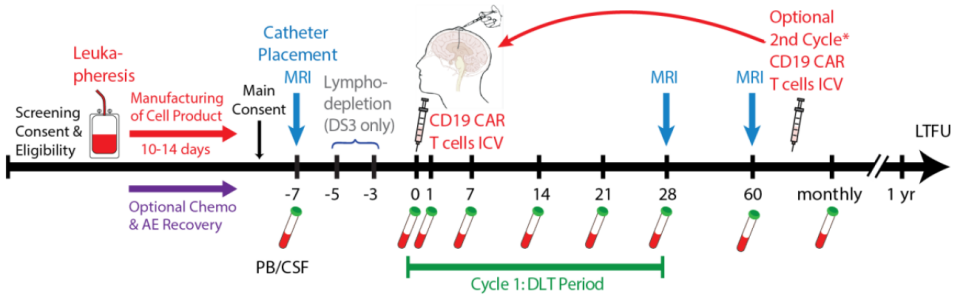


Table 1: CAR T Cell Dose Schedule (DS)

Agent	DS -1	DS 1 (Starting Dose)	DS 2	DS 3
Lymphodepletion#	none	none	Yes#	Yes#
CAR T Dose^	4M*	10M	10M	30M

Main questions to address:

- Safety
- Activity
- CAR expansion in CSF
- CAR trafficking to peripheral blood

CAR T Cell Immunotherapy in advanced prostate cancer

Tanya Barauskas Dorff, M.D.
Professor of Medicine
Department of Medical Oncology & Experimental Therapeutics
Section Chief, Genitourinary Cancers

Saul Priceman, Ph.D.
Associate Professor
Department of Hematology and Hematopoietic Cell Transplantation

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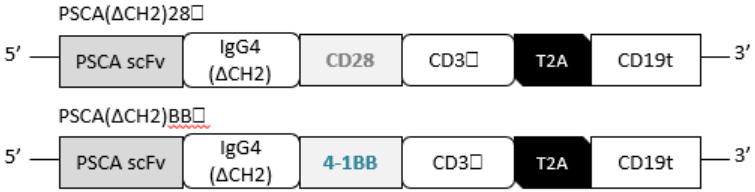
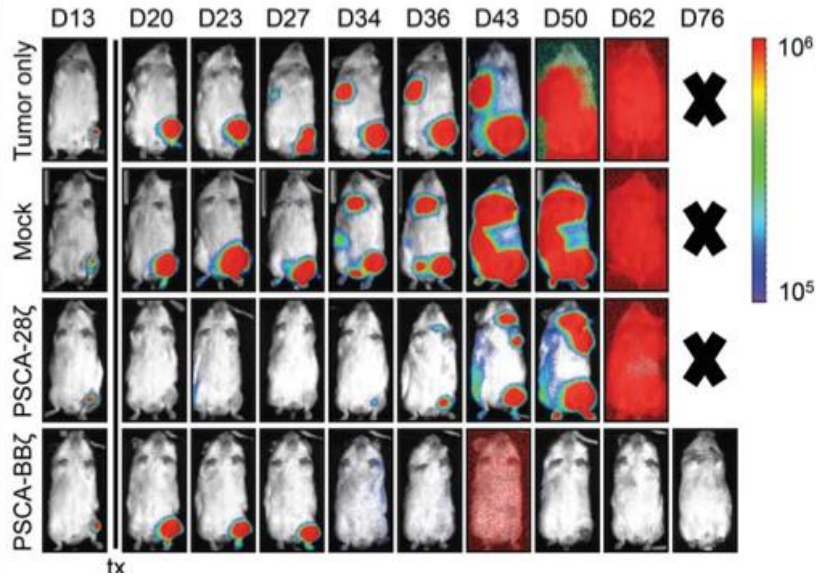
CAR T cells for Prostate Cancer

PSCA-41BBζ (COH)
Priceman



No “kill switch”
Lentiviral transduction
Standard Selection/ Expansion



Priceman SJ et al. Oncoimmunology 2018 e1380764

Table 1. CAR+ Cell Dose Schedule

Dose -1	**Starting Dose 0a**	Dose 0b	Dose 1	Dose 2
50M	**100M**	100M +precond.	300M +precond.	600M + precond.

Prostate Cancer Foundation
Curing Together.

Congressionally Directed Medical Research Programs
CDMRP
Department of Defense

SPORE IN PROSTATE CANCER
UCLA

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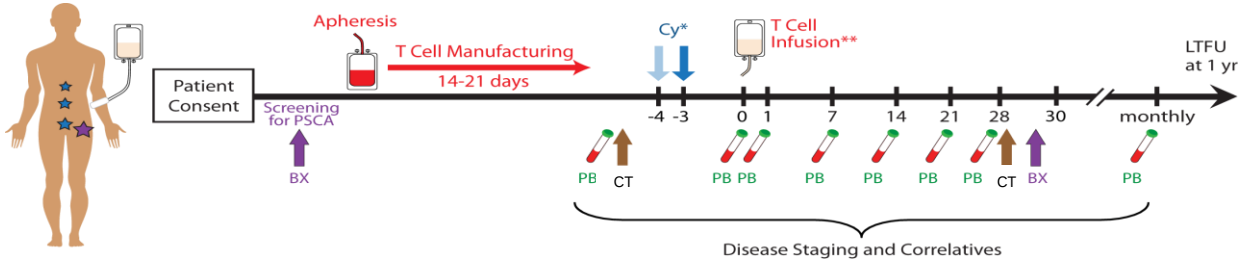
Phase 1 Trial to Evaluate PSCA-BBζ CAR T Cells in Patients with mCRPC

Prostate Cancer Foundation
Curing Together.

Tanya Dorff, MD

- **PSCA⁺ metastatic castration resistant prostate cancer**
  (Clinical PI: Tanya Dorff, MD, Research PI: Saul Priceman, PhD) – Phase 1 complete
- PSCA⁺ metastatic pancreatic and bladder cancers – TBD



- 14 patients treated (11 with LD)
- 14/14 at least 1 prior AR-targeted therapy
- 13/14 prior Taxane

Table 1: Dose Level		
1	2	3
100M CAR⁺ T cells	100M CAR⁺ T cells + LD	100M CAR⁺ T cells + LD^{mod}
n=3	n=6	n=5

ASCO 2023
Abstract: 5019
Poster: 113

Priceman, et al. *OncoImmunology* 2018
Murad, et al. *Mol Ther* 2021

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Therapeutic Responses in mCRPC Patients Treated with PSCA-CAR T Cells

Prostate Cancer Foundation
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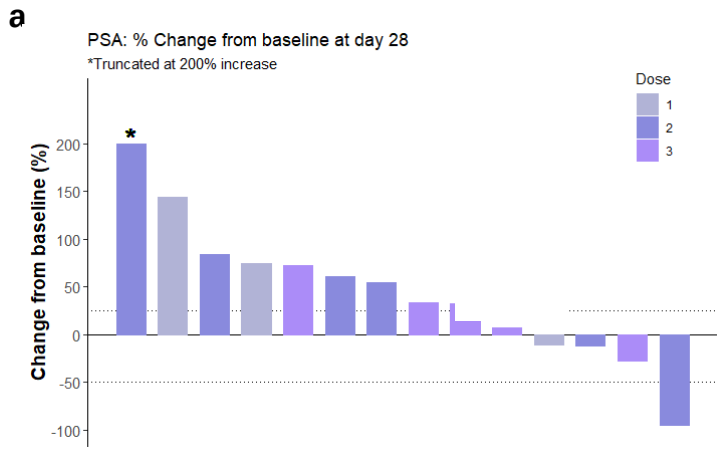

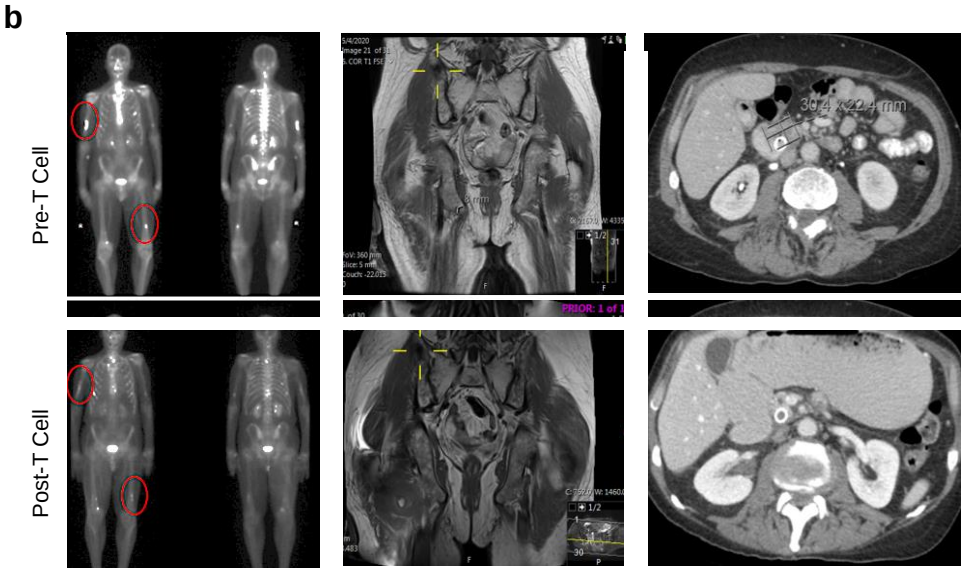

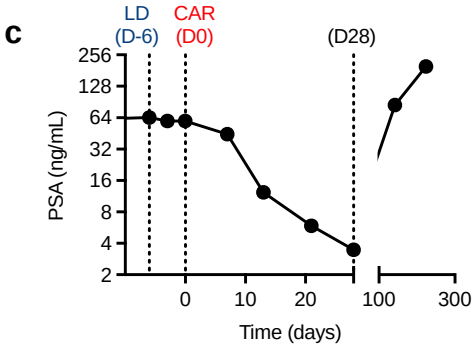

-PSCA-CAR T cells induced biochemical and radiographic responses in patients on trial

Dorff et al. *manuscript in preparation*

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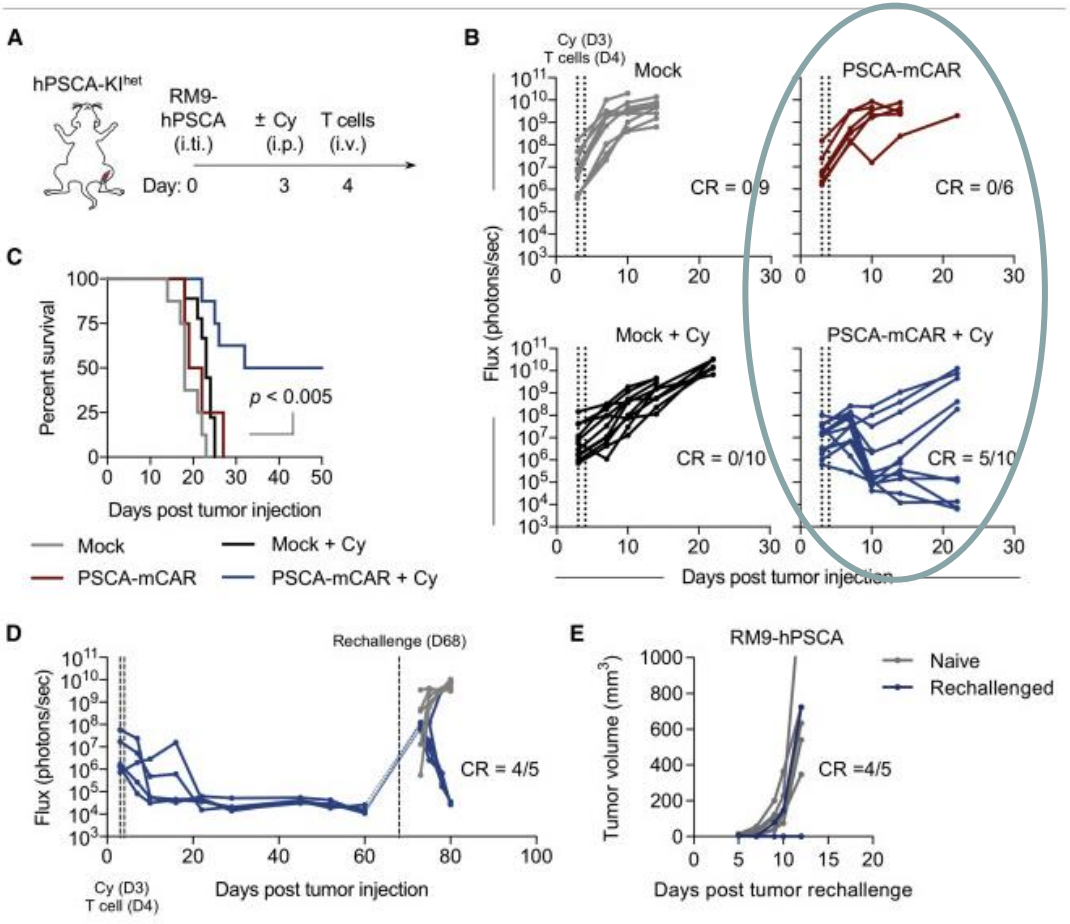
(Lymphodepletion) Preconditioning necessary for CAR T Cell Efficacy



Cyclophosphamide (Cy) pre-conditioning combined with PSCA-mCAR T cell treatment is effective *in vivo* against bone-metastatic RM9-hPSCA prostate tumors and promotes protective anti-tumor immune memory upon rechallenge

- converts to immunologically "warm" tumors with increased CD11c+ DCs and reduced CD206+ M2 macrophages

Murad et al. Molec Ther 2021: S1525-0016
https://doi.org/10.1016/j.ymthe.2021.02.024

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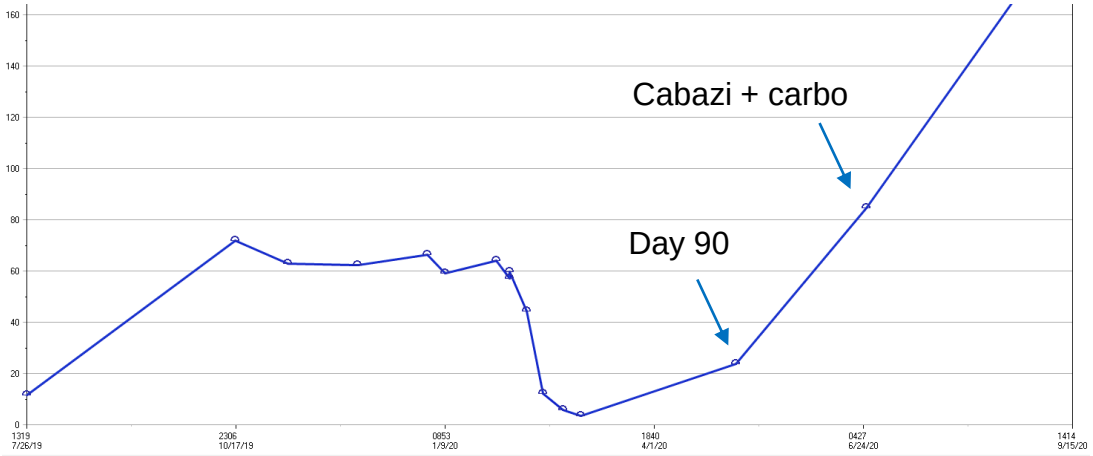
Challenge: Lack of durability of response

- PSA began to rise within 3 months after CarT
- Got permission to give a 2nd dose of CarT – but never proceeded
- 1 dose of cabazi + carbo given to bridge



Would a 2nd dose (or multiple doses) improve efficacy?
Does LD chemo need to be repeated?

What would toxicity look like with 2nd dose?

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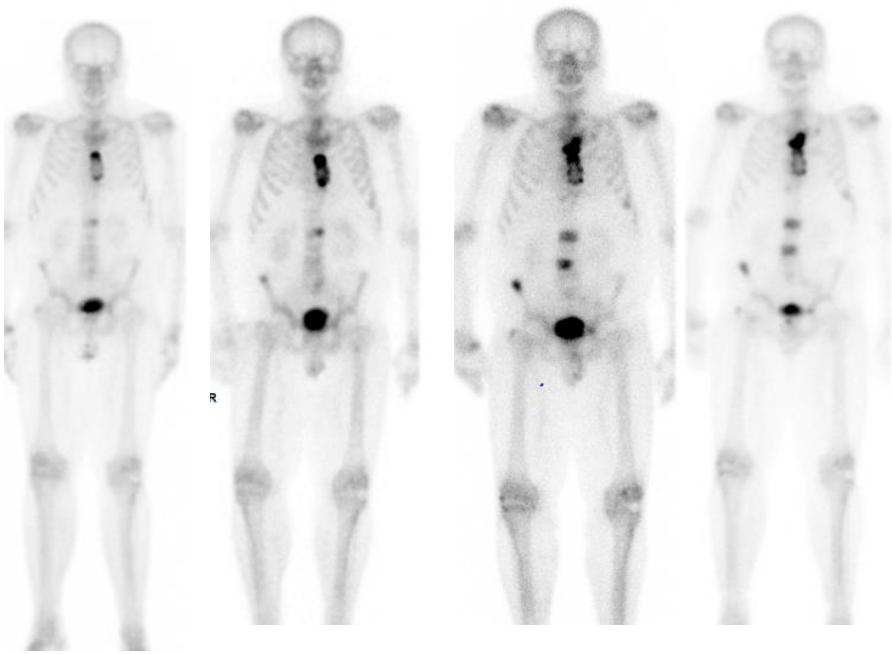
Preliminary experience: multiple doses

- 71 yo mets at dx, tx ADT + docetaxel then Abiraterone for mCRPC, enrolled in CAR T trial
  - Bridging cabazi dropped PSA to 0.75 but PSA rose to 2.4 by time of CAR T infusion #1
- PSA dropped to 1.66 by day 60 post CAR T, but day 28 imaging shows no change
- **Grade 2 cystitis**
- 6 months after CAR T #1 his PSA is rising (15.3) and he has cancer-related pain
- Treated with **2nd infusion** of 100M PSCA CAR T cells
  - Within 1 week pain resolved
  - D28 scans with improvement
  - PSA did not decline (up to 18.2)
  - Symptomatic and radiographic PD at day 90
- **No cystitis**



Pre CAR T | D28 Post CAR T | Pre CAR T 2nd dose | D28 post 2nd CAR T dose

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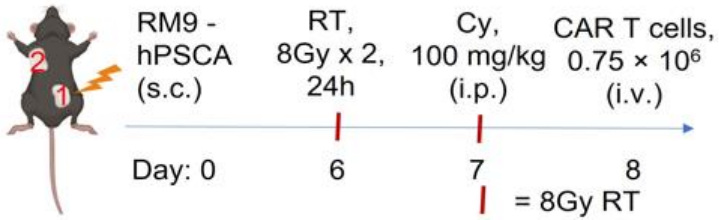
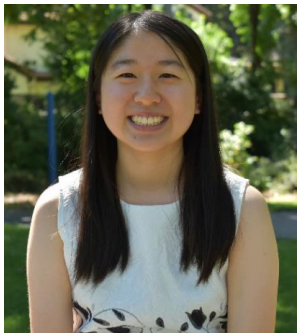
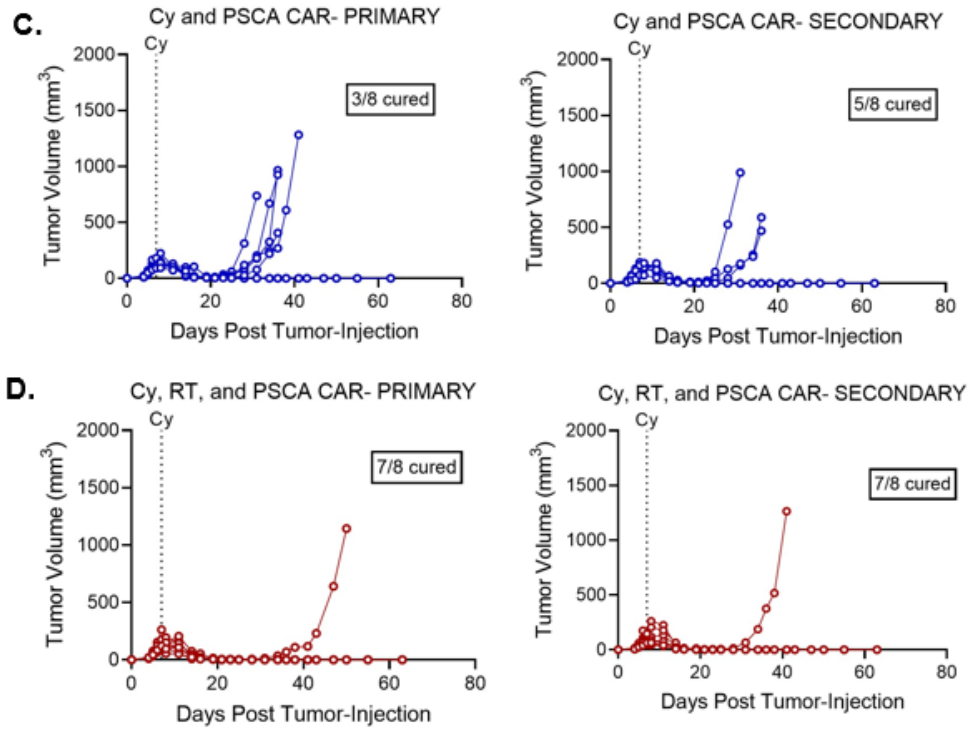
Combining LD + RD + CAR T





Cari Young, PhD
Post-doc
Priceman lab



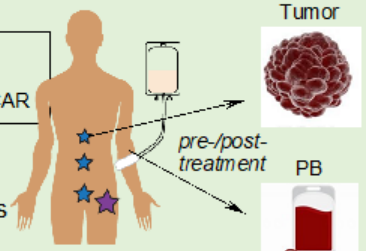
Multi-dose PSCA CAR T and combination with SBRT

Specific Aim 1: Phase 1b trial evaluating MDRT and PSCA-CAR T cell therapy combination for patients with mCRPC

Phase 1b trial safety/activity design:

- ***Year 1***: TP1: multi-dosing PSCA-CAR T cells
  - ***Years 2-5***: TP2: MDRT + PSCA-CAR T cells

Day -14 … -6: MDRT
Day -5 … 0: LD
Day 0, 14, 28: PSCA-CAR



pre-/post-treatment

Patient correlatives studies:

- CAR T cell persistence, expansion, and phenotype in blood (PB) and tumors
- Immune landscape changes in PB and tumors
- Tumor evolution (tumors, CTCs, cfDNA)

Specific Aim 2: Refine the combination regimen of RT and PSCA-CAR T cells experimentally and mathematically.

2a: Optimization of RT to improve CAR T cell and systemic immune responses targeting prostate cancer.

2b: Apply a mathematical model to optimize dose schedule of focal radiation combined with PSCA-CAR T cells.

Hypothesis: Cystitis will be minimal with multiple smaller doses of Car T+ cells, but total higher dose of cells will improve response

Priceman, Rockne, Li, Dorff

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Effective Targeting of TAG72^{+} Peritoneal Ovarian Tumors via Regional Delivery of CAR-Engineered T Cells

John P Murad, Anna K Kozlowska, Hee Jun Lee, Maya Ramamurthy, Wen-Chung Chang, Paul Yazaki, David Colcher, John Shively, Mihaela Cristea, Stephen J Forman, Saul J Priceman

Front Immunol. 2018 Nov 19;9:2268. doi: 10.3389/fimmu.2018.02268.

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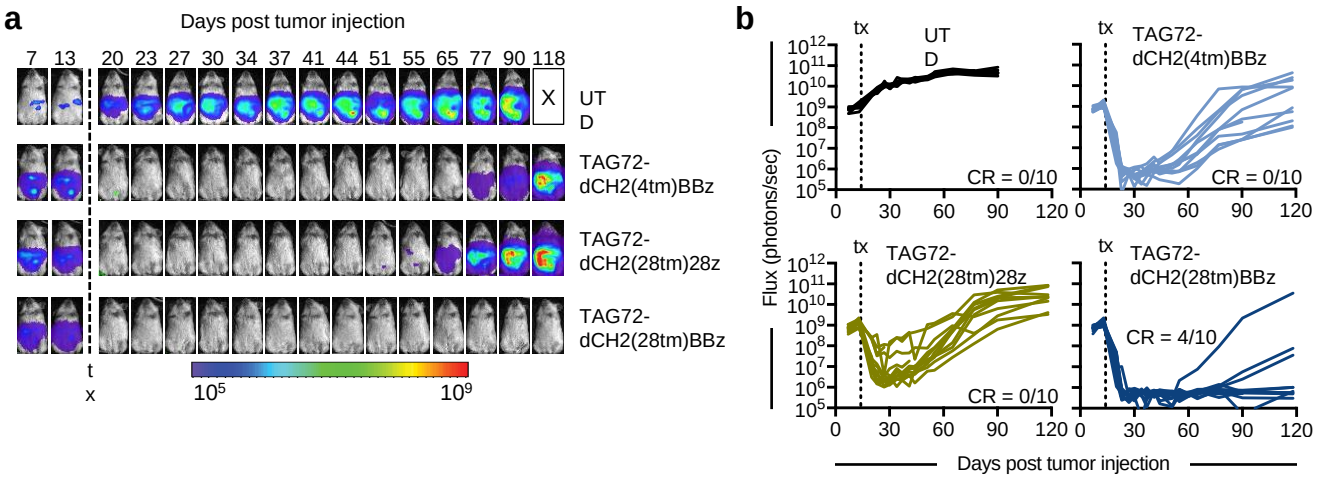
Optimized TAG72-CAR T Cells Provide Curative Responses against Ovarian Cancer Peritoneal Metastasis Xenograft Models



- TAG72-CARs with optimized backbone greatly improves *in vivo* anti-tumor efficacy

Lee et al. *in revision*

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Phase 1 Clinical Trial to Evaluate TAG72-CAR T Cells in Recurrent Ovarian Cancer

NIH R01

- **TAG72+ platinum-resistant metastatic epithelial ovarian cancer**
  (Clinical PI: Lorna Rodriguez, MD PhD, Research PI: Saul Priceman, PhD) – Open to enrollment

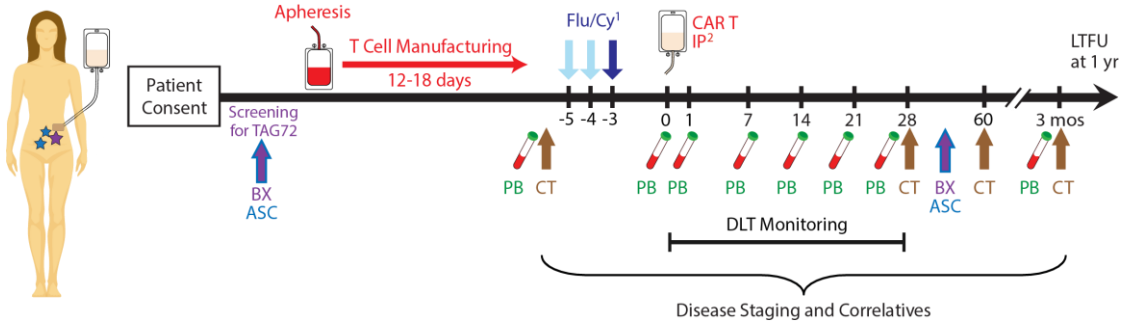

Table 1. CAR+ Cell Dose Schedule				
Dose -1	**Starting Dose 0a**	Dose 0b	Dose 1	Dose 2
50M	**100M**	100M +precond.	300M +precond.	600M + precond.

Murad et al. *Front Immunol* 2018
Lee et al. *in revision*

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AML CAR Program

Researchers
Budde Laboratory
Forman Laboratory
Caligiuri/Yu Laboratory
Marcucci Laboratory

Supporting staff
Regulatory group
Manufacturing group
Statisticians
project managers
Many more…

Leukemia Center Physicians
CRNs & CRCs

Our pipeline: Preclinical → Phase 1

CD123CAR
CD33CAR
CLL1CAR
IL-1RAPCAR — Collaboration with Marcucci group
FLT-3CAR — Collaboration with Caligiuri/Yu; phase 1 planned

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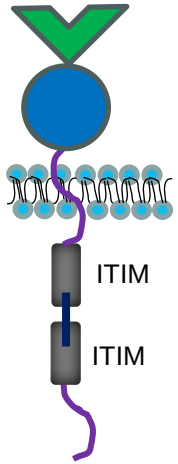
CD33: An Immunotherapeutic Target for AML



- Ig family with 2 extracellular domains.
- Expression:

  myeloid blasts in **87% - 98%** AML cases[1,2];

  leukemic stem/progenitor cells (LSPCs) and hematopoietic stem cells (HSCs)[4]

  myeloid-derived suppressor cells (MDSCs)[3]
- Function of CD33:

  cell adhesion and activation

- Clinically valídated target:
  - Gemtuzumab Ozogamicin (GO, Mylotarg) approved for CD33^{+} AML

[1]Ehninger et al. *Blood Cancer J*. 2014;4:e218.
[2]Andrews et al. *J Exp Med*. 1989:169:1721-1731.
[3]Elliott et al. *Front. Immunol*. 2017;8:86.
[4]Walter et al. *Blood*. 2012;119:6198-6208.

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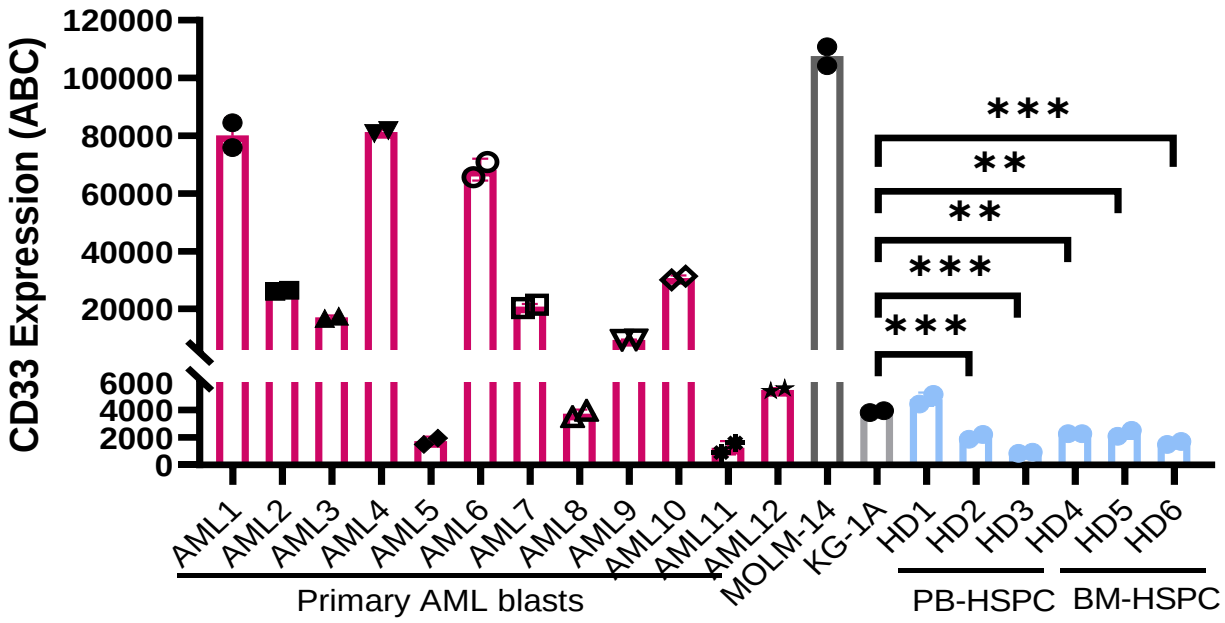
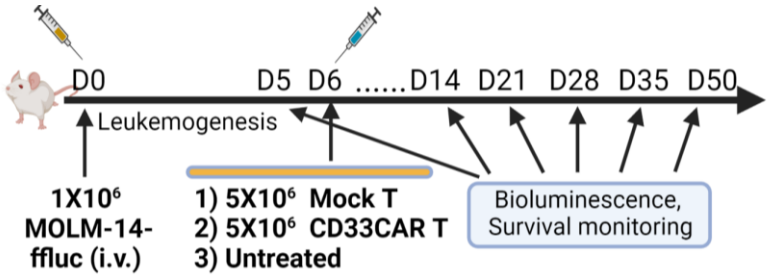
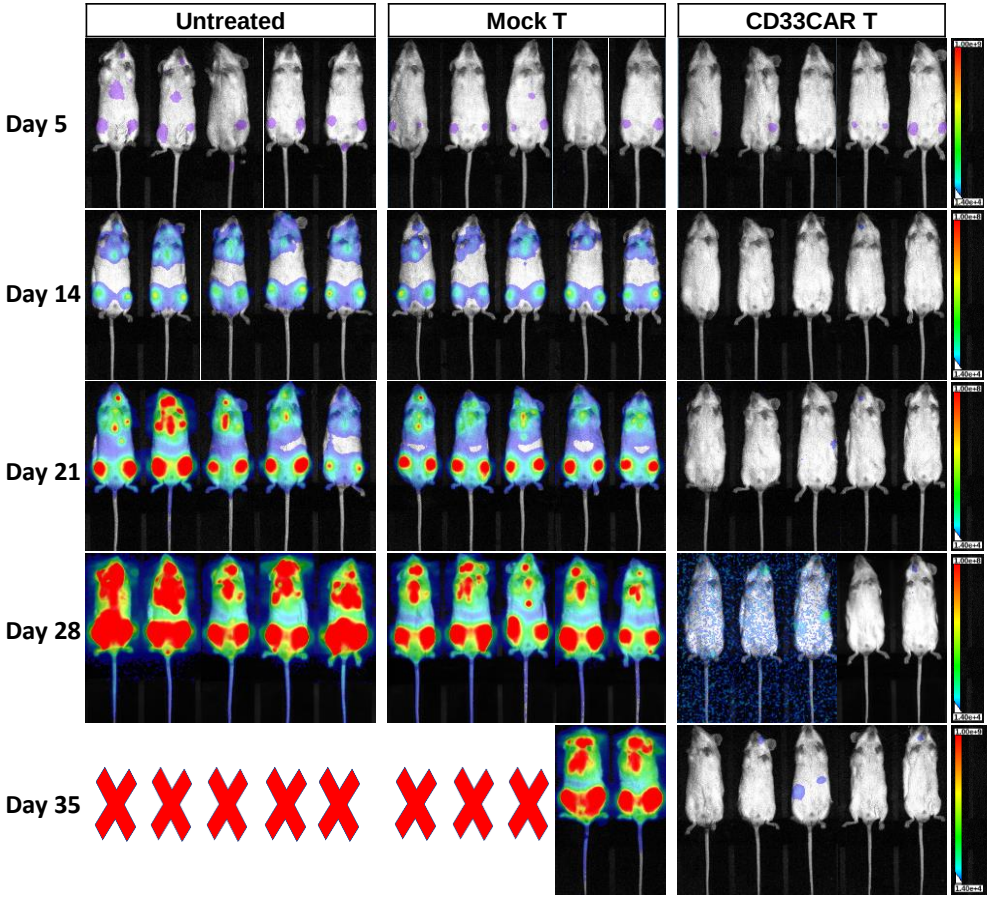
Differential CD33 Expression:

low on normal hematopoietic stem/progenitor cells



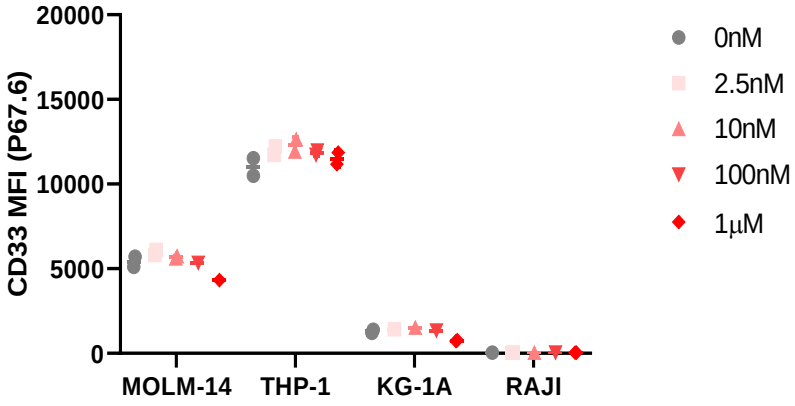
Potential Antileukemic Activity of CD33CAR T Cells *In Vivo*



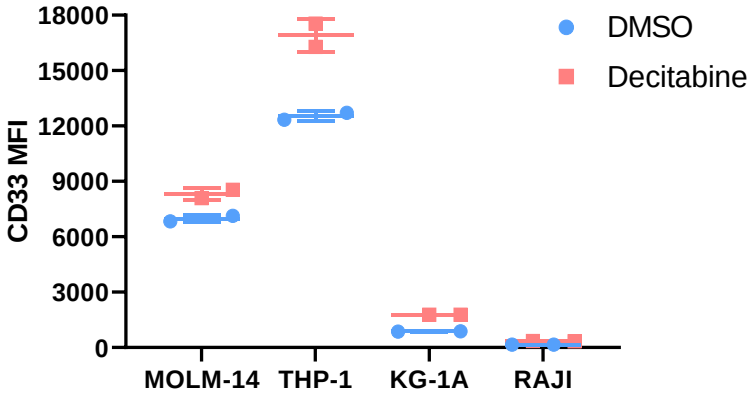


Impact of anti-leukemia drugs on CD33 expression

FLT3 inhibitor: no change of CD33 expression



Decitabine: increased CD33 expression



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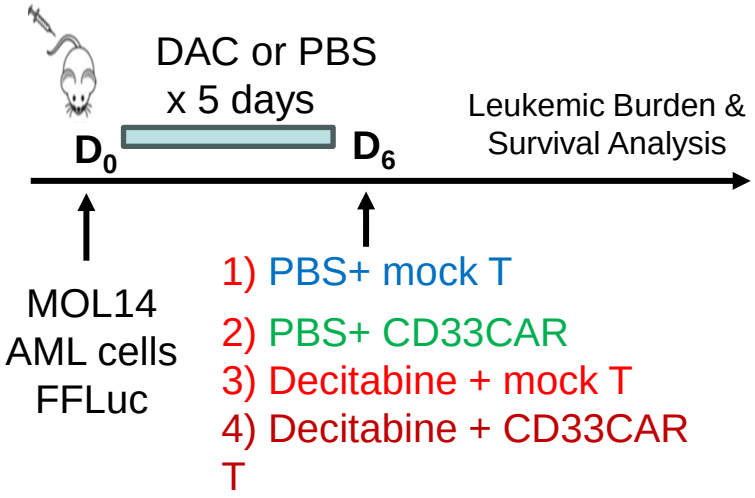
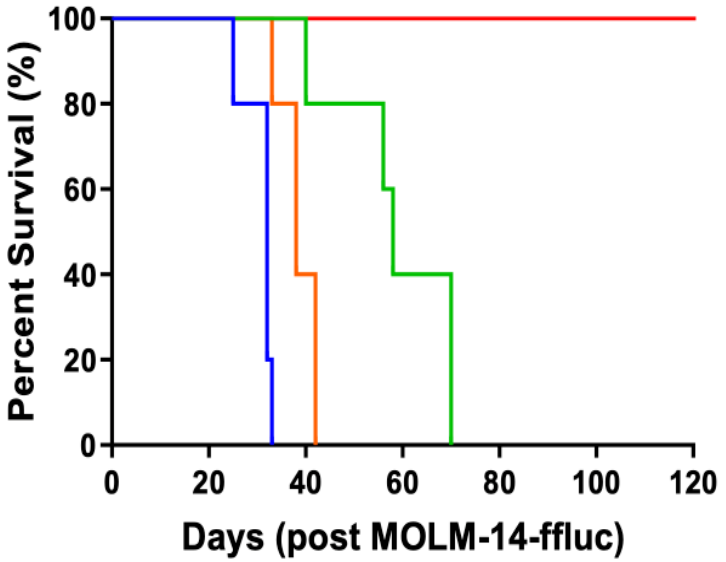
Decitabine Pretreatment Sensitizes AML Cells to Killing by CD33 CAR T cells



Decitabine + CD33CAR T: 100% survival



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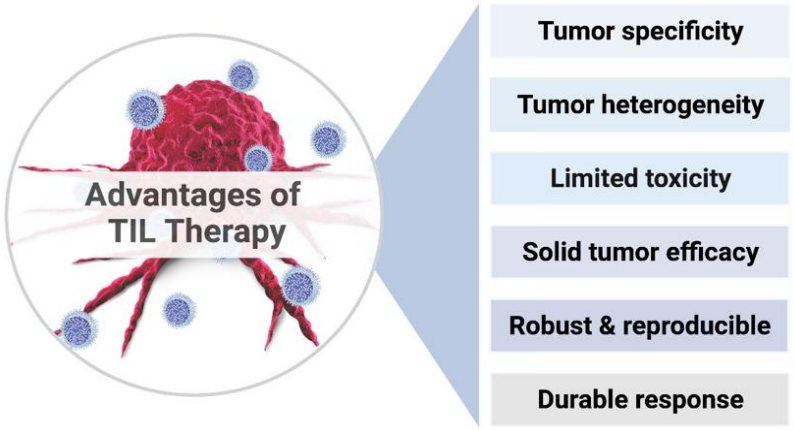
Advantages of
TIL Therapy
Tumor specificity
Tumor heterogeneity
Limited toxicity
Solid tumor efficacy
Robust & reproducible
Durable response

Snap TILs

- The Translational Genomics Research Institute (Tgen) at City of Hope lead by Sunil Sharma, has developed a personalize neo antigen pipeline to augment the activity of these T cells by stimulating the harvested T cells with peptide antigens derived from the patients own tumor (personalized immunotherapy)

- These cells have potential to overcome the tumor intrinsic resistance mechanisms that make cancer, not responsive to the current immune based therapies

- The technology augments tumor cell recognition and we hypothesis will be a more effective TIL therapy approach and make immunotherapy an option for patients with cancer

tgen part of City of Hope

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Tumor-Infiltrating Lymphocyte Therapy or Ipilimumab in Advanced Melanoma

The NEW ENGLAND JOURNAL of MEDICINE

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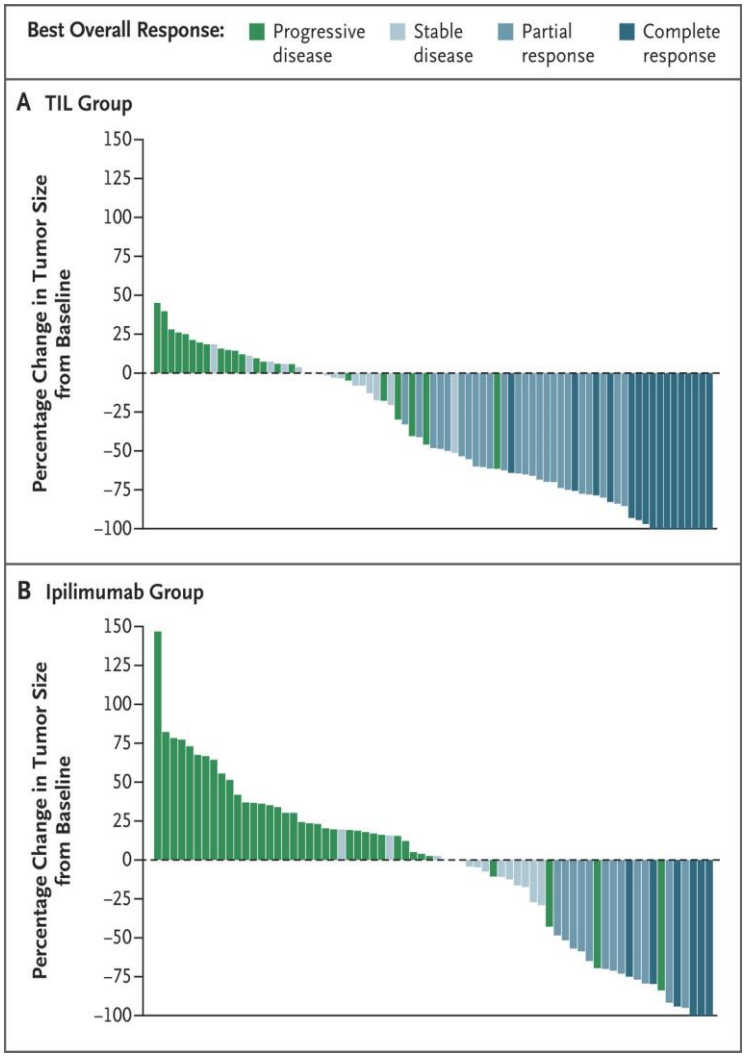
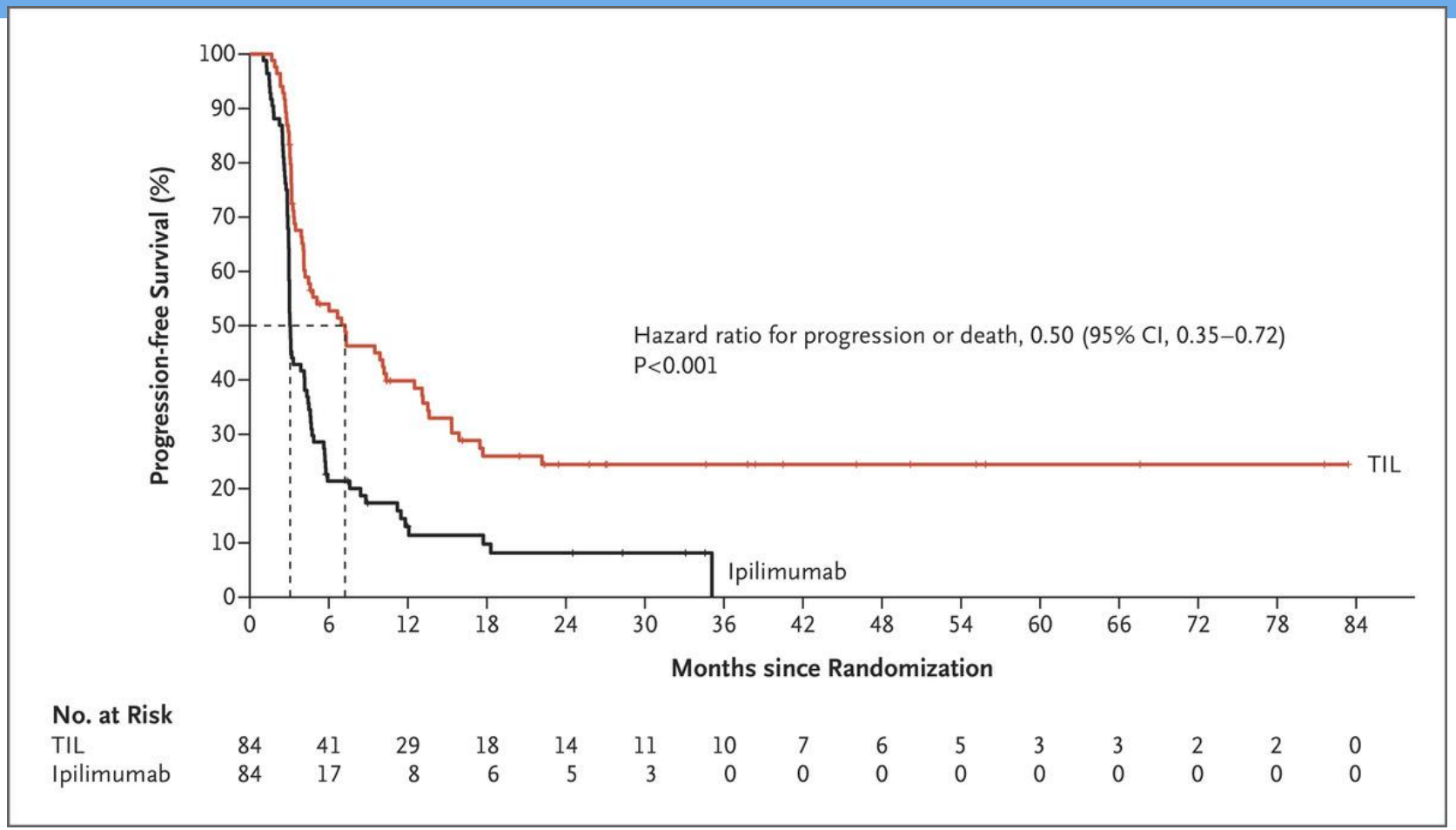


MW Rohaan et al. N Engl J Med 2022;387:2113-2125.

Progression-free Survival.



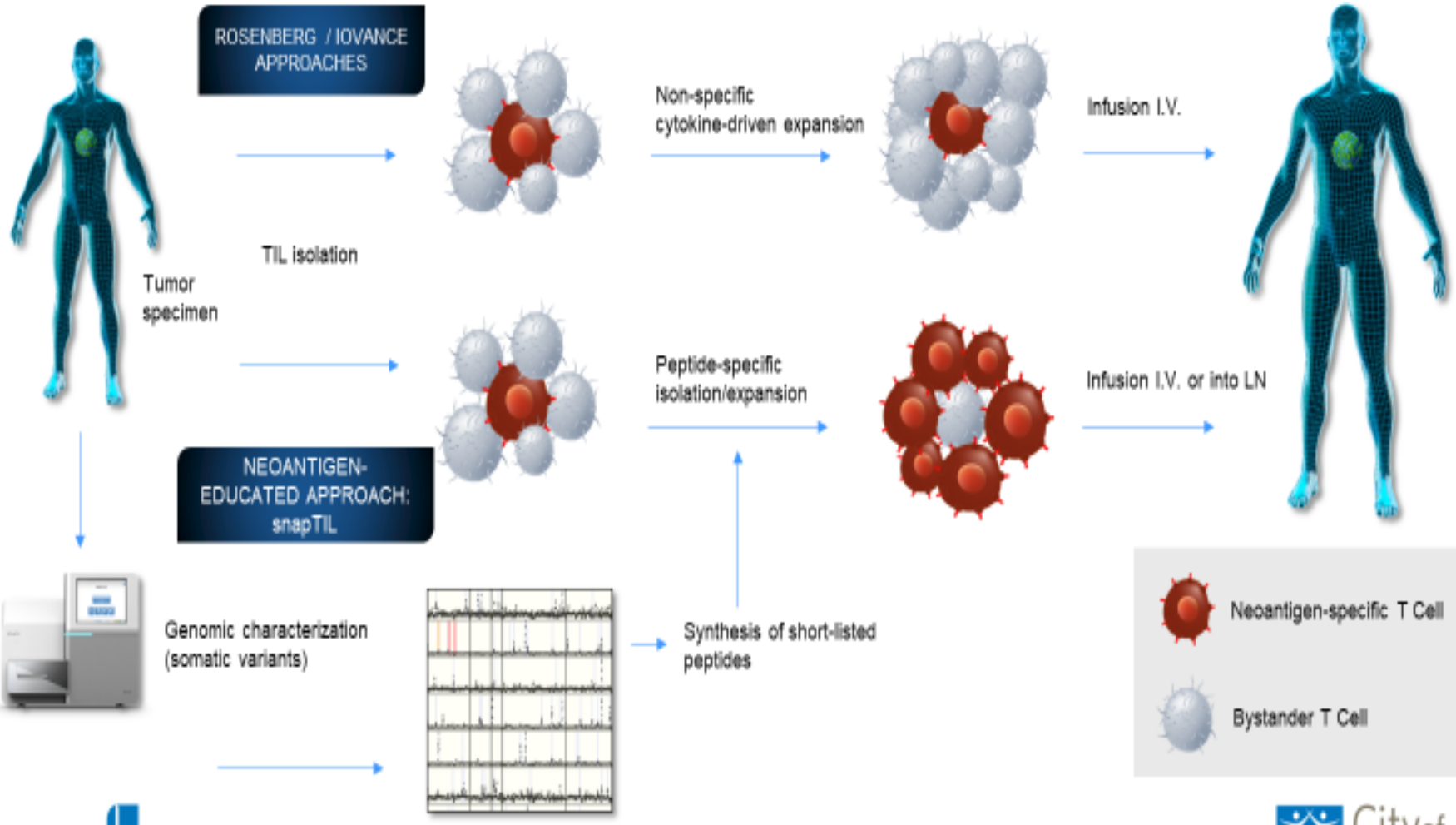
Progression-free survival assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, is shown for all patients who were randomly assigned to receive tumor-infiltrating lymphocyte (TIL) therapy or ipilimumab (the intention-to-treat population). The patients were stratified according to *BRAF* V600–mutation status, line of treatment, and treatment center. Hazard ratios were estimated with the use of the stratified Cox regression model. The P value was calculated with the use of the stratified log-rank test with a two-sided 95% confidence interval. Tick marks indicate censored data..

MW Rohaan et al. N Engl J Med 2022;387:2113-2125.

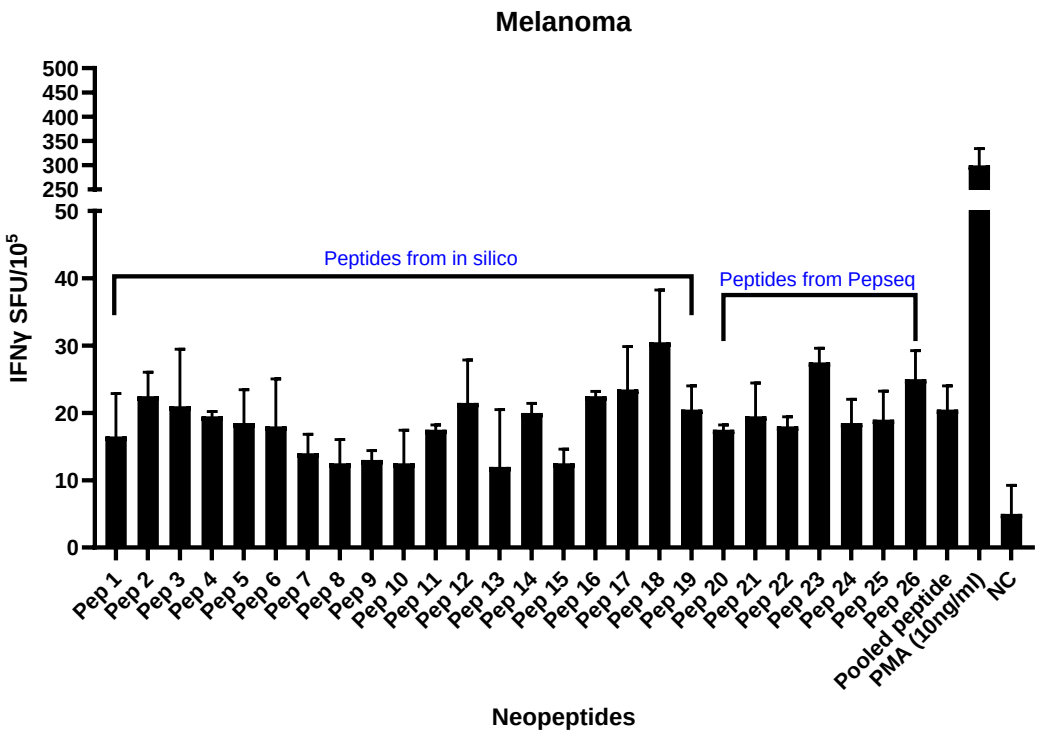
City of Hope™

OUR SCIENCE & TECHNOLOGY: *Selective NeoAntigen Peptides TIL (snapTIL™)*
snapTIL™ Versus Conventional TIL Therapies: Using Genomic Tools To Enrich snapTIL

SOURCE: Translational Genomics Research Institute



Educated snapTIL response to neopeptides

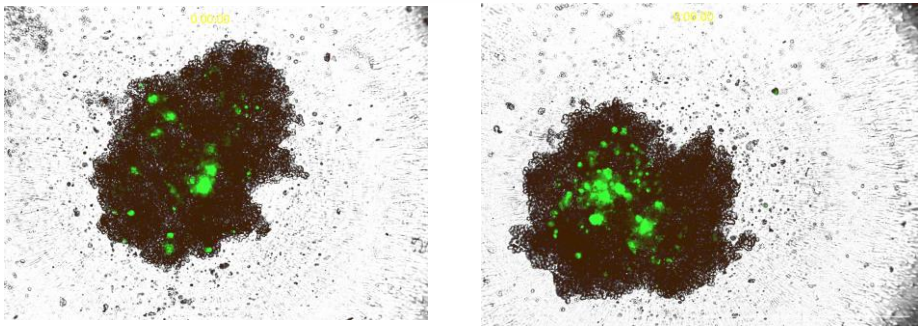


Immune response of autologous snapTIL educated with selected peptides

snapTIL show higher cytotoxicity compared to conventional TILs

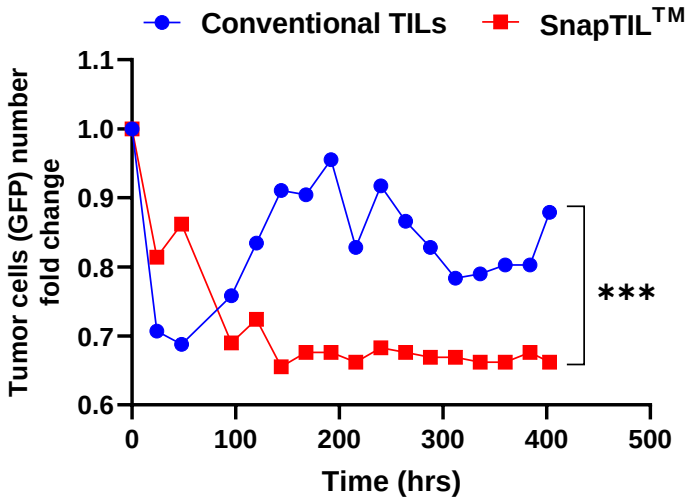
snapTIL™ Conventional TILs

10 days



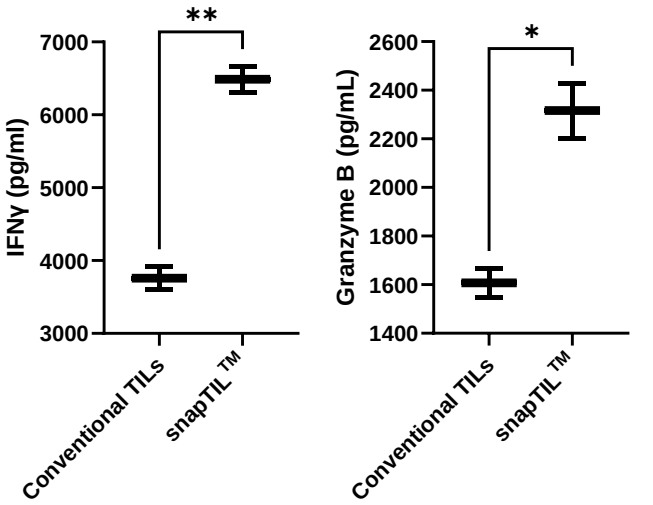
Tumor cells (green)
Stroma cells (black)
TILs (orange)

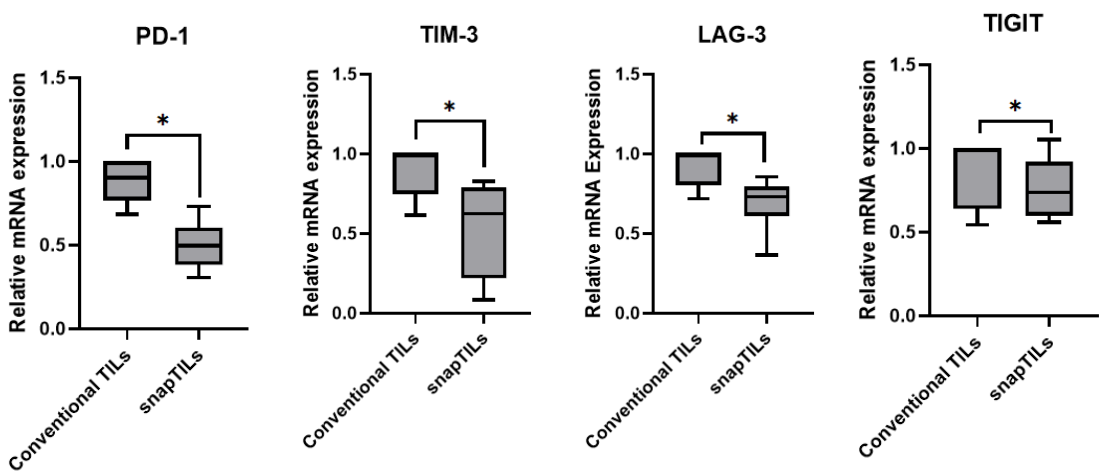
Melanoma patient-derived tumoroids



snapTIL™ kill all tumor cells.

snapTIL™ show higher activation status and less exhaustion status compared to conventional TILs



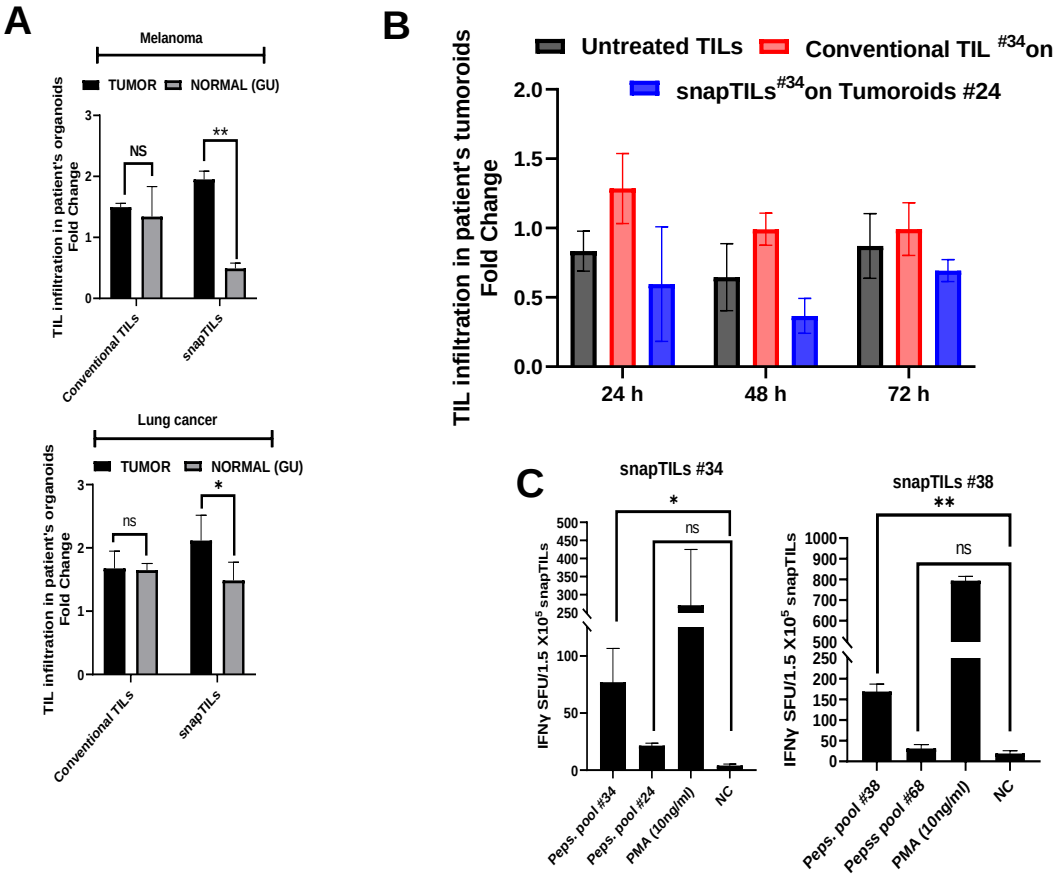


snapTIL™ show higher activation status and cytotoxicity compared to Conventional TILs

snapTIL™ show less exhaustion status after Rapid Expansion compared to Conventional TILs

Representative response of cohort of 15 patients

snapTIL™ are highly selective toward the patient's tumor



(A) snapTIL™ preferentially recognize tumor tissue: representative from Melanoma (top) and Lung cancer (bottom) patient. GU=general un-involved tissue.

(B) Specificity of immune response as measured by ex-vivo immune infiltration assay of allogeneic peptides. Representative response from snapTIL™ and Conventional TILs from pancreatic cancer patient #34 incubated with allogeneic tumoroids from melanoma patient #24

(C) Specificity of immune response as measured by ex-vivo IFNγ ELISpot assay to allogeneic peptides versus autologous peptides. Representative response from pancreatic cancer patient #34 incubated with allogeneic peptides from melanoma patient #24 (left panel), and from colorectal cancer patient #38 incubated with allogeneic peptides from pancreatic cancer #68 (right panel).

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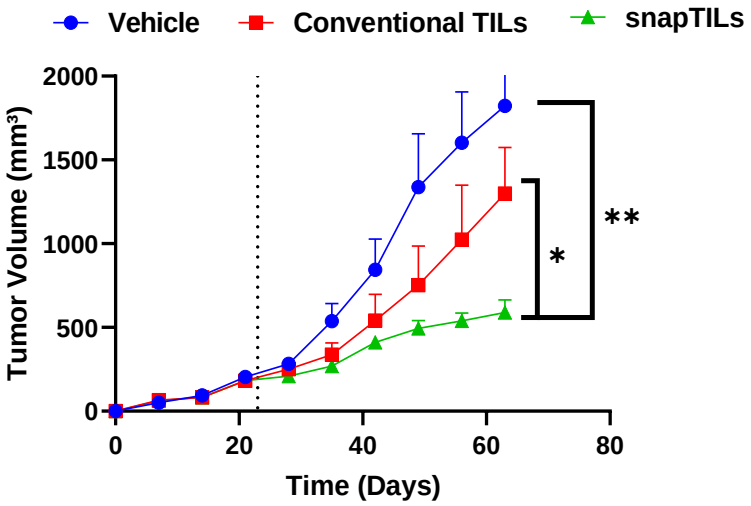
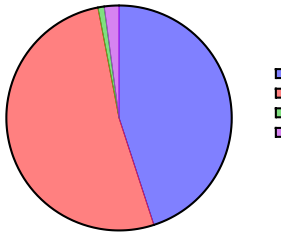
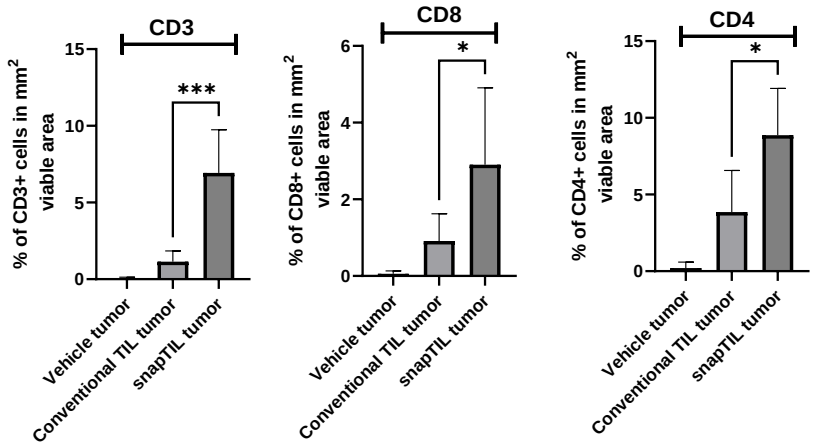
snapTILs efficacy *in vivo* studies: melanoma patient-derived xenograft model



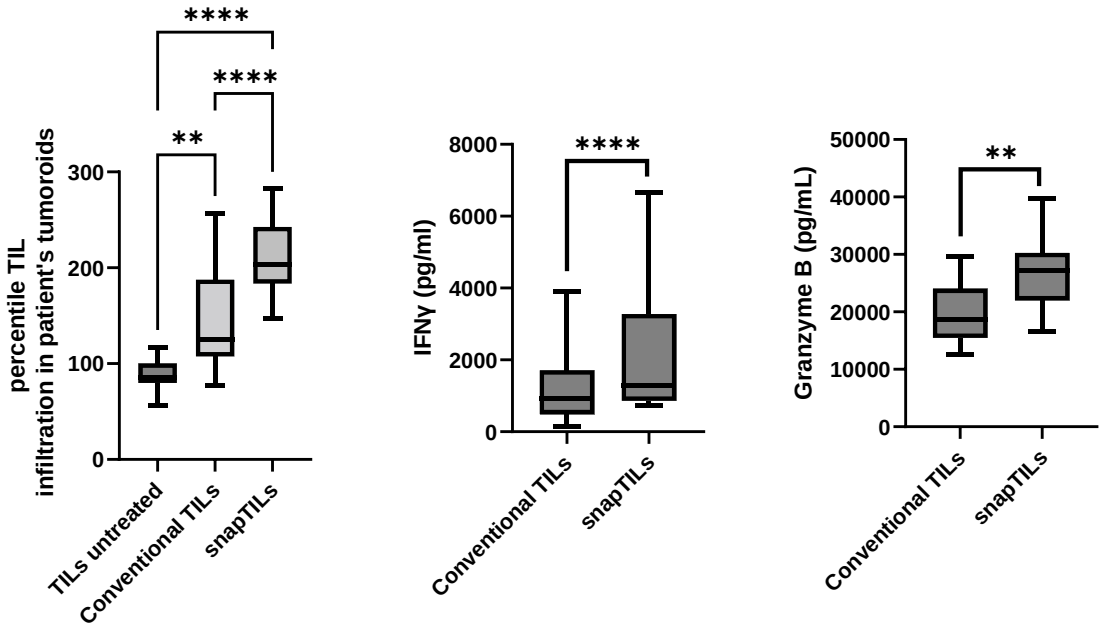
snapTIL™ treatment promotes ~70% tumor reduction. 72 days post-treatment, snapTIL™ CD3⁺CD8⁺ are still present in tumor core



TGI (Tumor Growth Inhibition)	
Conventional TILs	snapTIL™
28.70%	67.63%

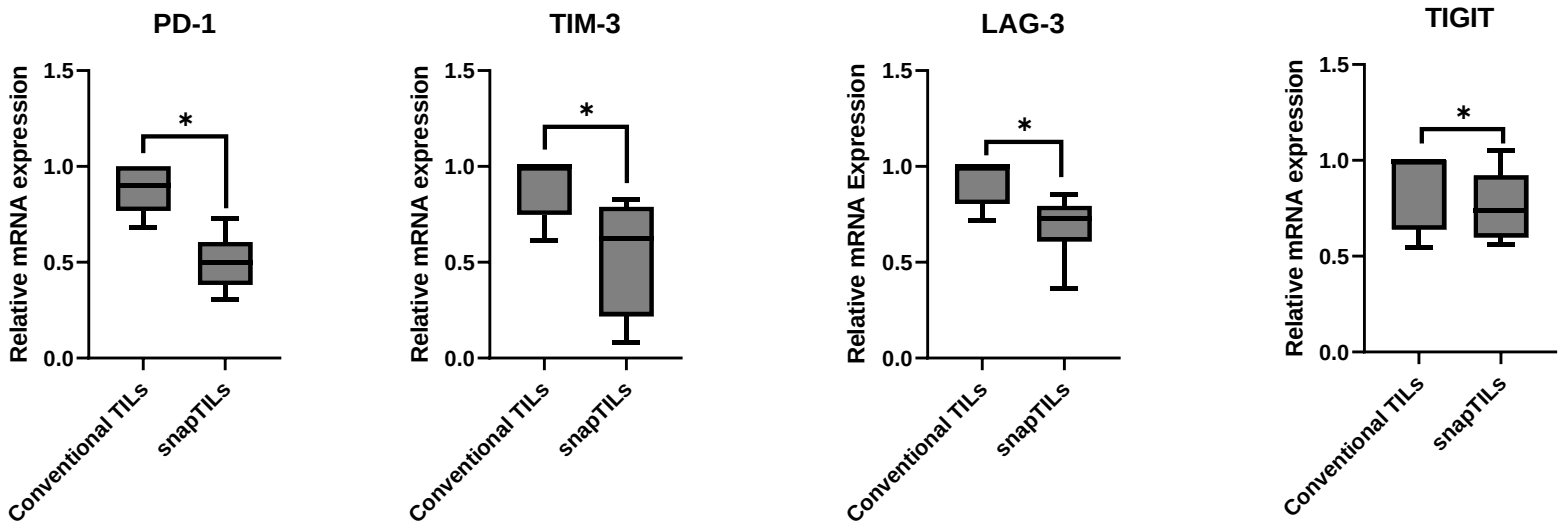


snapTIL™ efficacy, activation, and cytotoxicity in pancreatic cancer: ex-vivo model



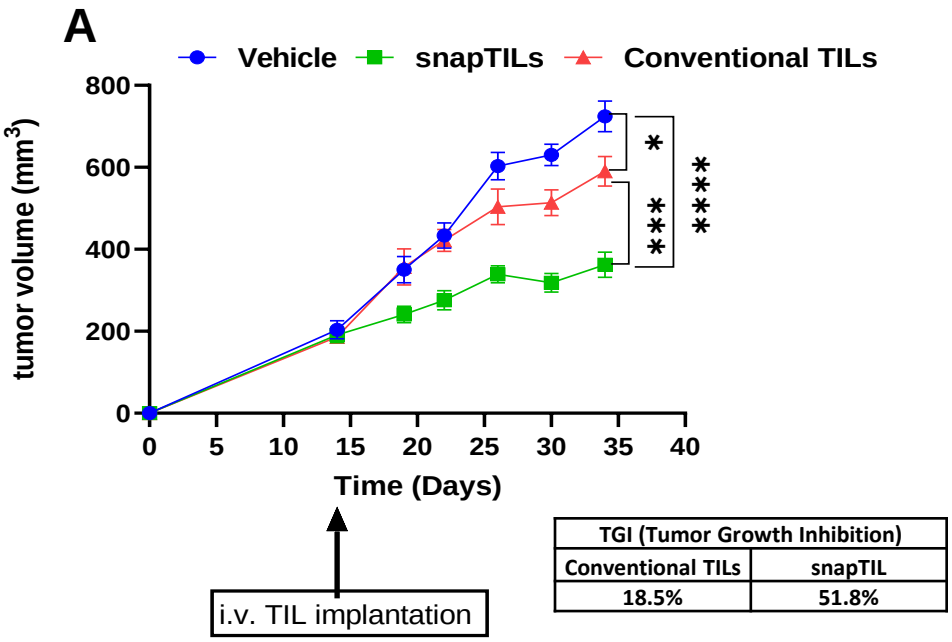
snapTIL™ show significant higher infiltration , enhanced activation and cytotoxicity properties in pancreatic cancer compared to Conventional Therapy. Data representative of 6 pancreatic cancer patients.

snapTIL™ efficacy in Pancreatic cancer patient's tumoroids

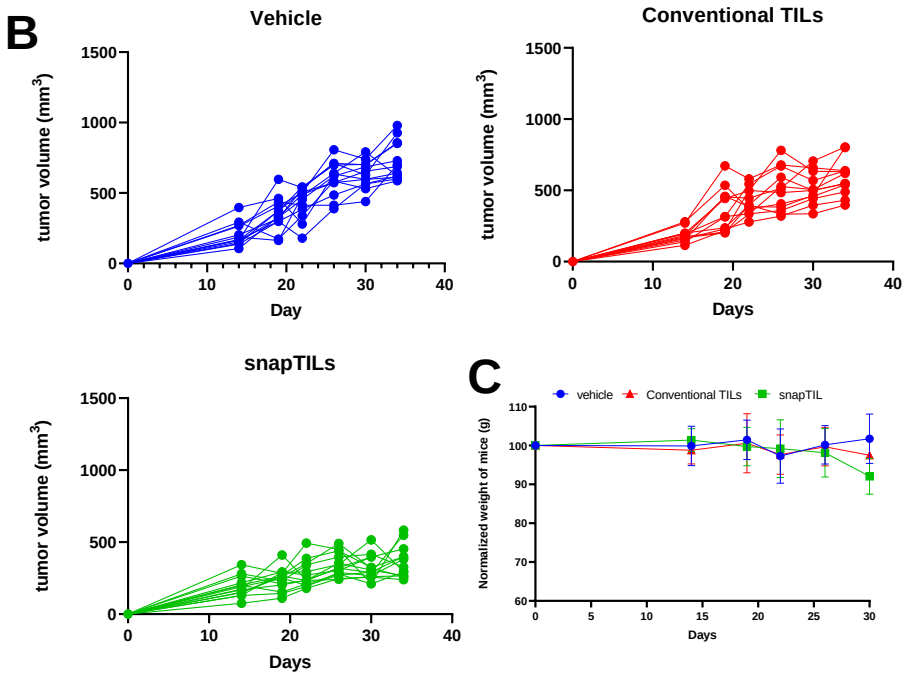


snapTIL™ show less exhaustion status after Rapid Expansion compared to Conventional Therapy. Data representative of 6 pancreatic cancer patients.

snapTILs efficacy *in vivo* studies: pancreatic cancer patient-derived xenograft model (study in progress)



TGI (Tumor Growth Inhibition)	
Conventional TILs	snapTIL
18.5%	51.8%



snapTILs show significant higher efficacy in pancreatic cancer compared to Conventional Therapy

Phase 1 Study of Adoptive Selective Neoantigen peptide stimulated Tumor Infiltrating Lymphocytes (snap TIL) Therapy for treatment of Advanced Pancreatic Cancer

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Protocol Goals and Design

- To determine the safety and feasibility of administering snap TIL in patients newly diagnosed incurable pancreatic cancer
- To determine response rate of treatment in patients as part of their upfront treatment
- At time of diagnosis, tumor is removed for generation of snap TILs, before any chemo is administered
- While cells being made, patients will get 4 cycles of initial treatment. Goal is tumor control while cells are made, as the initial chemotherapy treatment rarely induces a complete remission
- When cells are ready, patients will then undergo treatment with these personalized snap TIL cells to assess their efficacy, and toxicity

Universal Combinatorial Therapy: Oncolytic Viruses Deliver CAR Targets and 'Warm Up' Solid Tumors

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Saul Priceman, PhD,
Stephen Forman, MD
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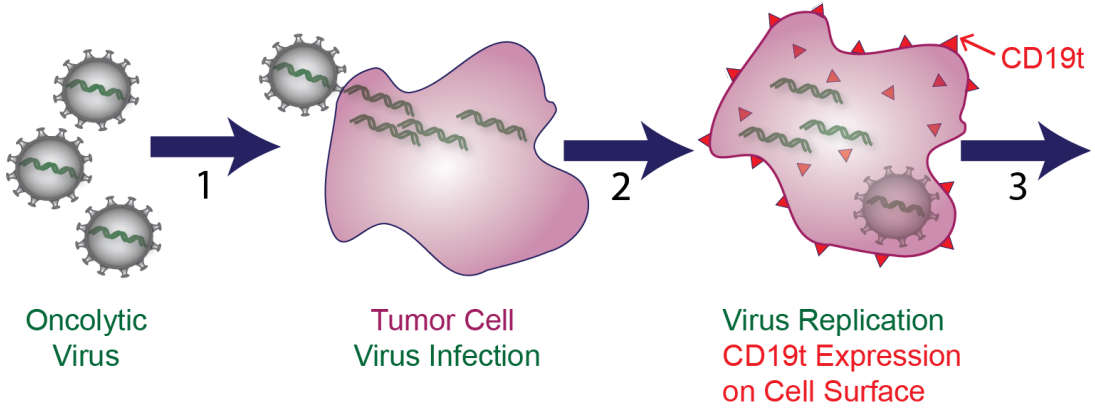

Image courtesy of Dr. Sandra Thomas

Now expanded to "off-the-shelf" using BiTEs (CD19, BCMA) with OV combination

Park et al. *Sci Transl Med* 2020 Sep 2; 12(559)

COH T Cell Therapy Research Program

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