Adoptive T-cell Therapy

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The University of Texas MD Anderson Cancer Center

SITC 2018 33rd Annual Meeting
Pre-Conference Primer on Tumor Immunotherapy and Cancer Immunotherapy
Thursday, November 8, 2018

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Making Cancer History®

Disclosures

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Cytotoxic T-lymphocytes Can Recognize and Kill Tumor Cells

(From UVA)

Necessary Steps for a Productive Immune Response

- Proliferation and activation of antigen-specific T-cells
- Migration of T-cells to the site of tumor or infection
- Recognition and killing of tumor cells or infected tissue

Generation of Antigen Specific T-cells

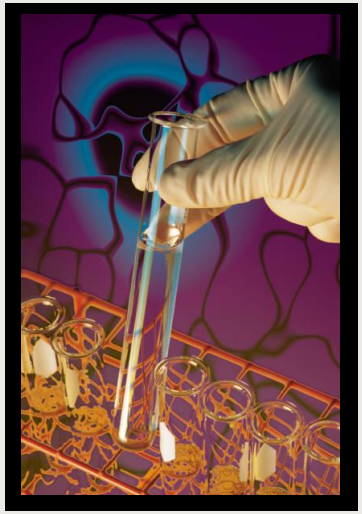
- **Adoptive T-cell Transfer**
  - TIL
  - Chimeric antigen receptor (CAR) transduced T-cells
  - TCR-transduced T-cells
- **Vaccines**
  - Peptides vs. Viral vs. Nucleic Acid Strategies
- **Intratumoral Immunomodulation**
  - Viruses
  - TLR Agonists
  - Antibodies (for example, anti-CD40)

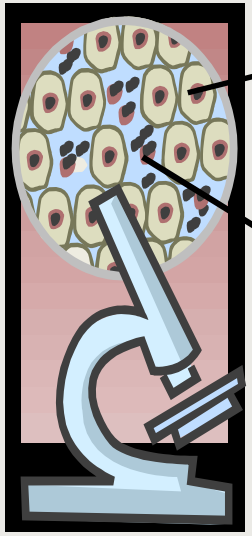
Neoantigens vs. Shared Antigen Strategies

Adoptive Cell Therapy (ACT) with Antigen Specific T-cells

Surgical Removal of Cancer Nodule

Single Cell Suspension Incubated with IL-2



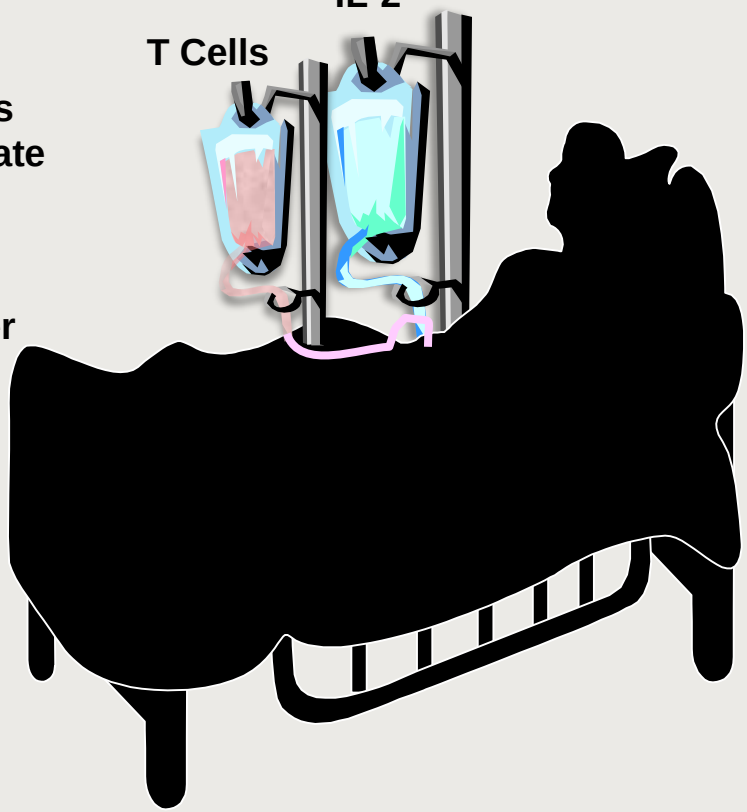


T Cells Proliferate

Cancer Cells Die

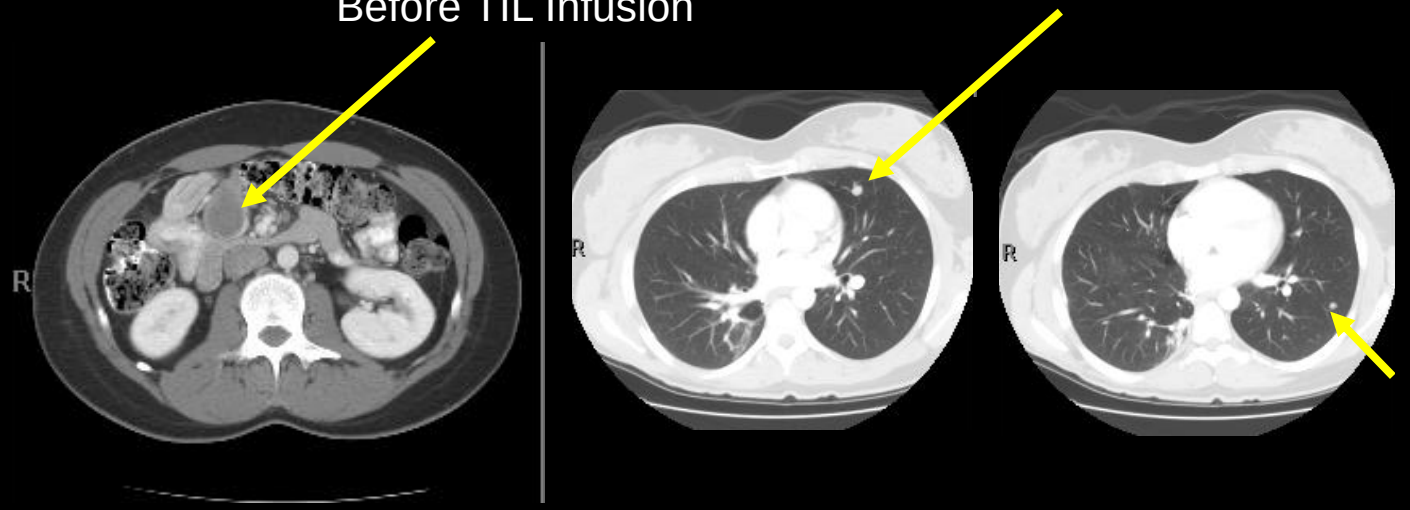
IL-2

T Cells

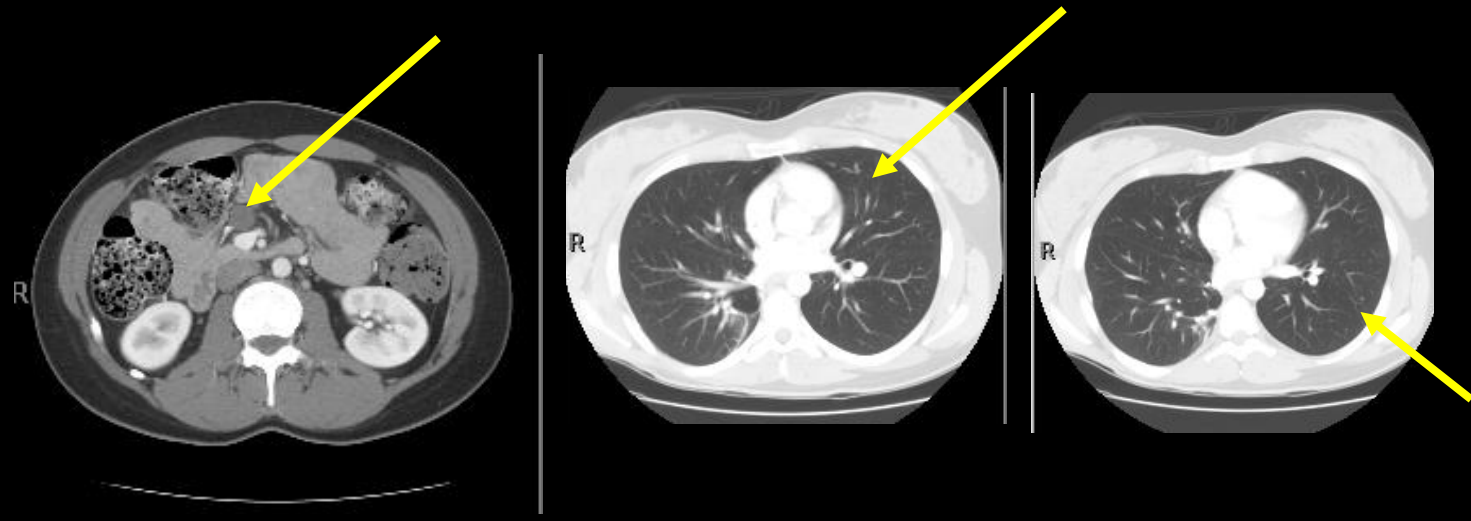


Clinical Response following Lymphodepletion + T-lymphocyte Infusion

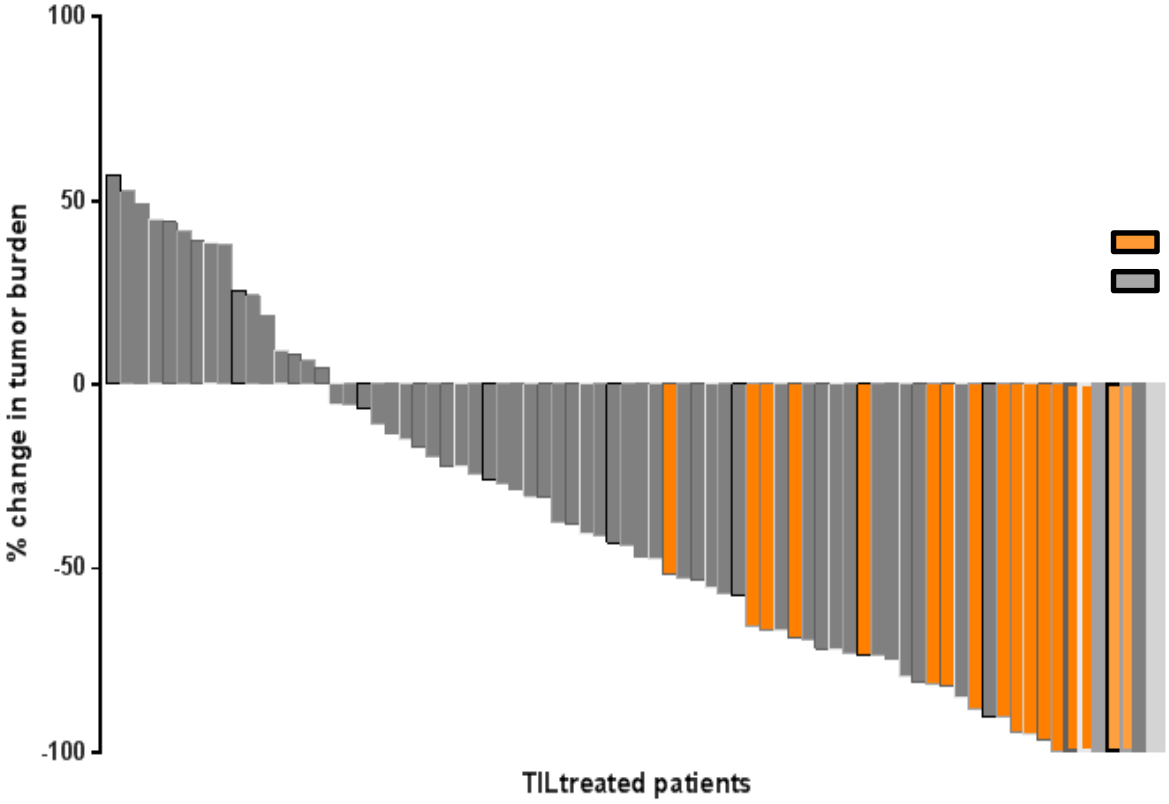
Before TIL Infusion



After TIL Infusion



Best Overall Response in TIL Treated Patients at MDACC

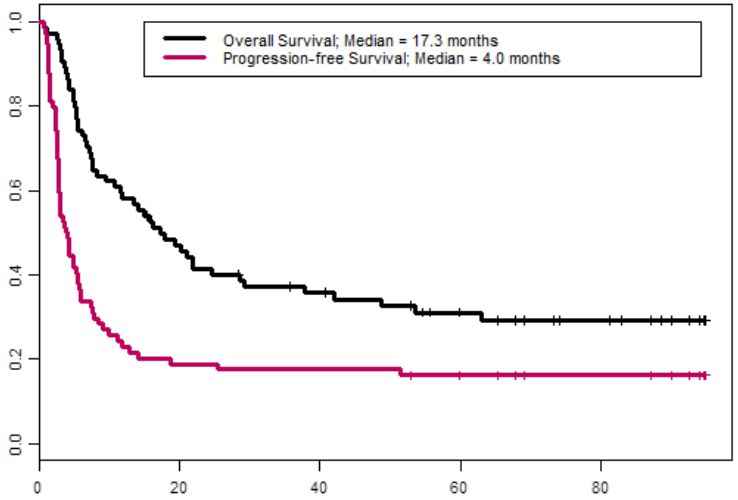


Most responses of >75% decrease in tumor burden are durable

N=80

Response as of 06/01/2015

Objective Tumor Response in Patients Receiving TIL Therapy at MDACC: 2007-2017



Number of Patients	CR	PR	CR + PR (%)
74	8 (11%)	23 (31%)	31 (42%)

Number of Patients	Prior anti-CTLA4	Prior anti-PD1	CR	PR	CR + PR (%)
43	No	No	5	15	20 (47%)
21[1]	Yes	No	3	5	8 (38%)
9[1]	Yes	Yes	0	3	3 (33%)
1	No	Yes	0	0	0

[1] Of the 30 patients treated after anti-CTLA4 therapy, 21 had TIL harvest after anti-CTLA4 and 9 had TIL harvest before anti-CTLA4

Forget, Haymaker et al.

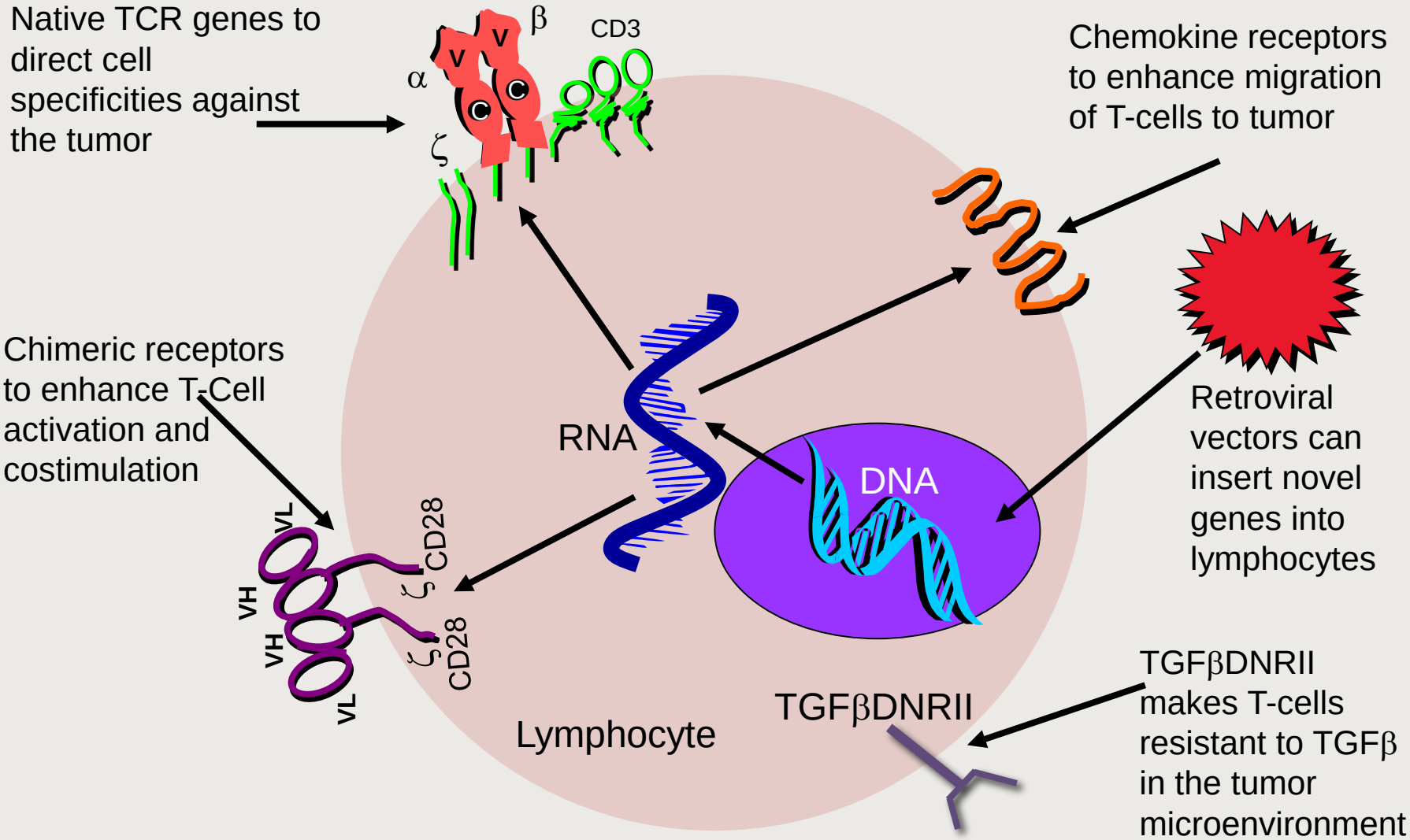
Response Rate to TIL Therapy has Decreased in the Modern Era of Checkpoint Inhibition

- **ORR 25% at NCI in patients with prior anti PD-1 therapy**

- **ORR 29% for 14 anti PD-1 refractory patients treated on multicenter Lion/Iovance melanoma trial**

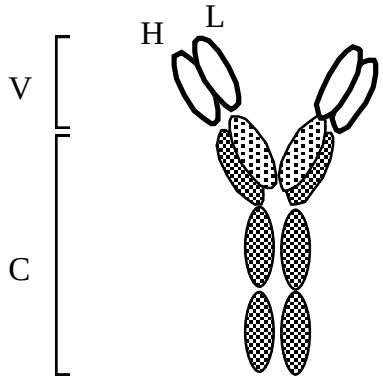
Goff et al. *J Clin Oncol* 2016; 34: 2389-2397
Sarniak et al. ASCO 2017

Insertion of Genes into Lymphocytes to Enhance Antitumor Properties

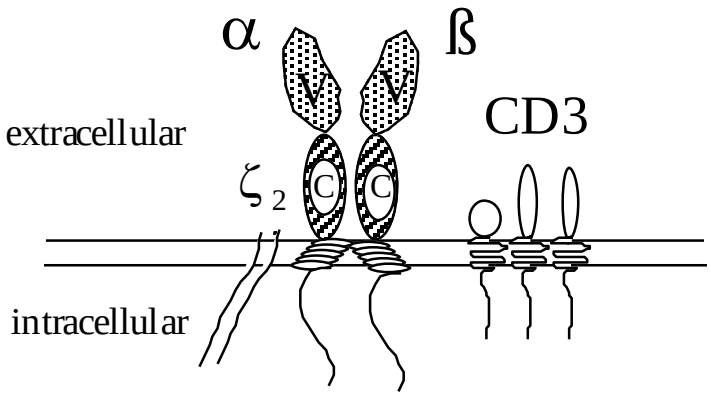


Chimeric Antibody / T-cell Receptor: Combines Antibody V Region and T-cell Signaling Chains

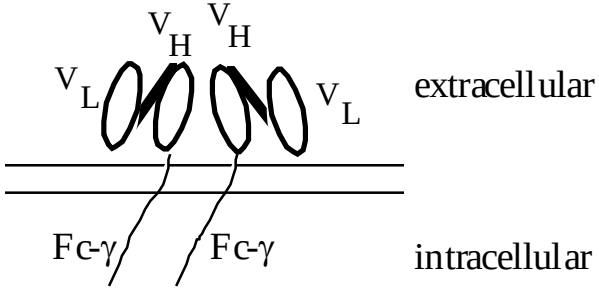
Antibody



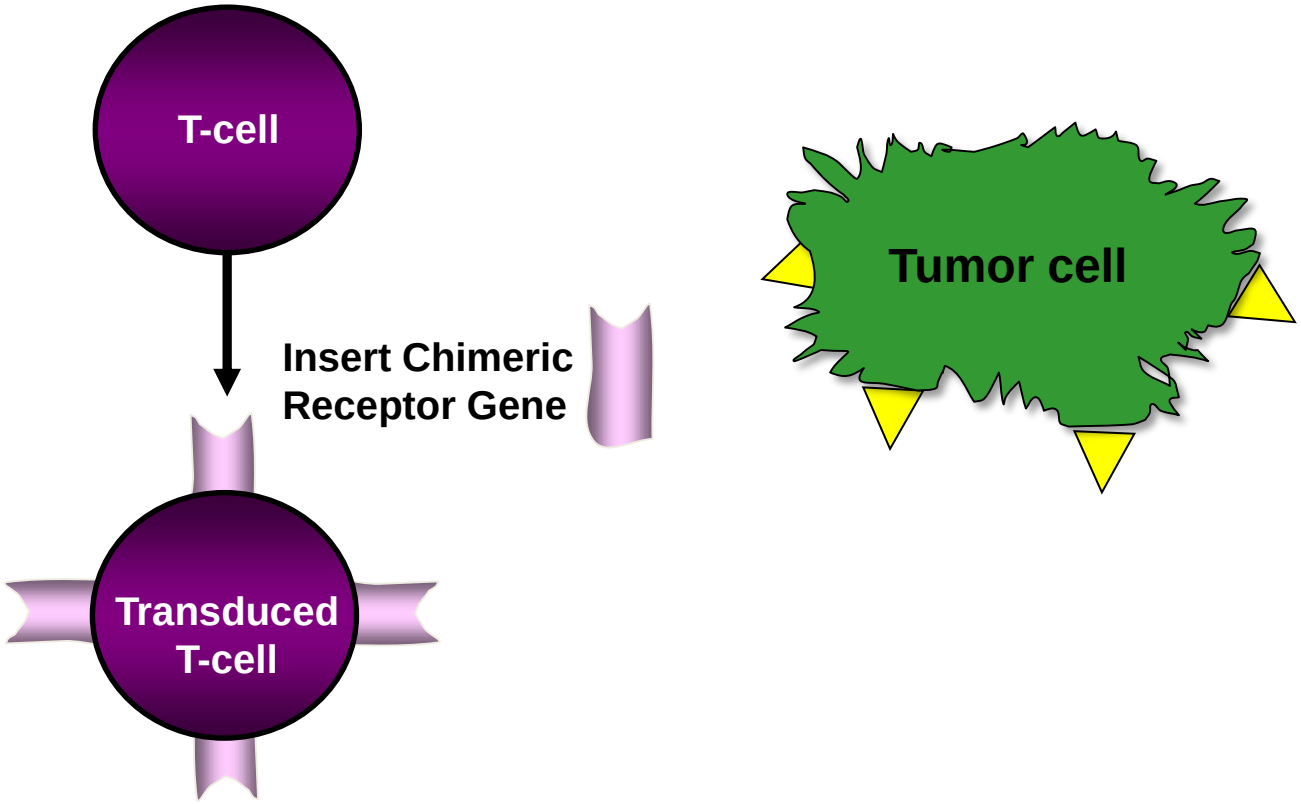
TCR



scFv-γ



Transduction of T-cells with Chimeric Receptor Genes to Direct T-cell Specificity



Brief Definitive Report

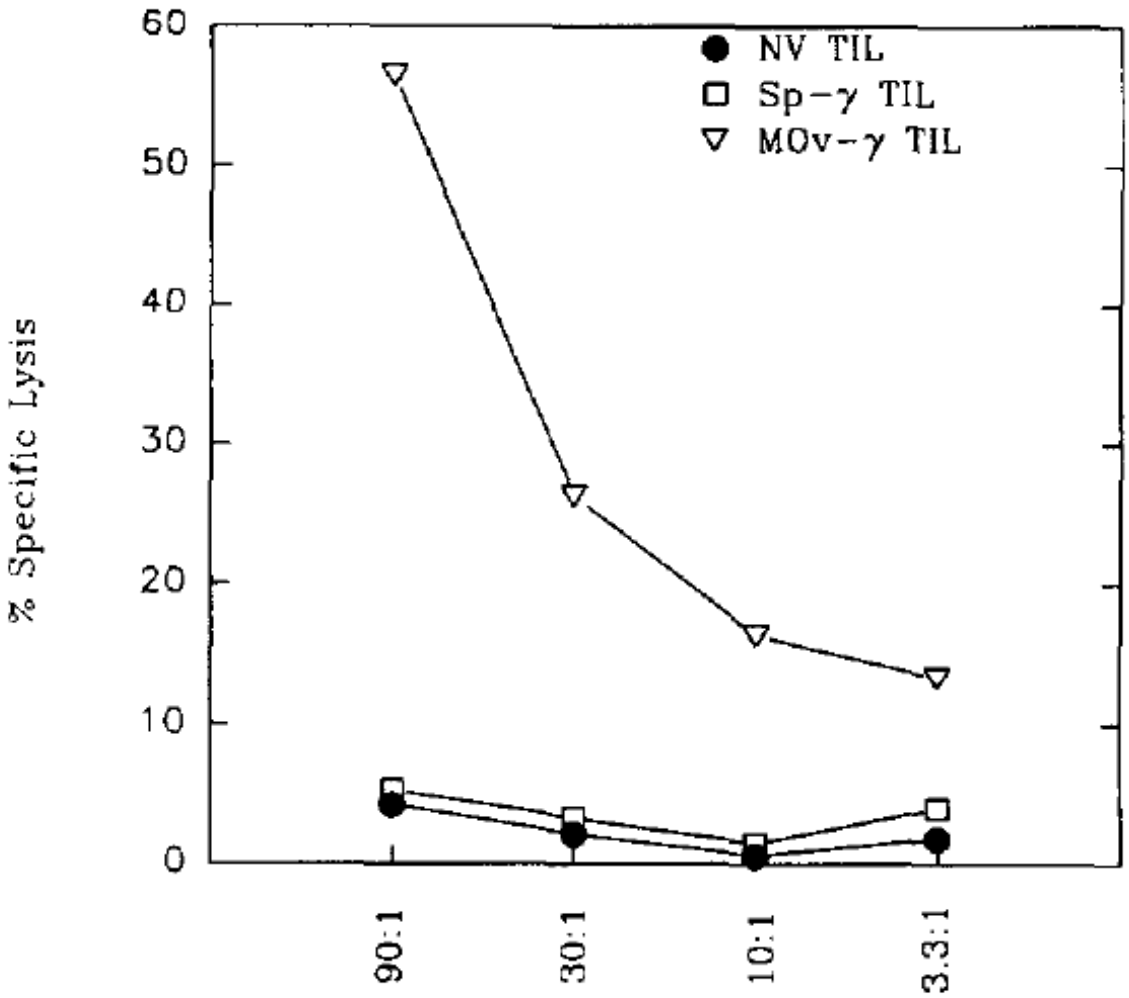
Lysis of Ovarian Cancer Cells by Human Lymphocytes Redirected with a Chimeric Gene Composed of an Antibody Variable Region and the Fc Receptor Gamma Chain.

By Patrick Hwu,* G. E. Shafer,* J. Treisman,* G. Schindler,‡ G. Gross,‡ R. Cowherd,* S.A. Rosenberg,* and Z. Eshhar‡

*From the *Surgery Branch, National Cancer Institute, National Institutes of Health Bethesda, Maryland 20892; and the ‡Department of Chemical Immunology, Weizmann Institute of Science, Rehovot 76100, Israel*

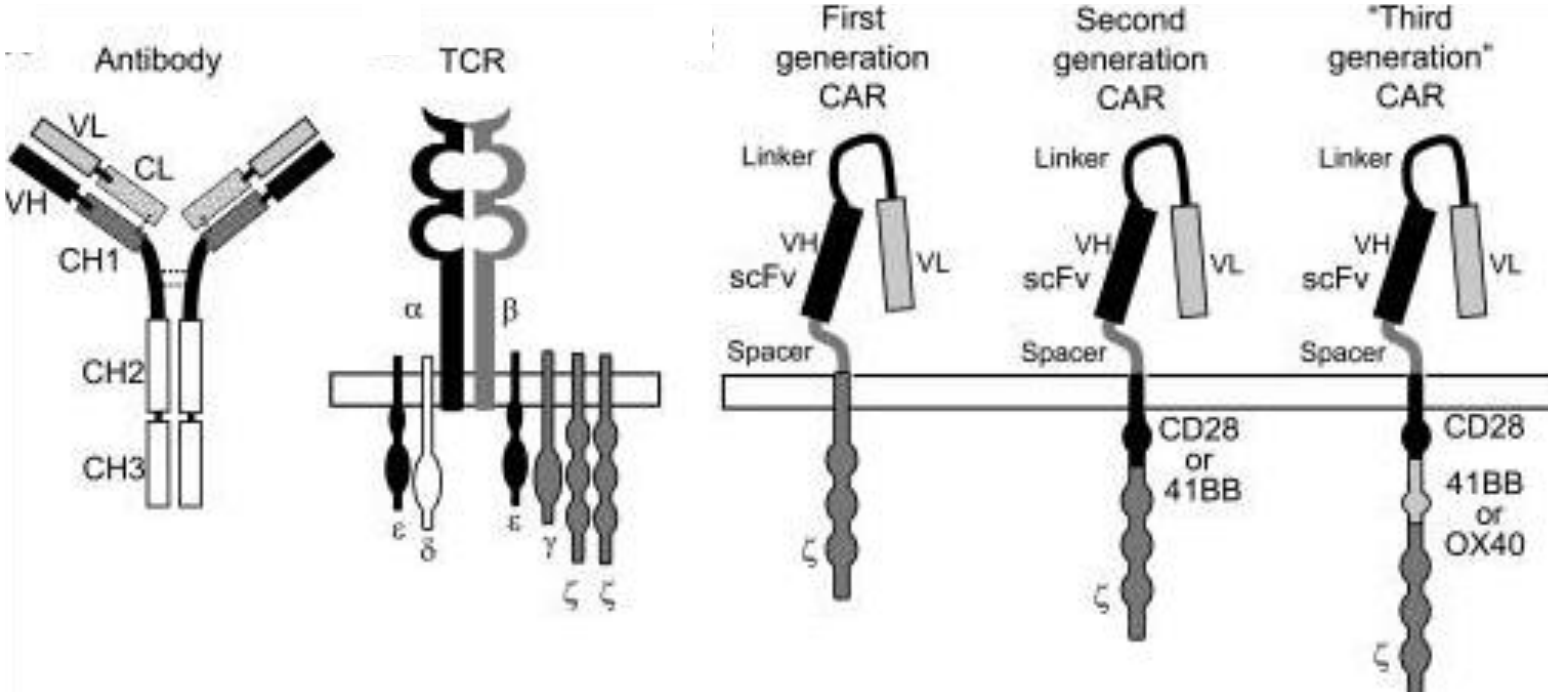
Hwu et al. *The Journal of Experimental Medicine*
Volume 178 July 1993 361-366

The Human Ovarian Carcinoma Cell Line IGROV-1 is Specifically Lysed by Mov-γ TIL



Hwu et al JEM 1993

Chimeric Antigen Receptors



Dotti G, Savoldo B, and Brenner M
Human Gene Therapy 2009

CD19 CAR T Products in Pivotal Trials in ALL and NHL

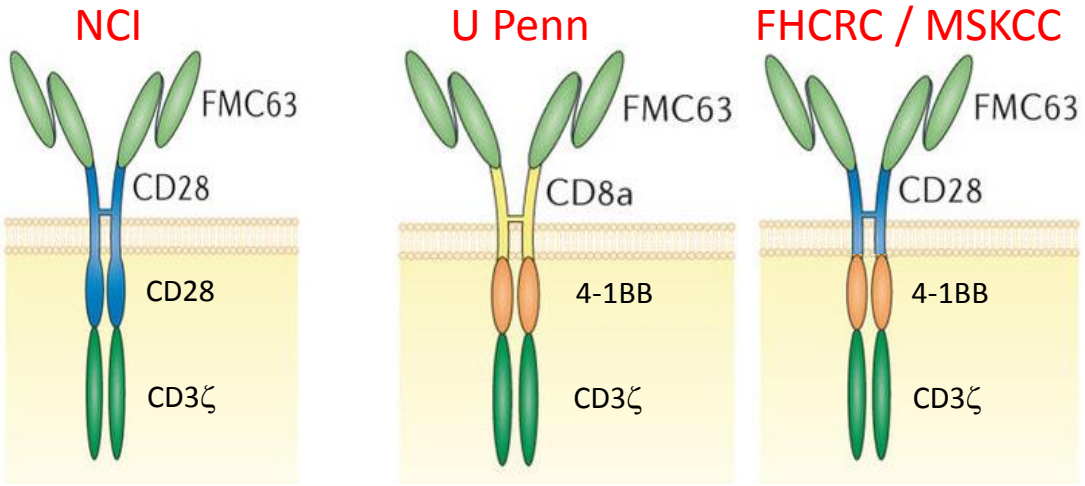
CD19 Ab

Hinge

Transmembrane

Signal 2

Signal 1



Gene transfer

Retrovirus	Lentivirus	Lentivirus
Kite Pharma	**Novartis**	**Juno Therapeutics**
KTE-C19	**CTL-019**	**JCAR017**
Axicabtagene ciloleucel	**Tisagenlecleucel**	**CD4:CD8 = 1:1**
Axi-cel		

Adapted from van der Steegen et al.
Nat Rev Drug Discov, 2015

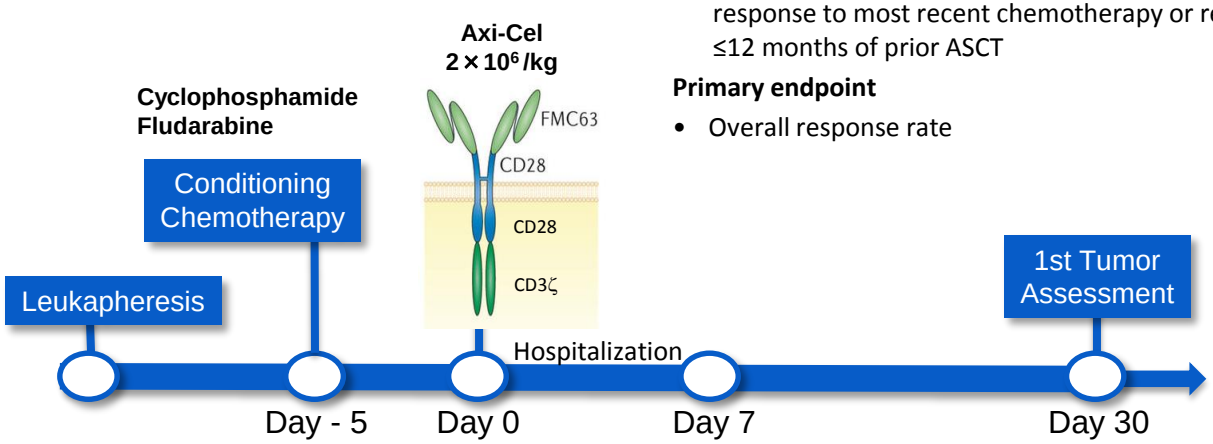
ZUMA1: 1st Multicenter Phase 2 Trial of CD19 CAR T-cell Therapy in Refractory Aggressive B-cell NHL

Eligibility criteria

- DLBCL, PMBCL, TFL
- Chemo-refractory disease: PD or SD as best response to most recent chemotherapy or relapse ≤12 months of prior ASCT

Primary endpoint

- Overall response rate



- **111 patients enrolled at 22 sites; 99% manufacturing success rate**
- **17-day average turnaround time from apheresis to delivery to clinical site**
- **91% (N=101) of enrolled patients received axi-cel**

Neelapu et al. *ICML* 2017, Abstract 8

ZUMA1: Efficacy with Axi-cel

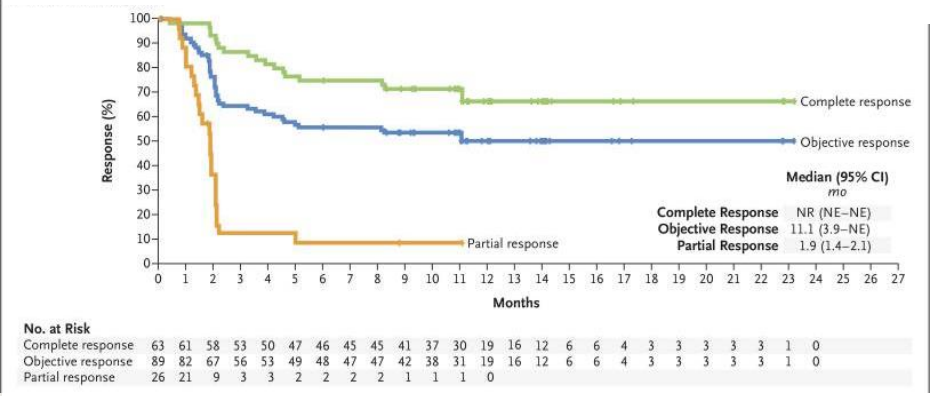
	DLBCL (N= 77)		PMBCL/TFL (N=24)		Combined (N=101)	
	ORR (%)	CR (%)	ORR (%)	CR (%)	ORR (%)	CR (%)
Best response	82	49	83	71	82	54
Med f/u 8.7 mo	36	31	67	63	44	39

- **Study met primary endpoint for ORR ($p < 0.0001$) at primary analysis**
- **Compares favorably with historical data (ORR-26%, CR-8%)**

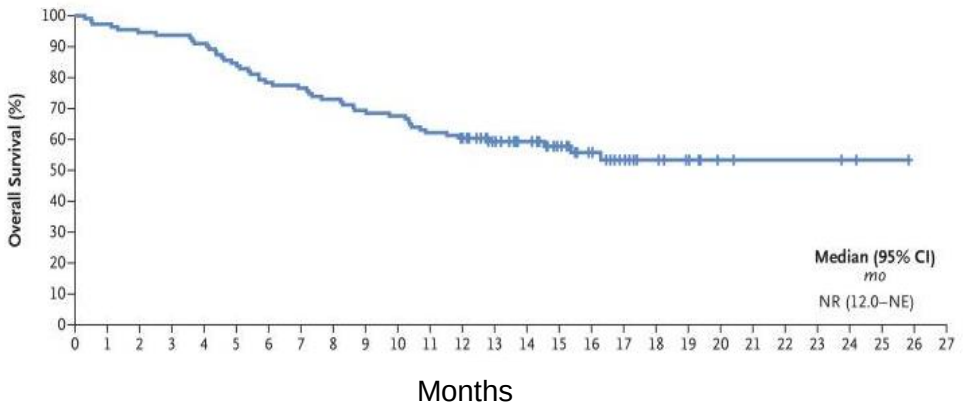
Neelapu et al. *ICML* 2017, Abstract 8

ZUMA1: Duration of Response and Overall Survival in NHL

Duration of Response



Overall Survival



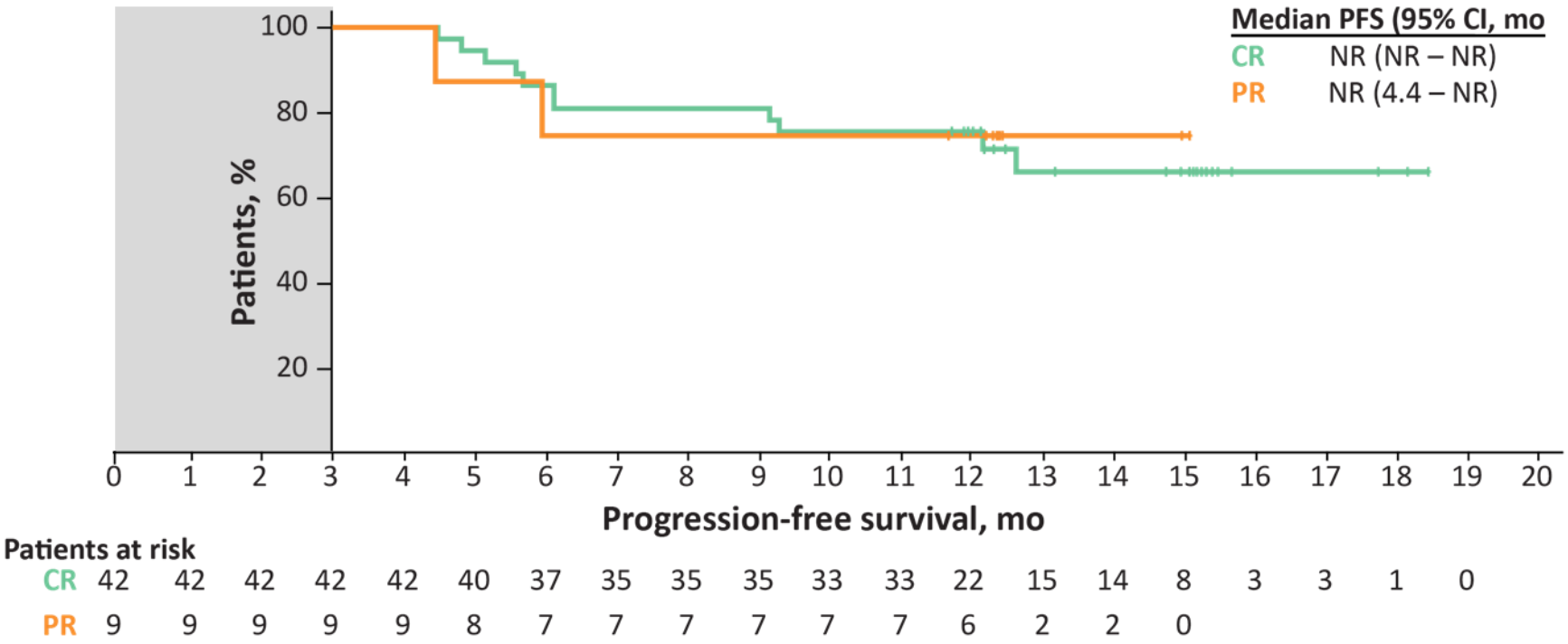
CR, complete response; NR, not reached;
ORR, objective response rate.

FDA approval of axicabtagene ciloleucel (Yescarta) on October 18, 2017 for adults with relapsed or refractory large B-cell lymphoma failing at least two lines of systemic therapy

- DLBCL, PMBCL, High-grade B-cell lymphoma, Transformed follicular lymphoma

Neelapu et al. *NEJM* 377(26):2531-44, 2017

ZUMA1: Phase 2 Study of Axi-Cel in Patients with Refractory Large B-cell Lymphoma PFS by Response at Month 3

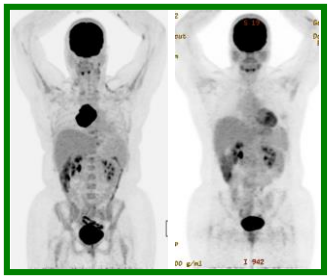


Includes 1 patient who converted from SD to CR at >Month 12. Forty-one percent (41%; 18/44) patients with PR converted to CR.

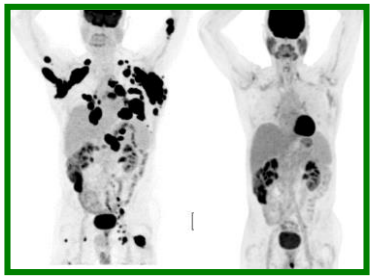
BOR, best objective response

Locke…Neelapu. Abstract #3003 ASCO 2018

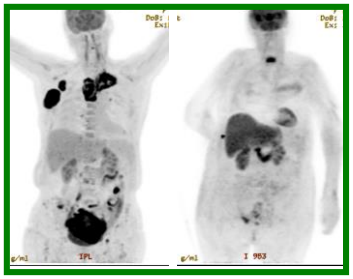
ZUMA1: Representative CRs after Axi-cel



28/F/PMBCL
- R-CHOP - SD
- R-ICE - PR
- R-DHAP - PD



62/M/DLBCL
- R-CHOP - PR
- R-GDP - PD
- R-ICE - PD
- R-Rev - PD

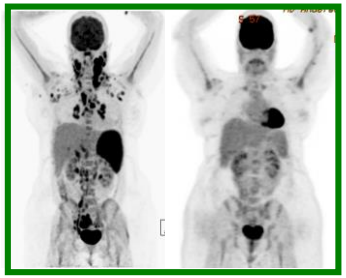


66/F/DLBCL
- R-CHOP - PR
- R-ICE - SD

R-EPOCH - PD
O-DHAP - PD

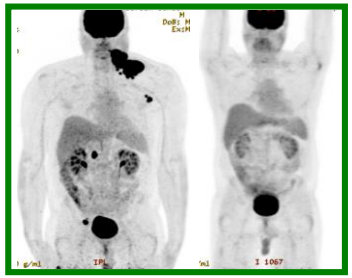
- Ofat-Ibr - PD
- Idela - PD

60/M/TFL
- R-Benda - CR
- R-EPOCH - PD
- R-HCVAD - PD

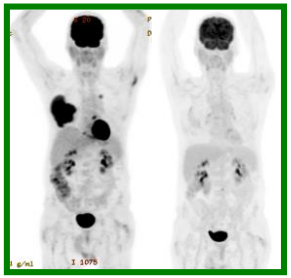


40/F/DLBCL
- R-CHOP - CR
- R-ICE - CR
- ASCT - CR

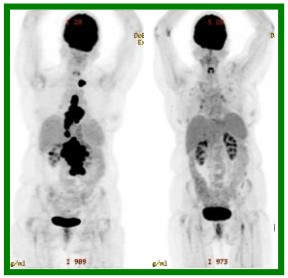
PNT2258 - PD
R-Gem-Ox - PD



59/M/DLBCL
- R-CHOP - CR
- R-ICE - PD



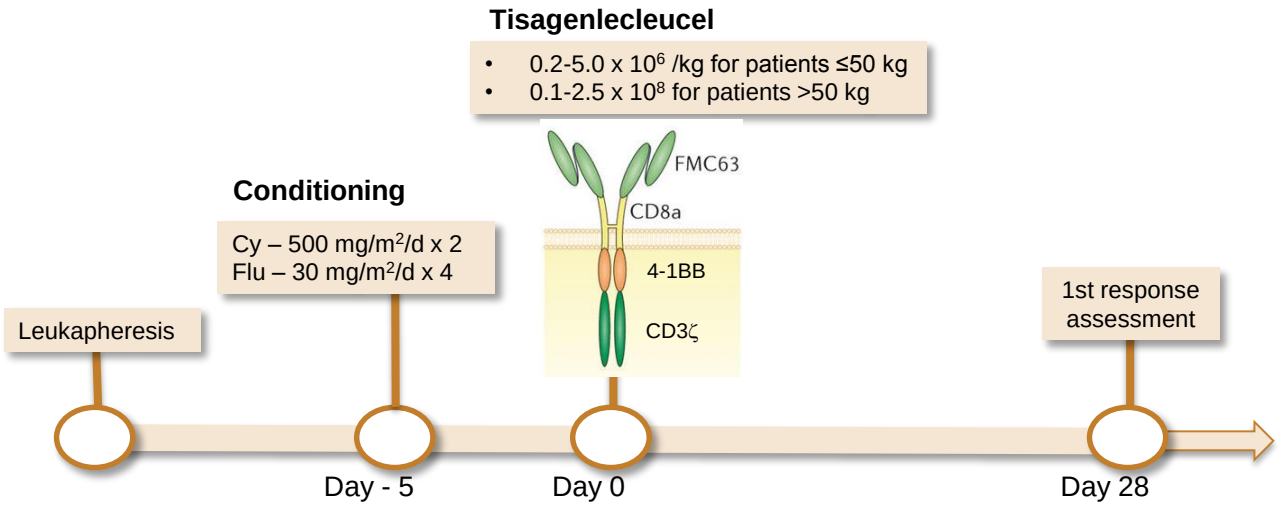
75/M/DLBCL
- R-EPOCH - PD
- R-Gem-Ox - PD



66/F/TFL
- R-CHOP - CR
- R-ICE - PD

Neelapu et al. *ICML* 2017, Abstract 8

ELIANA: 1st Multicenter Trial of CTL019 in Relapsed/Refractory Pediatric and Young Adult ALL



- **Eligibility**
  - **r/r ALL with ≥5% lymphoblasts in BM**
  - **Ages 3 yrs at screening to 21 yrs at initial diagnosis**

Primary Endpoint

- ORR within 3 months, 4-week maintenance of remission

Grupp et al, ASH 2016, Abstract 221

ELIANA: Efficacy with Tisagenlecleucel (N = 63)

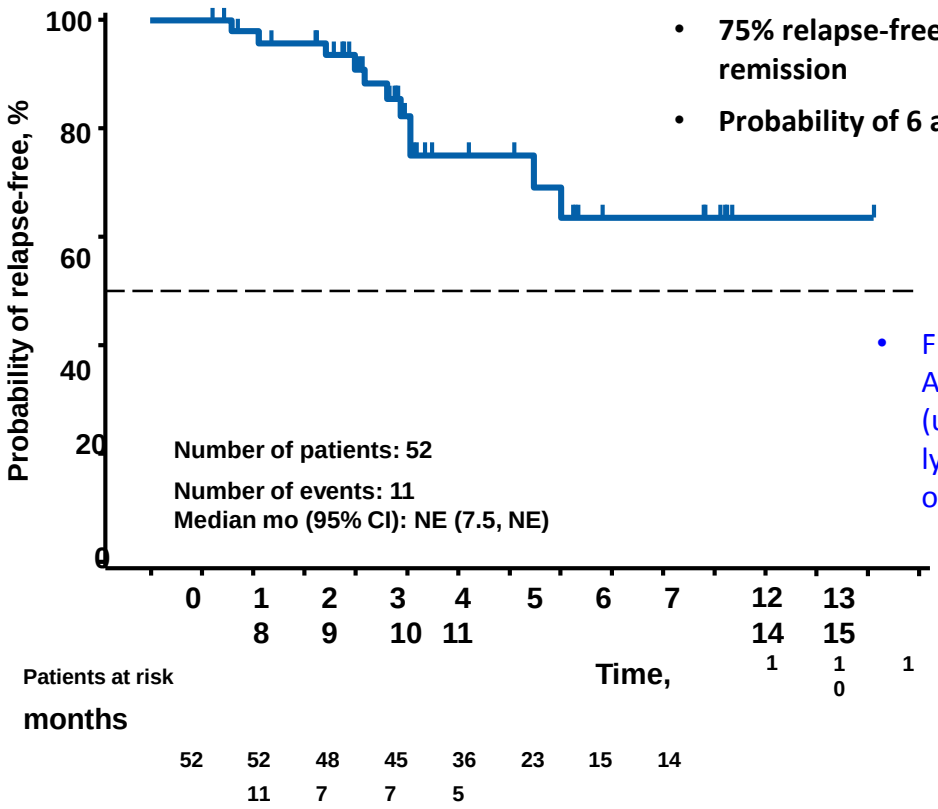
	N (%)
ORR (CR+CRi) within 3 months	52 (83)*
CR	40 (63)
CRi	12 (19)
Day 28 response	53 (84)
CR or CRi with MRD negative bone marrow	52 (83)*

***P* < 0.0001**

- **CR = Complete remission**
- **CRi = Complete remission with incomplete blood count recovery**
- **MRD negative = Flow cytometry of < 0.01%**

Grupp et al, ASH 2016, Abstract 221
Updated ODAC meeting, July 2017

ELIANA: Duration of Response in ALL



- **Median duration of RFS and OS not reached**
- **75% relapse-free at 6 months after onset of remission**
- **Probability of 6 and 12 mos OS 89% and 79%**

- FDA approval of tisagenlecleucel (Kymriah) on August 30, 2017 for pediatric and young adult (up to 25 years) with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

Grupp et al, ASH 2016, Abstract 221
Updated ODAC meeting, July 2017

CD19 CAR T-cell Therapy: Safety

ZUMA1: Safety (N = 101)

Adverse Event	All Grades	Grade ≥3
CRS	93%	13%
CRES	64%	28%

- CRS – Cytokine Release Syndrome
- CRES – CAR-Related Encephalopathy Syndrome
- 3 deaths on ZUMA1 due to AEs – 2 CRS and 1 pulmonary embolism

Neelapu et al. ICML 2017, Abstract 8

ELIANA: Safety (N = 62)

Adverse Event	All Grades	Grade ≥3
CRS	79%	48%
CRES	45%	15%

- 2 deaths within 30 days of CTL019 (1 ALL, 1 cerebral hemorrhage)
- All patients who achieved CR/CRi developed B-cell aplasia

Grupp et al, ASH 2016, Abstract 221
Updated ODAC meeting, July 2017

Enhancing Patient Safety: MD Anderson CARTOX Program

Drs. George Wilding, Aman Buzdar, Patrick Hwu

Co-Chairs – EJ Shpall, MD and Sattva Neelapu, MD

Charles Levenback, MD
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- Nitin Jain

Lymphoma and Myeloma
- Sattva Neelapu
- Jason Westin
- Michael Wang

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- Michael Rytting

Sarcoma Medical Oncology
- Dejka Araujo

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- George Blumenschein
- Vincent Lam

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- Krina Patel, MD
- Naveen Pemmaraju, MD
- Dejka Araujo, MD
- Sajad Khazal, MD

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Critical Care
- Cristina Gutierrez
- Joseph Nates

Emergency Medicine
- Patricia Brock
- Terry Rice

Neuro-Oncology
- Sudhakar Tummala
- Monica Loghin
- John de Groot

Neuroradiology
- Linda Chi

Nursing
- Patty Johnston
- Joaquin Buitrago
- Venice McDougle

Pharmacy
- Alison Gulbis
- Sandra Horowitz

EHR / Information Services
- Andrew Lee
- Cary Goodman

MD Anderson CARTOX Program Activities

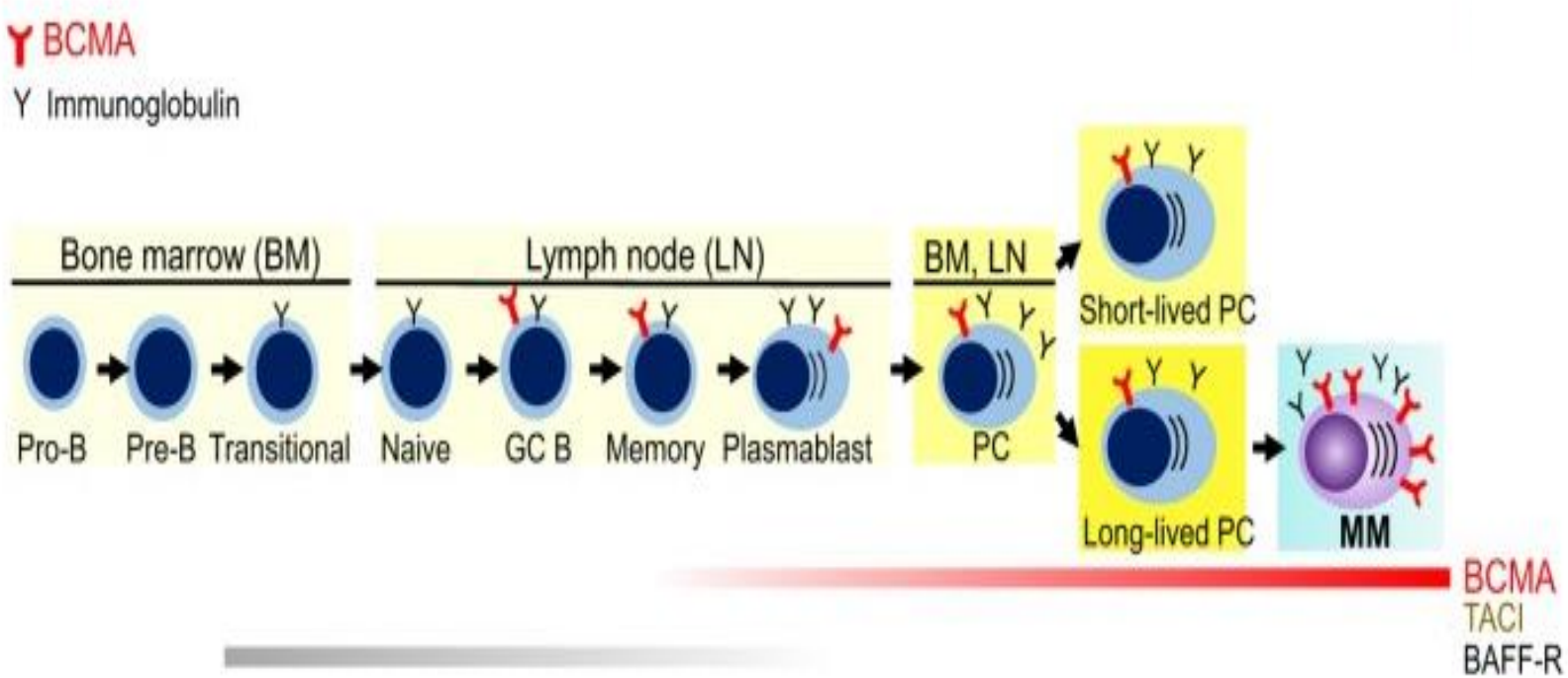
REVIEWS

Nat Rev Clin Oncol, Sep 2017

Chimeric antigen receptor T-cell therapy — assessment and management of toxicities

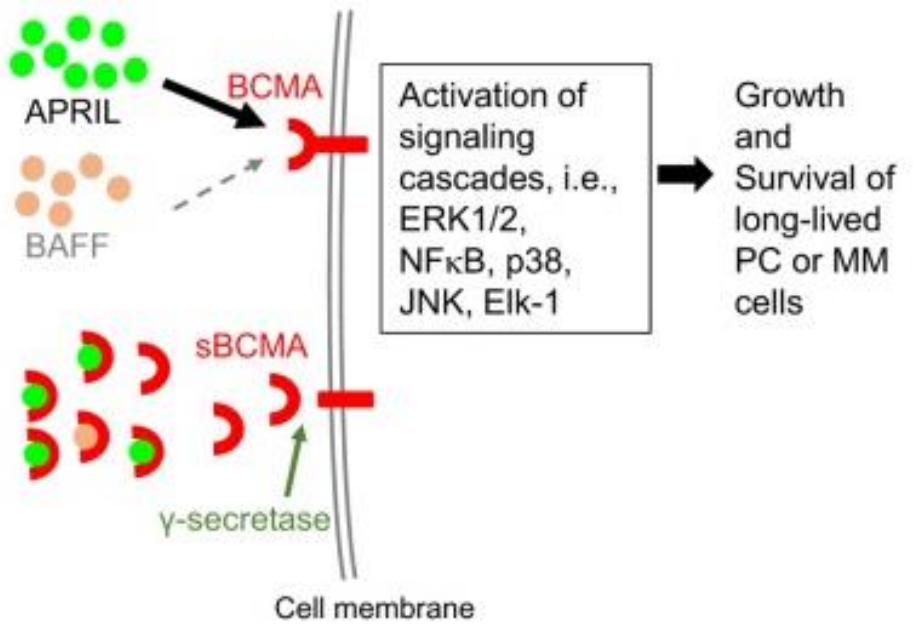
Sattva S. Neelapu[1], Sudhakar Tummala[2], Partow Kebriaei[3], William Wierda[4], Cristina Gutierrez[5], Frederick L. Locke[6], Krishna V. Komanduri[7], Yi Lin[8], Nitin Jain[4], Naval Daver[4], Jason Westin[1], Alison M. Gulbis[9], Monica E. Loghin[2], John F. de Groot[2], Sherry Adkins[1], Suzanne E. Davis[10], Katayoun Rezvani[3], Patrick Hwu[10], Elizabeth J. Shpall[3]

BCMA is Selectively Induced During Plasma Cell Differentiation



Shih-Feng Cho et al. *Front Immunol* 9:1821, 2018

A Proliferation-inducing Ligand (APRIL) and BAFF are Two Natural Ligands for BCMA



BCMA expression in PC

In normal physical functions

- Support survival of long-lived PCs
- Production of antibodies
- Class switch of immunoglobulin

In MM

- Promote proliferation and survival of MM cells.
- Associated with immunosuppressive BM microenvironment.
- Increased sBCMA level is associated with disease progression and poorer outcome.

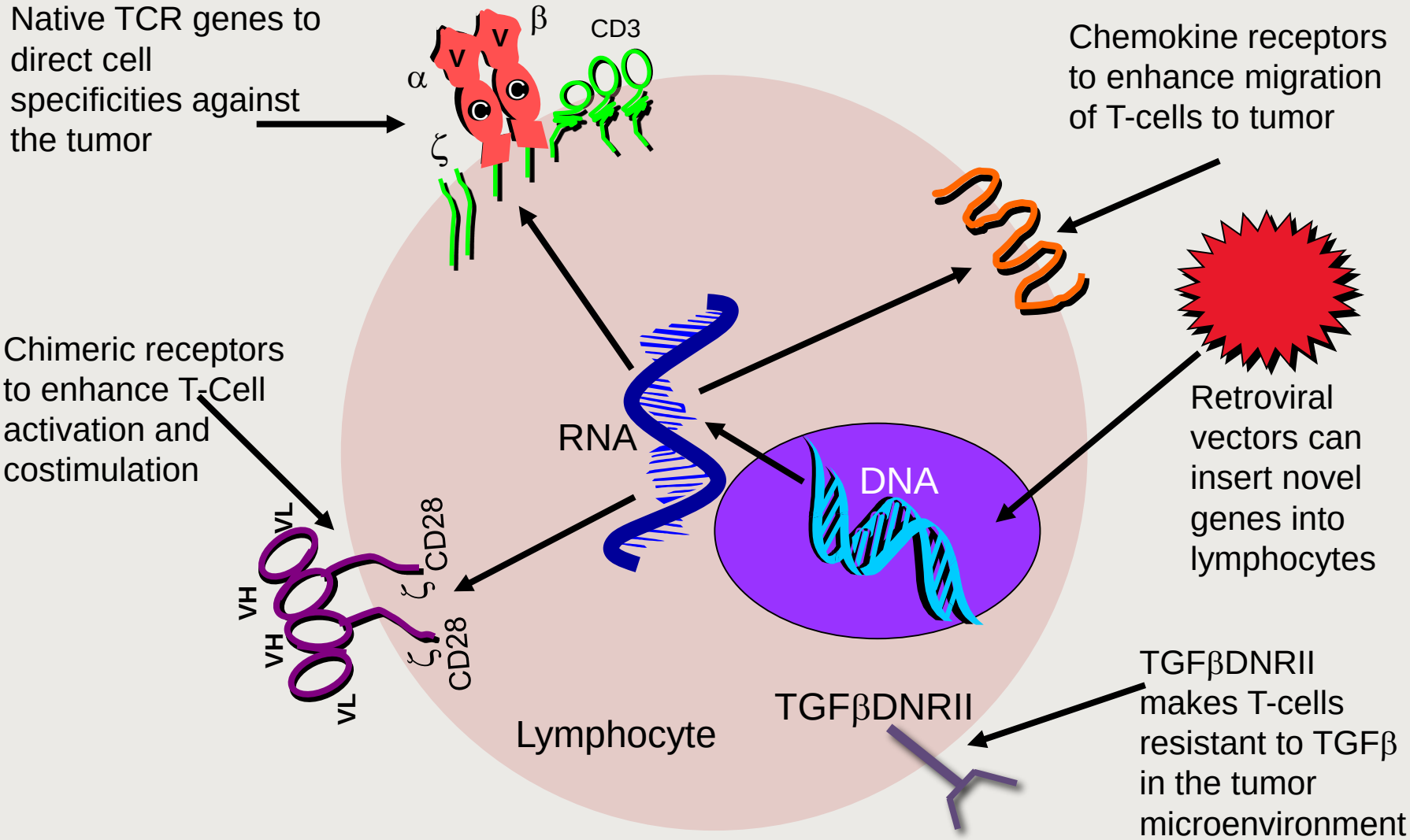
Shih-Feng Cho et al. *Front Immunol* 9:1821, 2018

BCMA CAR-T Trials

Anti-BCMA chimeric antigen receptor (CAR)	National Cancer Institute	Phase 1
Bb2121	Bluebird Bio / Celgene	Phase 1
LCAR-B38M	Nanjing Legend Biotech	Phase 1
CART-BCMA	Novartis	Phase 1
KITE-585	Kite Pharma	Preclinical
BCMA CAR	Pfizer / Cellectis SA	Preclinical
P-BCMA-101	Poseida Therapeutics	Preclinical
FHVH74-CD828Z FHVH32-CD828Z FHVH33-CD828Z FHVH93-CD828Z	Tenebrio	Preclinical
Descartes-08	Cartesian Therapeutics	Preclinical
P-BCMA-ALLO1	Poseida Therapeutics	Preclinical
EGFRt/BCMA-41BBz	Juno	Phase 1 (recruiting)

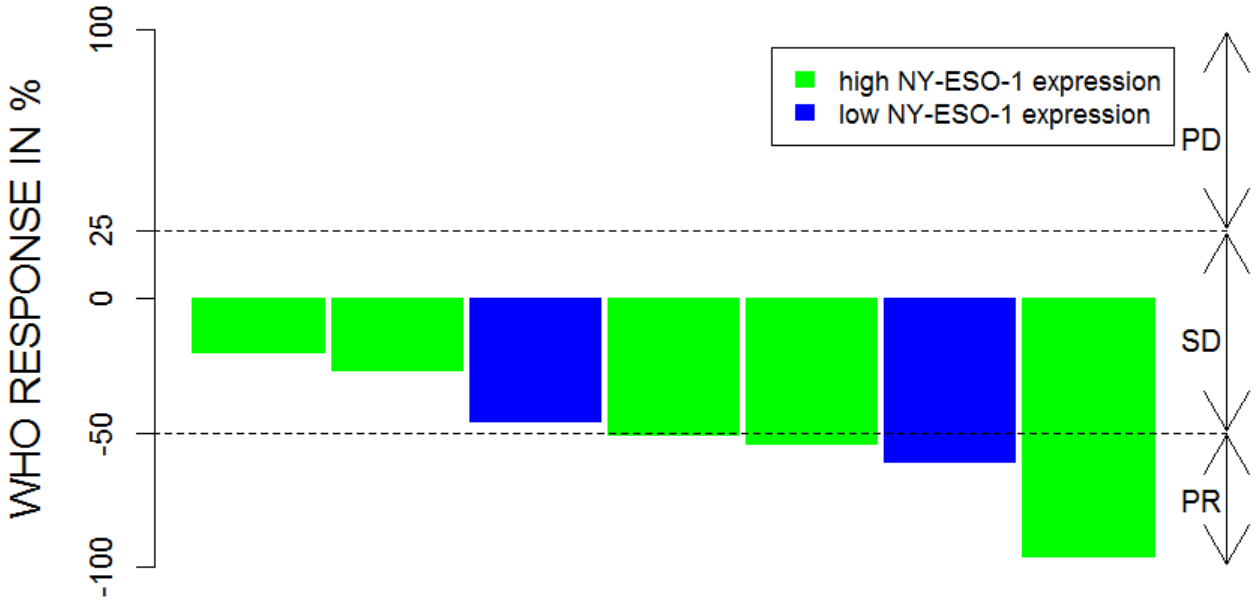
Shih-Feng Cho et al. *Front Immunol* 9:1821, 2018

Insertion of Genes into Lymphocytes to Enhance Antitumor Properties



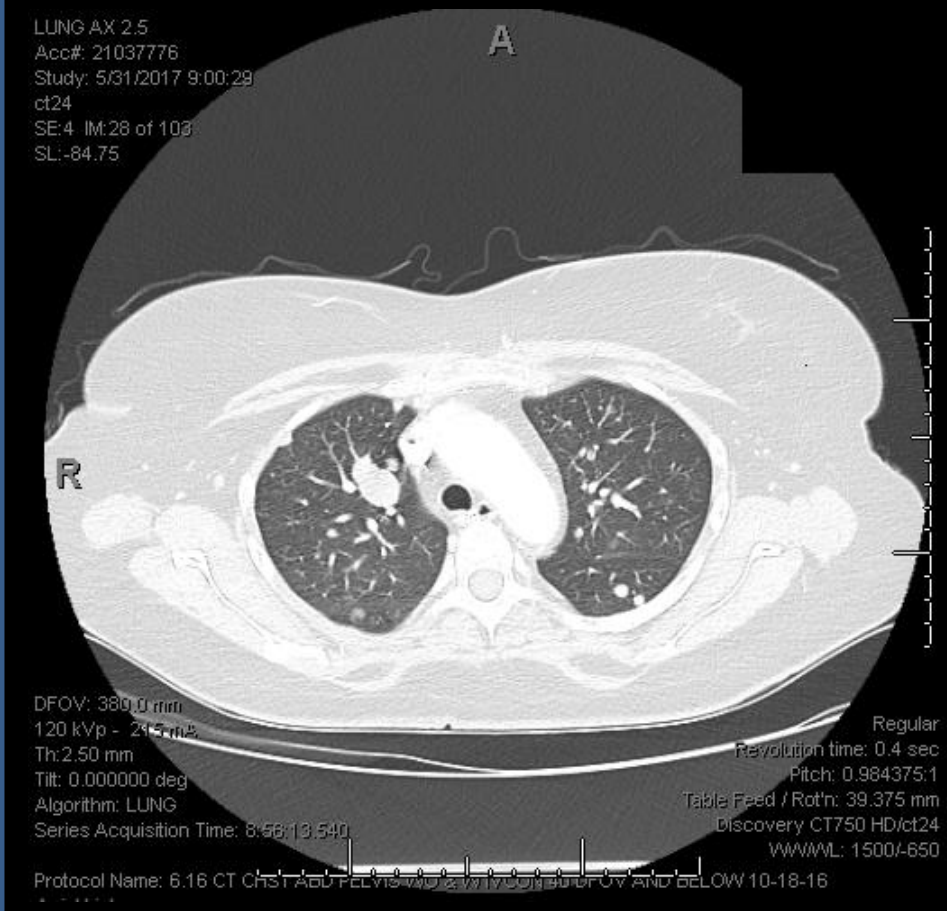
T-cell Therapy for Synovial Sarcoma

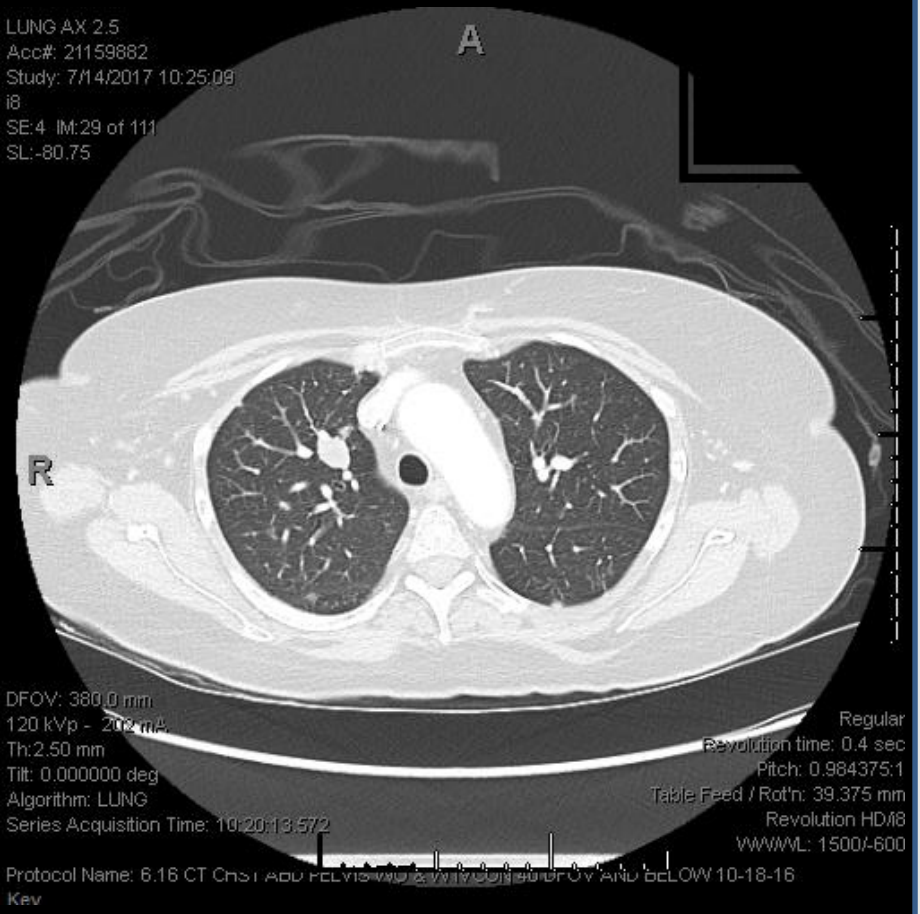
Best Response: WHO Criteria



Source: Dejka Araujo
Assoc. Professor Sarcoma Medical Oncology
M.D. Anderson Cancer Center

T-cell Therapy for Synovial Sarcoma
Patient 7: SD - 29% at Week 4





Source: Dejka Araujo
Assoc. Professor Sarcoma Medical Oncology
M.D. Anderson Cancer Center

T-cell Therapy for Synovial Sarcoma
Patient 4: PR, -84% at Week 8

Source: Dejka Araujo
Assoc. Professor Sarcoma Medical Oncology
M.D. Anderson Cancer Center

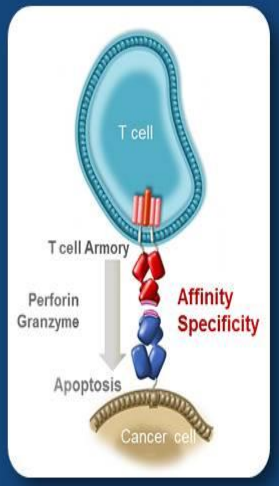
NY-ESO-1^{c259}TCR: Efficacy in Synovial Sarcoma

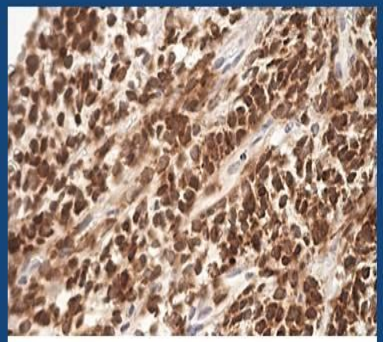
NY-ESO-1^{c259}TCR is an affinity-matured HLA-A*02-restricted TCR recognizing NY-ESO-1 peptide (*SLLMWITQC*)

NY-ESO-1^{c259}TCR led to responses in 50% of synovial sarcoma patients (D'Angelo *et al. Cancer Discovery*, in press)

NY-ESO-1 is expressed in 80-90% of MRCLS

This experience prompted interest in exploring a similar approach in MRCLS

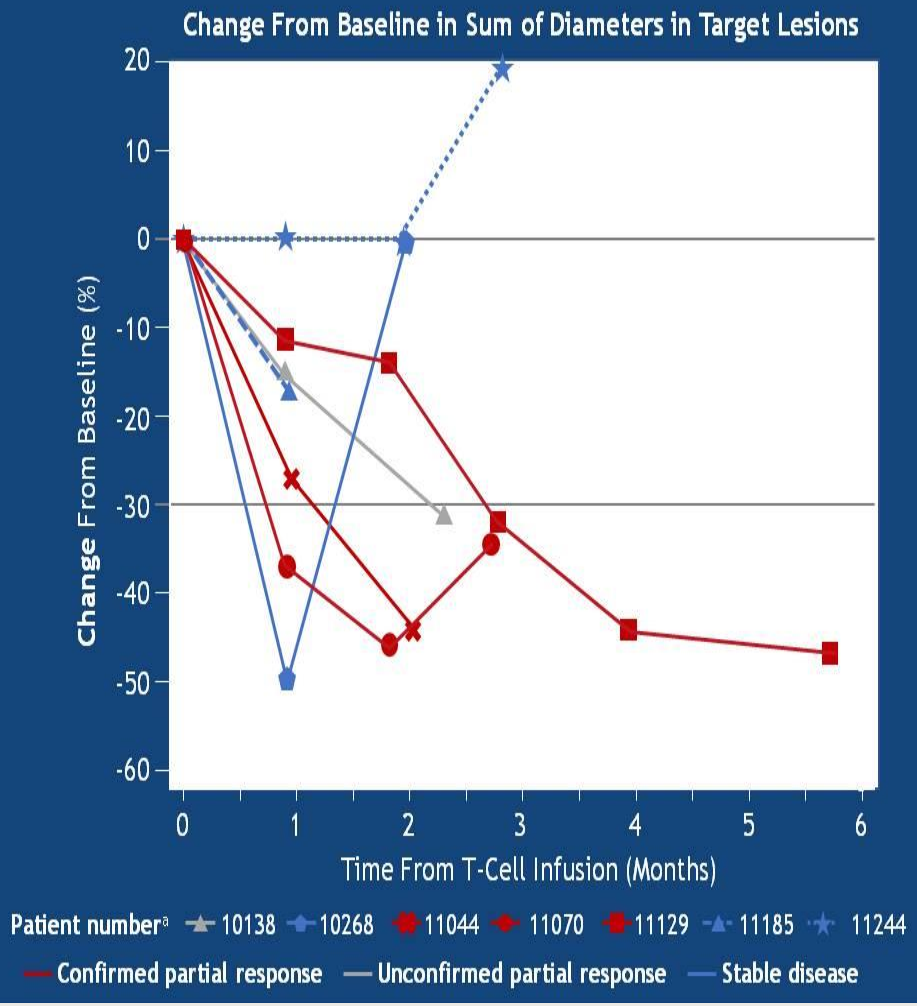




NY-ESO-1 IHC staining of MRCLS tissue

Presented By Sandra D'Angelo
at 2018 ASCO Annual Meeting

Response Summary

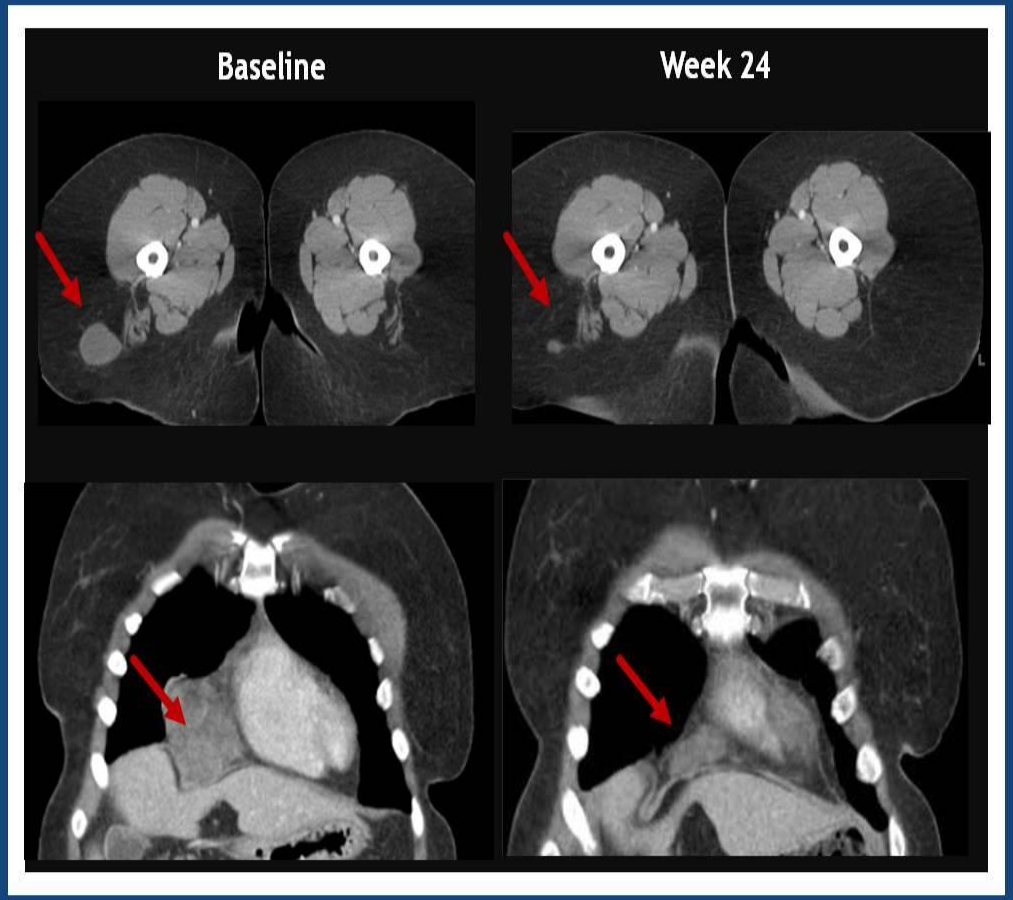


Best Overall Response (BOR)	N=8
Confirmed complete response	0
Confirmed partial response	3
Unconfirmed partial response	1
Stable disease	3
Progressive disease[b]	0
Not assessed[a]	1
Overall (Unconfirmed) Response	**4**

[a]Patient 11832 recently treated and post-infusion disease assessment is not yet available
[b]Three patients have progressed

Data cutoff May 30, 2018

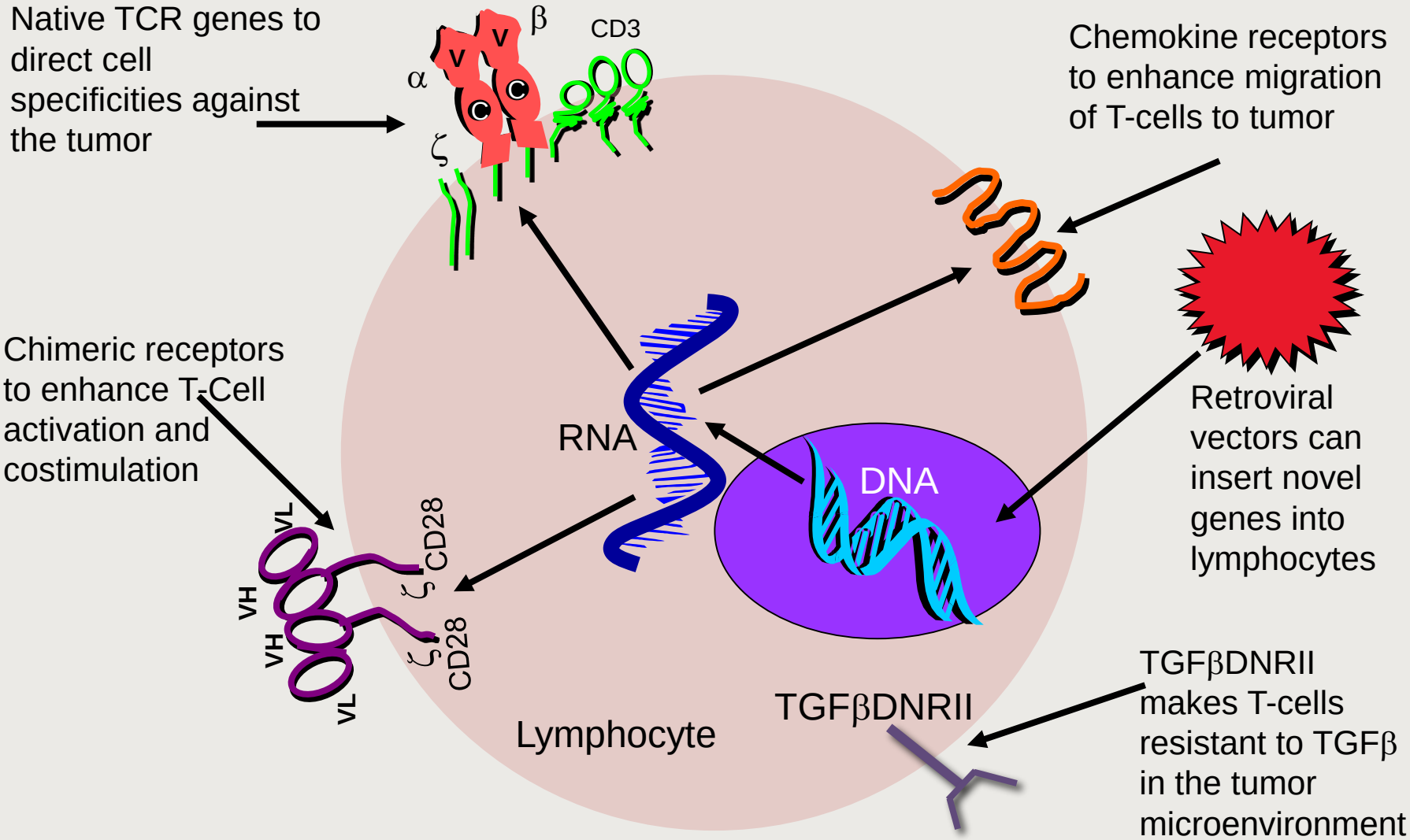
Patient 11129: Radiographic Assessments Demonstrate Tumor Shrinkage



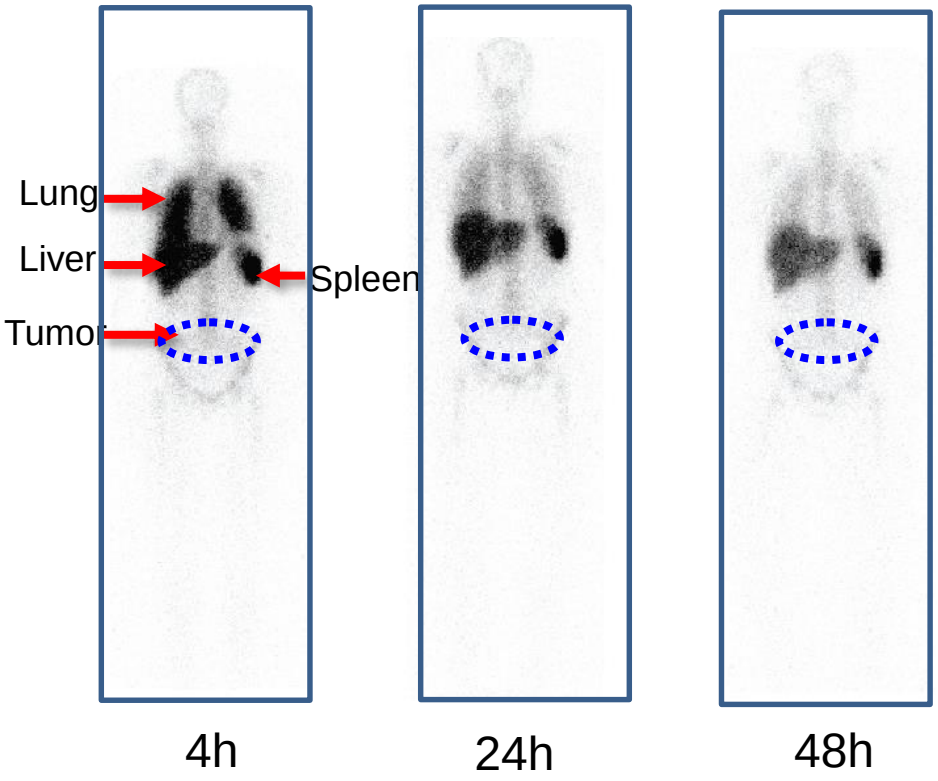
Images from patient at Washington University in St. Louis

Presented By Sandra D'Angelo at June 2018 ASCO Annual Meeting

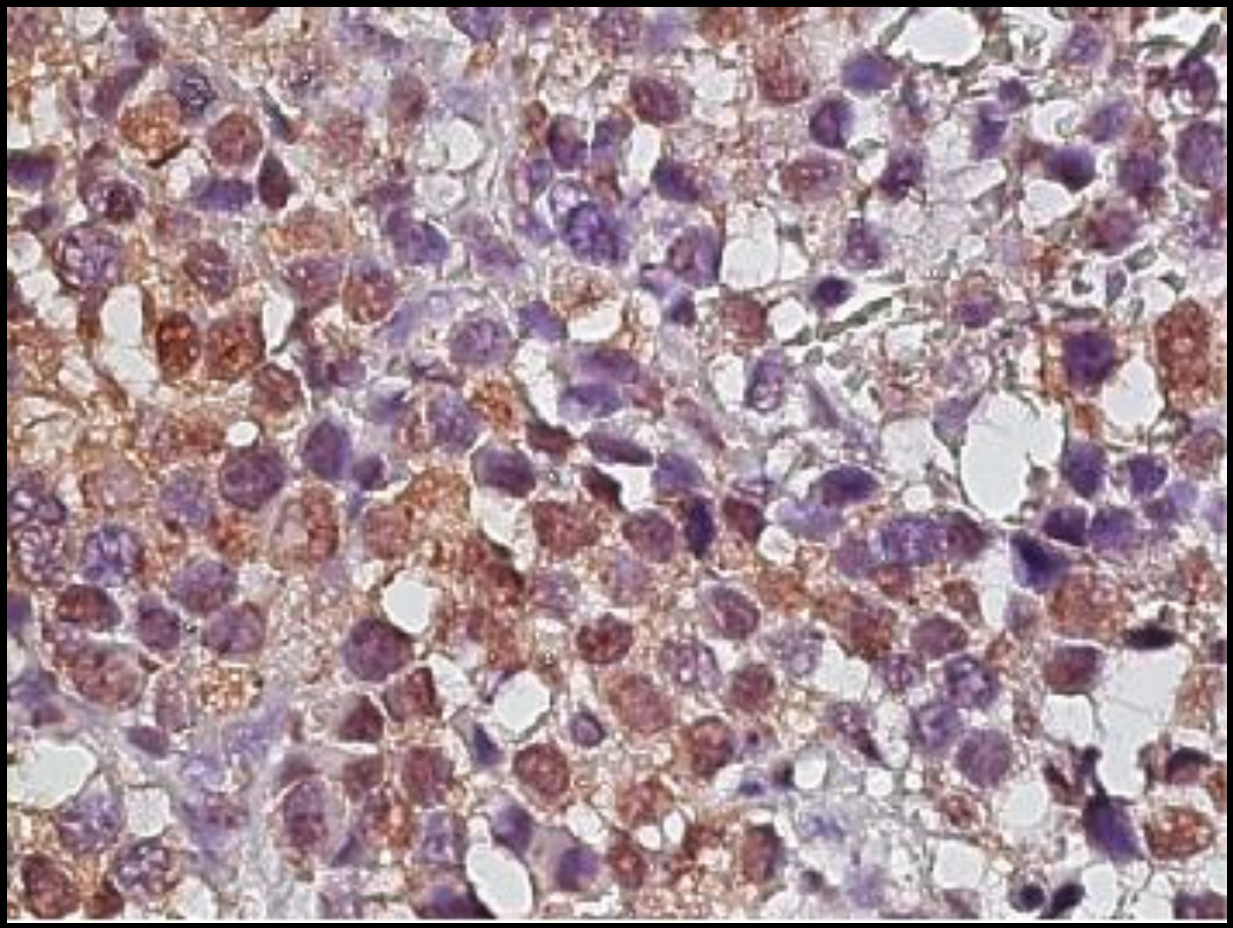
Insertion of Genes into Lymphocytes to Enhance Antitumor Properties



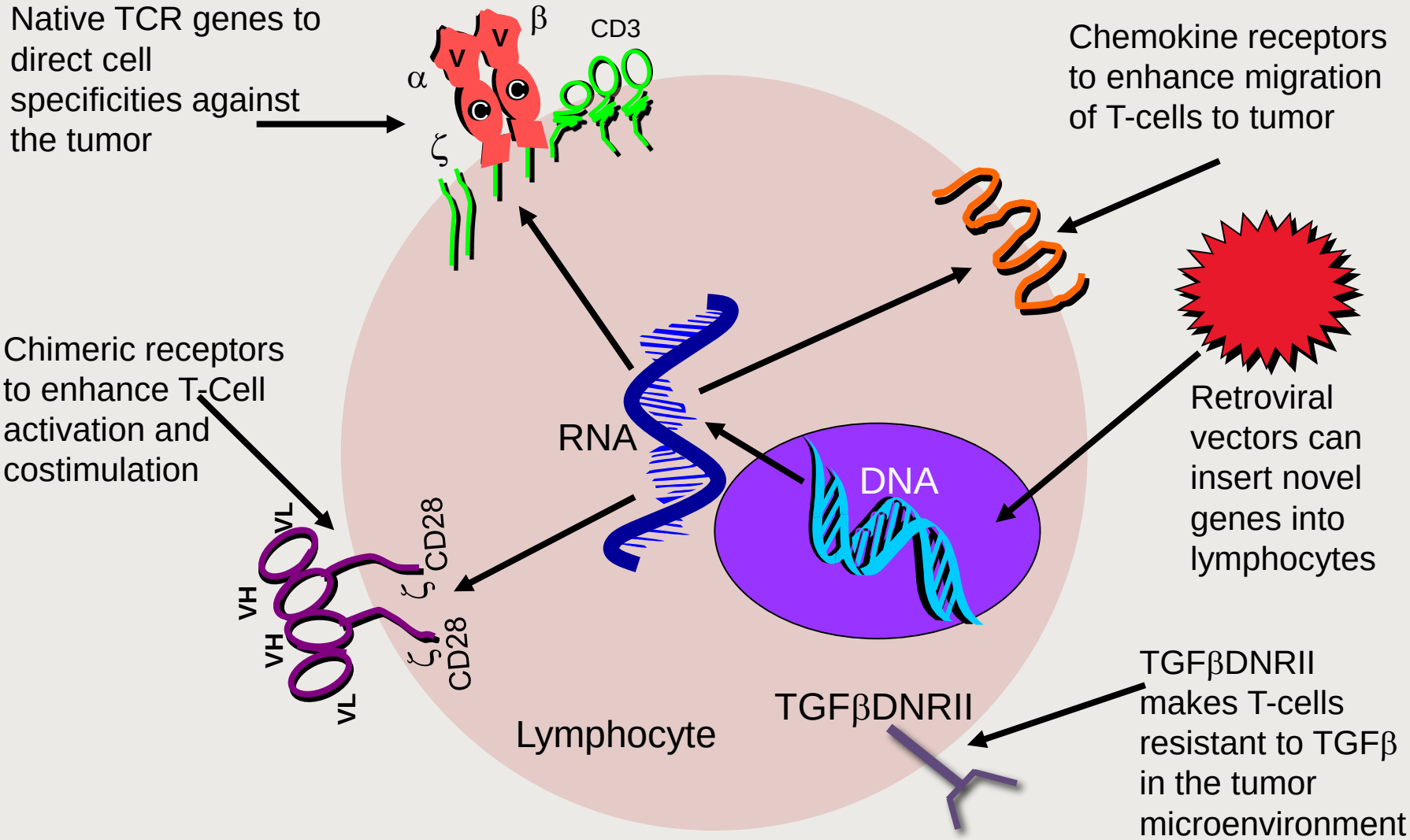
One of the Rate-limiting Steps in ACT is the Inefficient Migration of T-cells to Tumor



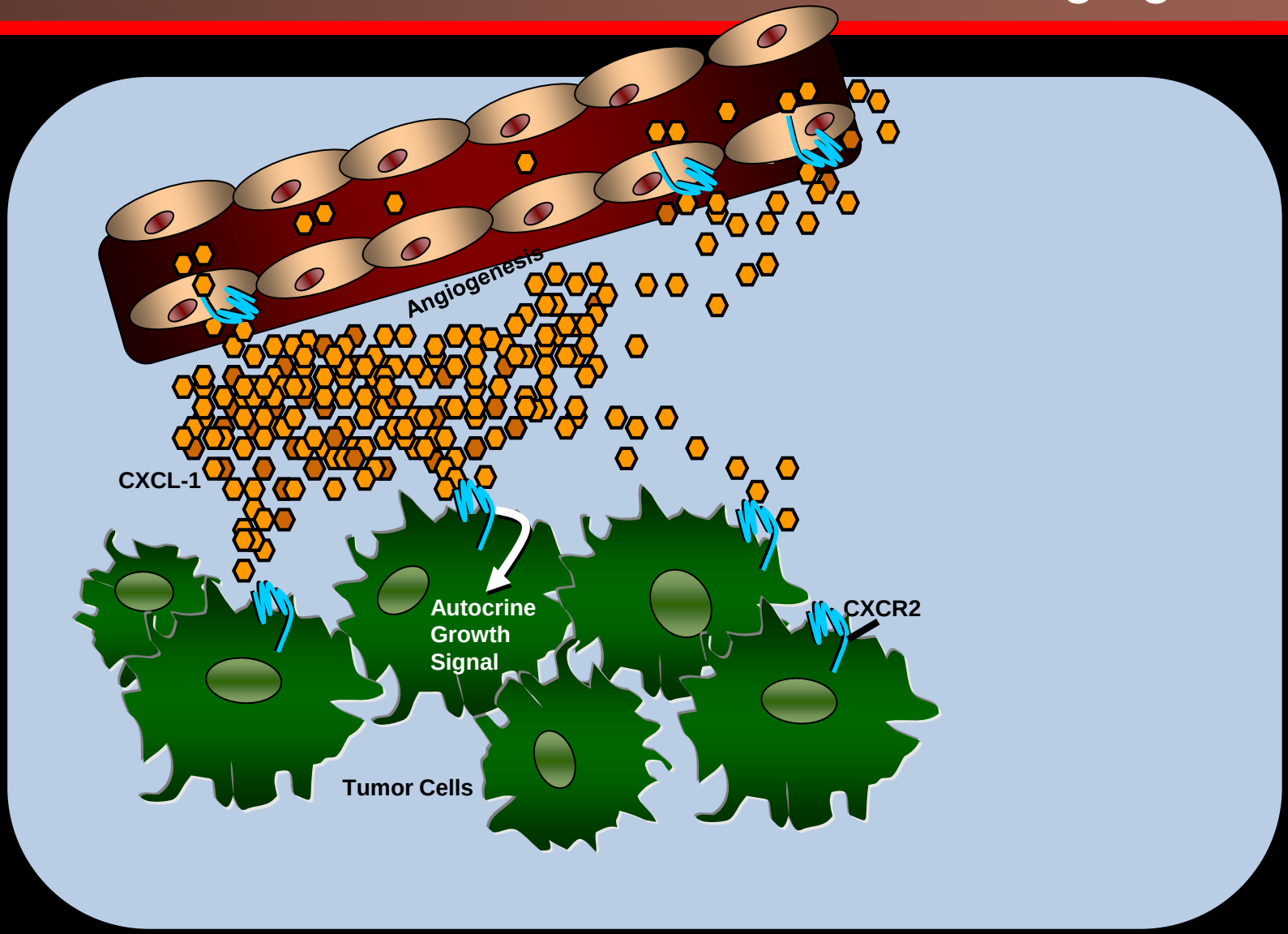
The Presence of CXCL1 in the Tumor Microenvironment



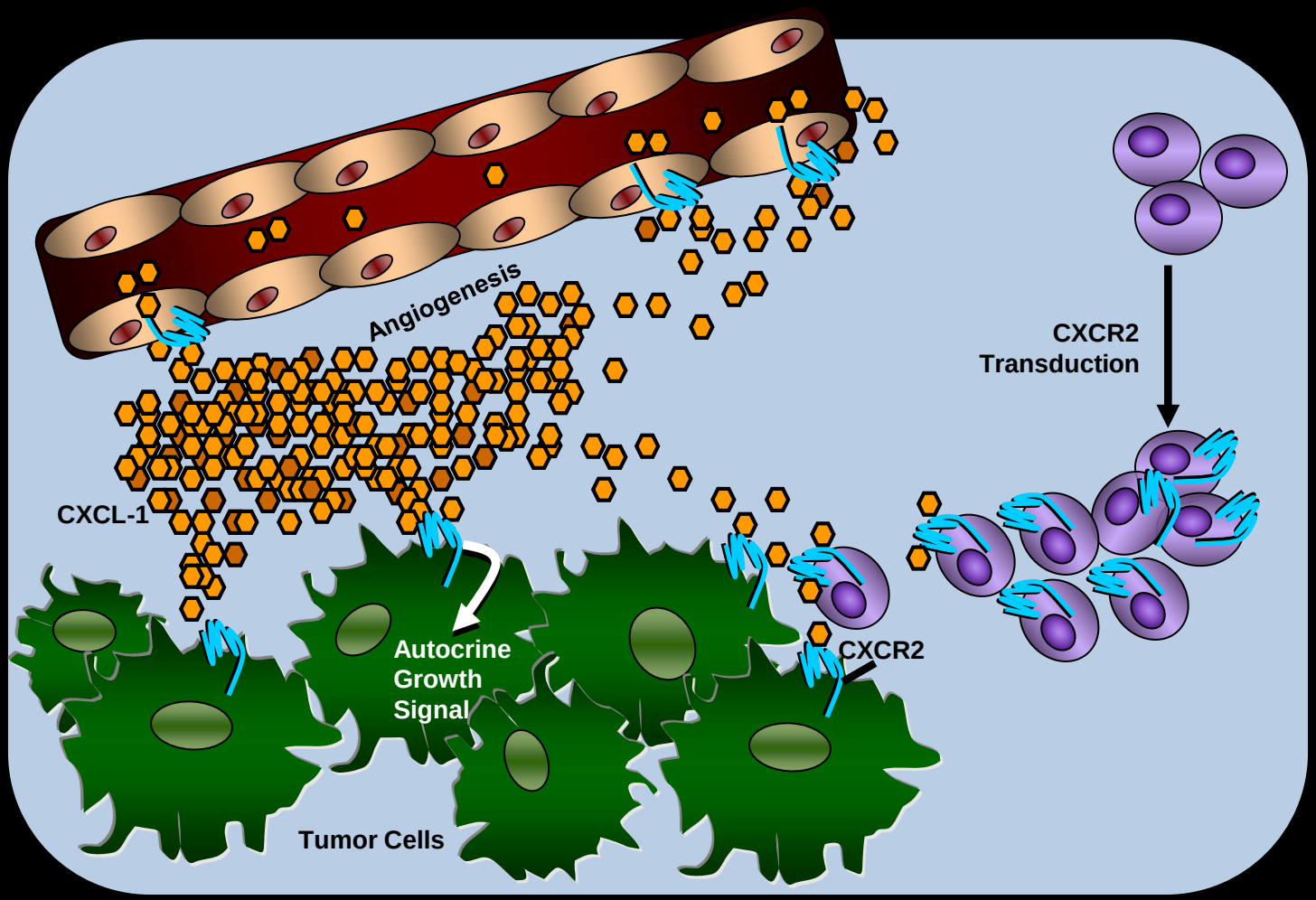
Insertion of Genes into Lymphocytes to Enhance Antitumor Properties



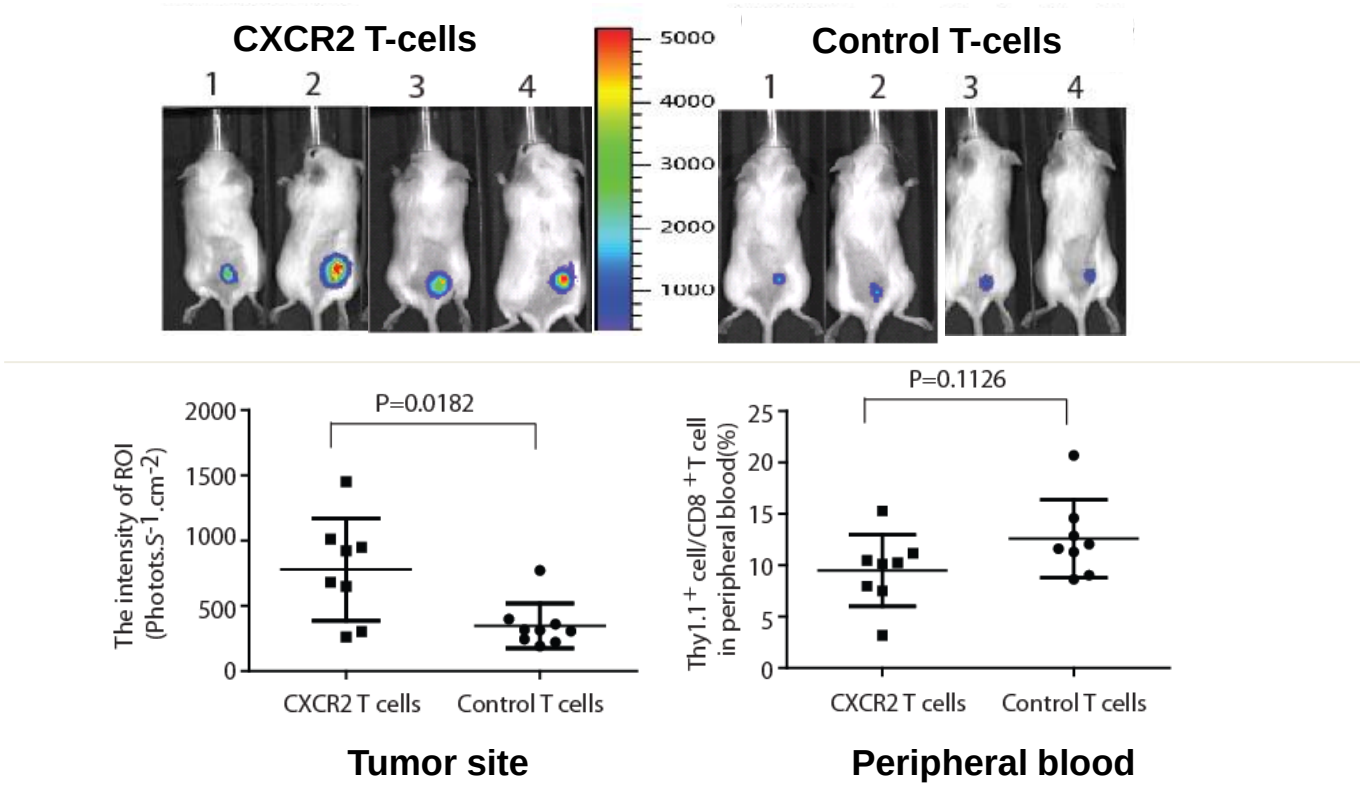
Melanoma Cells Produce CXCL1 which Serves as an Autocrine Growth Factor and Stimulates Angiogenesis



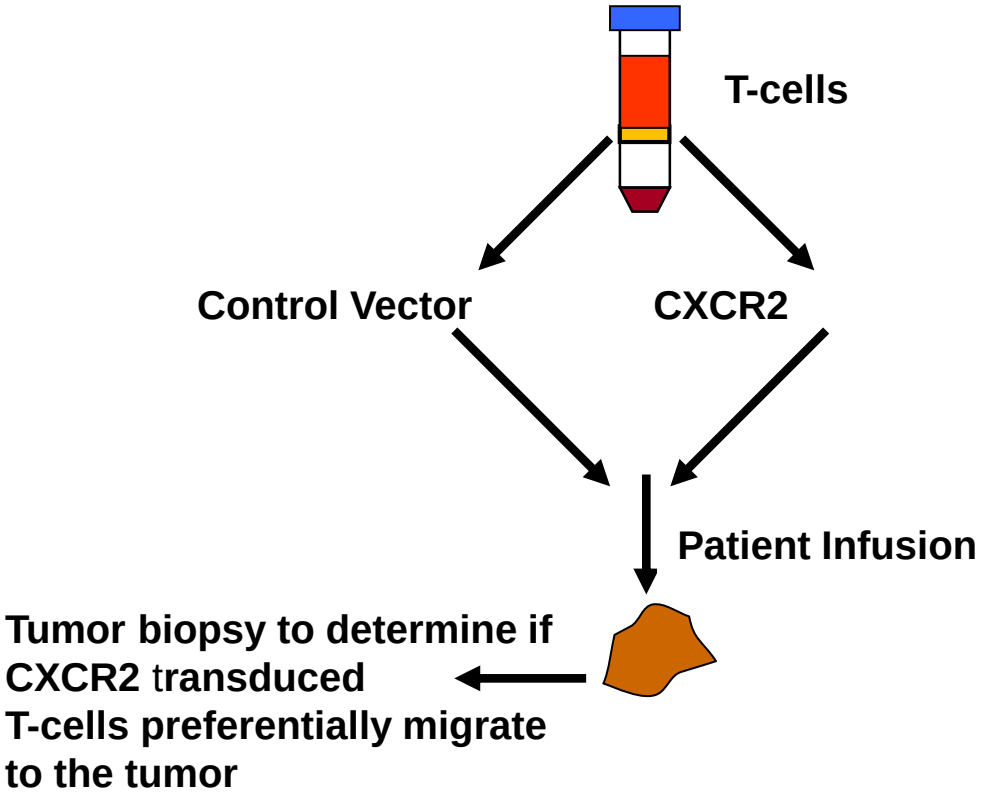
Transduction of T-cells with CXCR2 May Allow Them to Migrate to Tumor Sites



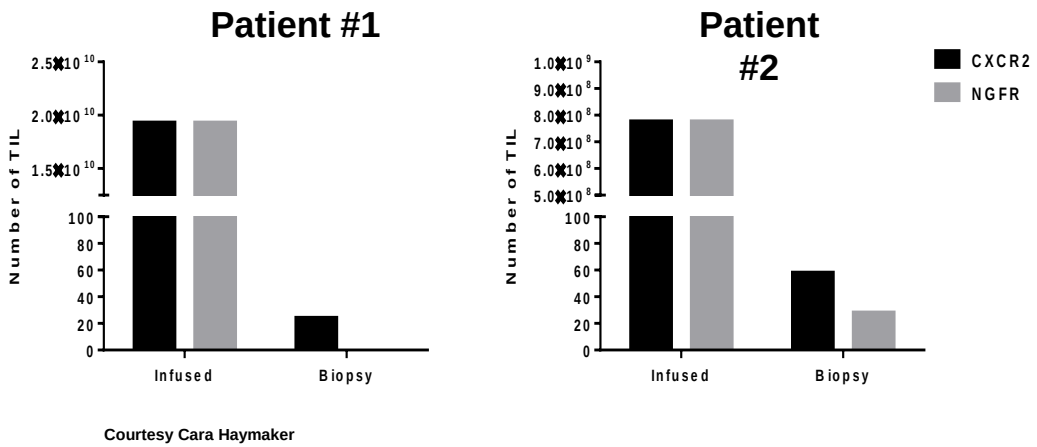
CXCR2-expressing T-cells Display Enhanced Accumulation in Tumor Site



Clinical Trial Plans



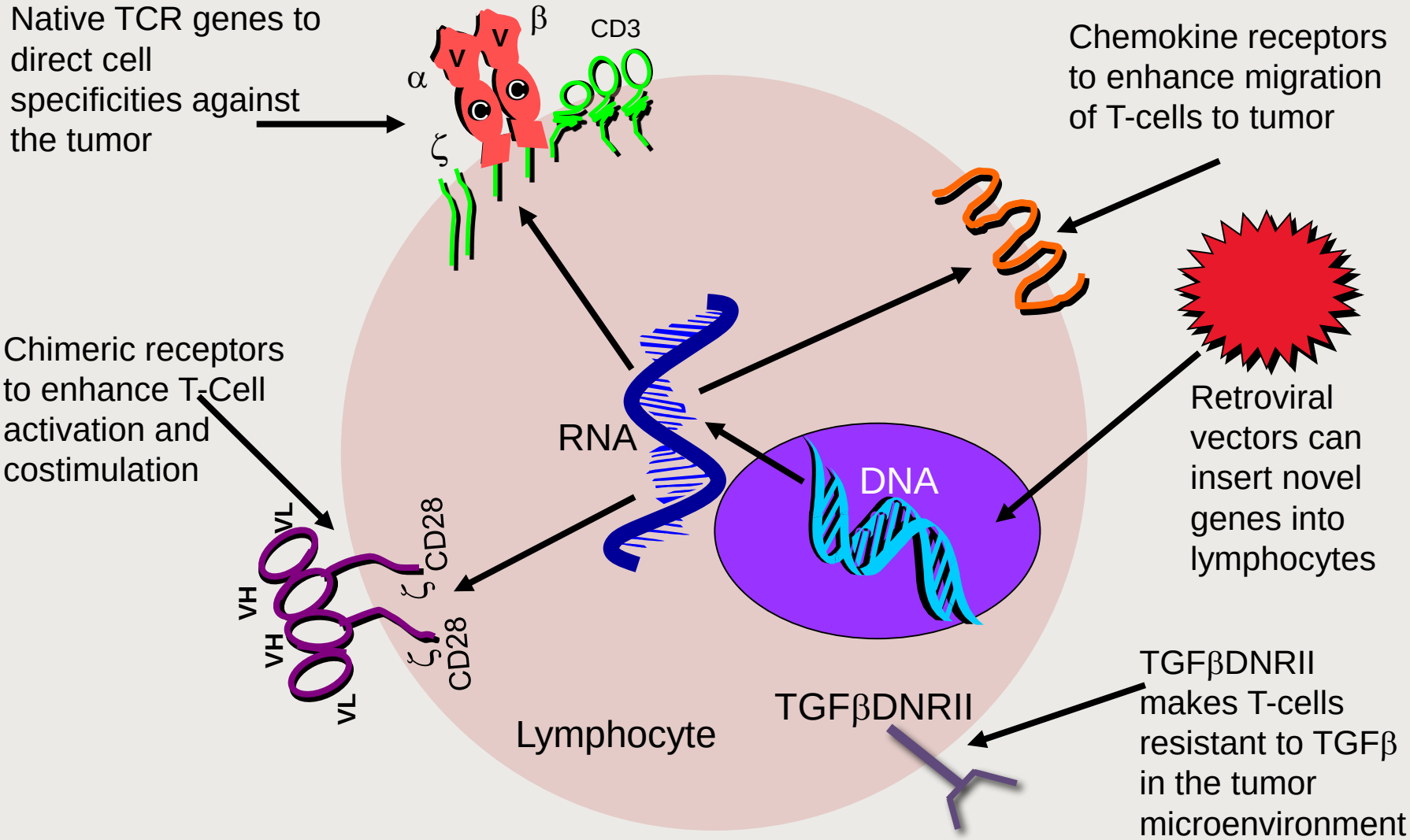
MDACC TIL ACT Treatment with CXCR2 Genetically Modified TIL



Courtesy Cara Haymaker

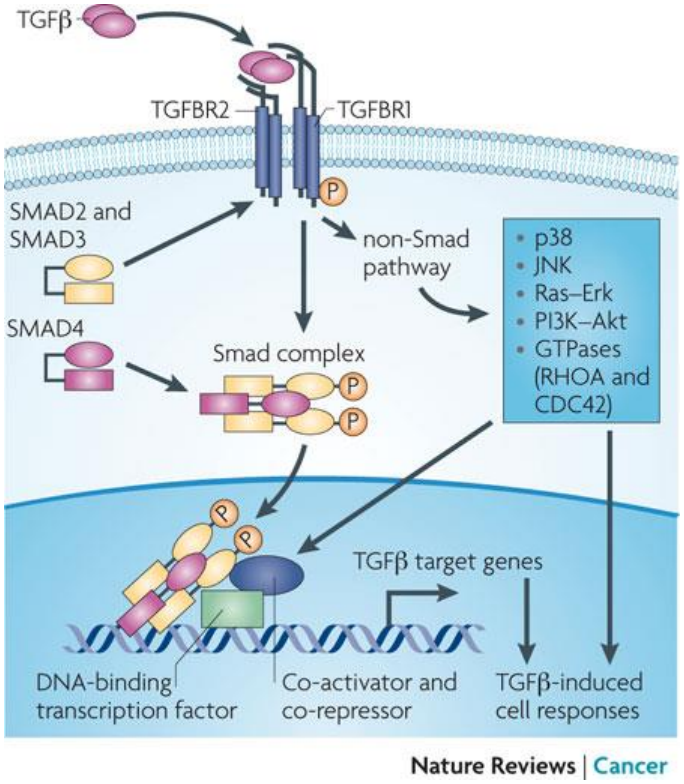
Number of CXCR2 or NGFR positive cells infused and at time of post treatment biopsy (D21-D26)

Insertion of Genes into Lymphocytes to Enhance Antitumor Properties



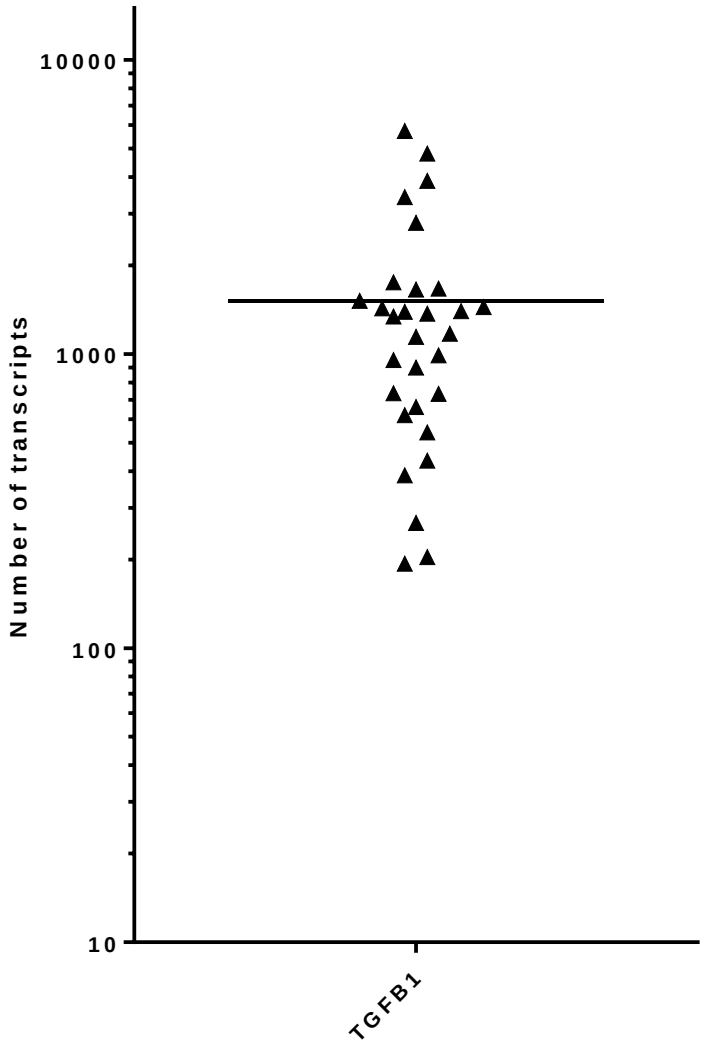
Transforming Growth Factor-β

- Ubiquitous cytokine with pleiotropic effects on cell growth and differentiation
  - Tumor suppressive in early cancer stages and becomes tumor promotional with later-stage malignancies
  - Limits immune responses to antigen presentation by inducing immune tolerance
  - Inhibits the function and proliferation of T-cells
  - Found elevated in the blood in patients with advanced stage cancer



Ikushima and Miyazono. *Nat Rev Cancer* 10: 415-424, 2010
Pickup et al. *Nat Rev Cancer* 13(11) 788-799, 2013

Advanced Stage Melanomas have Elevated TGF-β Levels

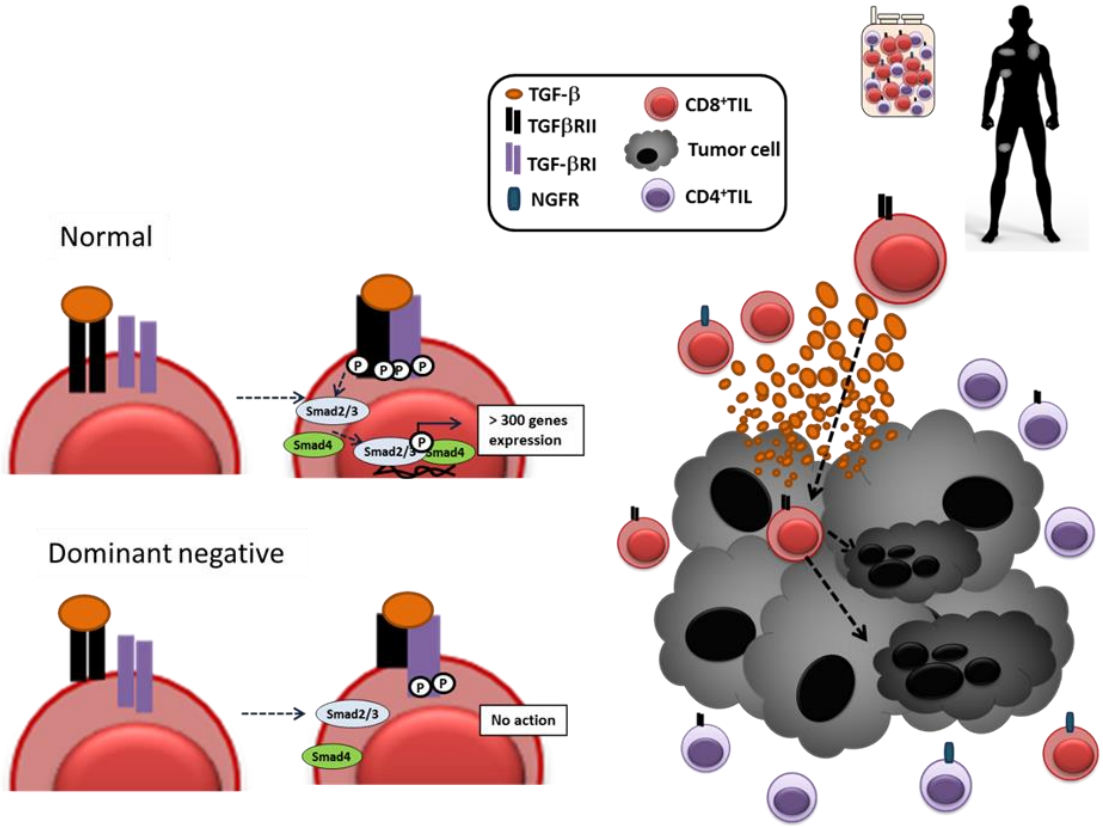


N = 30, metastatic melanoma tissue

Number of TGFB1 RNA transcripts measured by Nanostring

TGFβ-DNRII Transduced TIL

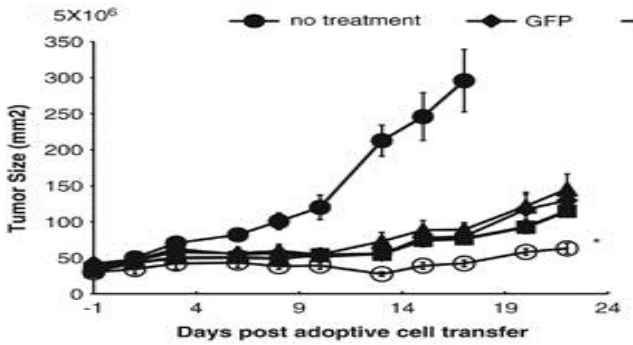
- TGF-β dominant negative receptor has been engineered to have a truncated intracellular domain. It fails to transmit signals/activation of SMAD transcription factors to abrogate TGF-β signaling.
- TGF-β DNR can be efficiently introduced into TIL by a retroviral vector (over 60% transduction efficacy)
- Viral transduction of TIL does not affect the ability to expand TIL
- A truncated version of the nerve growth factor receptor (NGFR) is used as a control. Each patient becomes their own control.

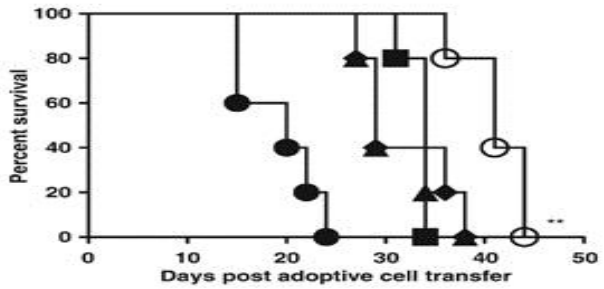


Forget, Tavera et al *Front Immunol* 2017

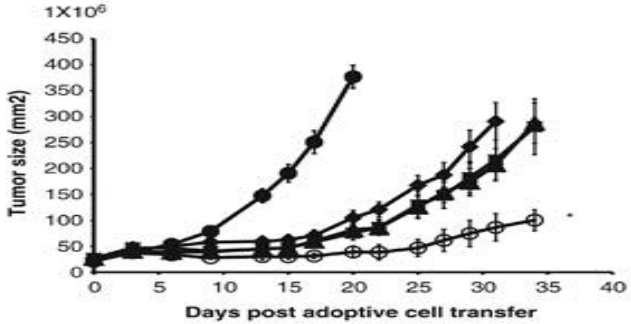
DNRII Expressing pmel-1 T-cells had Enhanced Anti-Tumor Activity Against B16 Melanoma

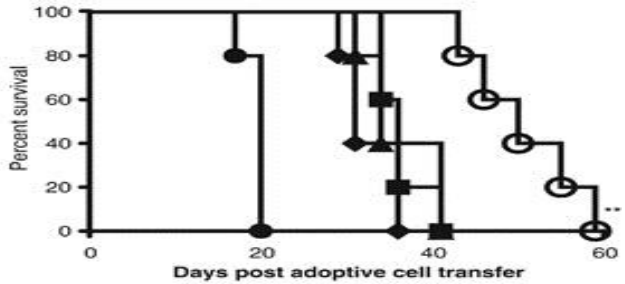
5x10^6



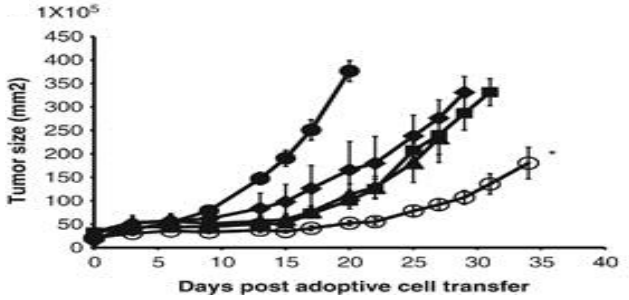


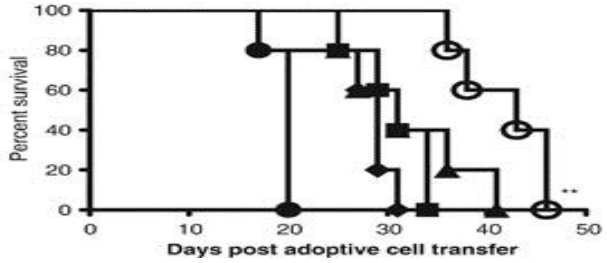
1x10^6





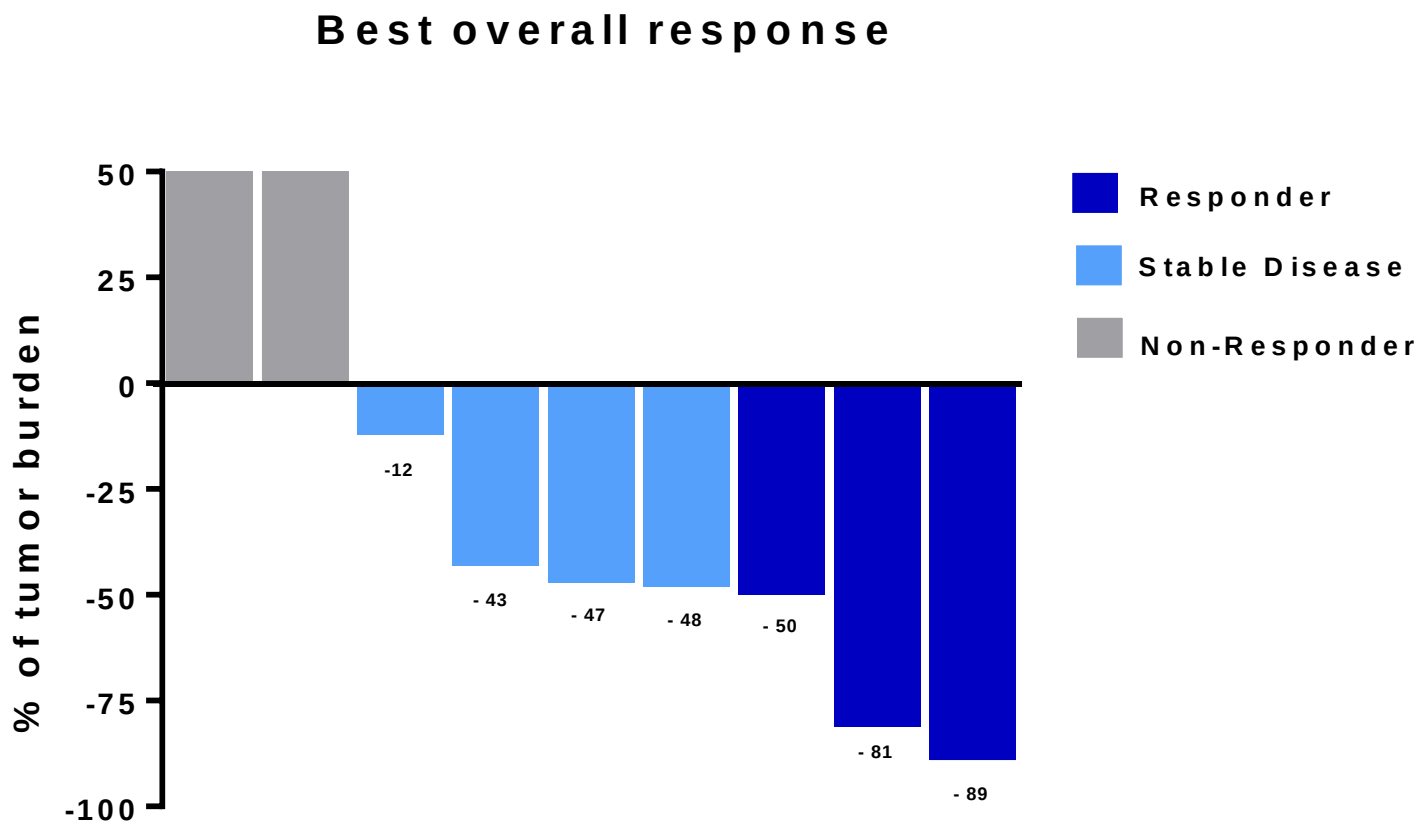
1x10^5





Zhang et al.
Gene Therapy 10: 575-80, 2013

Clinical Response for the TGFbDNRII TIL Trial



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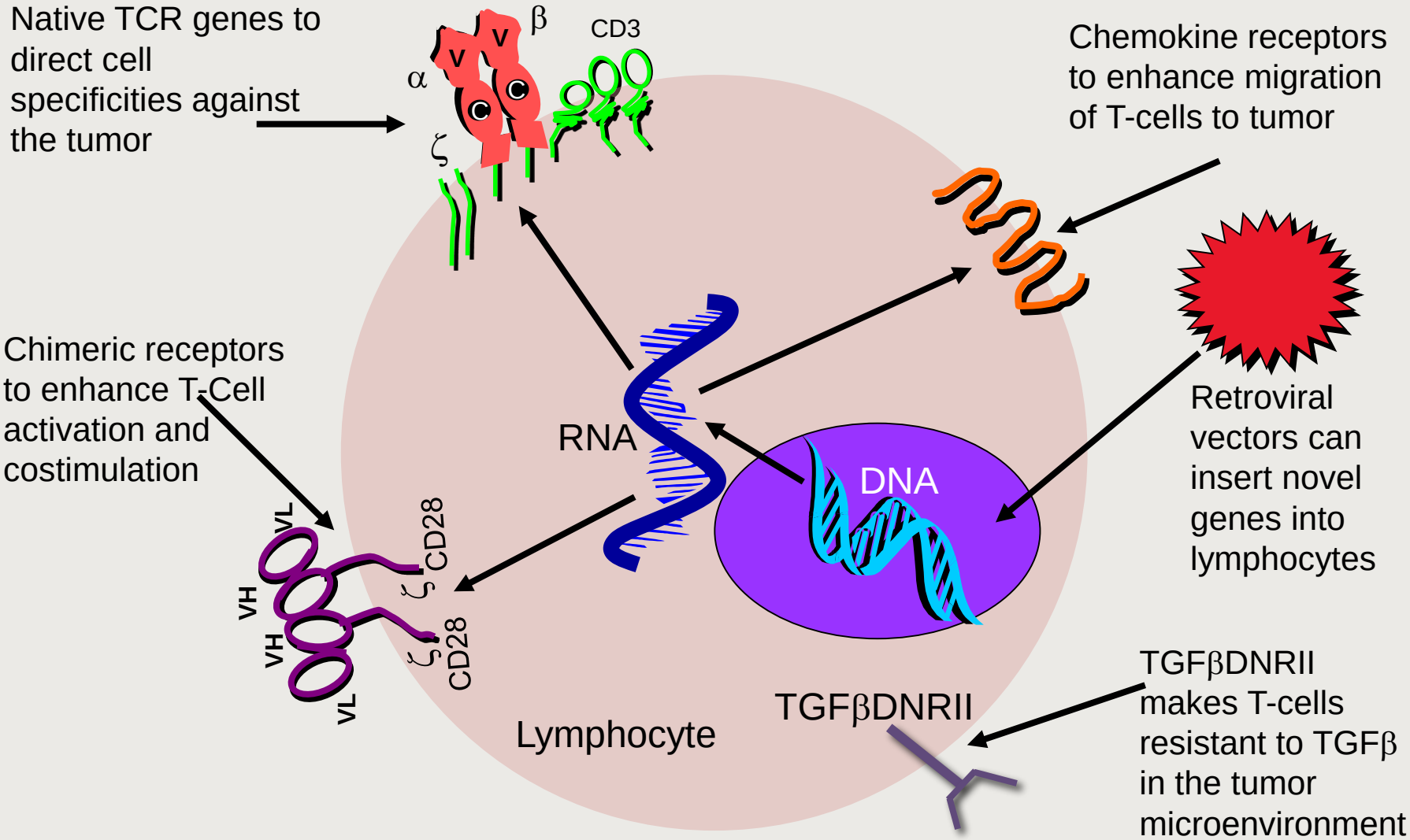

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