Adoptive T-cell Transfer

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Melanoma Medical Oncology

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

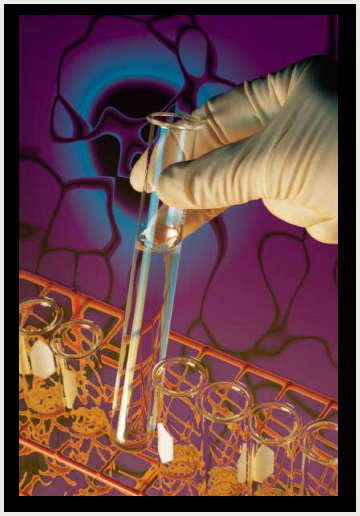
Disclosures

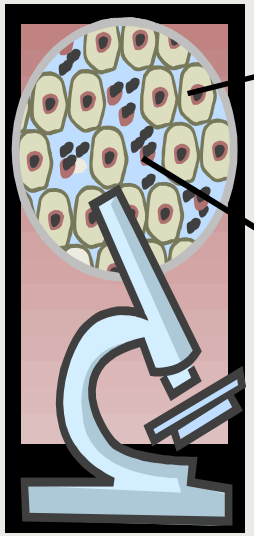
None

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

Surgical Removal of Cancer Nodule

Single Cell Suspension Incubated with IL-2



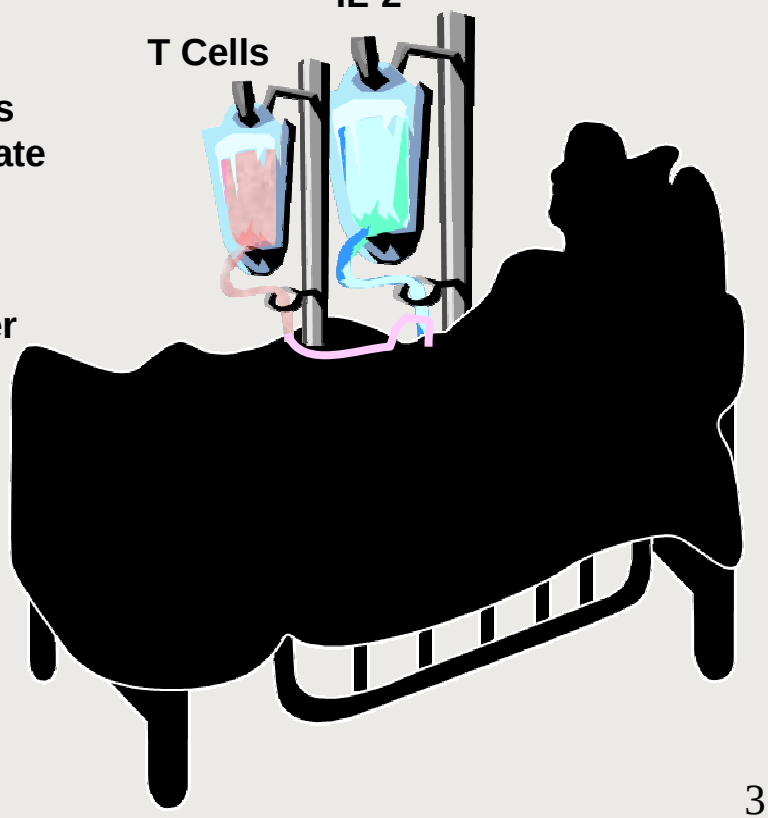


T Cells Proliferate

Cancer Cells Die

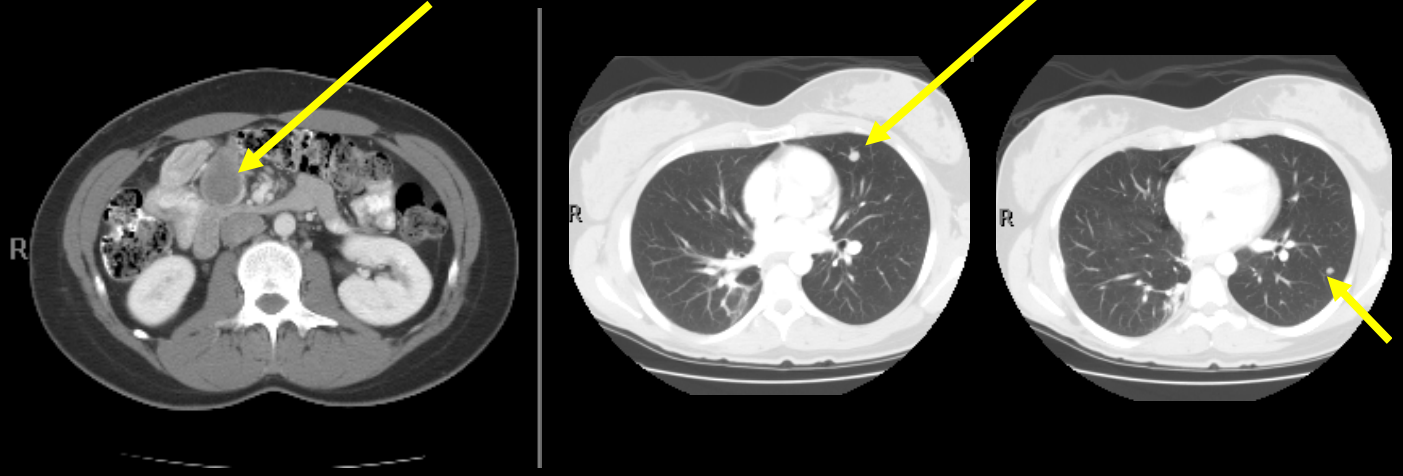
IL-2

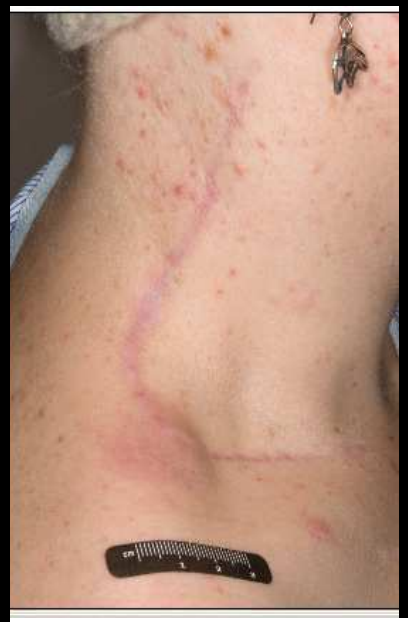
T Cells



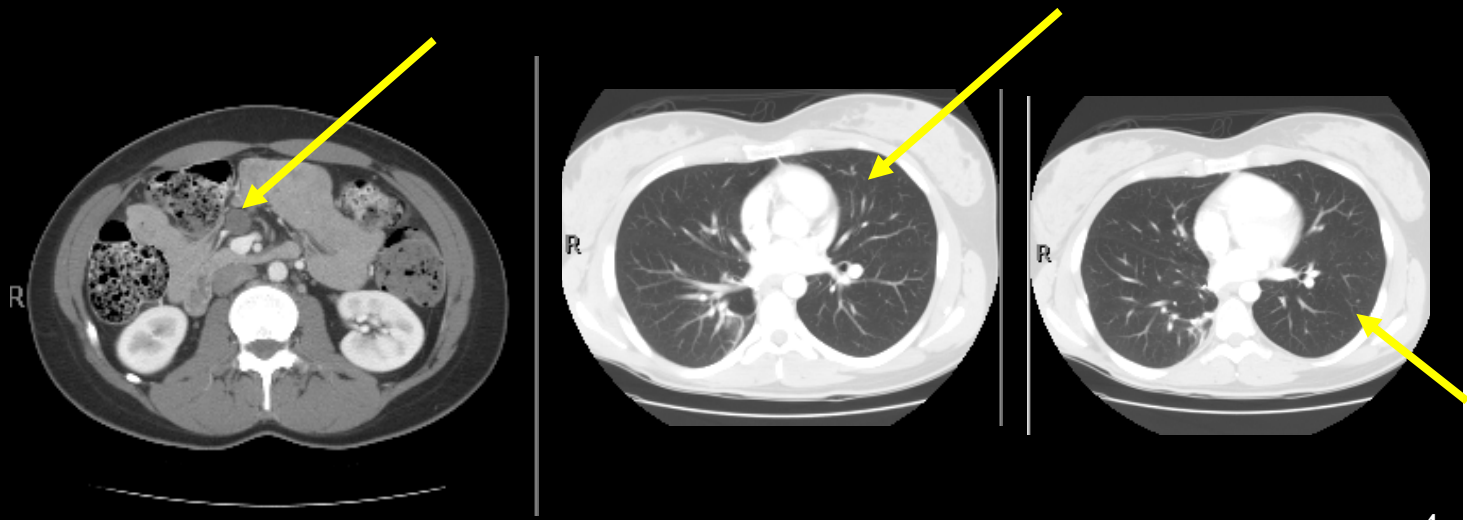
Clinical Response following Lymphodepletion + T-lymphocyte Infusion

Before TIL Infusion



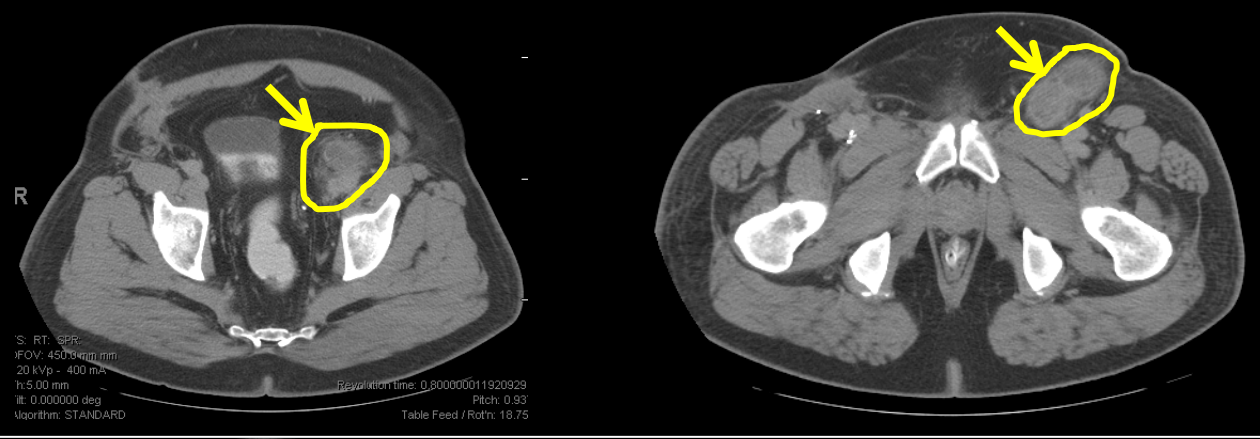


After TIL Infusion

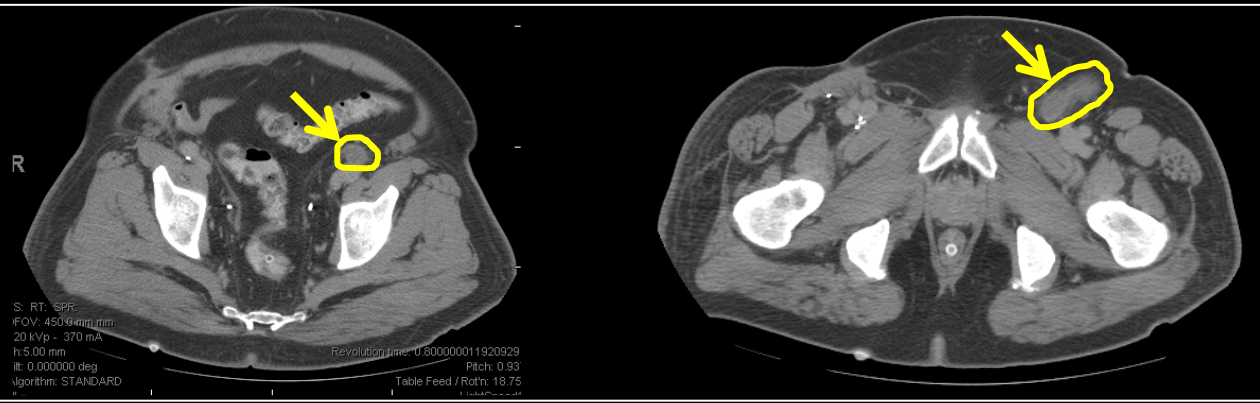


Response to TIL Therapy

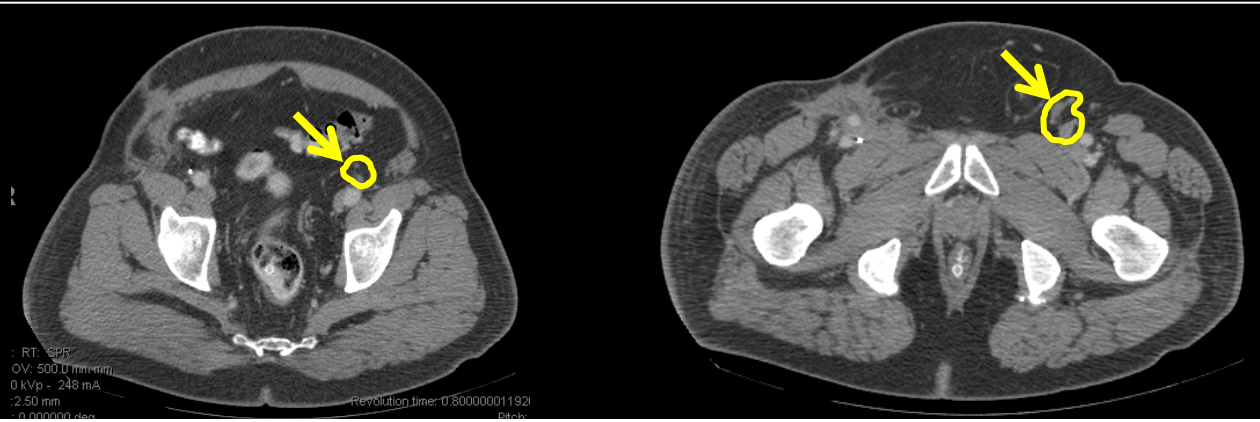
pre-treatment



4 weeks post-treatment



18 months post-treatment durable response noted



Clinical Response Data from MDACC TIL Clinical Trial

Best overall response:

Number of patients	CR*	PR*	Total
51	2 (4%)	21(41%)	23 (45%)

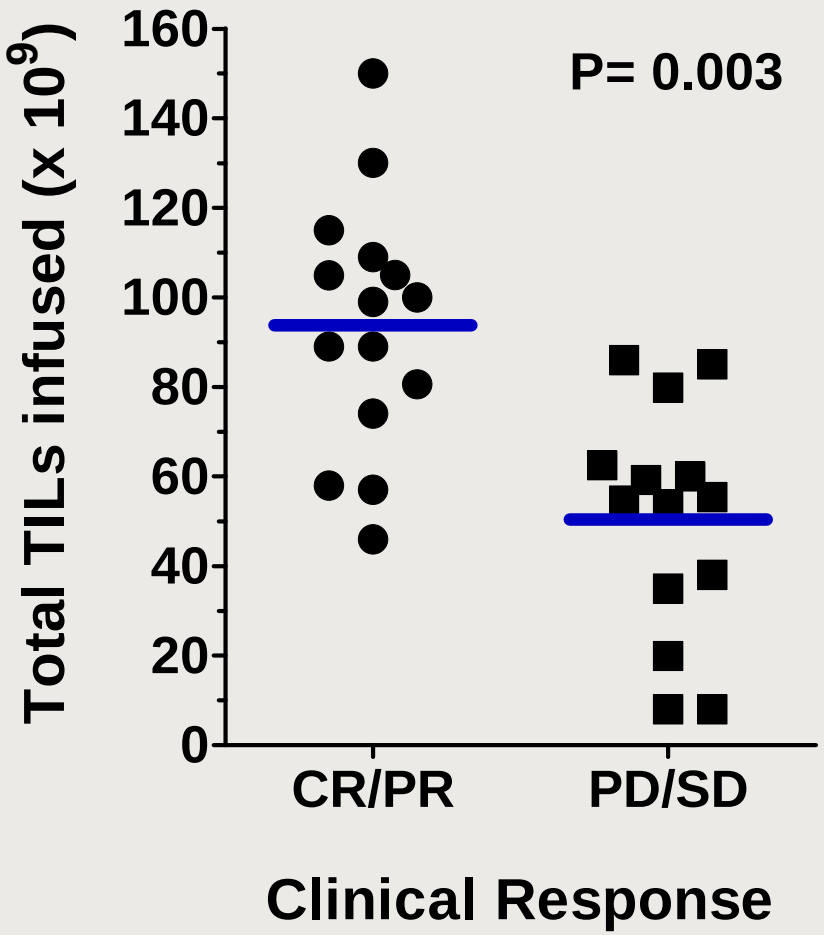
*Some patients are still undergoing clinical response

Clin Cancer Res 18: 6758-6770, 2012
Radvanyi … Hwu

Progression-free and Overall Survival

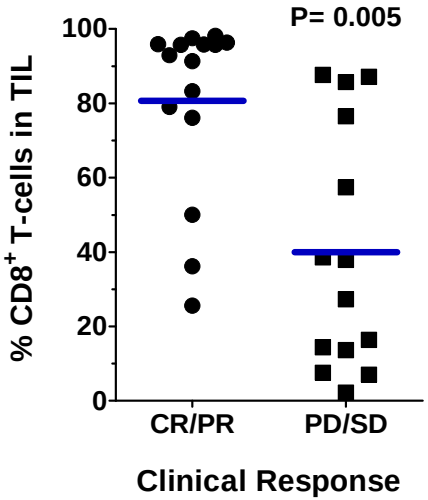
	Best Overall Response (n=51)			
	irRC Responders (45%)		irRC Non- Responders (55%)	
	CR	PR	SD	PD
Number of patients	2	21	17	11
Progression-free survival (months)	29, 20+	37+, 37+, 36+, 33+, 31+, 30+, 29+, 27+, 22+ 22+, 22, 11+, 11, 10, 9, 9, 8, 8, 8, 3, 3	38+, 7, 6+, 6+, 6, 6, 6, 5, 4, 4, 4, 4, 3, 3, 3, 2+, 1	3, 3, 3, 2, 2, 2, 1, 1, 1, 1, 1
Overall survival (months)	29+, 20+	38+, 37+, 37+, 36+, 33+, 31+, 30+, 29+, 27+, 27+, 25+, 23+, 22+, 22+, 15, 12+, 11+, 10+, 9+, 9+, 3+	38+, 25, 14+, 14, 11+, 10+, 8, 8, 7+, 6+, 6+, 6, 6, 6, 5, 4, 2+	21, 18, 14, 10+, 6, 5, 4+, 4, 3+, 3, 2

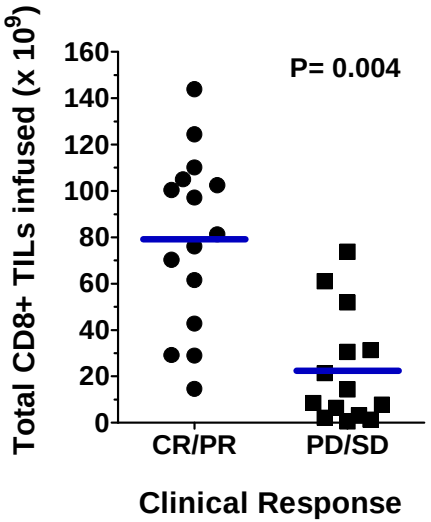
Numbers of Total TIL Infused and Type of Clinical Response

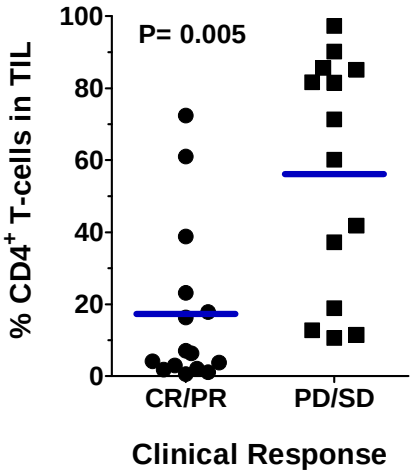


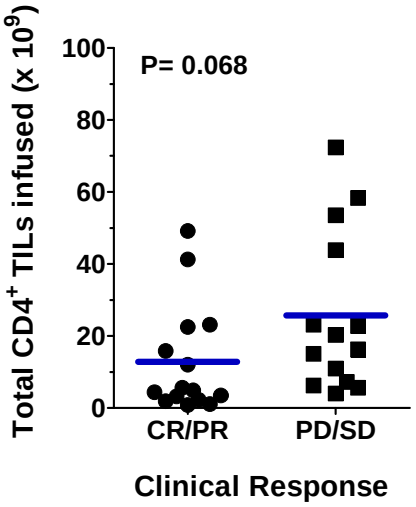
Clin Cancer Res 18: 6758-6770, 2012
Radvanyi … Hwu

CD8+ TIL are Critical



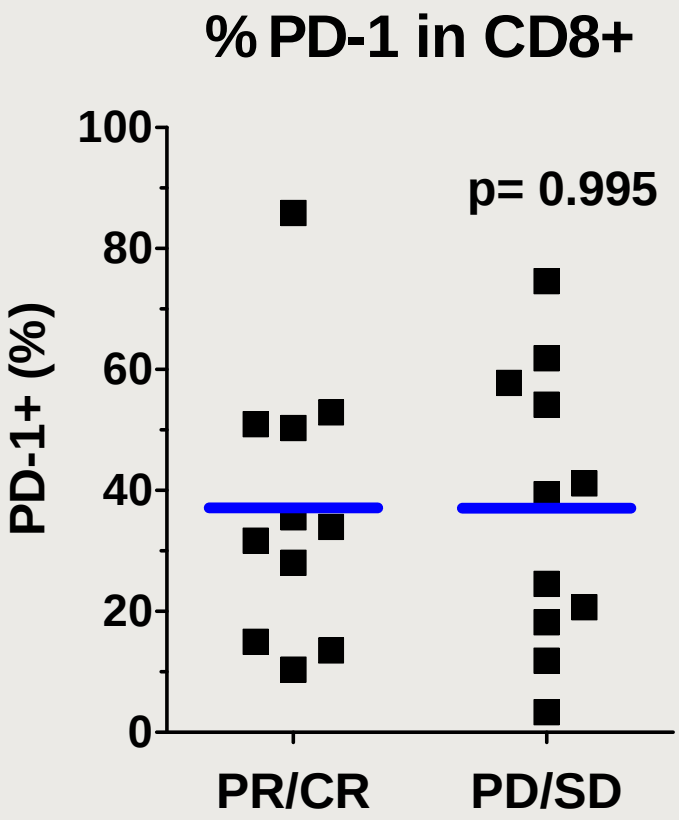


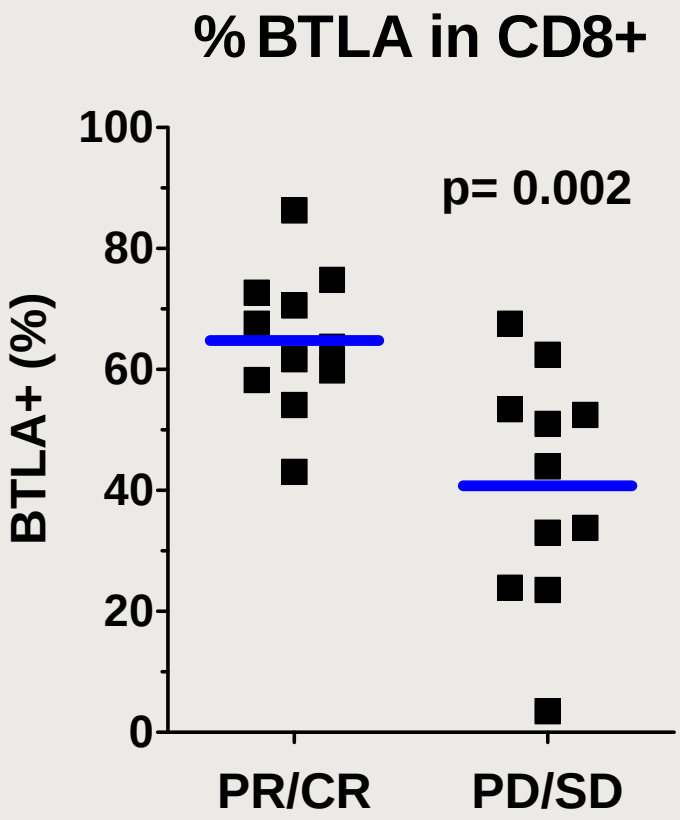




Clin Cancer Res 18: 6758-6770, 2012
Radvanyi … Hwu

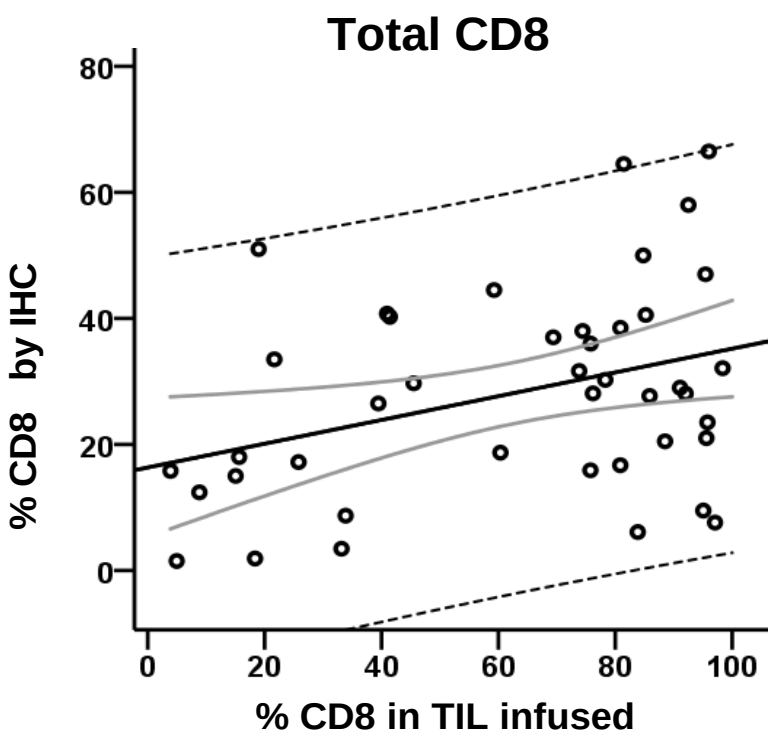
Higher Proportion of CD8+ TILs Co-expressing BTLA in Responders



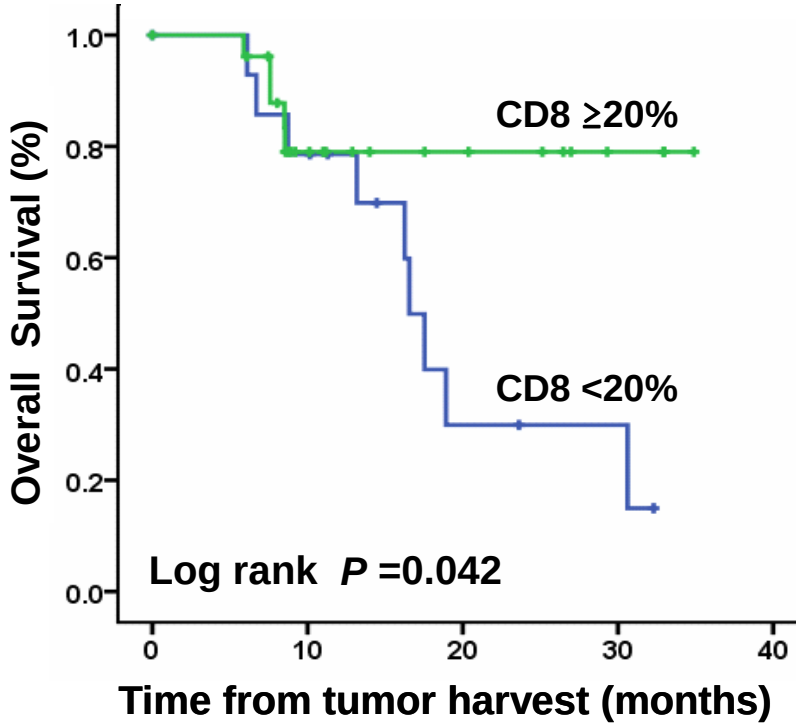


Clin Cancer Res 18: 6758-6770, 2012
Radvanyi … Hwu

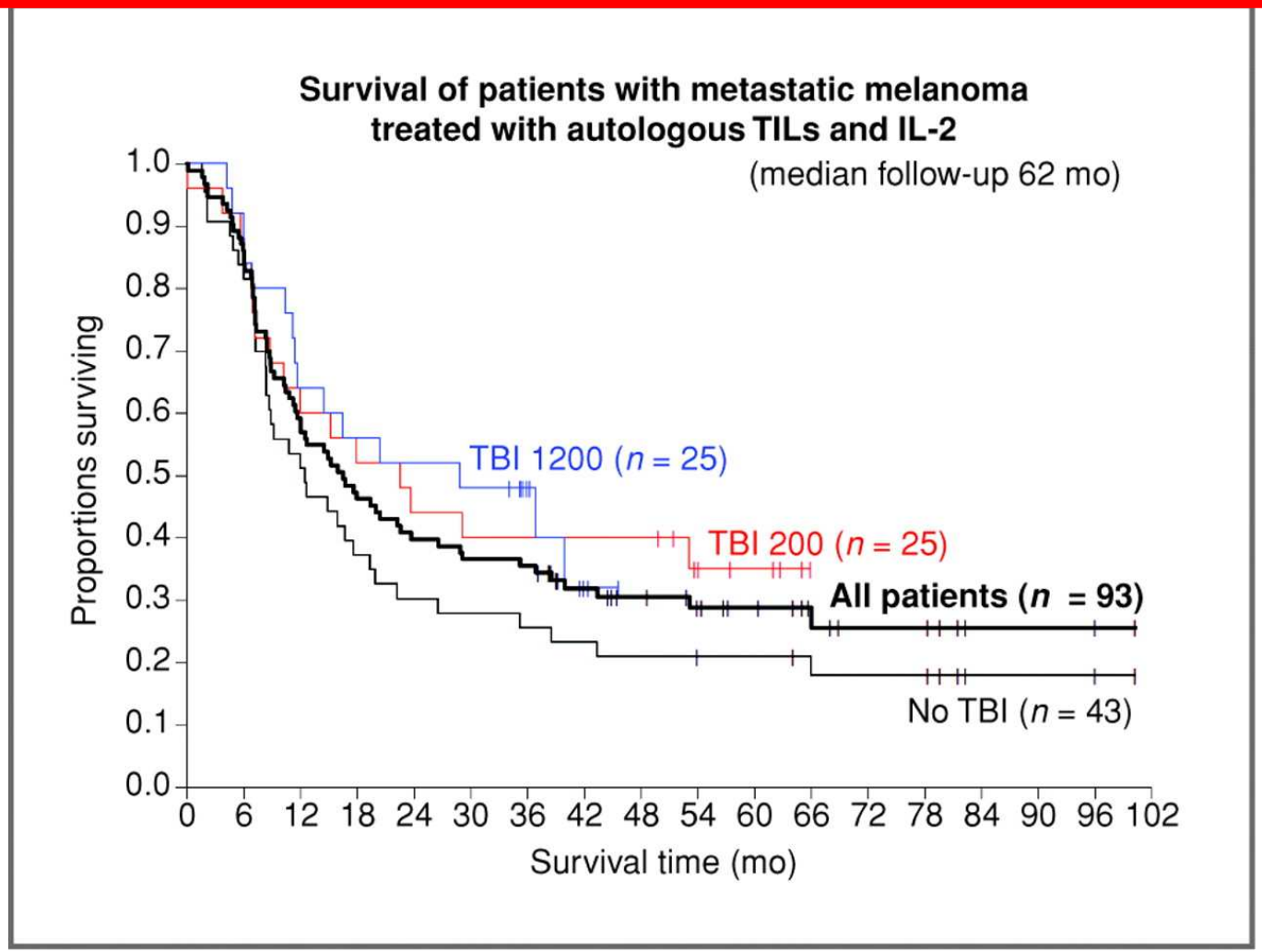
CD8 by IHC in Original Metastases is Associated with CD8 % in Expanded TIL and Survival



$P = 0.049$, $r^2 = 0.305$



Overall Survival of Patients Receiving TILs with the Chemotherapy Preparative Regimen Alone (no TBI) or plus 2 or 12 Gy TBI.



Rosenberg SA et al. CCR 2011

Durable Complete Responses in Heavily Pretreated Patients with Metastatic Melanoma Using T-Cell Transfer Immunotherapy
Cell Transfer Therapy

Treatment	*n* (%) of patients (duration in mo)			OR (%)
	Total	PR	CR	
No TBI	43	16 (37)	5 (12)	21 (49)
		84, 36, 29, 28, 14, 12, 11, 7, 7, 7, 7, 4, 4, 2, 2, 2	82+, 81+, 79+, 78+, 64+	
200 TBI	25	8 (32)	5 (20)	13 (52)
		14, 9, 6, 6, 5, 4, 3, 3	68+, 64+, 60+, 57+, 54+	
1,200 TBI	25	8 (32)	10 (40)	18 (72)
		21, 13, 7, 6, 6, 5, 3, 2	48+, 45+, 44+, 44+, 39+, 38+, 38+, 38+, 37+, 19	
Total	93	32 (34)	20 (22)	52 (56)

Rosenberg SA et al, CCR Jul 2011

Treatment Characteristics During TIL Therapy and Clinical Outcome

Patient	Age/sex	PS	Lactate dehydrogenase	Stage	Site of biopsy*	Evaluable metastasis	IL-2 doses	Resp.	PFS (mo)	OS (mo)
Responders (*n* = 10)										
05-LA	41/M	0	Normal	M1a	SC	SC nodules	10	CR	20†	20†
19-NS	66/M	1	Normal	M1c	Perito.	Peritoneum	3	CR	4†	4†
03-MG	36/M	0	Normal	M1c	LN	Soft tissue, lung, bone	15	PR	9	21†
06-TS	60/M	0	Normal	M1b	Lung	Lung	5	PR	18†	18†
09-SD‡	45/M	0	Normal	M1b	LN	Lung	7	PR	13†	13±
13-BS	61/M	0	Normal	M1b	Lung	Lung	9	PR	10†	10†
14-SV‡	71/M	0	Above	M1a	SC	SC, LN	9	PR	3	9†
16-SH	41/M	1	Normal	M1c	SC	Liver, adrenal, lung, LN	8	PR	6†	6†
18-WR	70/F	0	Normal	M1a	LN	SC, LN	8	PR	4	4†
20-TY	58/M	0	Normal	M1a	SC	SC, LN	7	PR	3†	3†
Median							8.1 ± 3.2		(7.3)	(9.3)
Nonresponders (*n* = 10)										
01-AY	56/M	0	Normal	M1c	Lung	Lung, SC, bone	9	SD	11	17
07-ZR	22/M	0	Normal	M1b	Lung	Lung	7	SD	3	15
08-RM	34/F	0	Normal	M1c	Liver	Liver	14	SD	5	6
12-VS‡	41/F	0	Normal	M1a	SC	SC, LN	11	SD	11†	11†
02-PE	36/M	0	Above	M1c	LN	LN, adrenal, periton.	9	PD	2	3
04-BA‡	57/M	0	Normal	M1c	Lung	LN, lung, adrenal,	13	PD	3	20†
10-BE	53/F	0	Normal	M1c	LN	SC, LN, adrenal	6	PD	1	5
11-KB	57/M	1	Above	M1c	LN	Lung, LN	6	PD	1	5
15-SM‡	52/M	1	Above	M1c	Liver	Bone, liver	10	PD	1	3
17-ZD‡	68/F	1	Above	M1c	Pleura	Lung, pleura, bone	5	PD	1	2
Median							9.0 ± 3.1		2.7	5.7

* **Site of tumor sample**
† **Ongoing**
‡ **Patients with HLA-A*0201.**

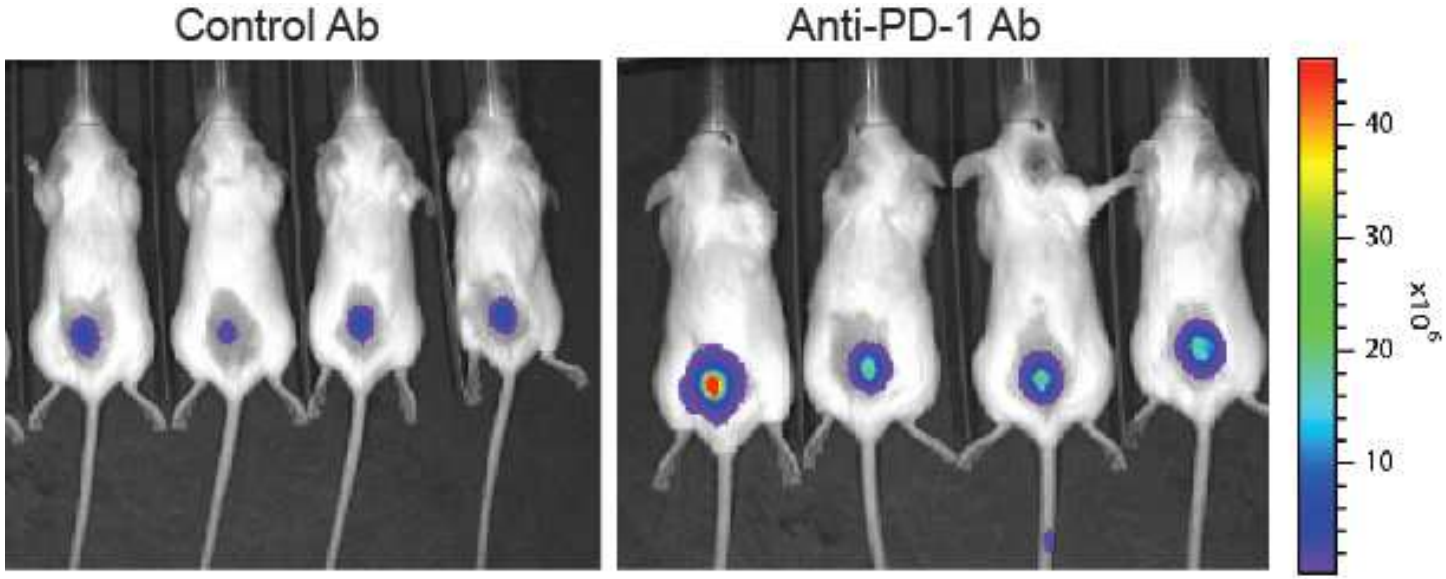
P = 0.53

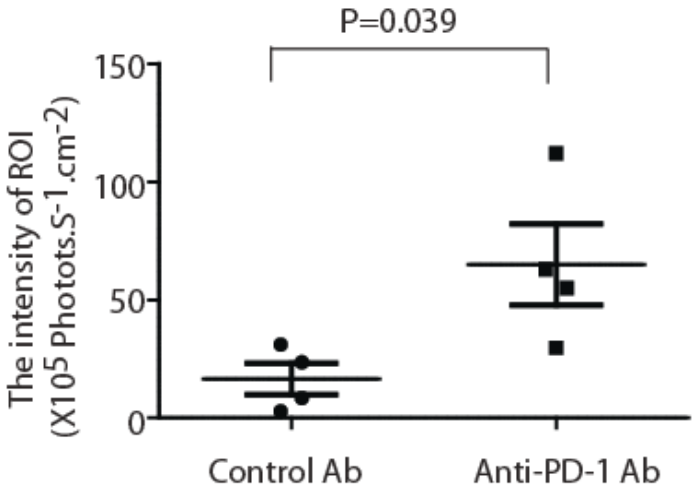
Besser et al, CCR May 2010

Question?

Does PD-1 inhibition enhance T-cell therapy?

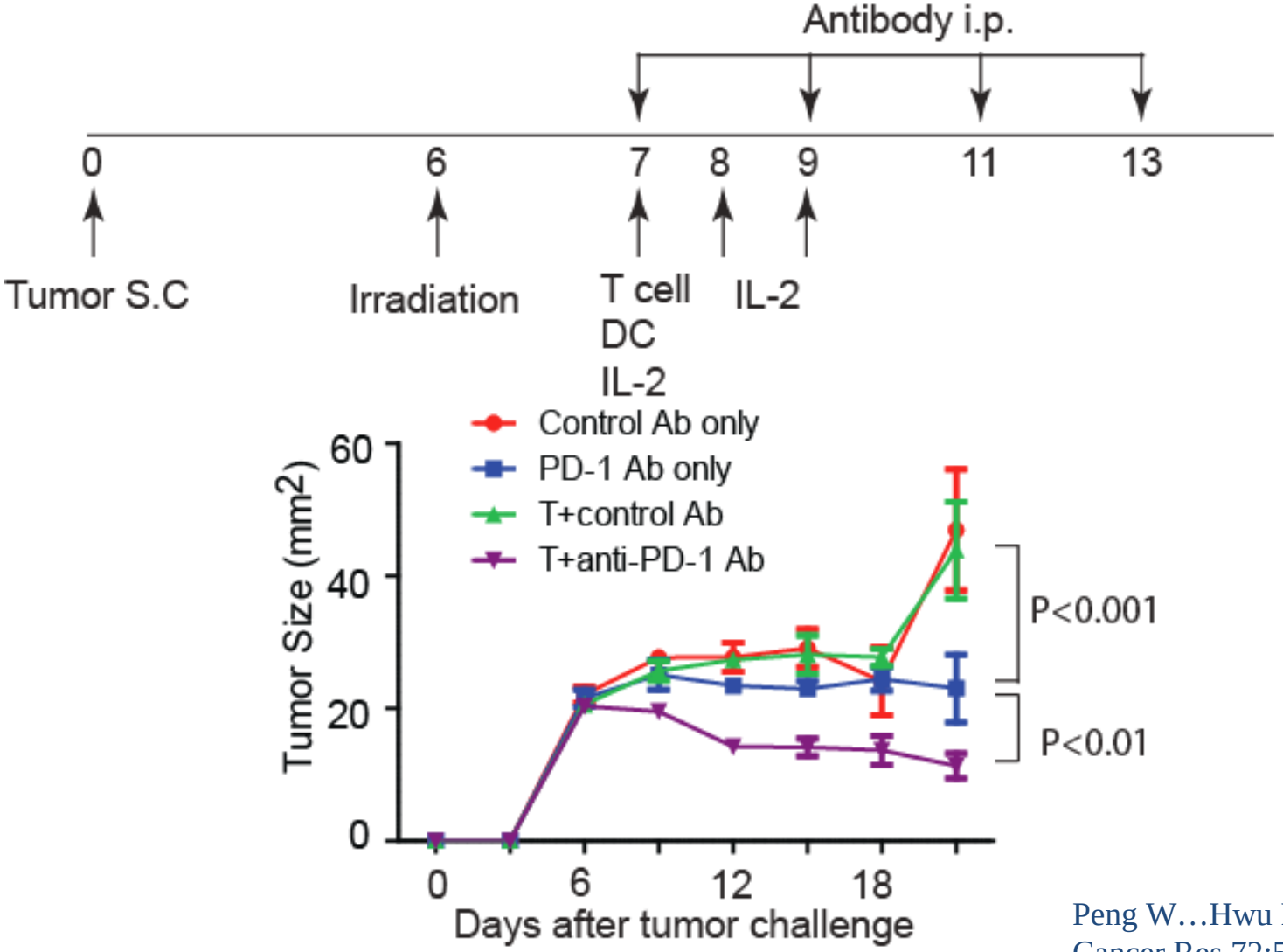
Increased Number of Transferred T-cells at the Tumor Site in Tumor-bearing Mice Receiving anti-PD-1 and ACT Treatment





Peng W…Hwu P.
Cancer Res 72:5209-18, 2012

Delayed Tumor Progression in Tumor-bearing Mice Receiving anti-PD-1 and ACT Treatment

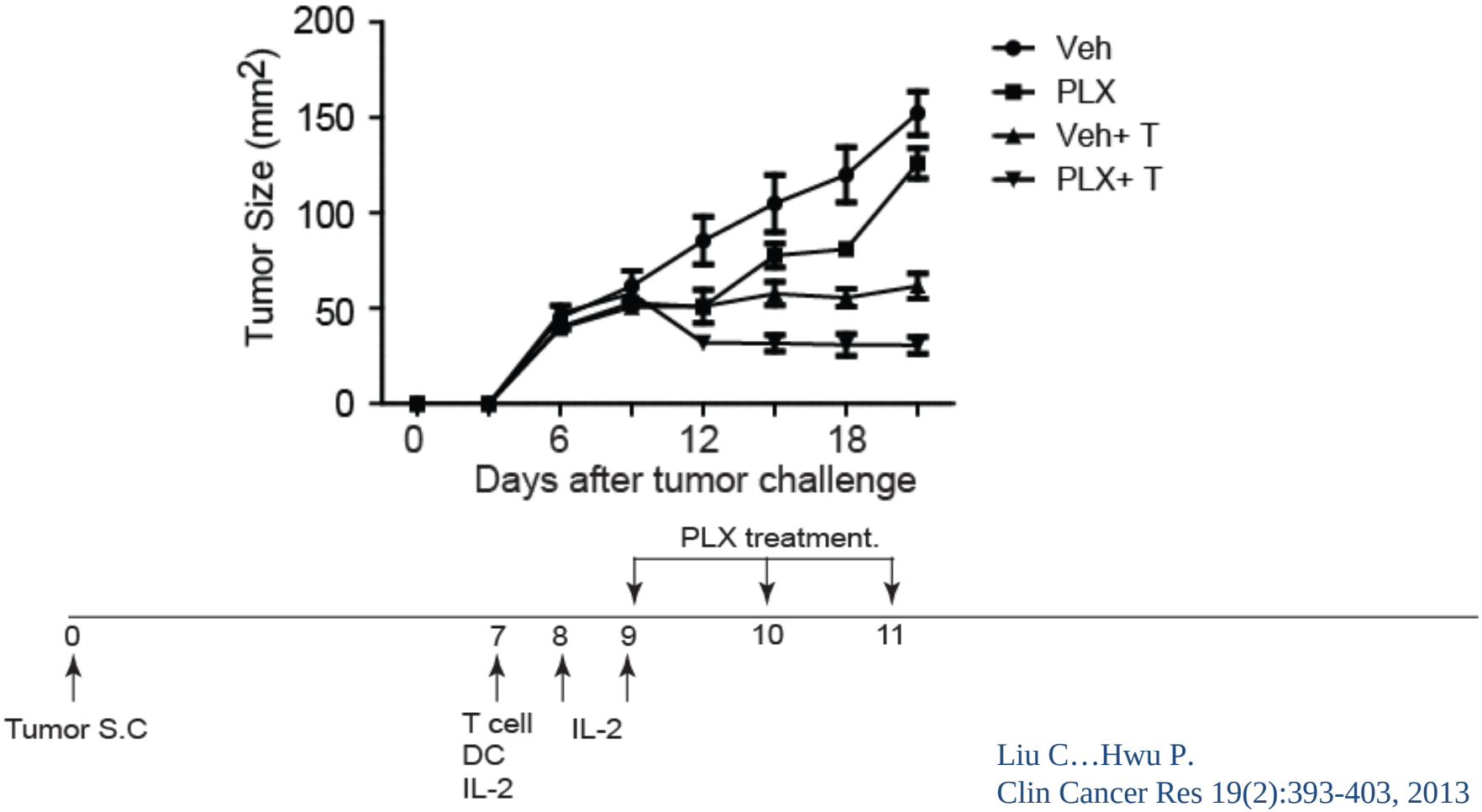


Peng W…Hwu P.
Cancer Res 72:5209-18, 2012

Question?

Does BRAF inhibition enhance T-cell therapy?

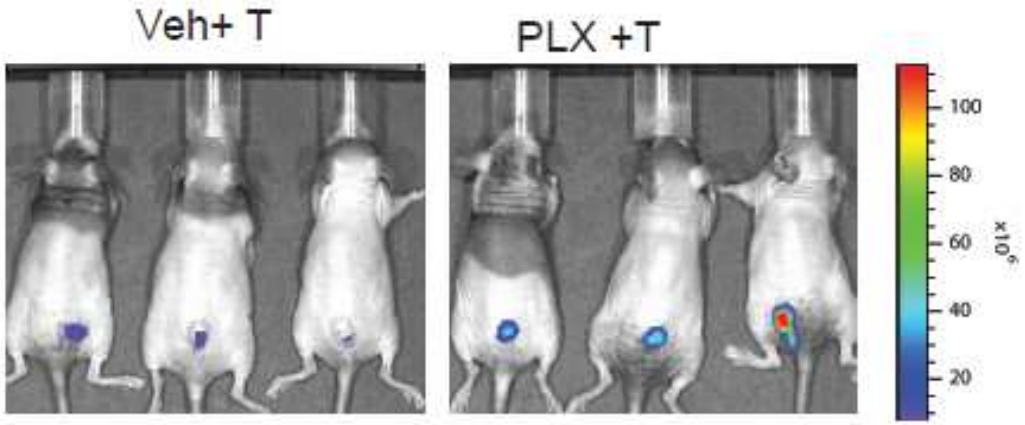
Combination of PLX4720 with Adoptive T-cell Therapy Leads to Enhanced Anti-tumor Activity (B6 nude mice)



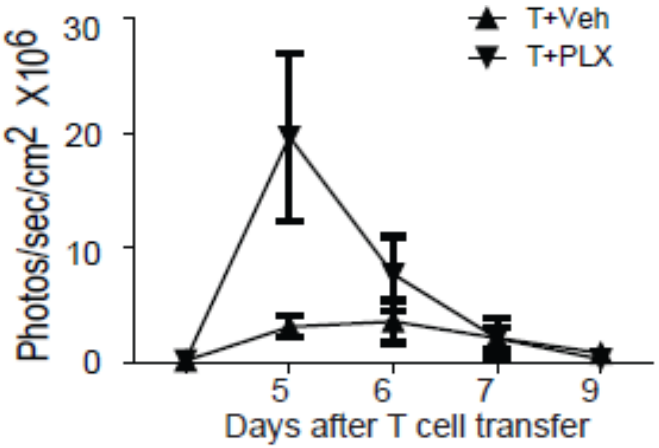
Liu C…Hwu P.
Clin Cancer Res 19(2):393-403, 2013

Administration of PLX4720 Increases Tumor Infiltration of Adoptively Transferred pmel-1 T-cells *in vivo*

A



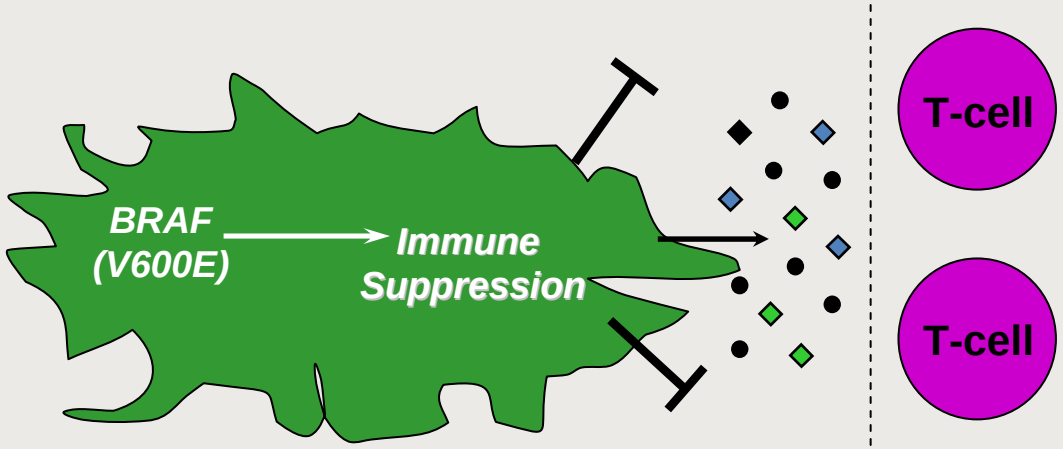
B



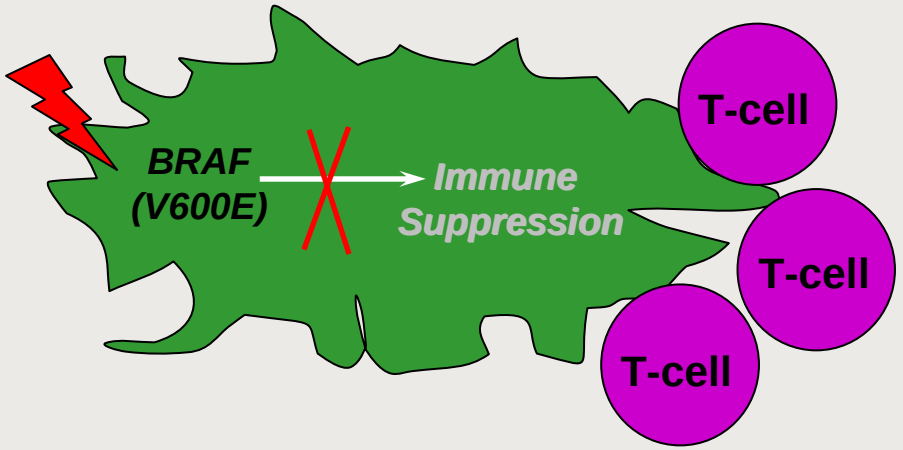
Liu C…Hwu P.
Clin Cancer Res 19(2):393-403, 2013

Combining BRAF(V600E) Inhibition and Immunotherapy

Immunotherapy Alone

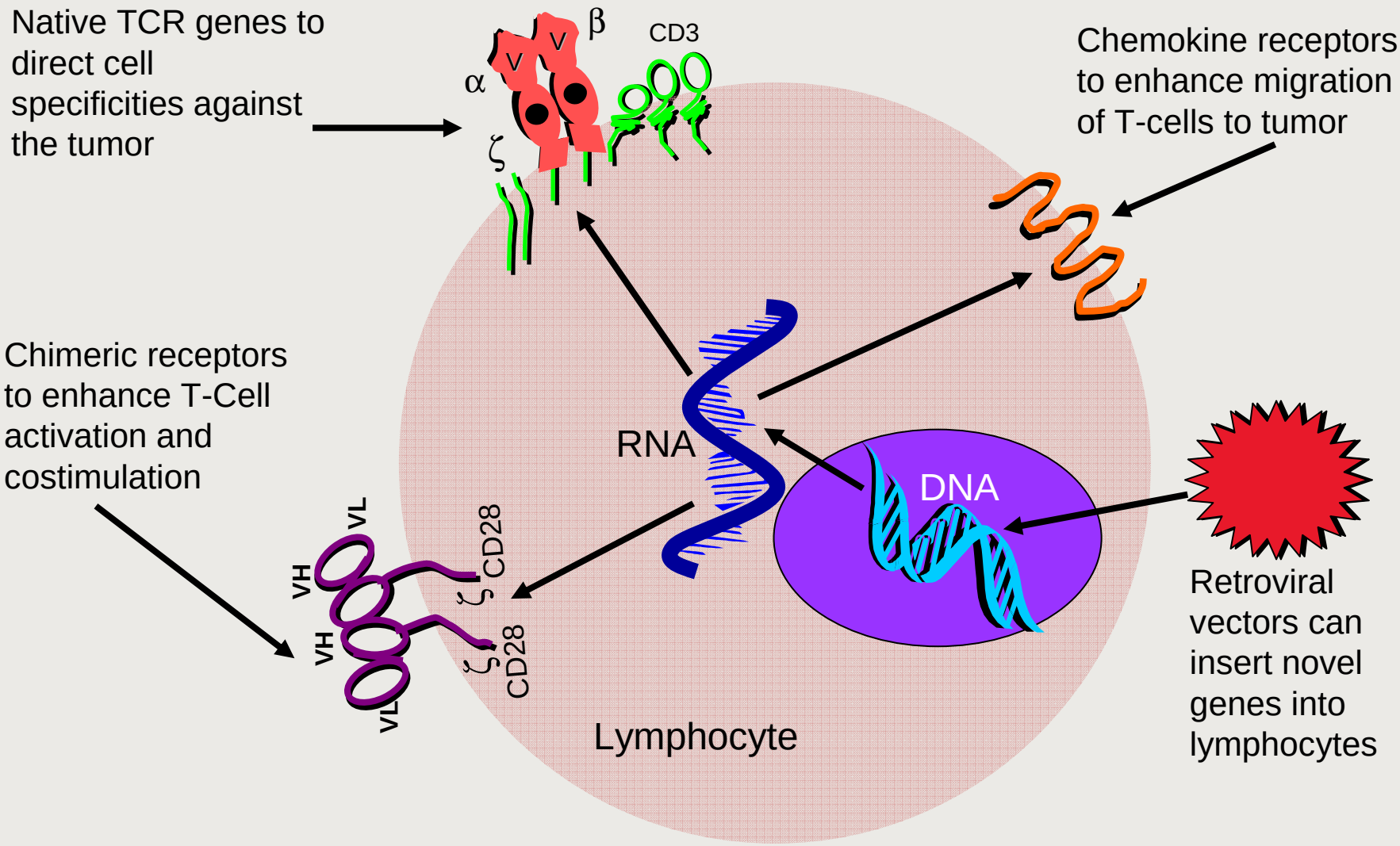


Immunotherapy Plus BRAF(V600E) Inhibition



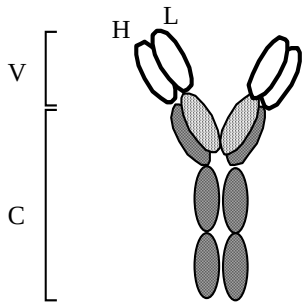
Jahan Khalili / Greg Lizee

Insertion of Genes into Lymphocytes to Enhance Antitumor Properties

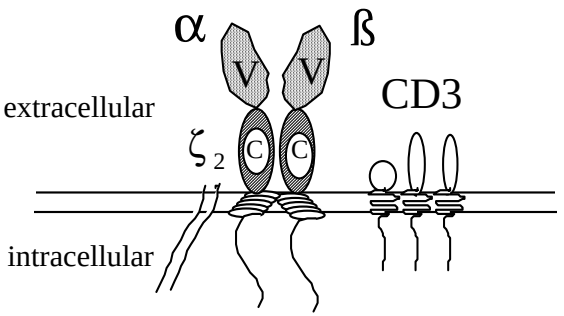


Chimeric Antibody/T Cell Receptor: Combines Antibody V Region and T-cell Signaling Chains

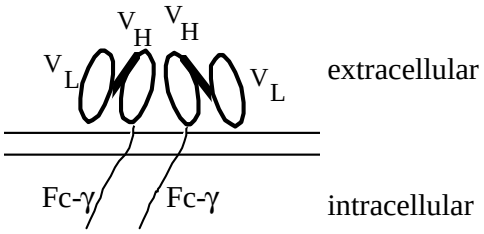
Antibody



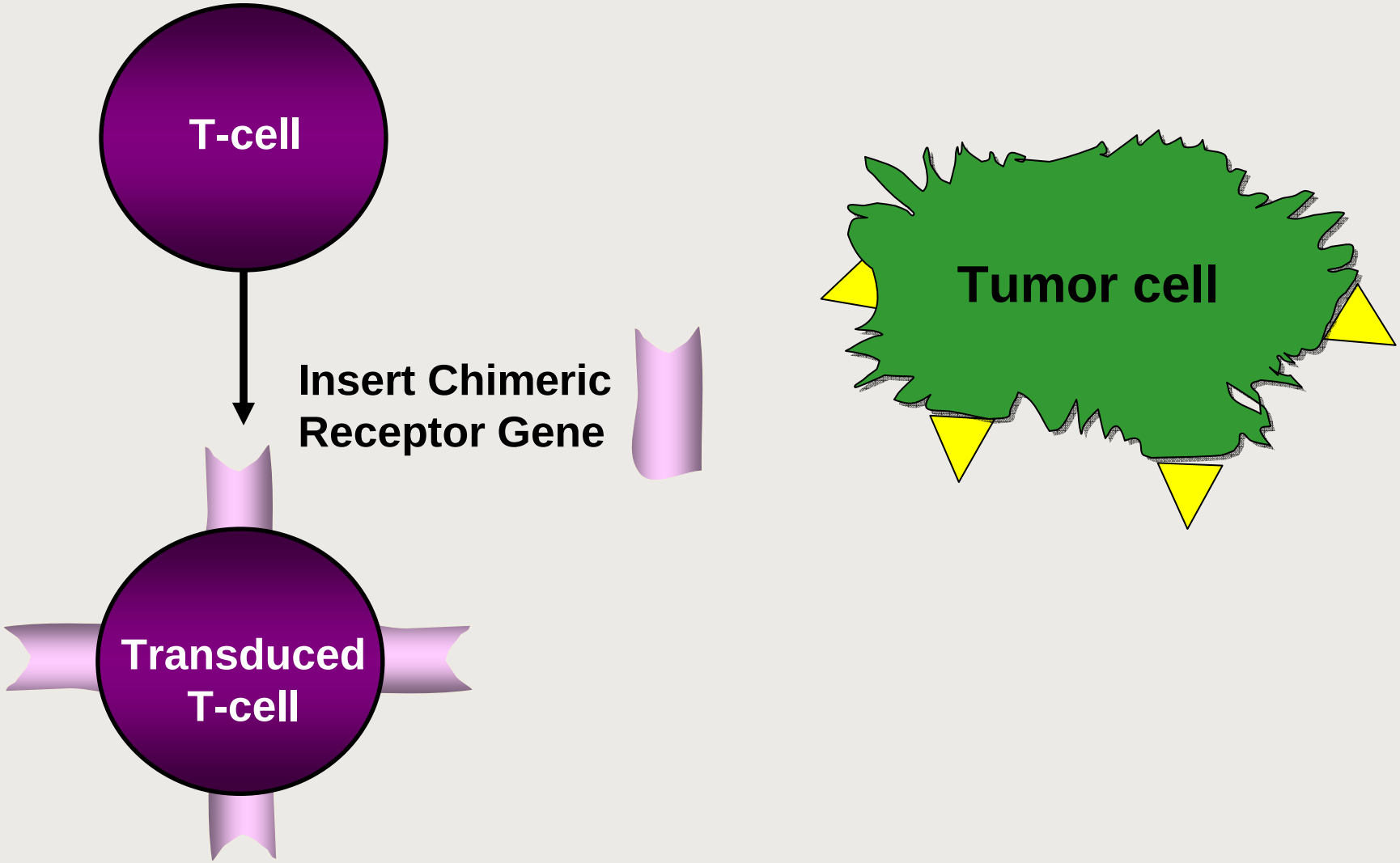
TCR



scFv-γ



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



Brief Definitive Report

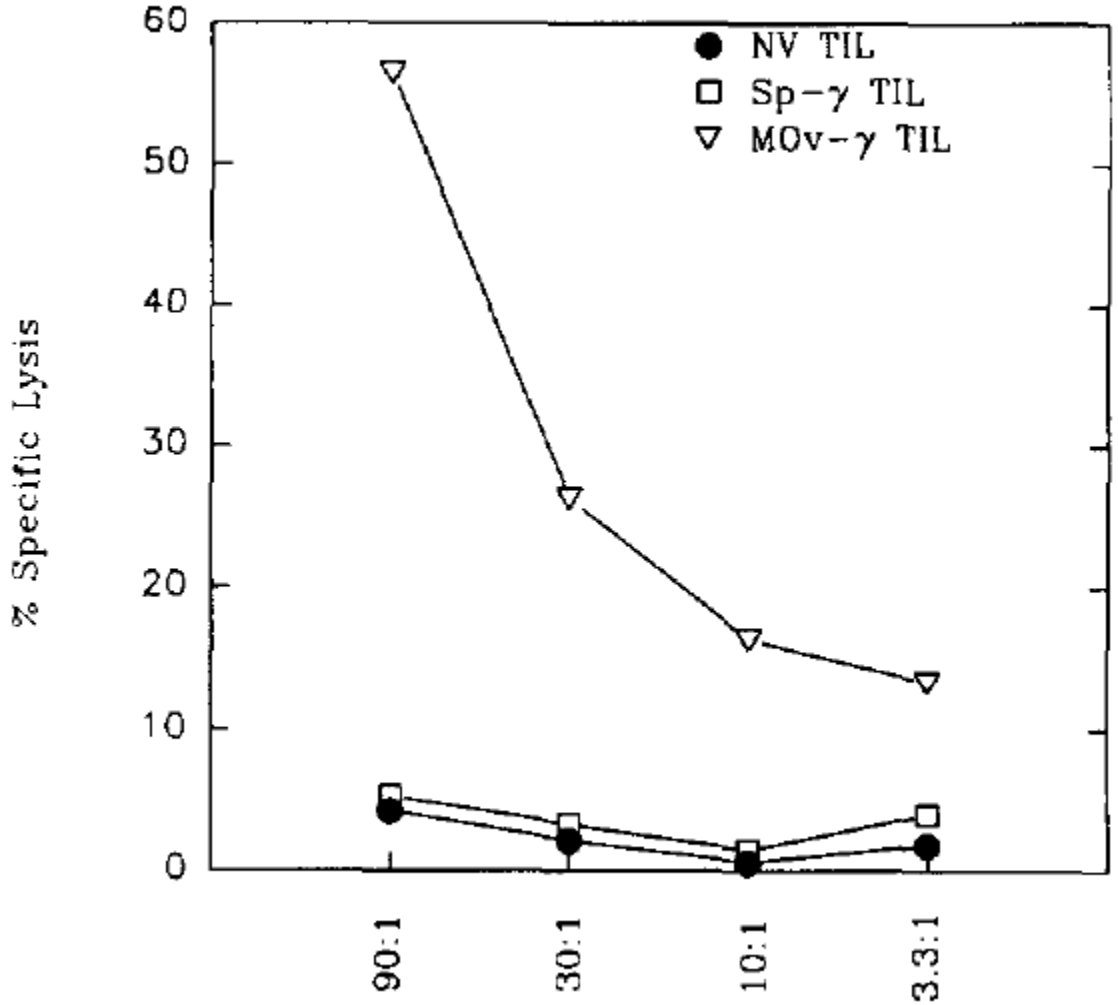
Lysis of Ovarian Cancer Cells by Human Lymphocytes Redirected with a Chimeric Gene Composed of an Antibody Variable Region and the Fc Receptor Gamma Chain.

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*

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

A T cell-independent antitumor response in mice with bone marrow cells retrovirally transduced with an antibody / Fc-γ chain chimeric receptor gene recognizing a human ovarian cancer antigen

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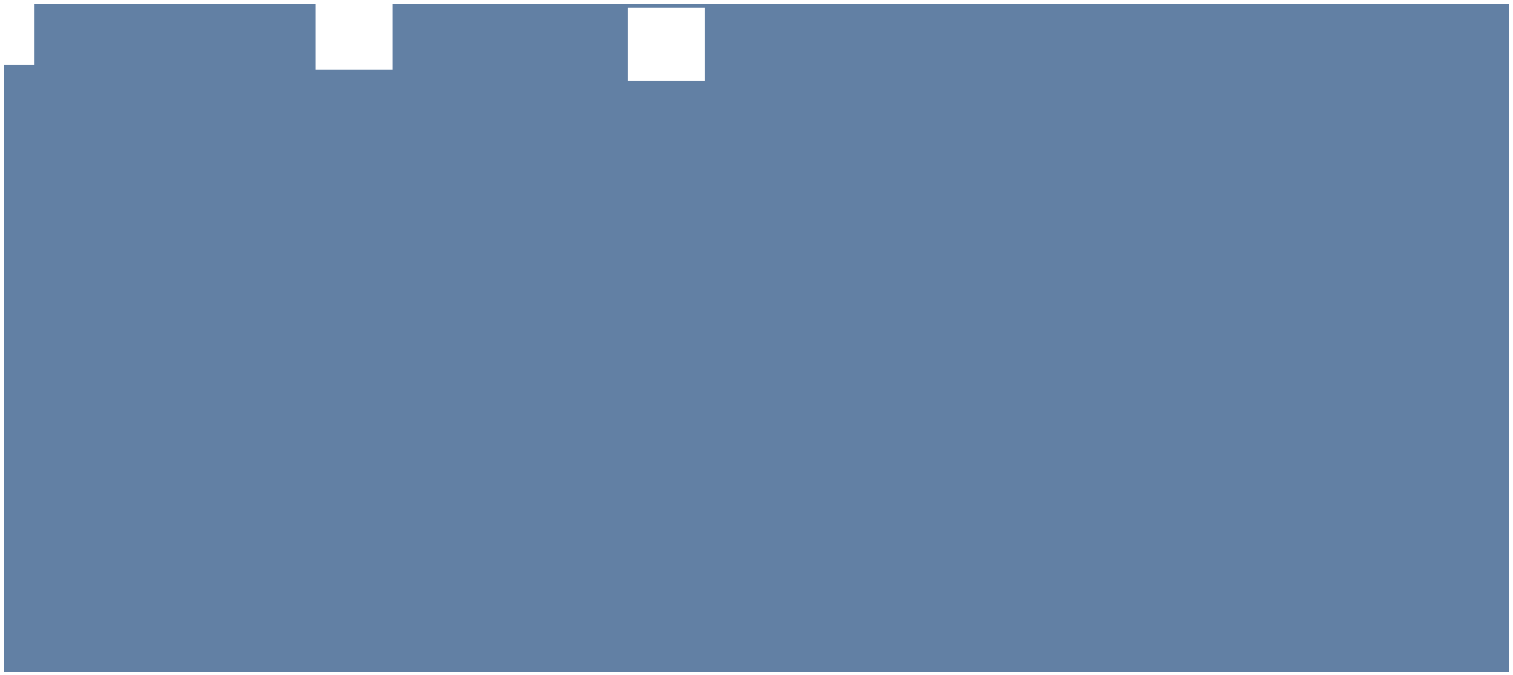
Gang Wang, Rajesh K. Chopra, Richard E. Royal, James C. Yang, Steven A. Rosenberg & Patrick Hwu

Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.

Nature Medicine ● Volume 4 ●Number 2 February 1998

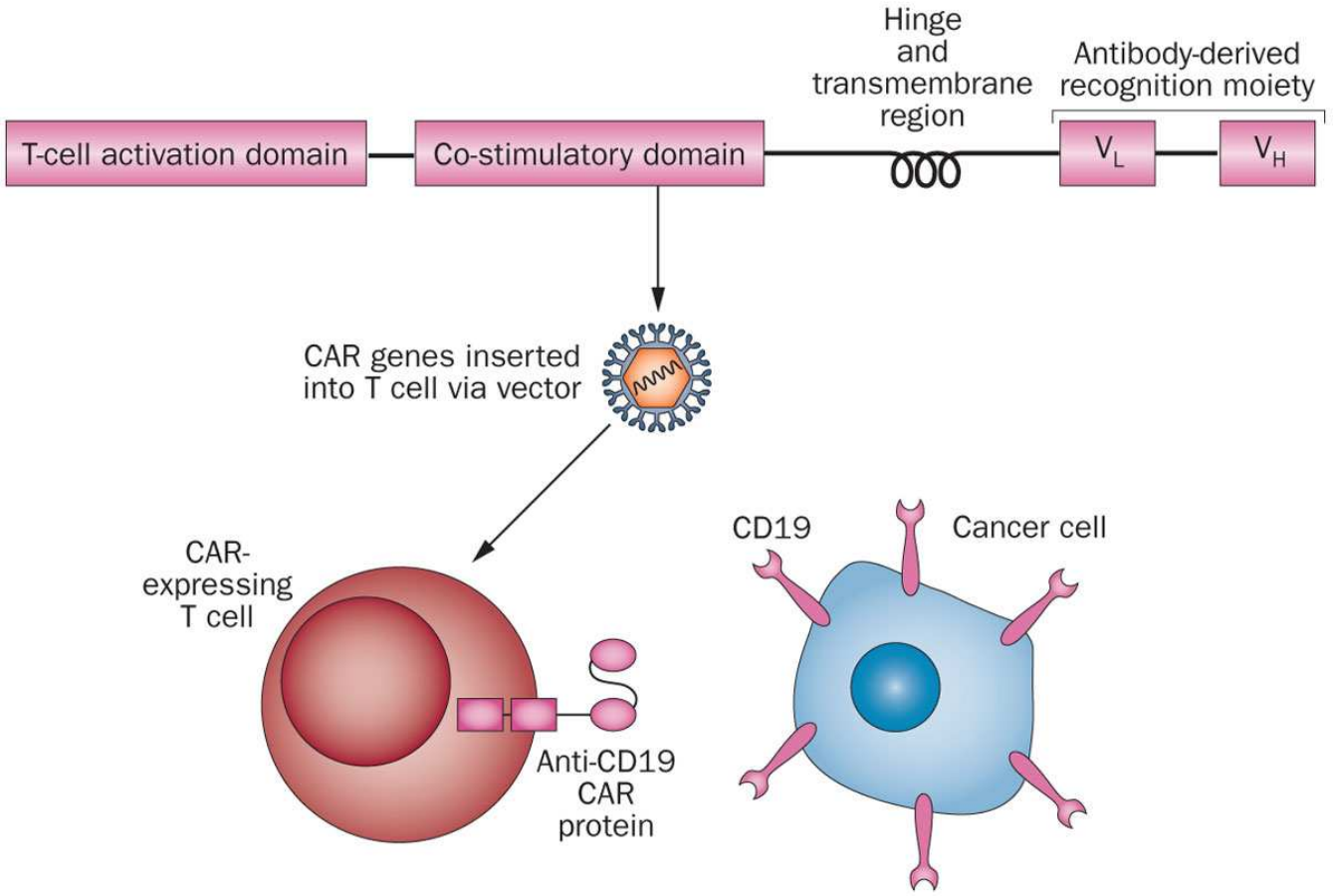
Tumor Growth in *MOvγ*-Reconstituted Mice after T-cell Depletion

Chimeric Antigen Receptors



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

Chimeric Antigen Receptor Domains



Kochenderfer JN, Rosenberg SA
Nature Review | Clinical Oncology 2013

Summary of Published anti-CD19 CAR Clinical Trial Results

Table 1 | Summary of published anti-CD19 CAR clinical trial results

Institution	Gene-transfer vector used	Antibody*	Co-stimulatory domain in CAR	Chemotherapy administered before cell infusion	Normal B-cell depletion‡	Regression of malignancy reported?	Cytokine-release-type toxicities§ reported?	*n*
Baylor College of Medicine[48]	Gamma-retrovirus	FMC63	CD28 or none	None	No	No	No	6
City of Hope[81]	Plasmid electroporation	FMC63	None	Fludarabine before some T cell infusions	No	No	No	2
Memorial Sloan–Kettering Cancer Center[30,84]	Gamma-retrovirus	SJ25C1	CD28	None or cyclophosphamide	No	Yes	Yes	9
National Cancer Institute[33,44]	Gamma-retrovirus	FMC63	CD28	Cyclophosphamide and fludarabine	Yes	Yes	Yes	8
University of Pennsylvania[31,51]	Lentivirus	FMC63	4-1BB	Variable	Yes	Yes	Yes	3

*The antibody that CAR antigen-recognition moiety was derived from. ‡Reported for >3 months. §For example, hypotension. Abbreviation: CAR, chimeric antigen receptor.

Kochenderfer JN, Rosenberg SA
Nature Review | Clinical Oncology 2013

Summary of the 1st Patients Treated on the NCI Adult Autologous anti-CD19 CAR Trial

Table 2 | Summary of the first patients treated on the NCI adult autologous anti-CD19 CAR trial[33]

Patient*	Age (years)	Malignancy	Number of unique prior therapies	Number of CAR-expressing T cells infused per kg	Response (duration in months after T-cell infusion)
1a‡	47	Follicular lymphoma	4	0.3×10^7	PR (7)
1b‡	48	Follicular lymphoma	5	1.3×10^7	PR (33)
2	48	Follicular lymphoma	5	0.3×10^7	NE
3	61	Chronic lymphocytic leukaemia	3	1.1×10^7	CR (24)
4	55	Splenic, marginal zone lymphoma	3	1.1×10^7	PR (12)
5	54	Chronic lymphocytic leukaemia	4	0.3×10^7	SD (6)
6	57	Chronic lymphocytic leukaemia	7	1.7×10^7	PR (7)
7	61	Chronic lymphocytic leukaemia	4	2.8×10^7	CR (21+)
8	63	Follicular lymphoma	7	3.0×10^7	PR (11)§

*All eight patients were male. ‡Patient 1 was treated twice. §Not evaluable for malignancy response beyond 11 months because the patient developed laryngeal carcinoma. Abbreviations: CAR, chimeric antigen receptor; CR, complete remission; NE, not evaluable for malignancy response because the patient died with influenza pneumonia; PR, partial remission; SD, stable disease.

Kochenderfer JN, Rosenberg SA
Nature Review | Clinical Oncology 2013

Antitumor activity and long-term fate of chimeric antigen receptor-positive T-cells in patients with neuroblastoma

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- Anti-GD2 CAR in EBV CTLs
- 3 of 11 patients with active disease experienced CR
- Persistence of CAR CTLs beyond 6 weeks was associated with superior clinical outcome.

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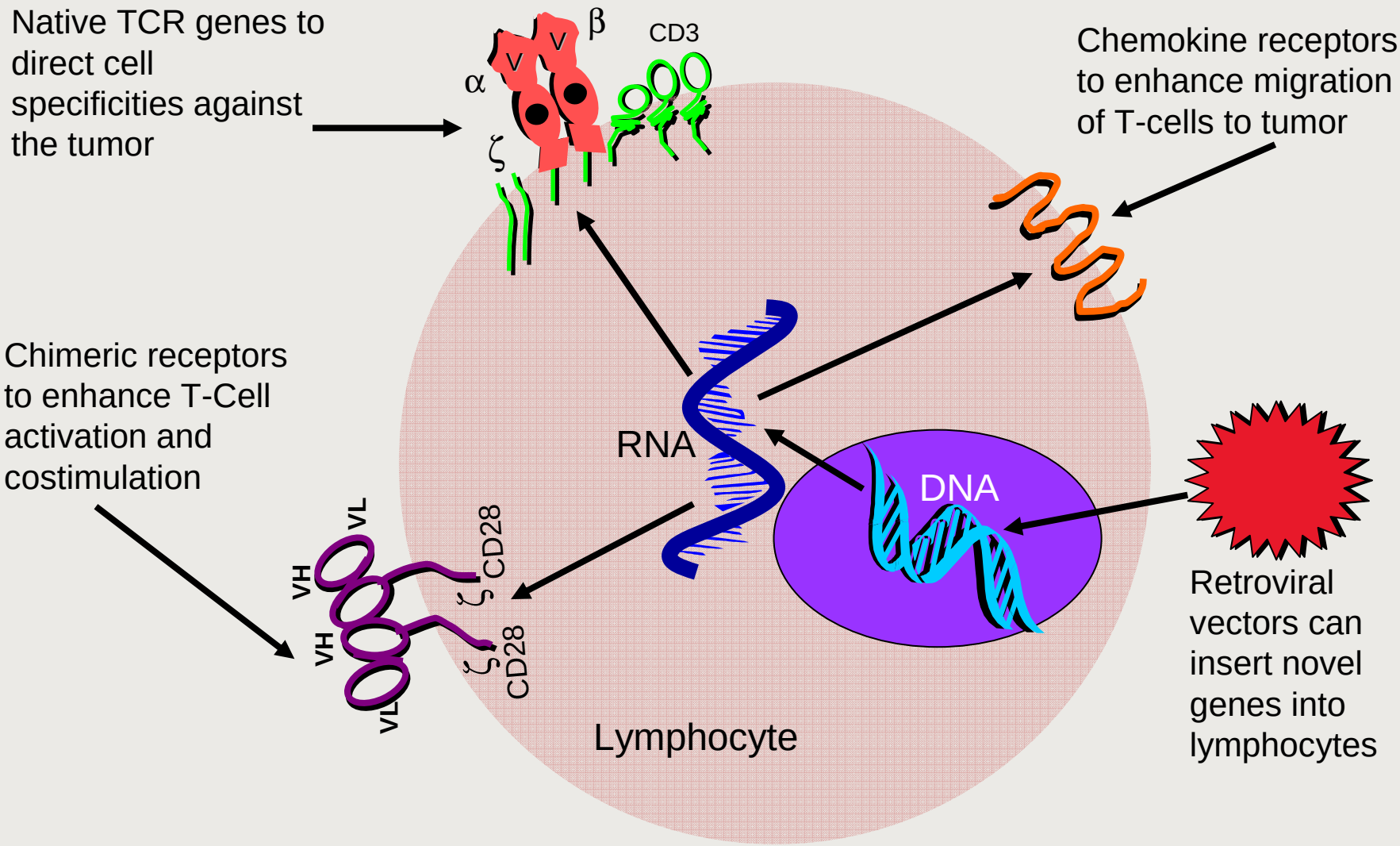
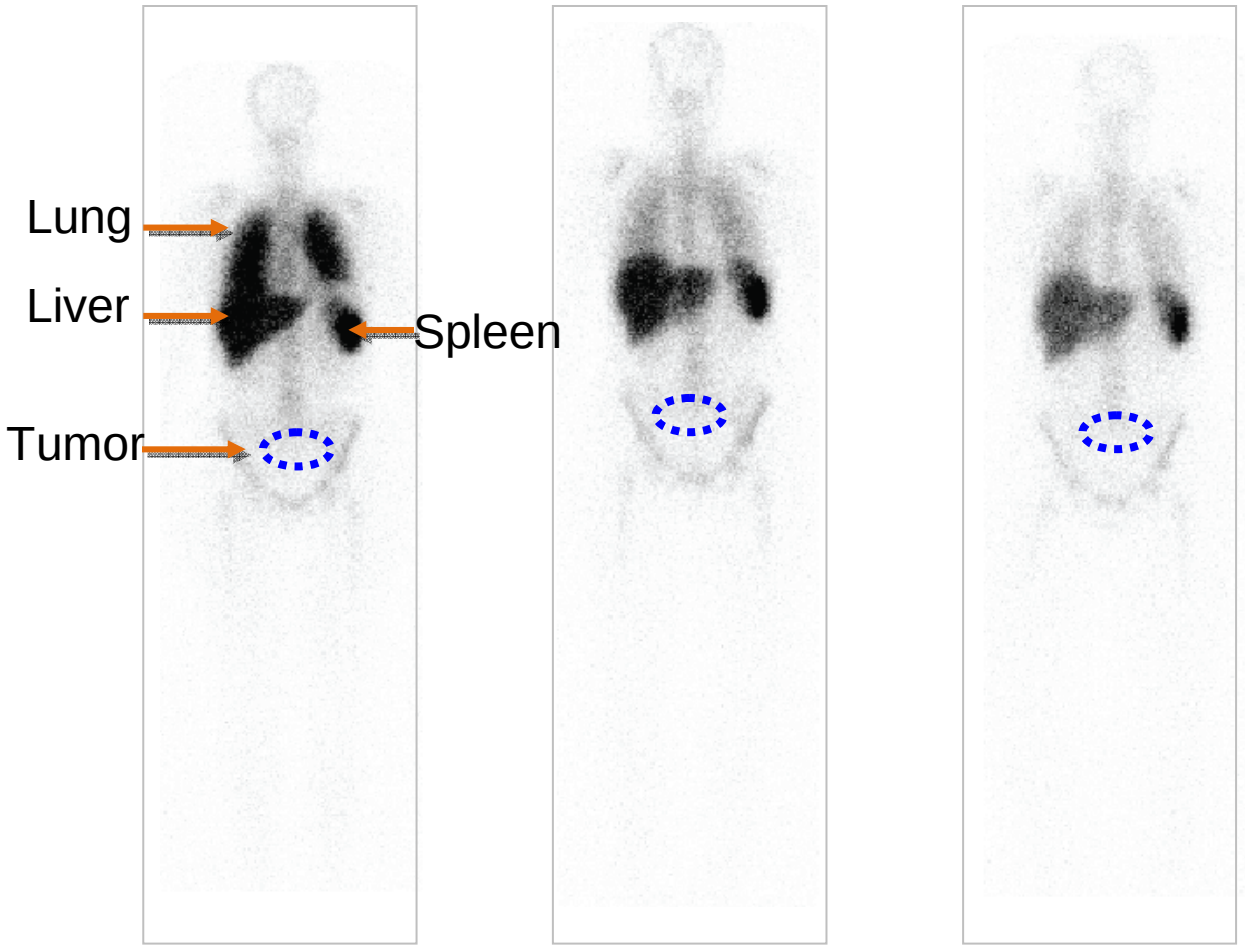
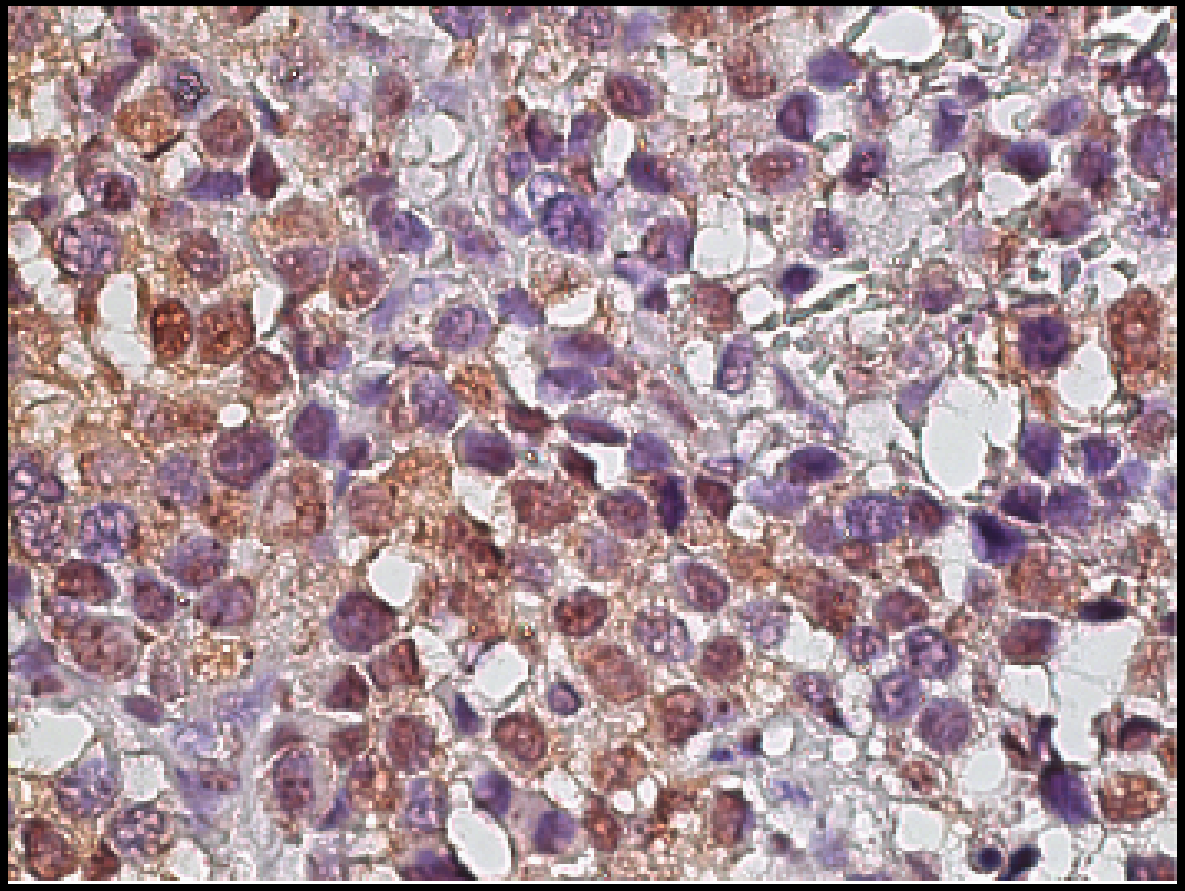
Insertion of Genes into Lymphocytes to Enhance Antitumor Properties



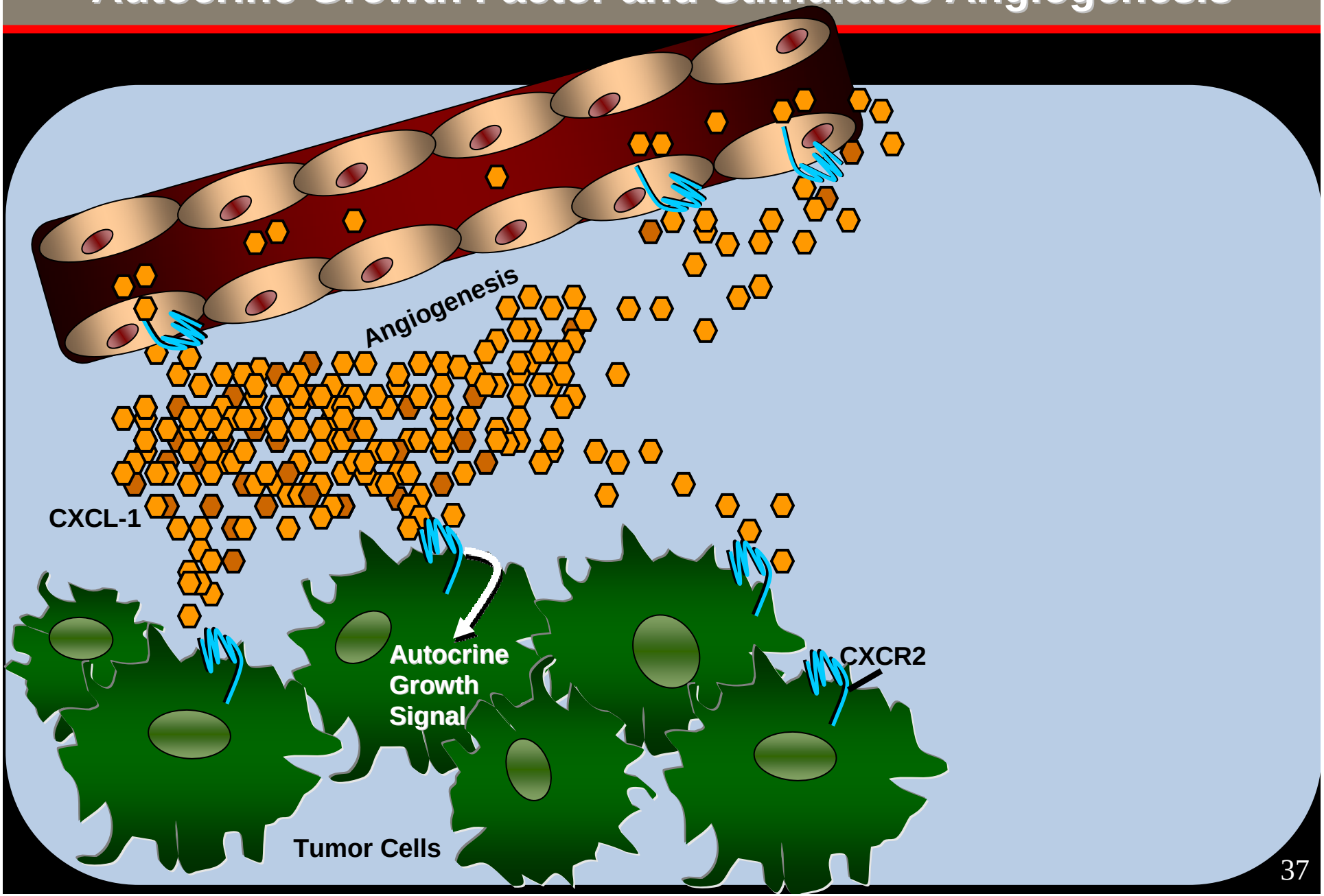
One of the Rate-limiting Steps in ACT is the Inefficient Migration of T-cells to Tumor



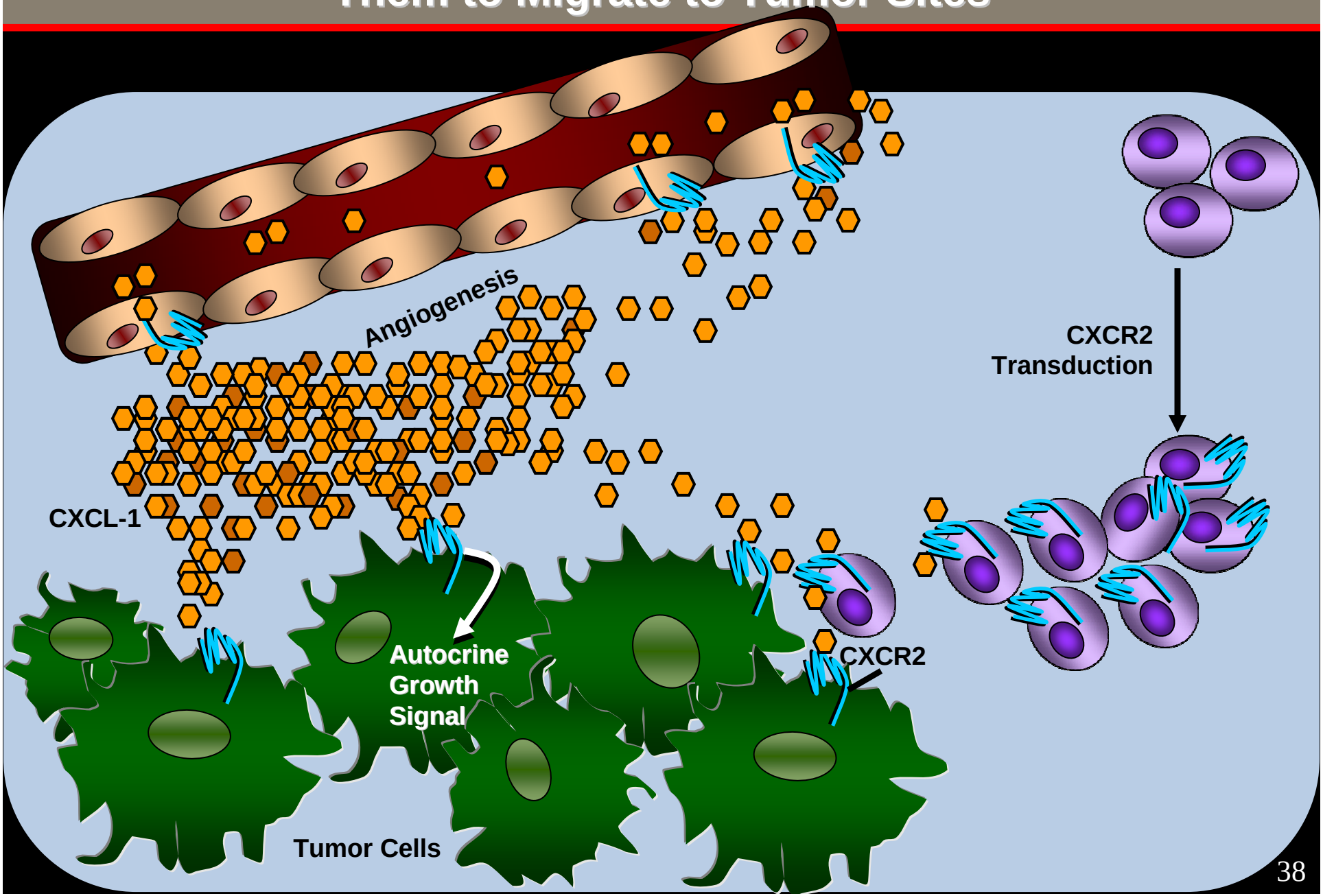
The Presence of CXCL1 in the Tumor Microenvironment



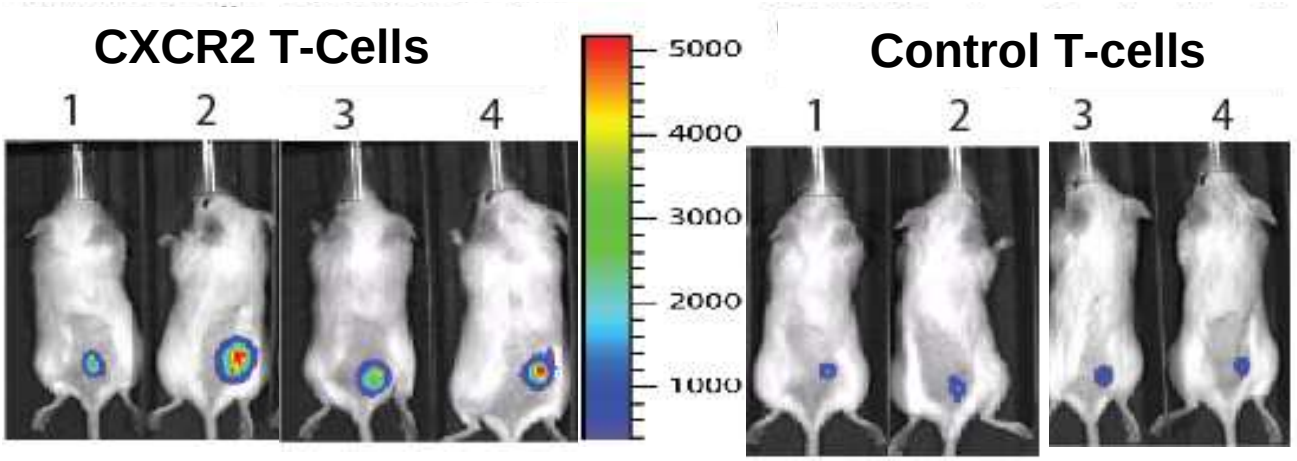
Melanoma Cells Produce CXCL1 which Serves as an Autocrine Growth Factor and Stimulates Angiogenesis

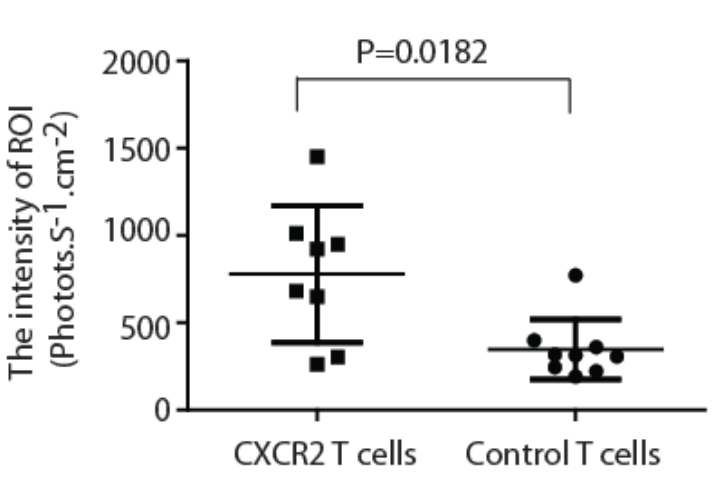


Transduction of T-cells with CXCR2 May Allow Them to Migrate to Tumor Sites

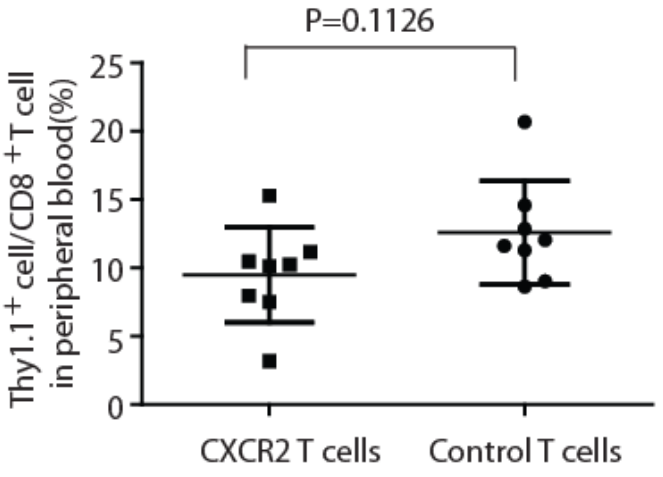


CXCR2-expressing T-cells Display Enhanced Accumulation in Tumor Site



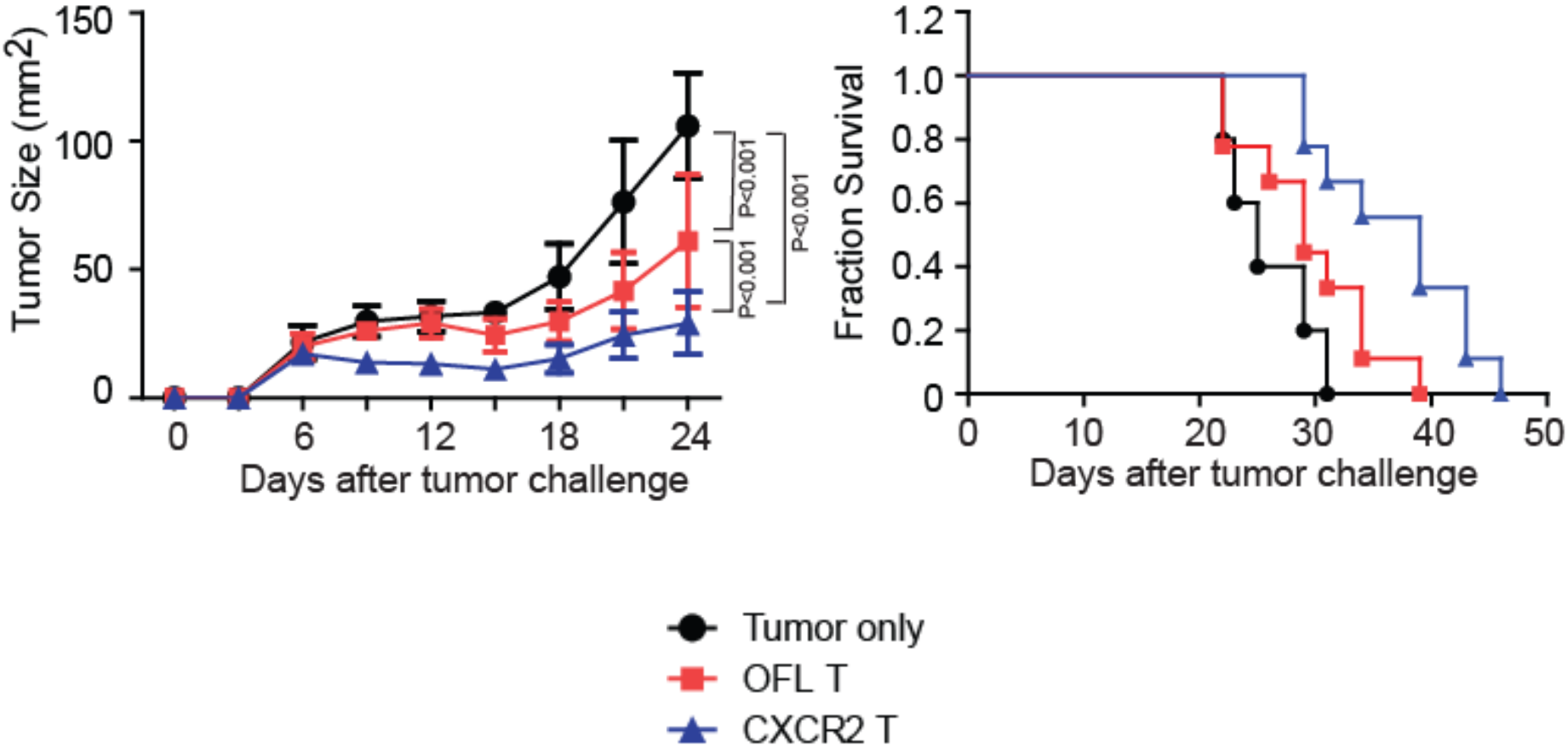


Tumor site

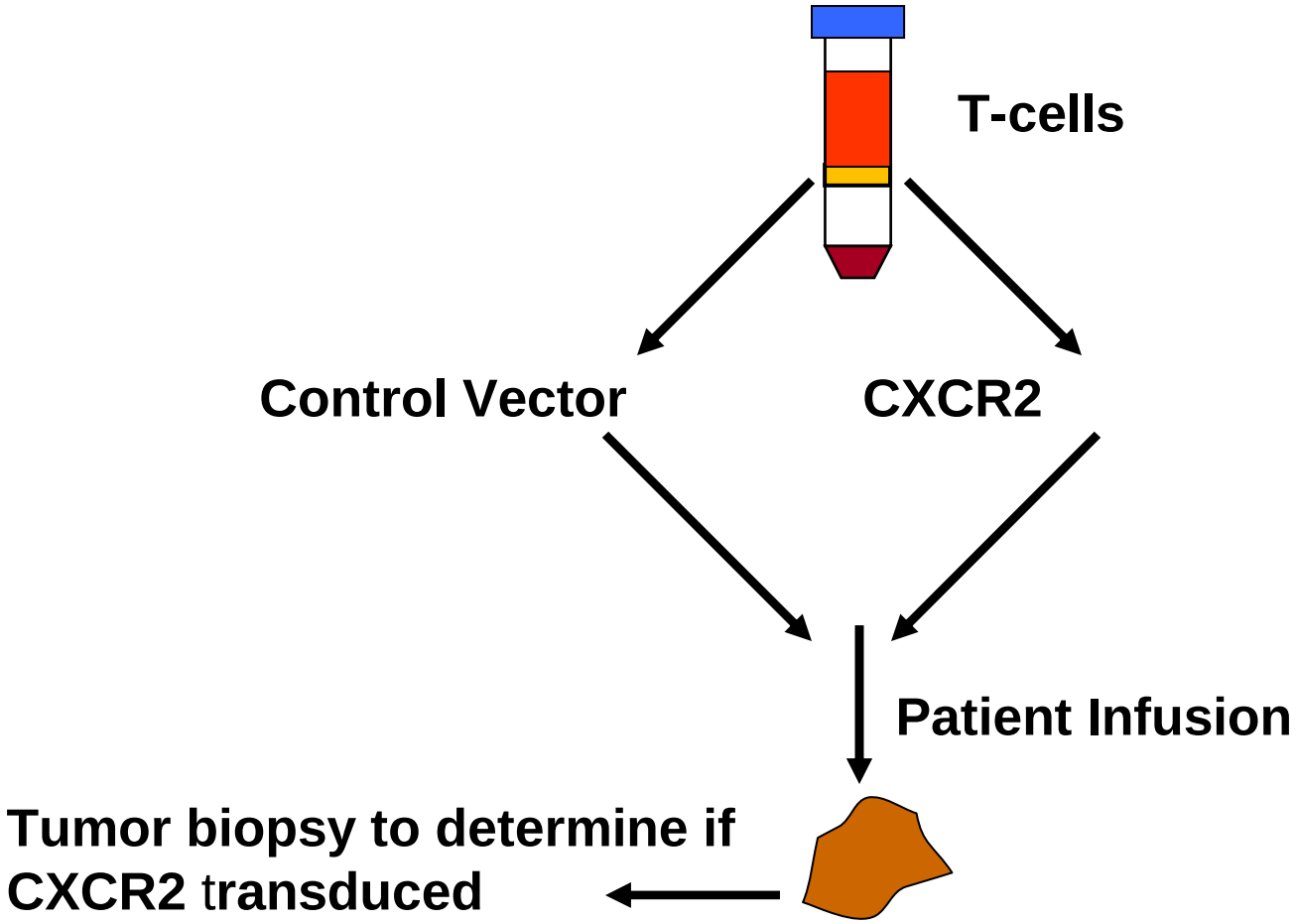


Peripheral blood

The Expression of CXCR2 in Pmel T-cells Delays Tumor Growth and Improves the Survival of Tumor-bearing Mice



Clinical Trial Plans



Tumor biopsy to determine if CXCR2 transduced T-cells preferentially migrate to the tumor

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