



Adoptive T-cell Transfer

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Professor and Chairman
Melanoma Medical Oncology

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THE UNIVERSITY OF TEXAS
MD Anderson
Cancer Center

Making Cancer History®

Disclosures

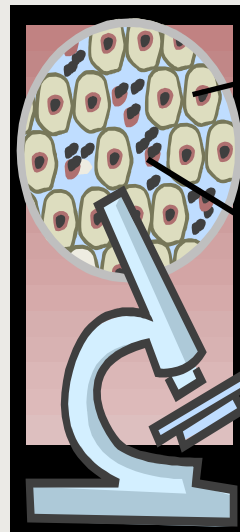
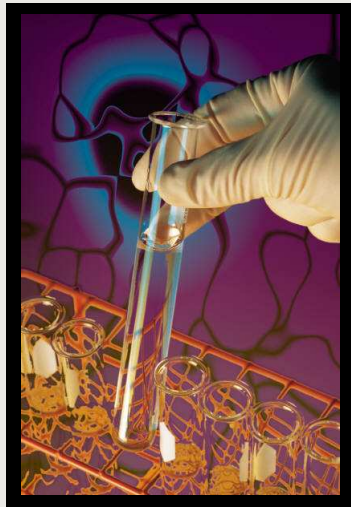
None

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

**Surgical
Removal of
Cancer Nodule**

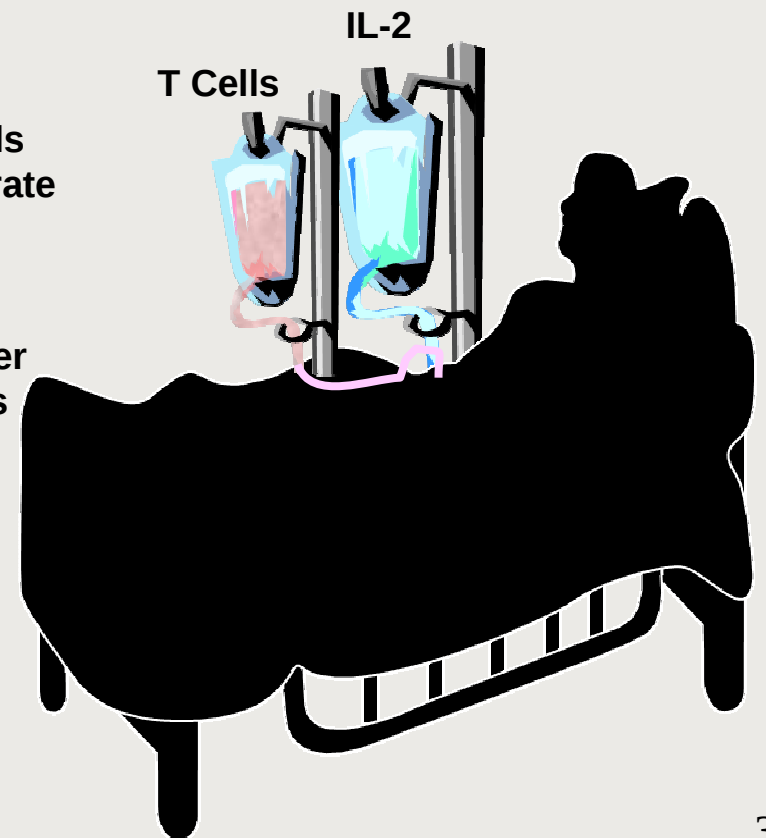


**Single Cell
Suspension
Incubated with IL-2**



**T Cells
Proliferate**

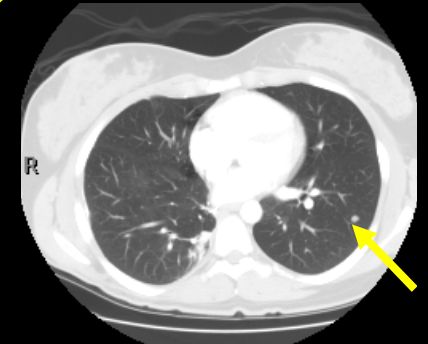
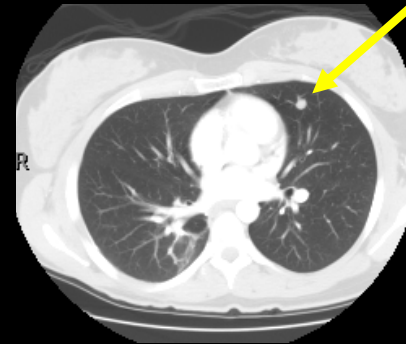
**Cancer
Cells
Die**



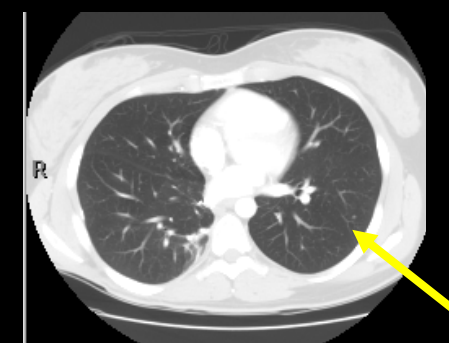
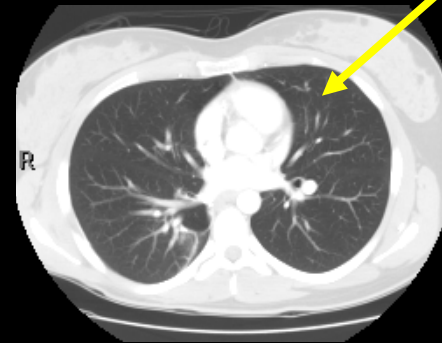
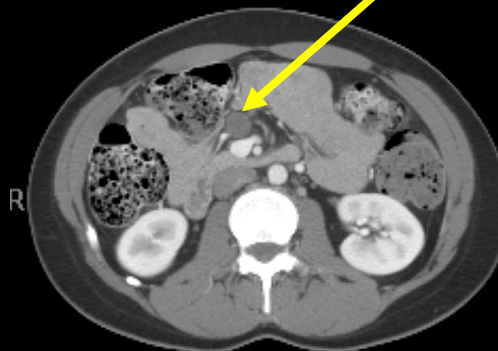
Clinical Response following Lymphodepletion + T-lymphocyte Infusion



Before TIL Infusion

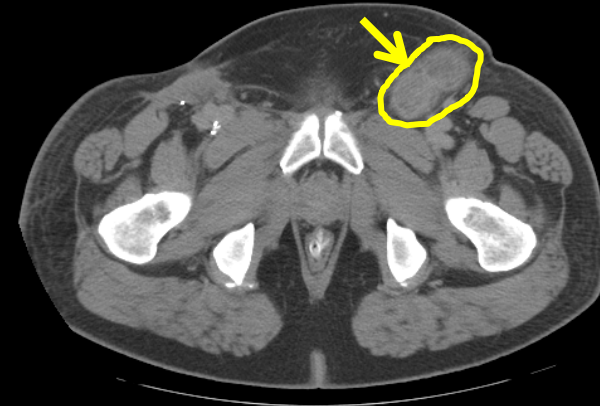
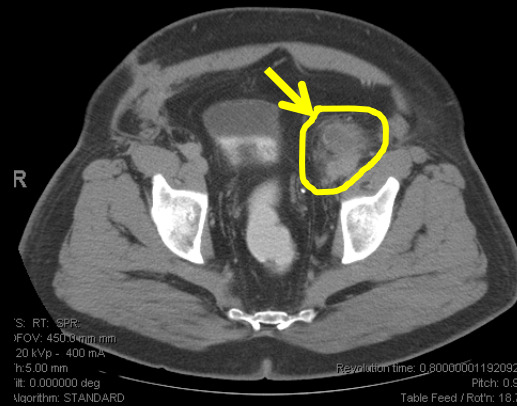


After TIL Infusion

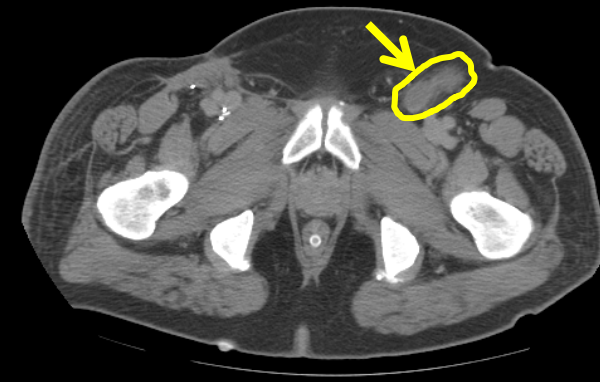
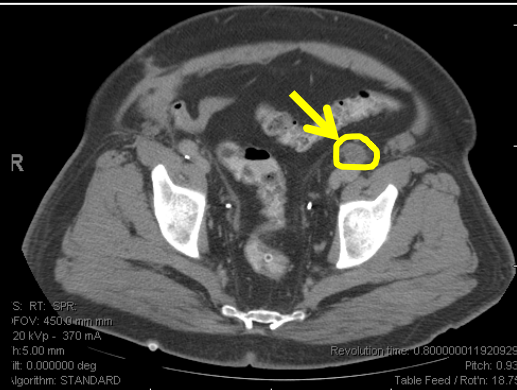


Response to TIL Therapy

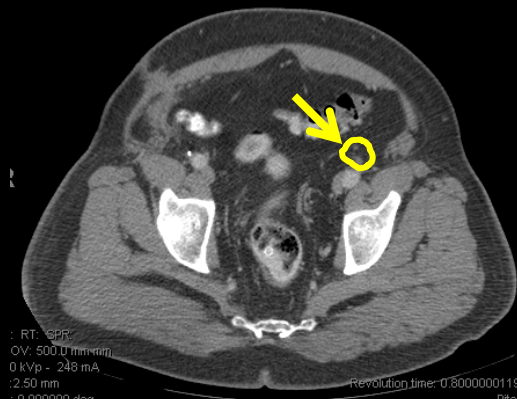
pre-treatment



4 weeks
post-treatment



18 months
post-treatment
durable
response
noted



Clinical Response Data from MDACC TIL Clinical Trial (as of September 2013)

Best overall response:

Number of patients	CR*	PR*	Total
71	3 (4%)	29(41%)	32 (45%)

*Some patients are still undergoing clinical response

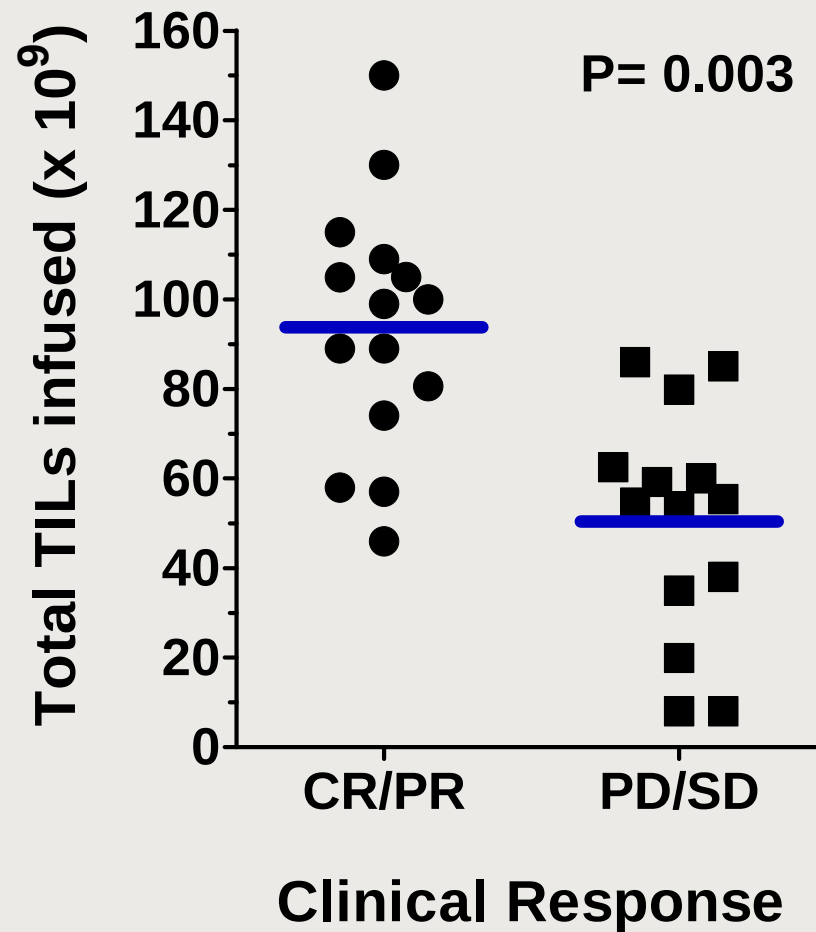
Progression-free and Overall Survival (as of September 2013)

Best Overall Response (n=71)

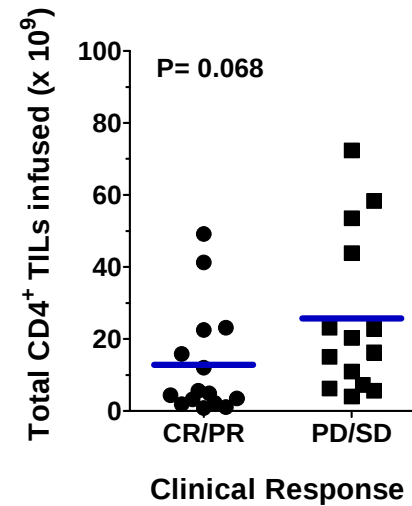
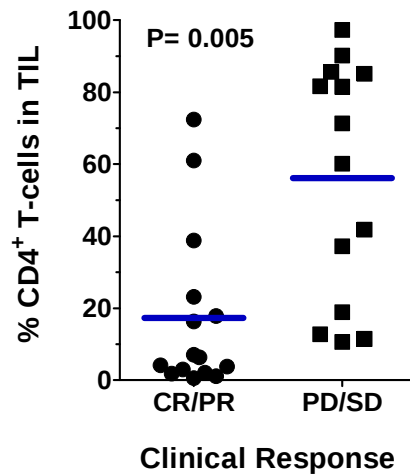
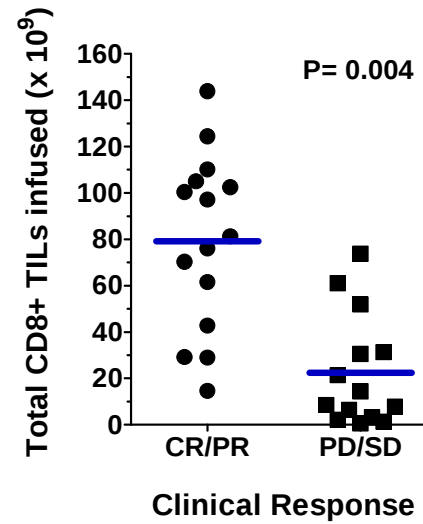
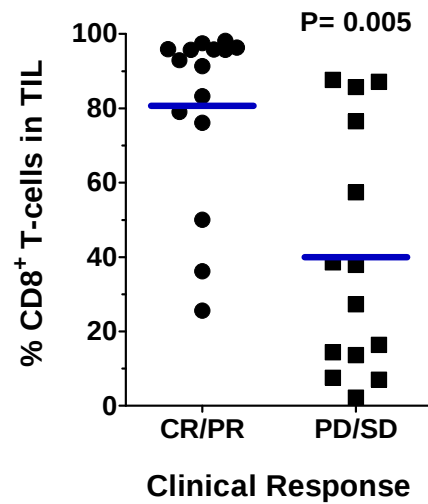
	irRC Responders (45%)		irRC Non-Responders (55%)	
	CR	PR	SD	PD
Number of patients	3	29	22	11
Progression-free survival (months)	42+, 34+ 9+	58+, 43, 58+, 15, 55+, 55+, 53+, 46+, 48+, 48+, 45+, 39+, 37+, 39+, 55+, 38+, 17, 25+, 30+, 26+, 23+, 7, 21+, 16+, 10+, 7, 11, 7+, 3	3, 3, 4, 4, 4, 7+, 7+, 6, 3, 5+, 6+, 3, 3+, 3+, 5, 3, 10+, 7+, 6+, 5+, 4+, 4+	
Overall survival (months)	42+, 34+ 9+	58+, 43+, 58+, 15, 55+, 55+, 53+, 46+, 48+, 48+, 45+, 39+, 37+, 39+, 55+, 38+, 17+, 25+, 30+, 26+, 17, 23+, 7, 21+, 16+, 10+, 10+, 7, 11	4, 12, 25, 6, 6, 8, 17+, 35+, 14, 5, 25+, 28+, 4, 17+, 21+, 7, 4, 10+, 6+, 5+, 4+, 4+	8, 18, 4, 5, 6, 21, 2, 14, 24+, 18+, 3
NR 4				
INE 2				

Updated Stats --- original data was published in 2012
Radvanyi,...Hwu Clin Cancer Res 2012

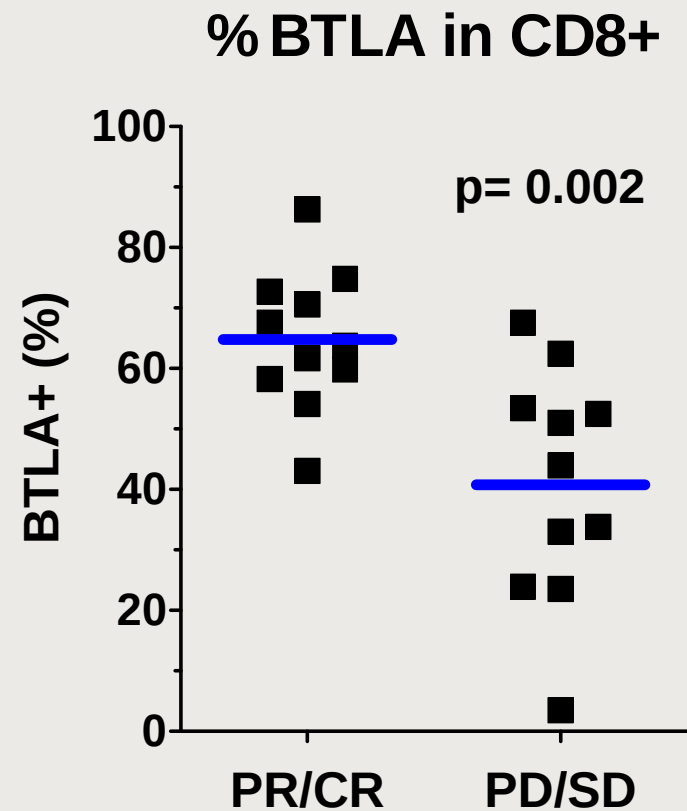
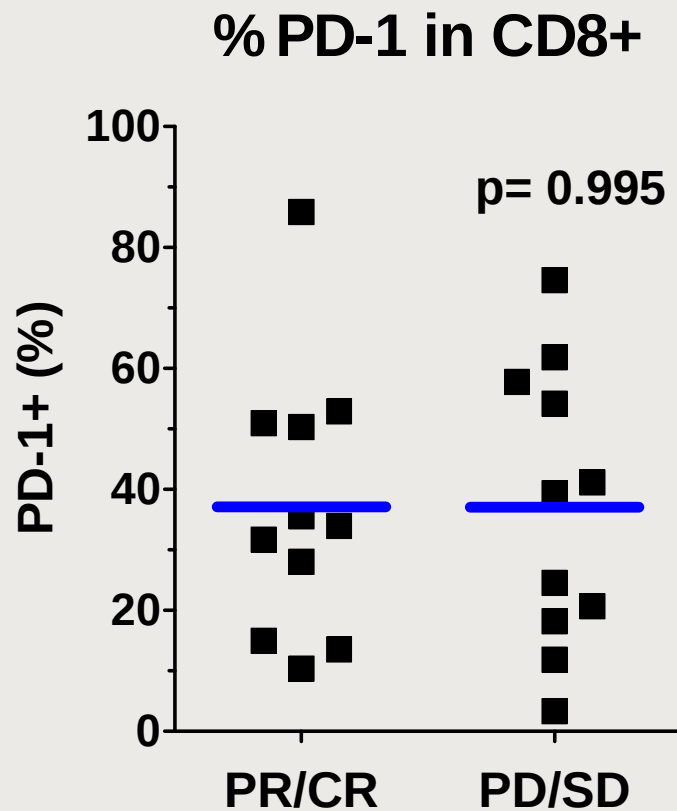
Numbers of Total TIL Infused and Type of Clinical Response



CD8+ TIL are Critical

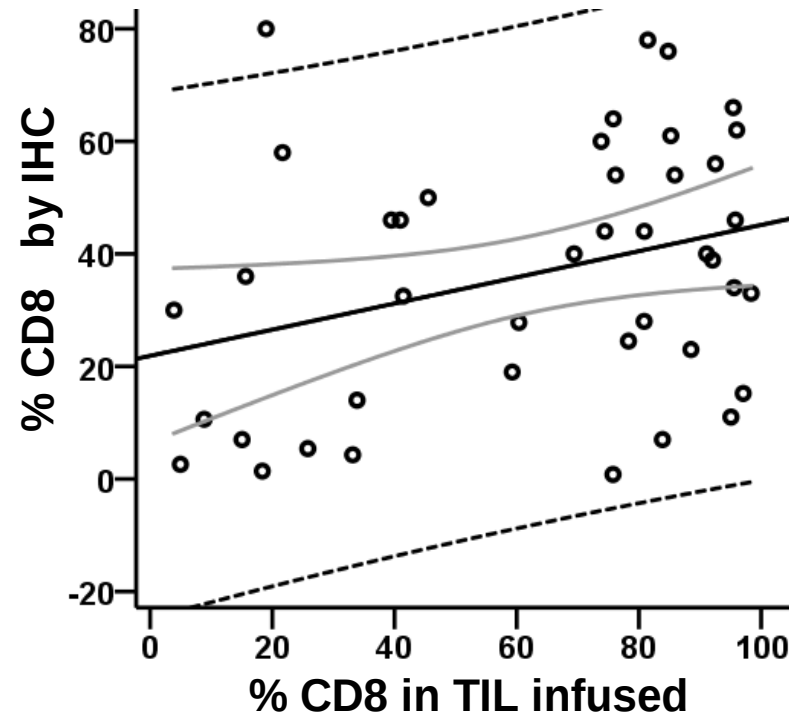
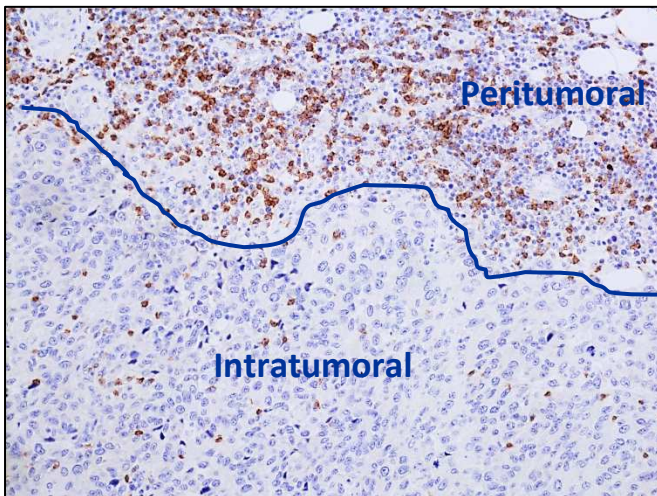
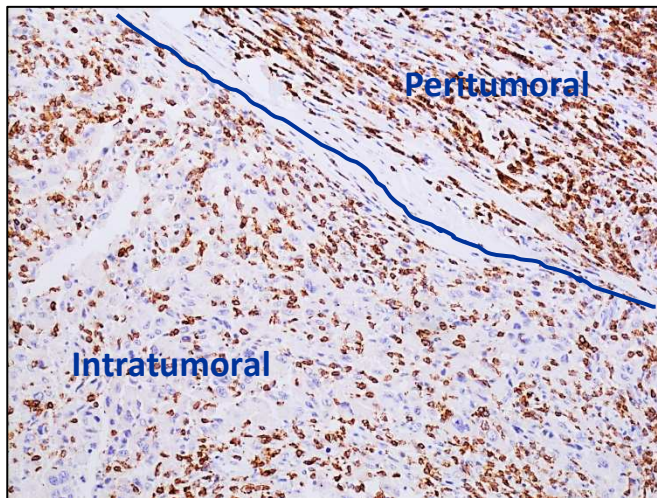


Higher Proportion of CD8+ TILs Co-expressing BTLA in Responders

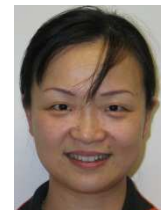


Clin Cancer Res 18: 6758-6770, 2012
Radvanyi ... Hwu

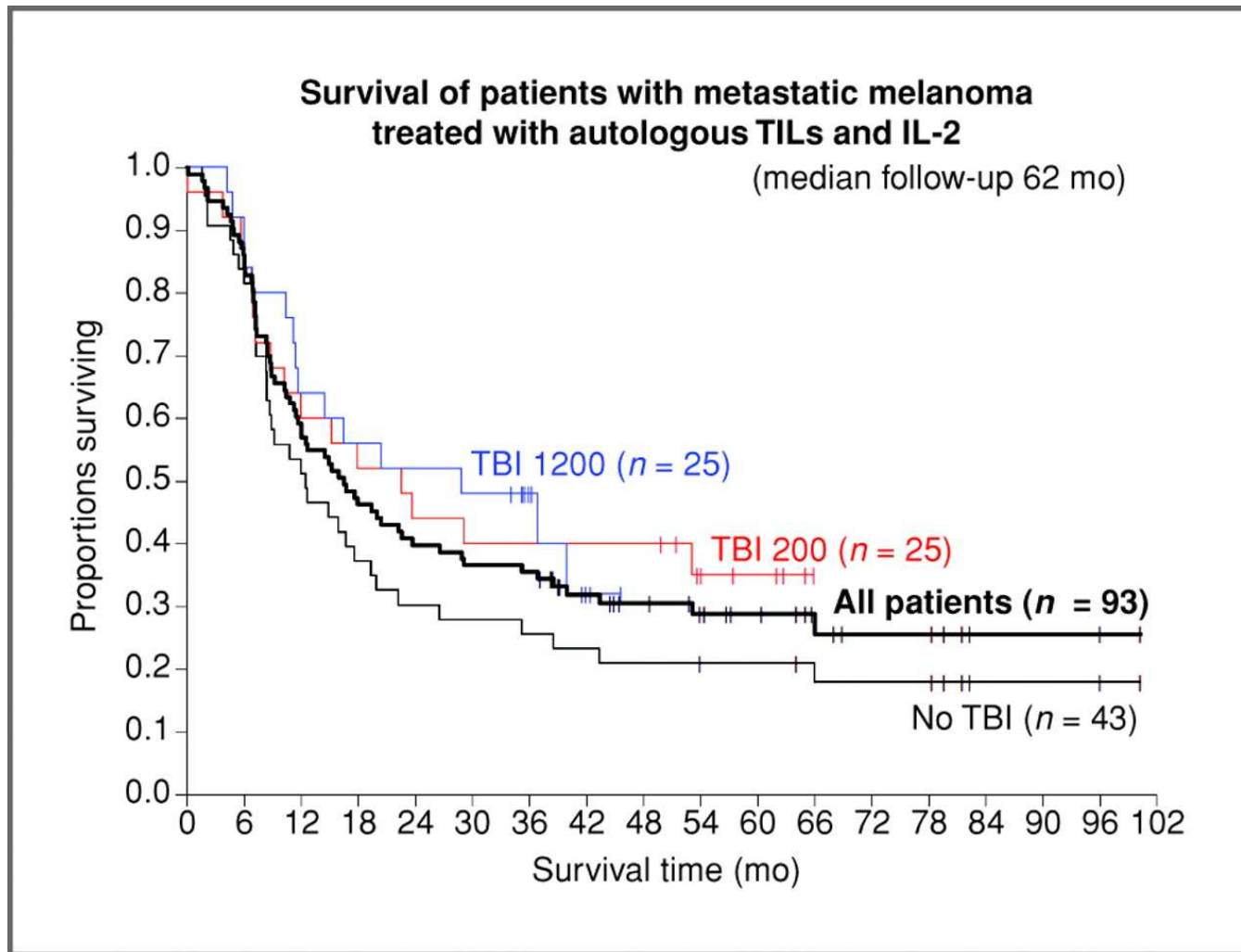
CD8 by IHC in Original Metastases is Associated with CD8 % in Expanded TIL



$P = 0.046, r^2 = 0.310$



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



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

Cell Transfer Therapy

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

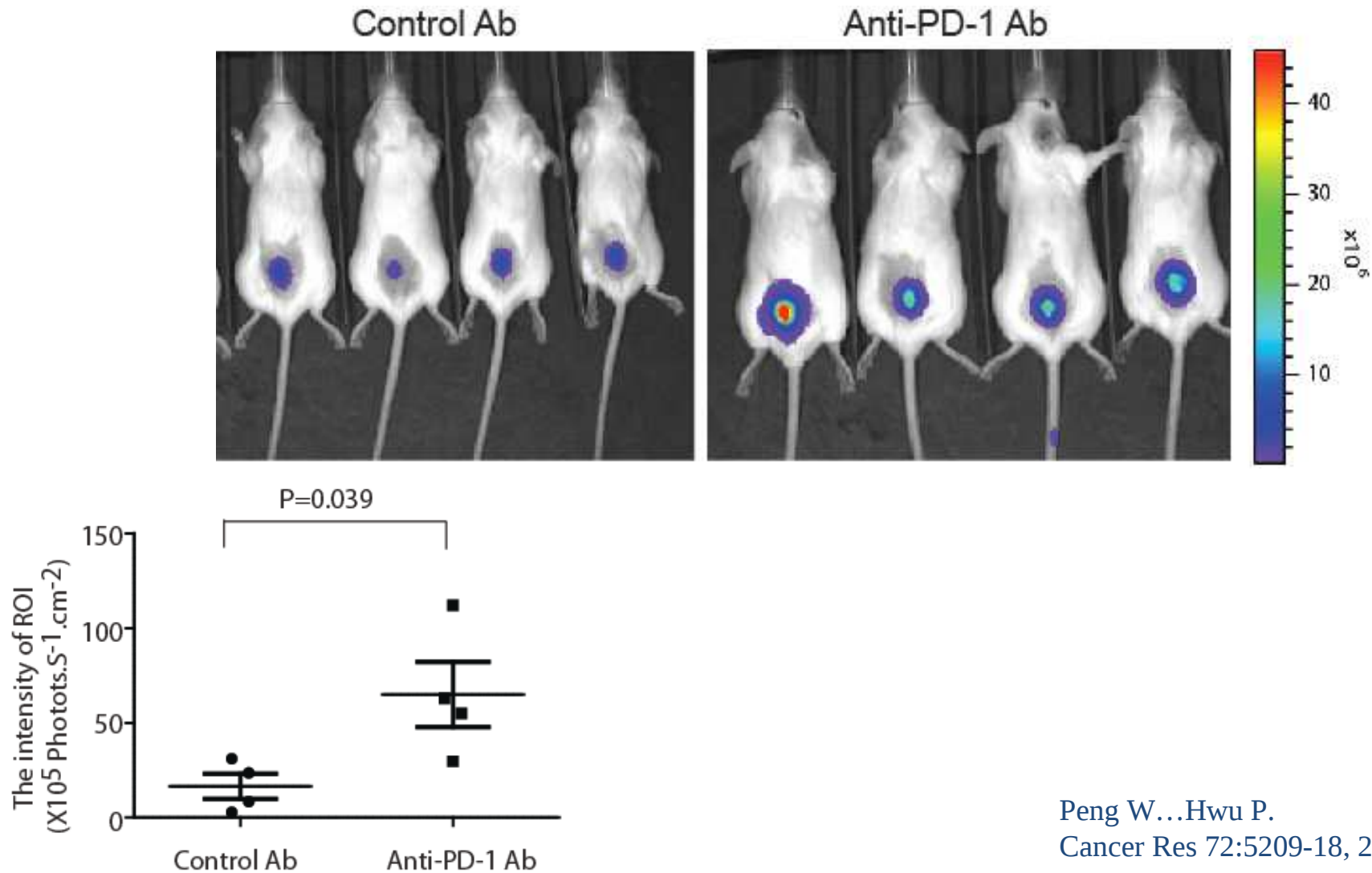
‡ Patients with HLA-A*0201.

P = 0.53 Besser et al, CCR May 2010

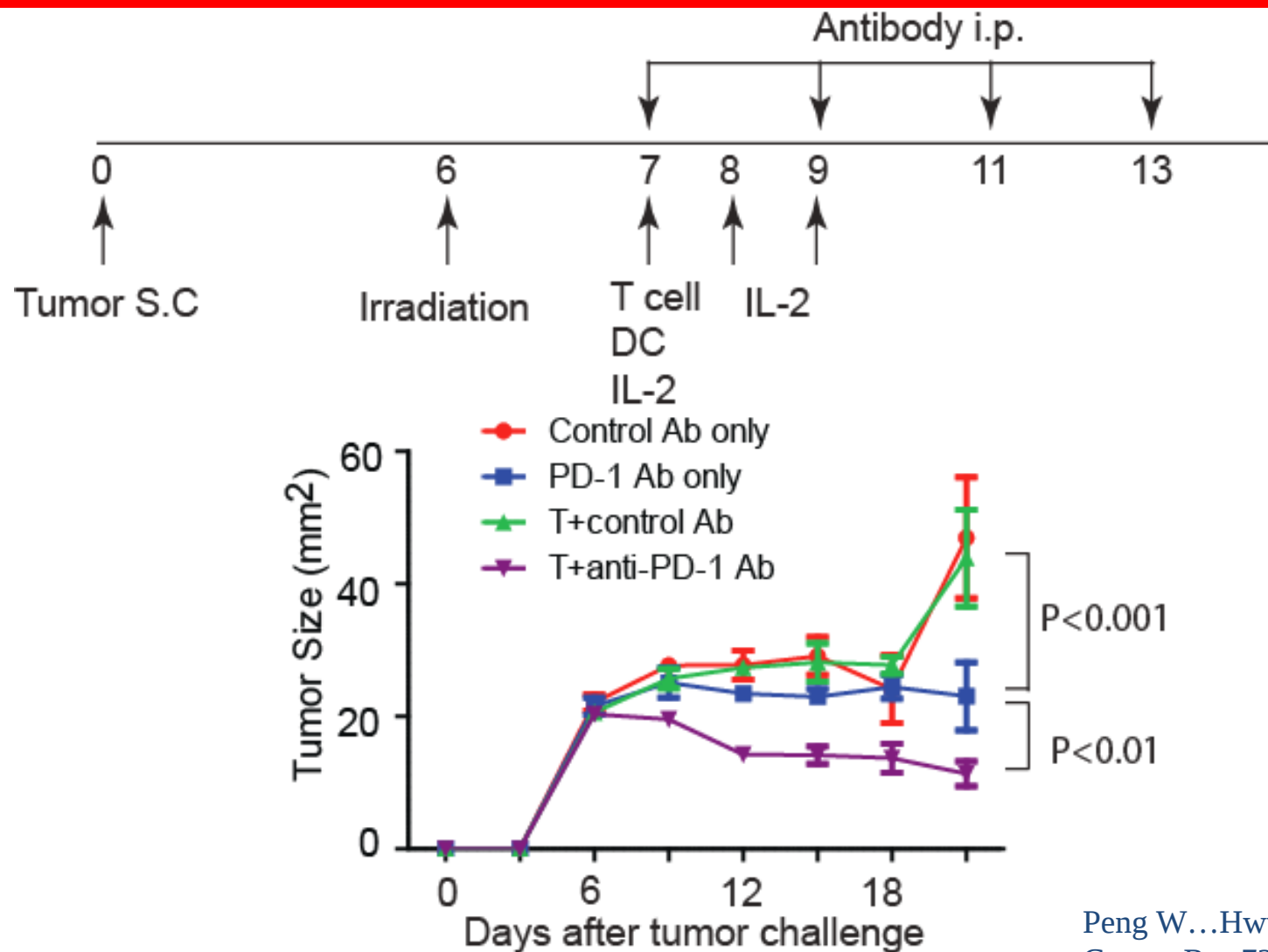
Question?

**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



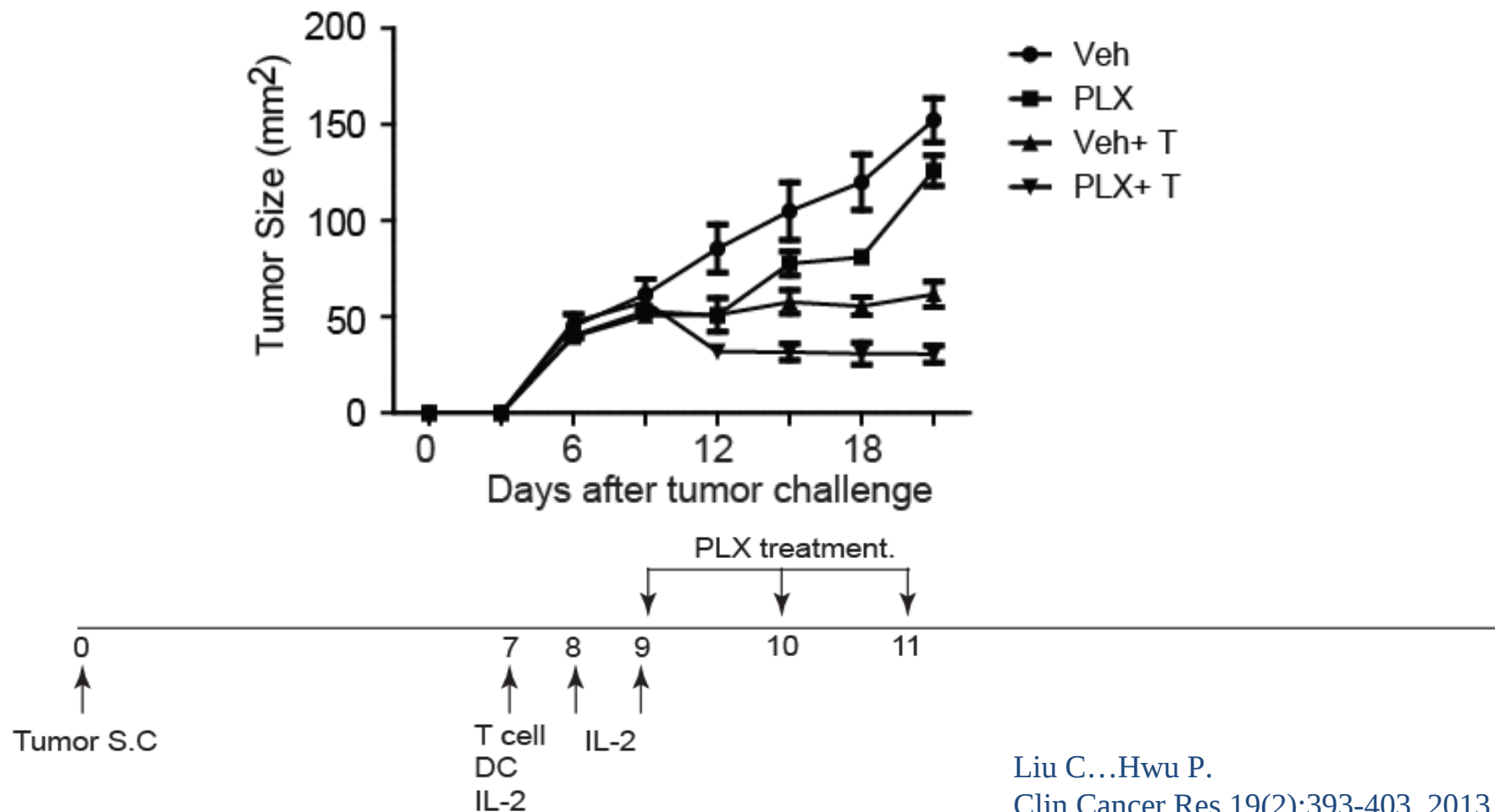
Delayed Tumor Progression in Tumor-bearing Mice Receiving anti-PD-1 and ACT Treatment



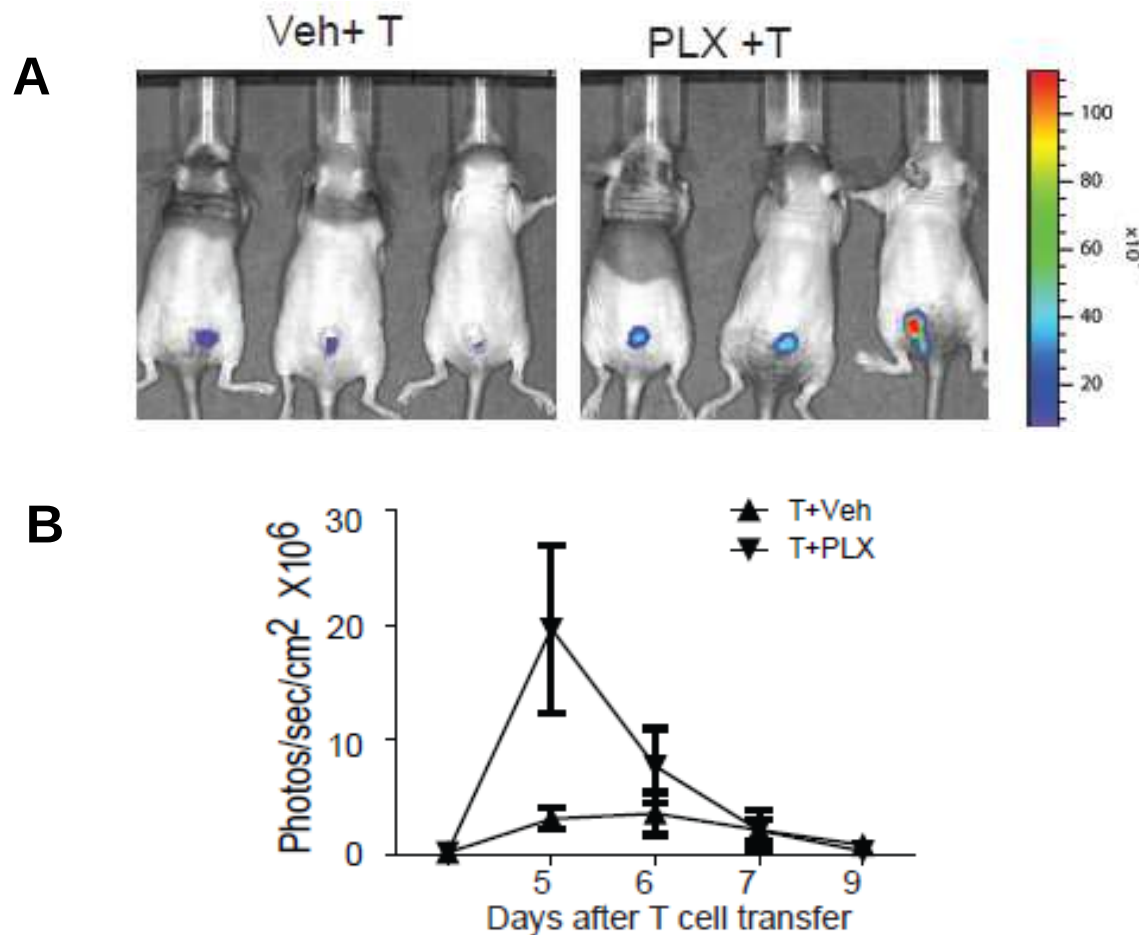
Question?

**Does BRAF inhibition enhance
T-cell therapy?**

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

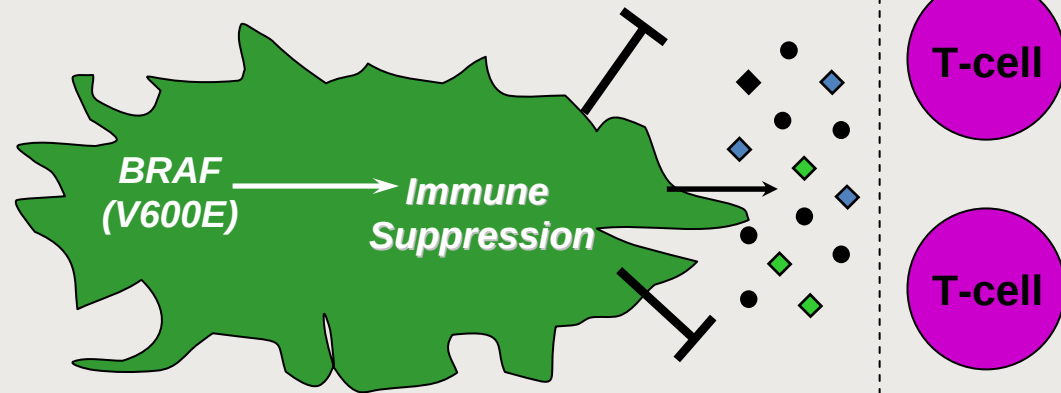


Administration of PLX4720 Increases Tumor Infiltration of Adoptively Transferred pmel-1 T-cells *in vivo*

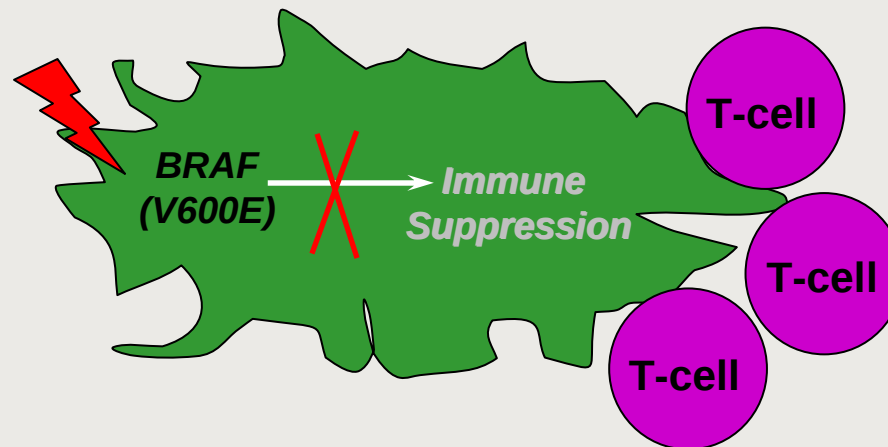


Combining BRAF(V600E) Inhibition and Immunotherapy

Immunotherapy
Alone

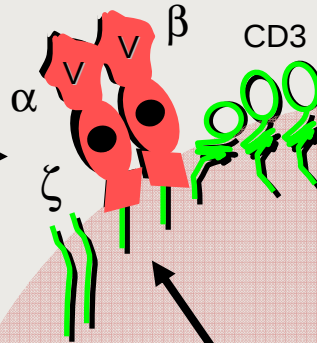


Immunotherapy
Plus BRAF(V600E)
Inhibition

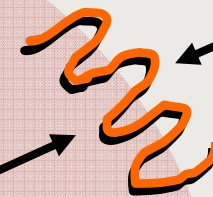


Insertion of Genes into Lymphocytes to Enhance Antitumor Properties

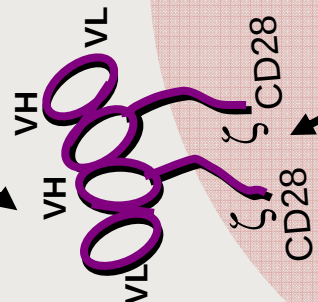
Native TCR genes to direct cell specificities against the tumor



Chemokine receptors to enhance migration of T-cells to tumor



Chimeric receptors to enhance T-Cell activation and costimulation

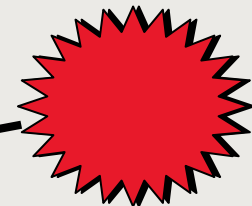


RNA

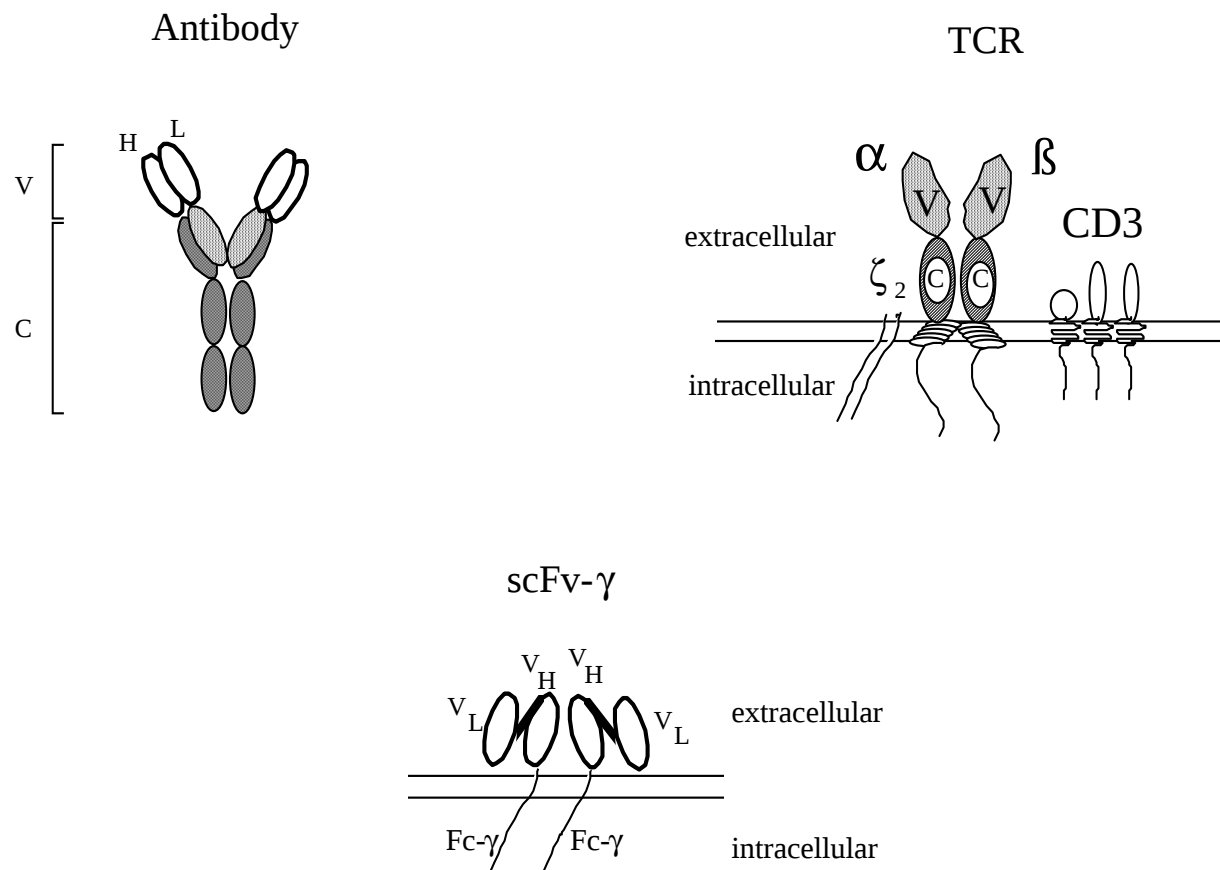
Lymphocyte

DNA

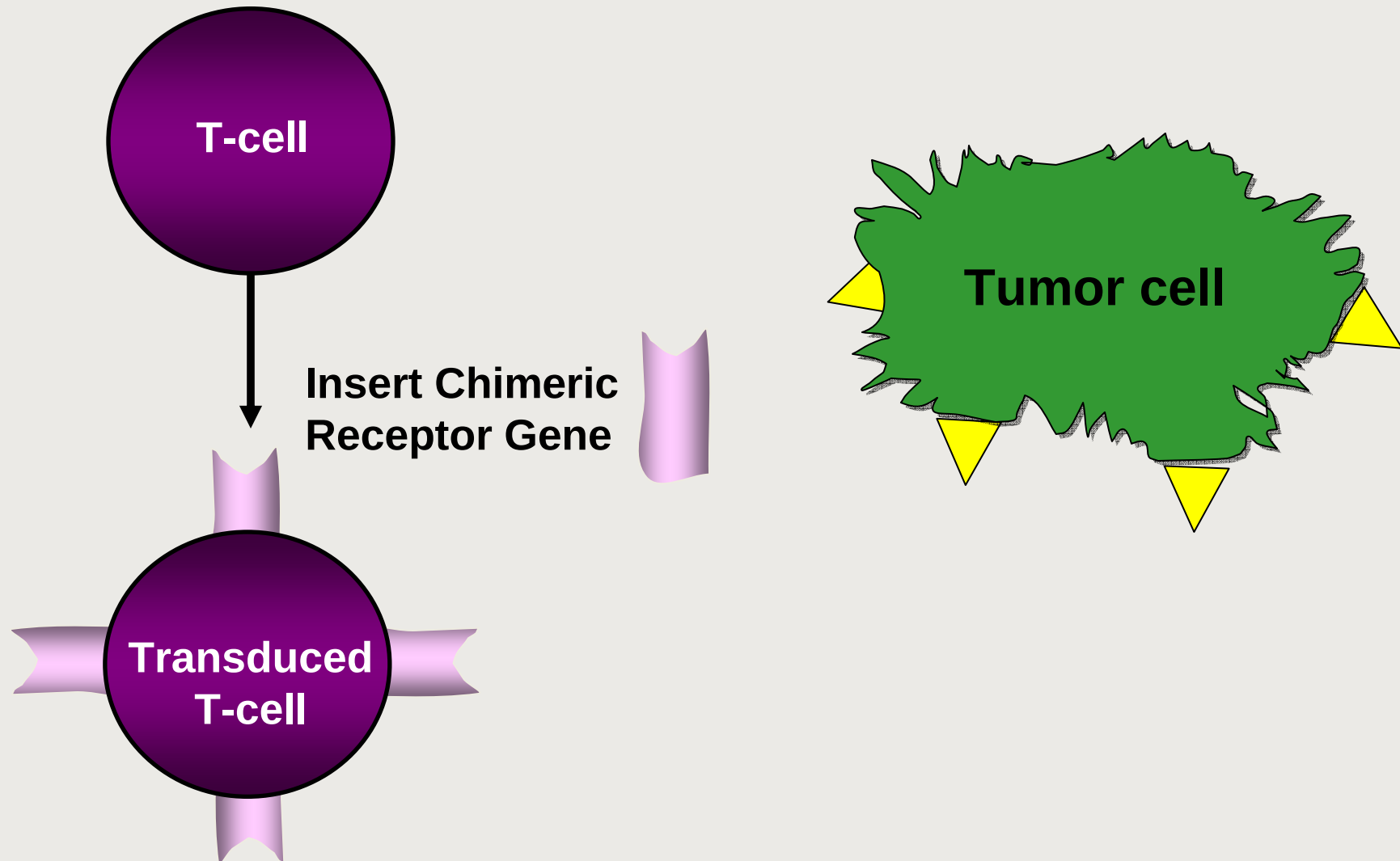
Retroviral vectors can insert novel genes into lymphocytes



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



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



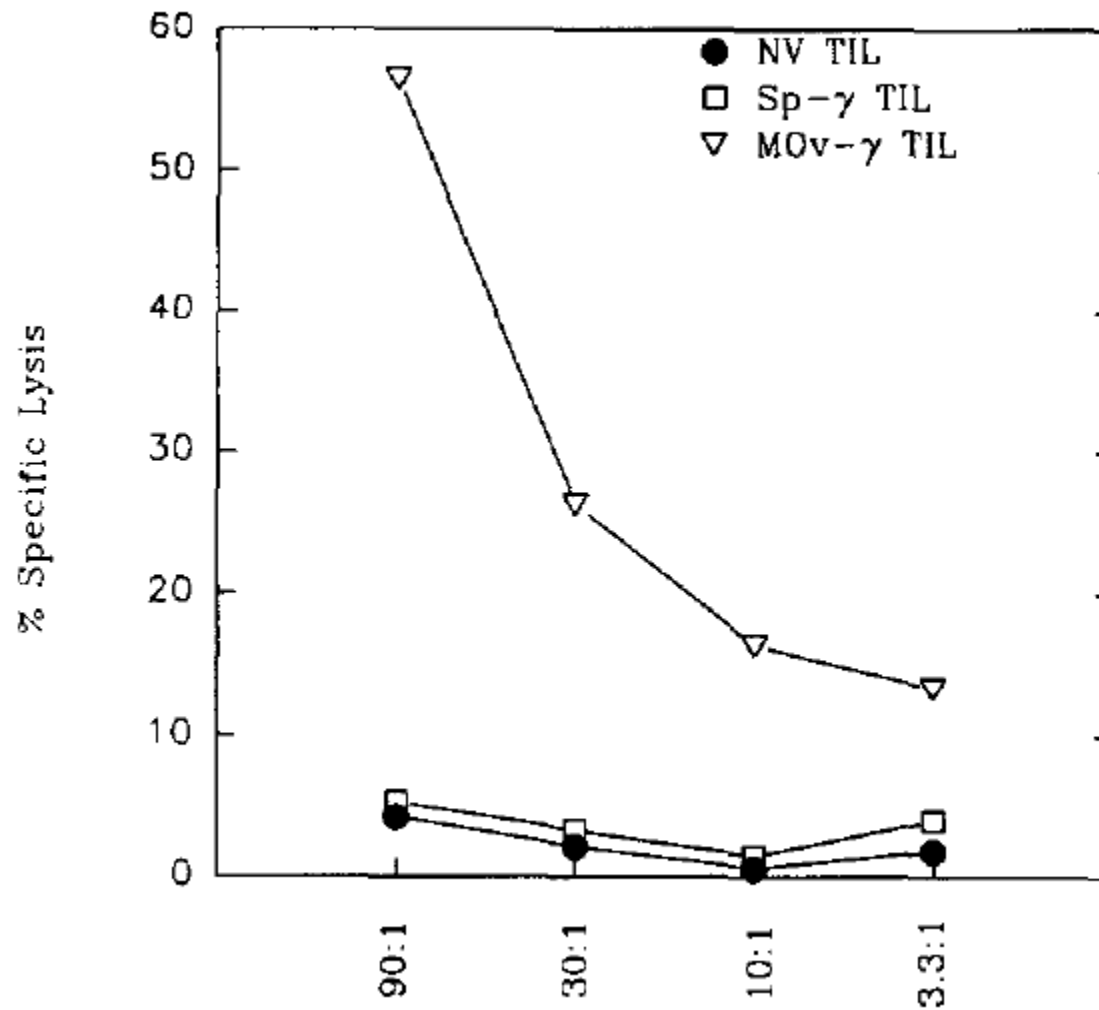
Brief Definitive Report

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



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

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.

Tumor Growth in *MOv γ* -Reconstituted Mice after T-cell Depletion

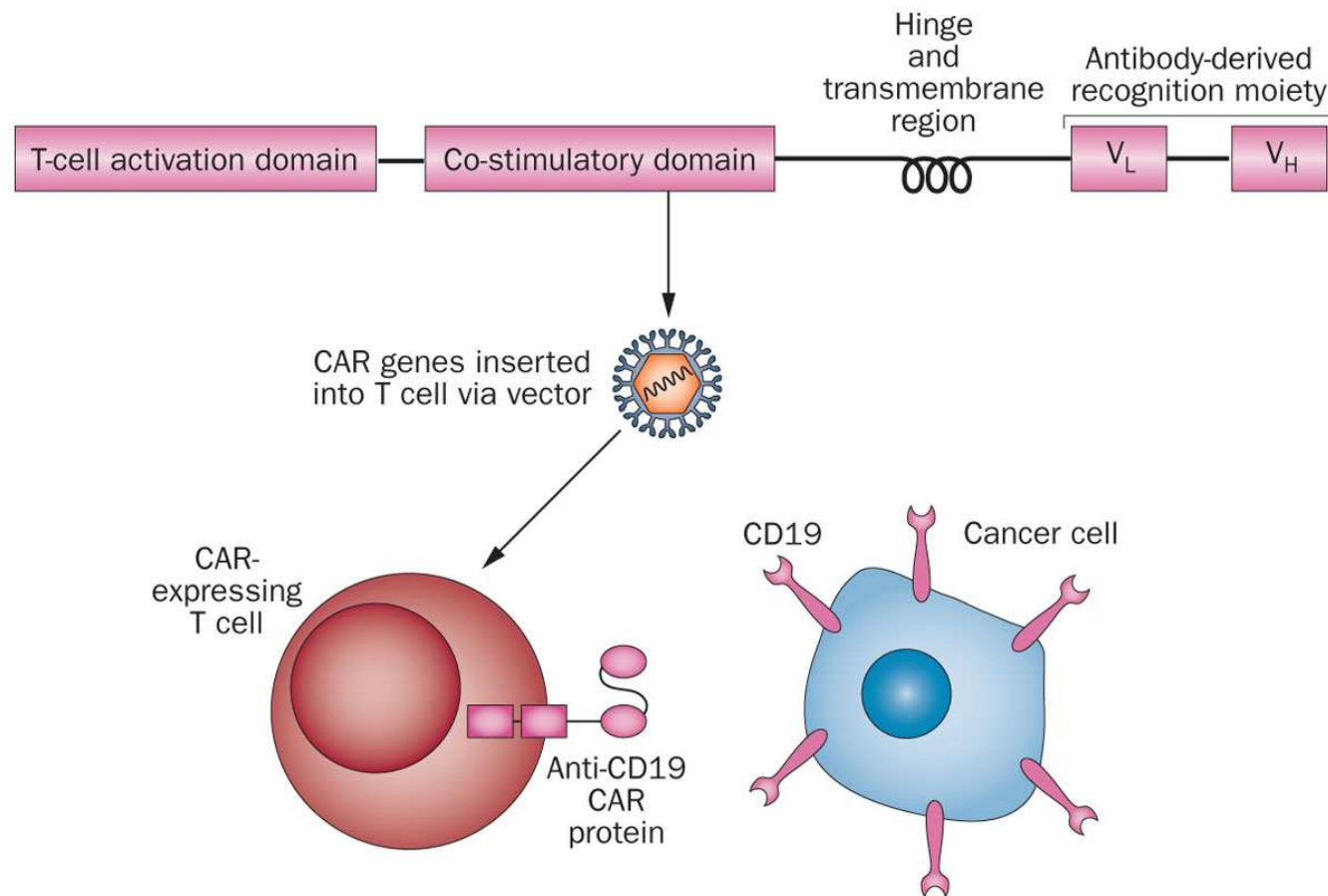


Chimeric Antigen Receptors



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

Chimeric Antigen Receptor Domains



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?	<i>n</i>
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.

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 trial³³

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.

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

Chrystal U. Louis,^{1,3} Barabara Savoldo,^{1,3} Gianpietro Dotti,^{1,4} Martin Pule,¹ Eric Yvon,¹ G. Doug Myers,¹ Claudia Rossig,¹ Heidi V. Russell,^{2,3} Oumar Diouf,^{1,3} Enli Liu,¹ Meng-Fen Wu,⁵ Adiran P. Gee,¹ Zhuhong Mei,¹ Cliona M. Rooney,^{1,3,6} Helen E. Heslop,^{1,4} and Malcolm K. Brenner,^{1,4}

¹Center for Cell and Gene Therapy, Baylor College of Medicine, Texas Children's Hospital, The Methodist Hospital Houston, TX; ²Texas Children's Cancer Center, Baylor College of Medicine, Houston, TX Departments of ³Pediatrics, and ⁴Medicine, Baylor College of Medicine, Houston, TX; ⁵Biostatistics Shared Resource Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, TX; and ⁶Department of Pathology and Immunology, Baylor College of Medicine, Houston TX

- 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.

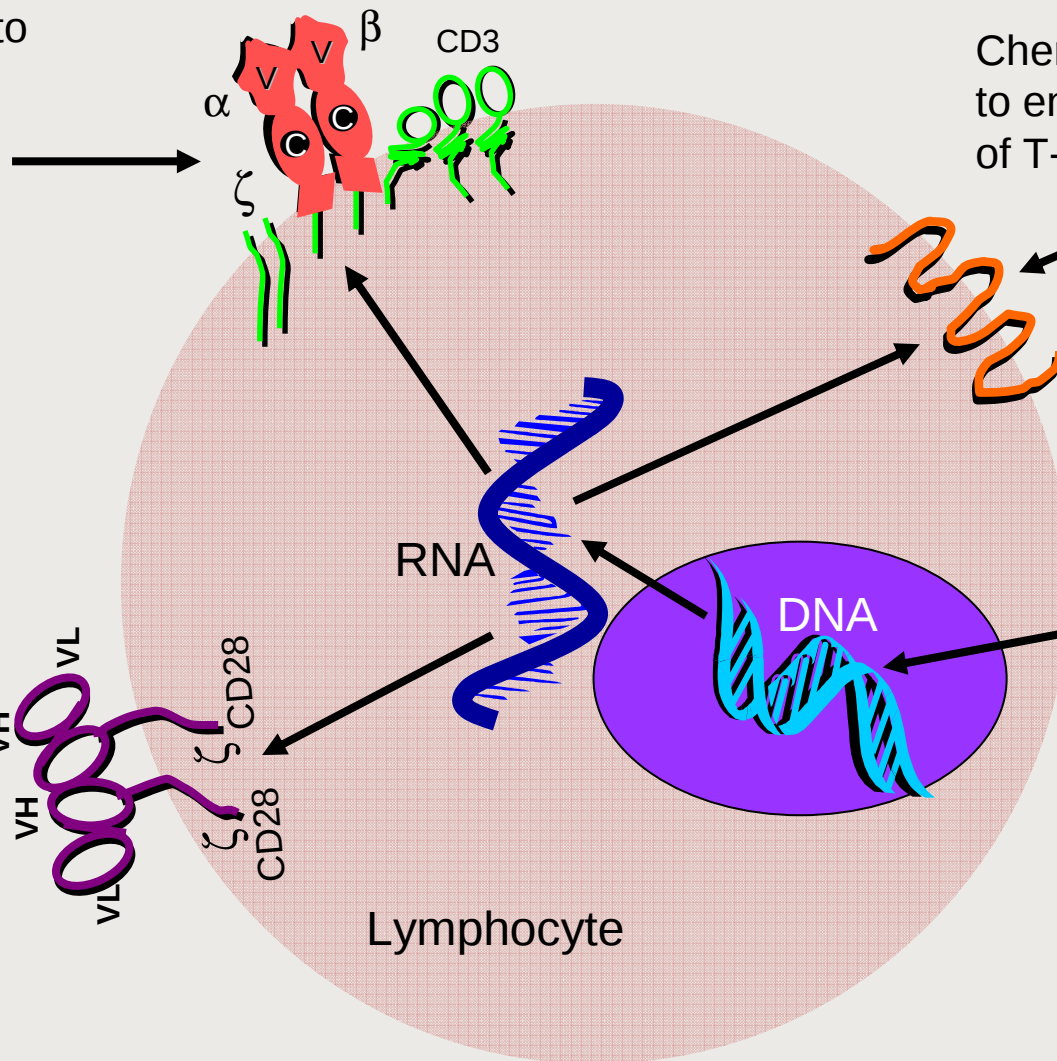
Insertion of Genes into Lymphocytes to Enhance Antitumor Properties

Native TCR genes to direct cell specificities against the tumor

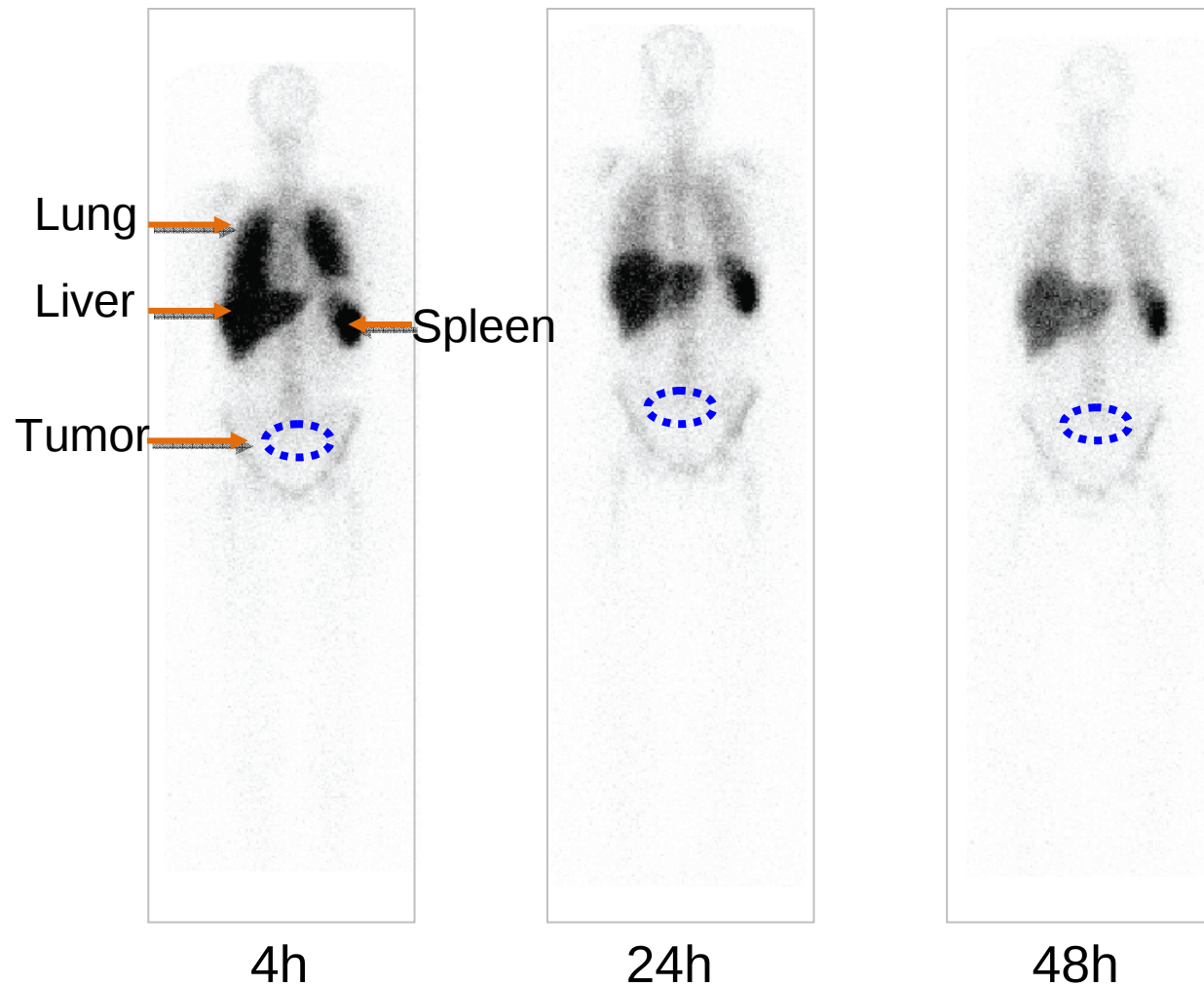
Chimeric receptors to enhance T-Cell activation and costimulation

Chemokine receptors to enhance migration of T-cells to tumor

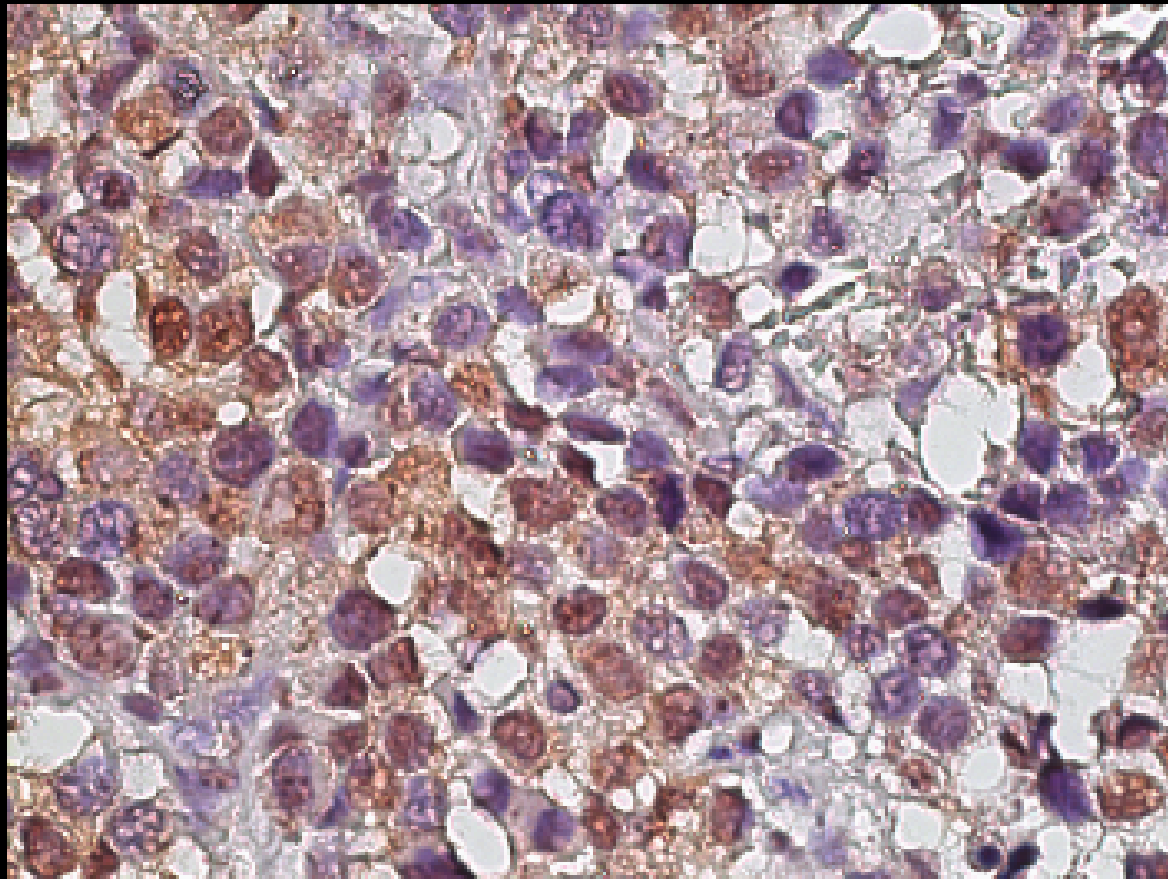
Retroviral vectors can insert novel genes into lymphocytes



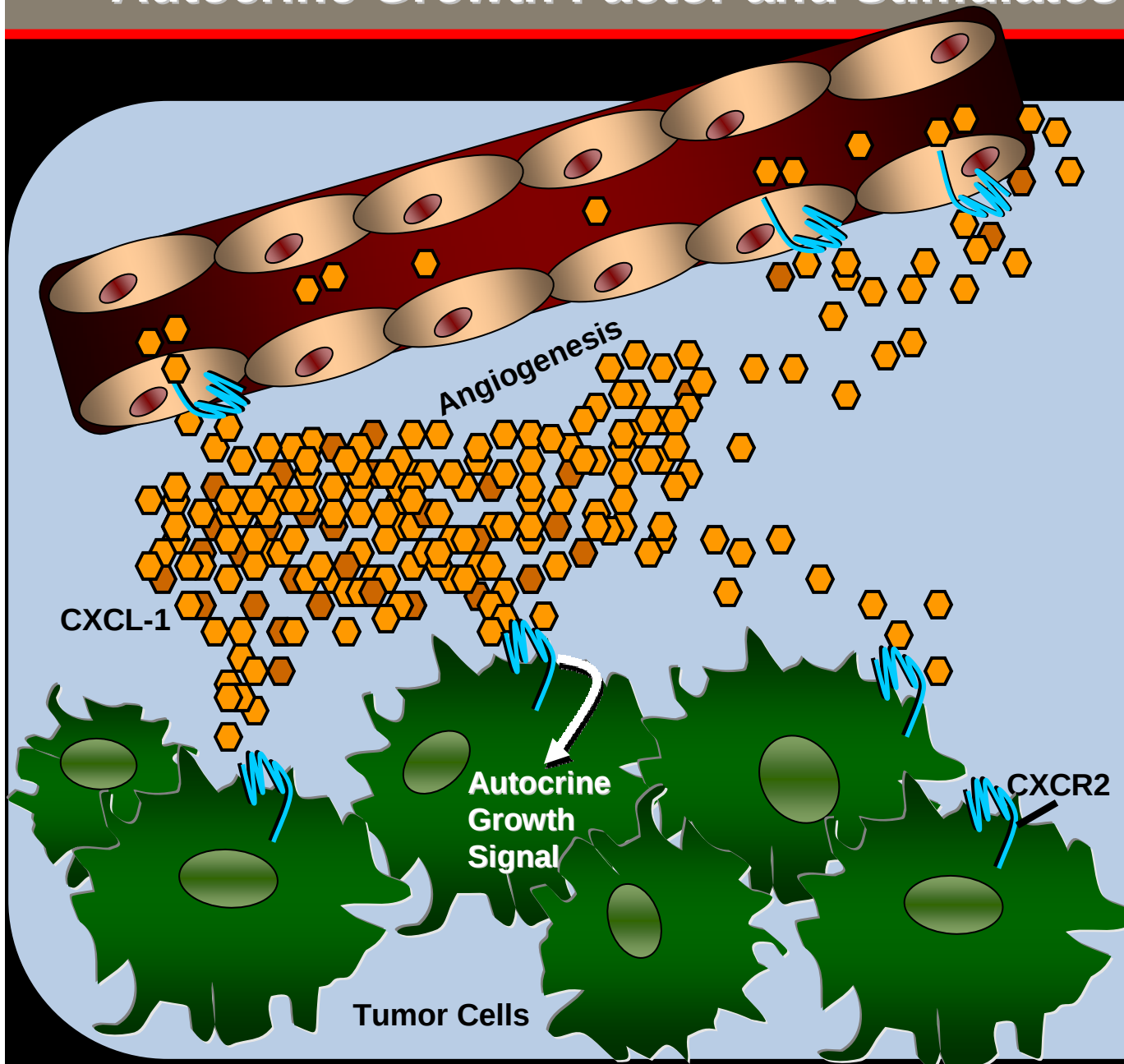
One of the Rate-limiting Steps in ACT is the Inefficient Migration of T-cells to Tumor



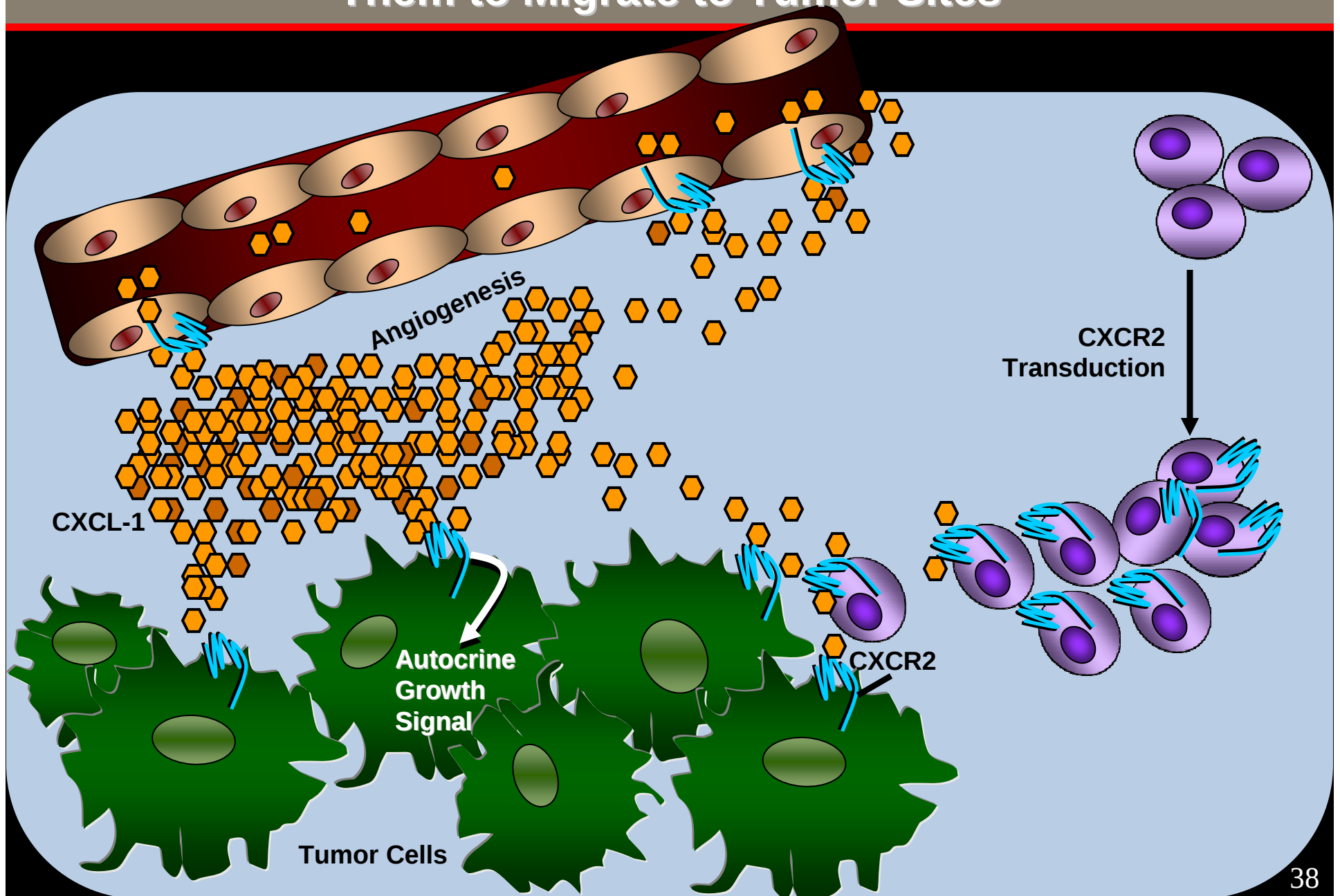
The Presence of CXCL1 in the Tumor Microenvironment



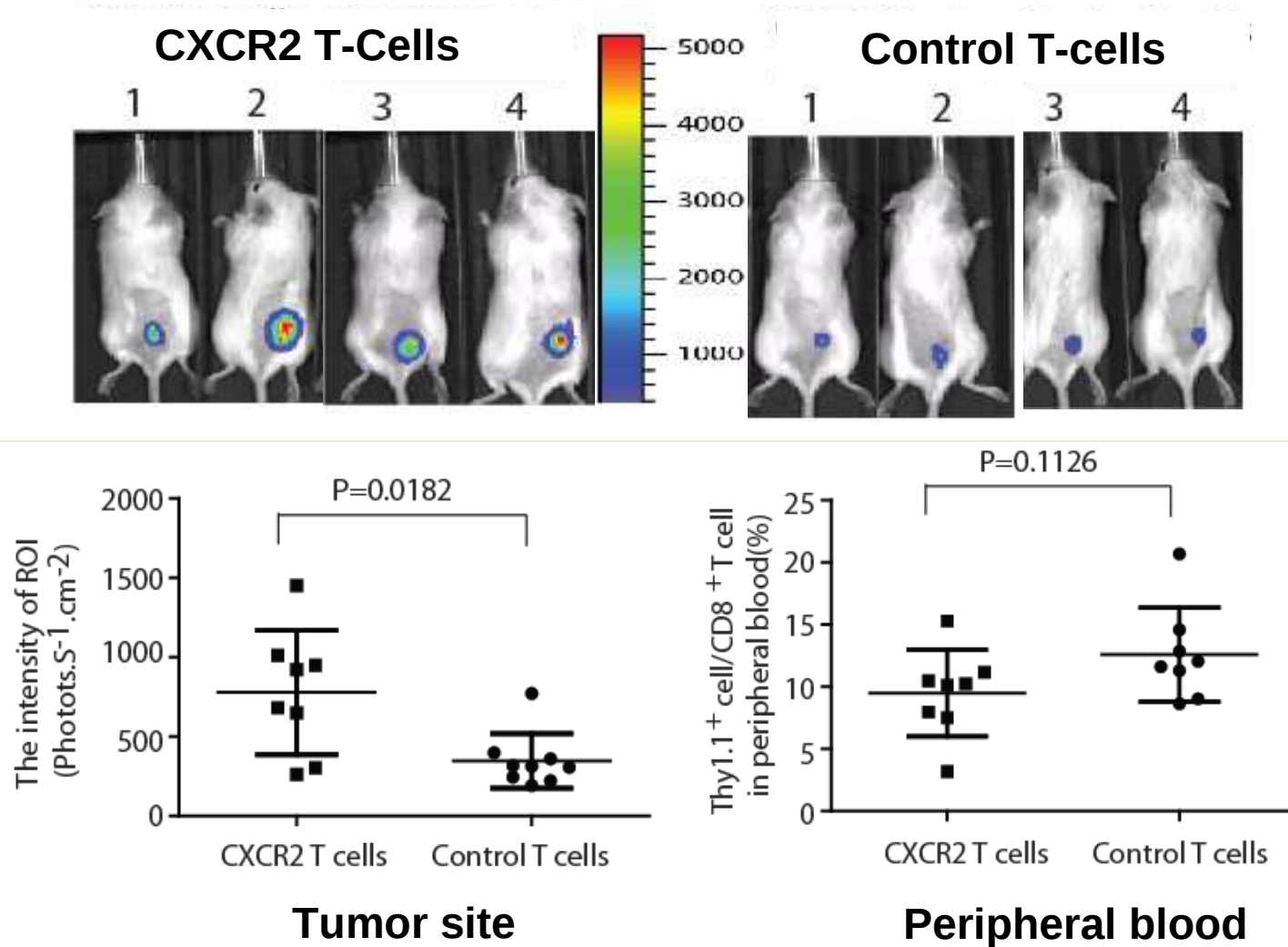
Melanoma Cells Produce CXCL1 which Serves as an Autocrine Growth Factor and Stimulates Angiogenesis



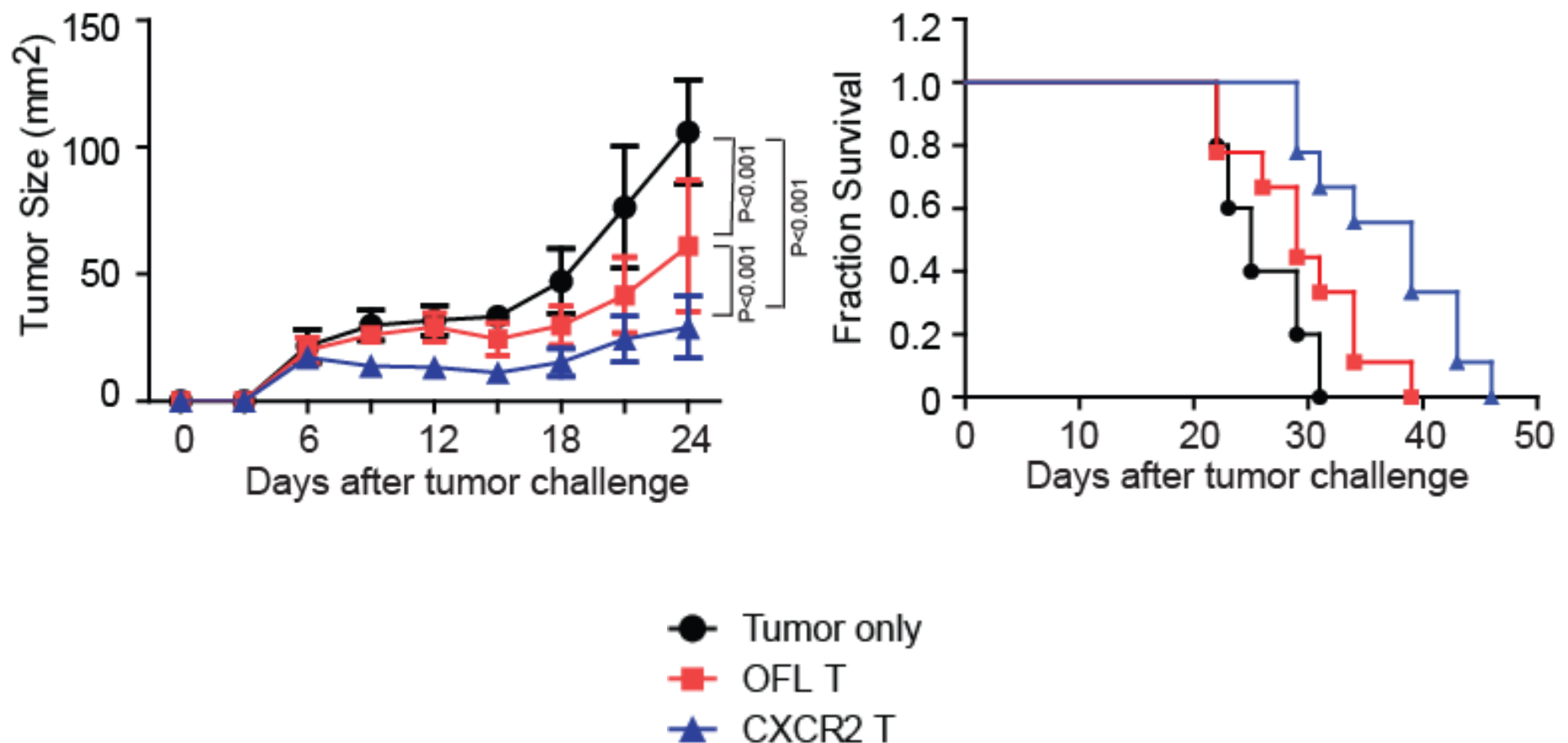
Transduction of T-cells with CXCR2 May Allow Them to Migrate to Tumor Sites



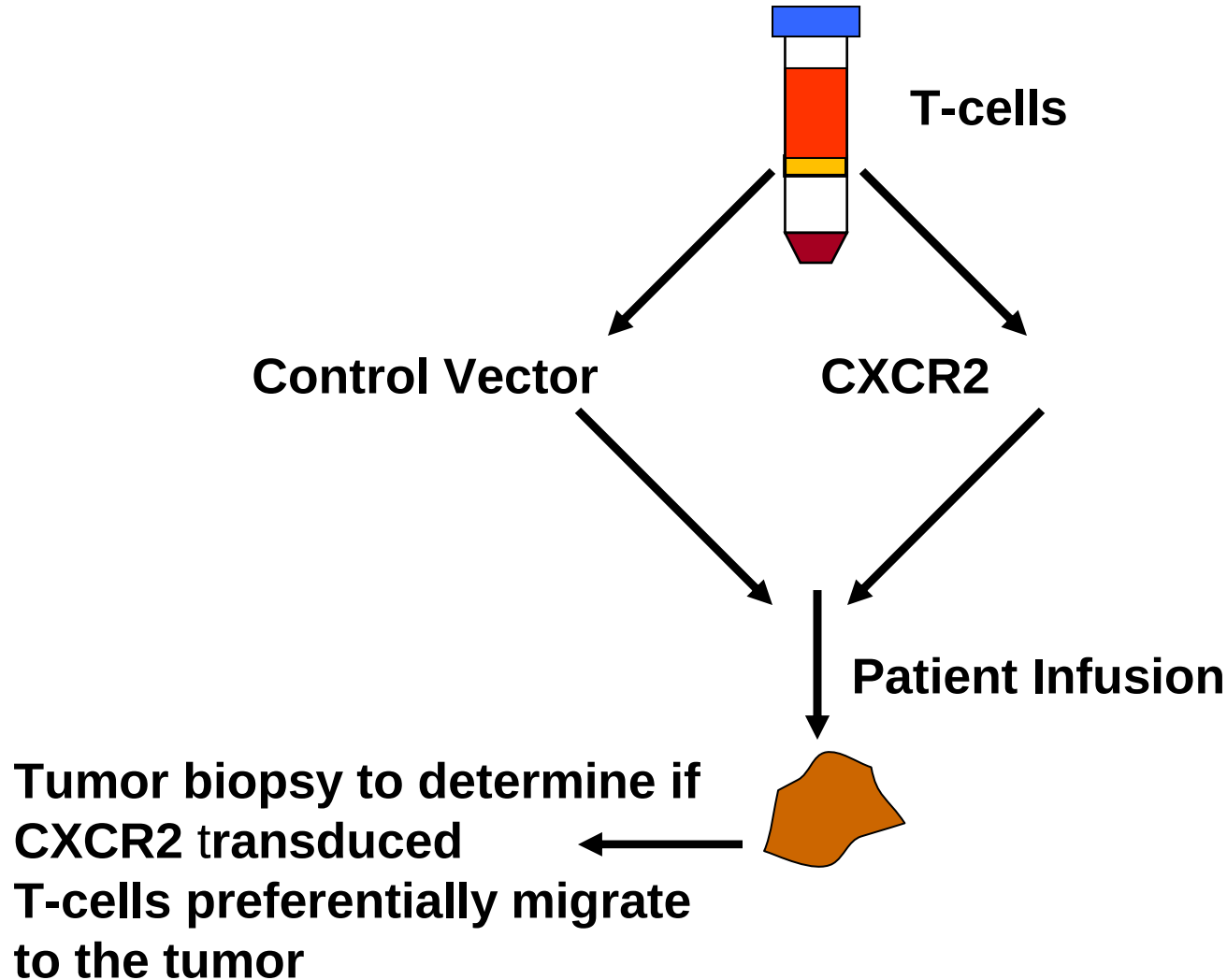
CXCR2-expressing T-cells Display Enhanced Accumulation in Tumor Site



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



Clinical Trial Plans



Acknowledgements

Preclinical Data

- Chengwen Liu
- Greg Lizee
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- Willem Overwijk
- Weiyi Peng
- Minying Zhang
- Jahan Khalili
- Tasuku Honjo (Kyoto)
- Mike Davies
- Scott Woodman

Laboratory Endpoints

- Chantale Bernatchez
- Laszlo Radvanyi
- Luis Vence
- IMCL

Clinical Research

- Melanoma Medical Oncologists
- Surgeons

- Pathologists
- Anna Vardeleon
- EJ Shpall
- TIL Lab
- Linda Duggan

Massachusetts General Hospital

- Keith T. Flaherty
- Jennifer A. Wargo

Surgery Branch, NIH

- Steven A. Rosenberg

Weizmann Institute of Science

- Zelig Eshhar

Adelson Medical Research Foundation

Ella Institute of Melanoma, Sheba Medical Center, Tel Hashomer, Israel

GSK

NCI

Prometheus

Roche/Genentech

Audience Participation Question 1:

T-cell therapy for metastatic melanoma has a reported approximate response rate of:

- a. 10%**
- b. 90%**
- c. 50%**
- d. 20%**

Audience Participation Question 2:

Patients with metastatic melanoma treated T-cell therapy can have a durable response.

- a. true**
- b. false**

Audience Participation Question 3:

There is evidence in animal models and clinical trials that combining T-cell therapy with the following approach can be helpful:

- a. total body irradiation (TBI)**
- b. BRAF inhibition for BRAF positive patients**
- c. anti-PD1 antibodies**
- d. all of the above**

Audience Participation Question 4:

There is evidence that T-cells transduced with chimeric antigen receptors (CARs) can induce responses in:

- a. pancreatic cancer**
- b. neuroblastomas**
- c. B-cell lymphoma**
- d. b and c**