Adoptive T-cell Therapy

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER
Making Cancer History™

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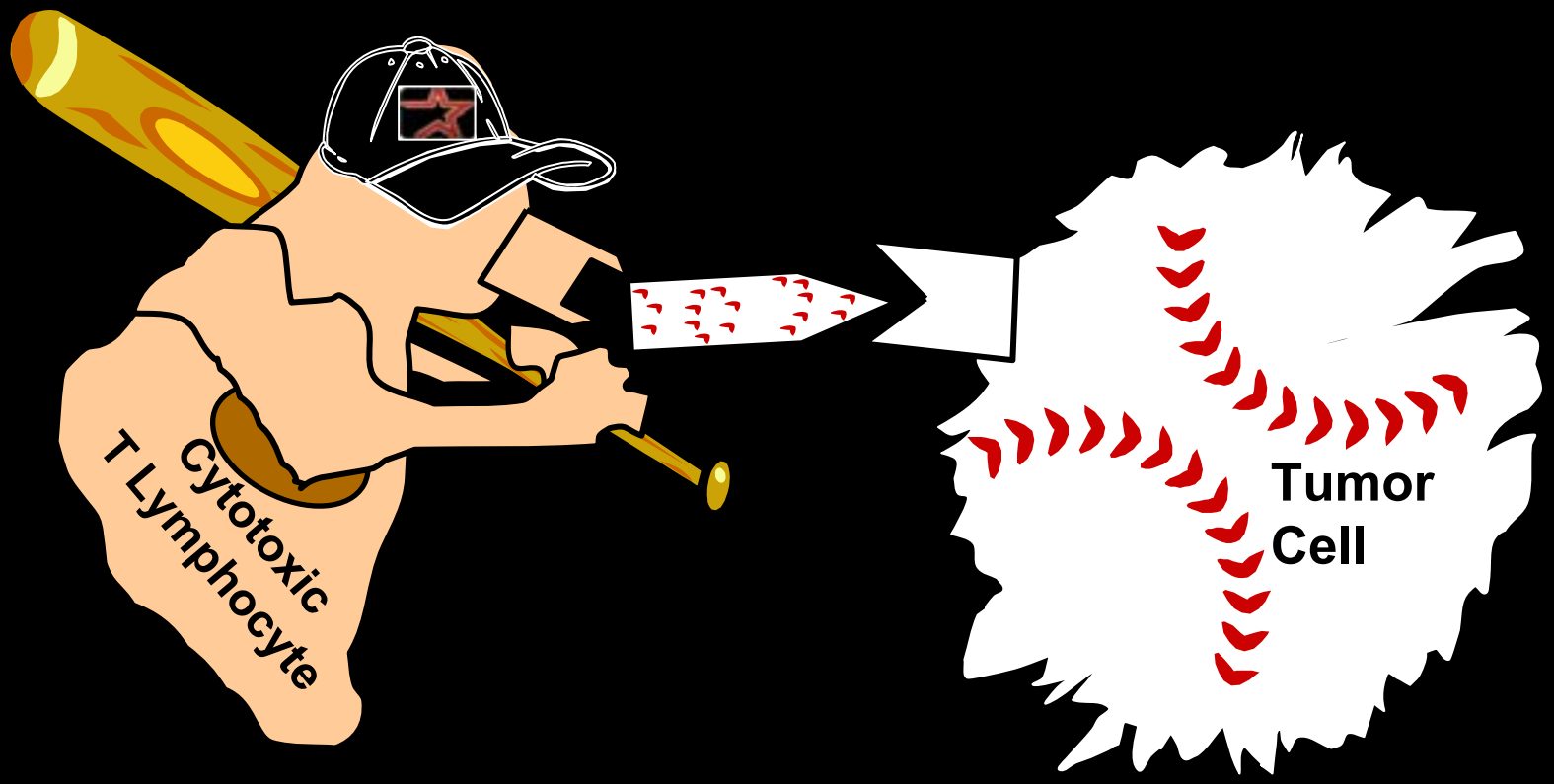
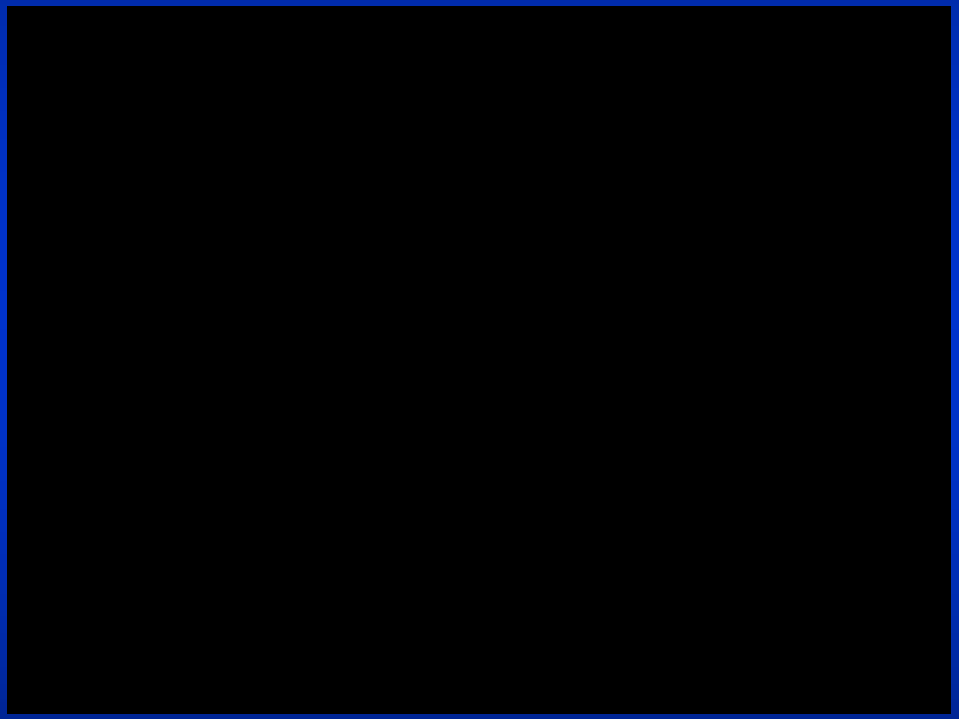
Stimulating the body's immune system against cancer: T-cells can kill tumor cells

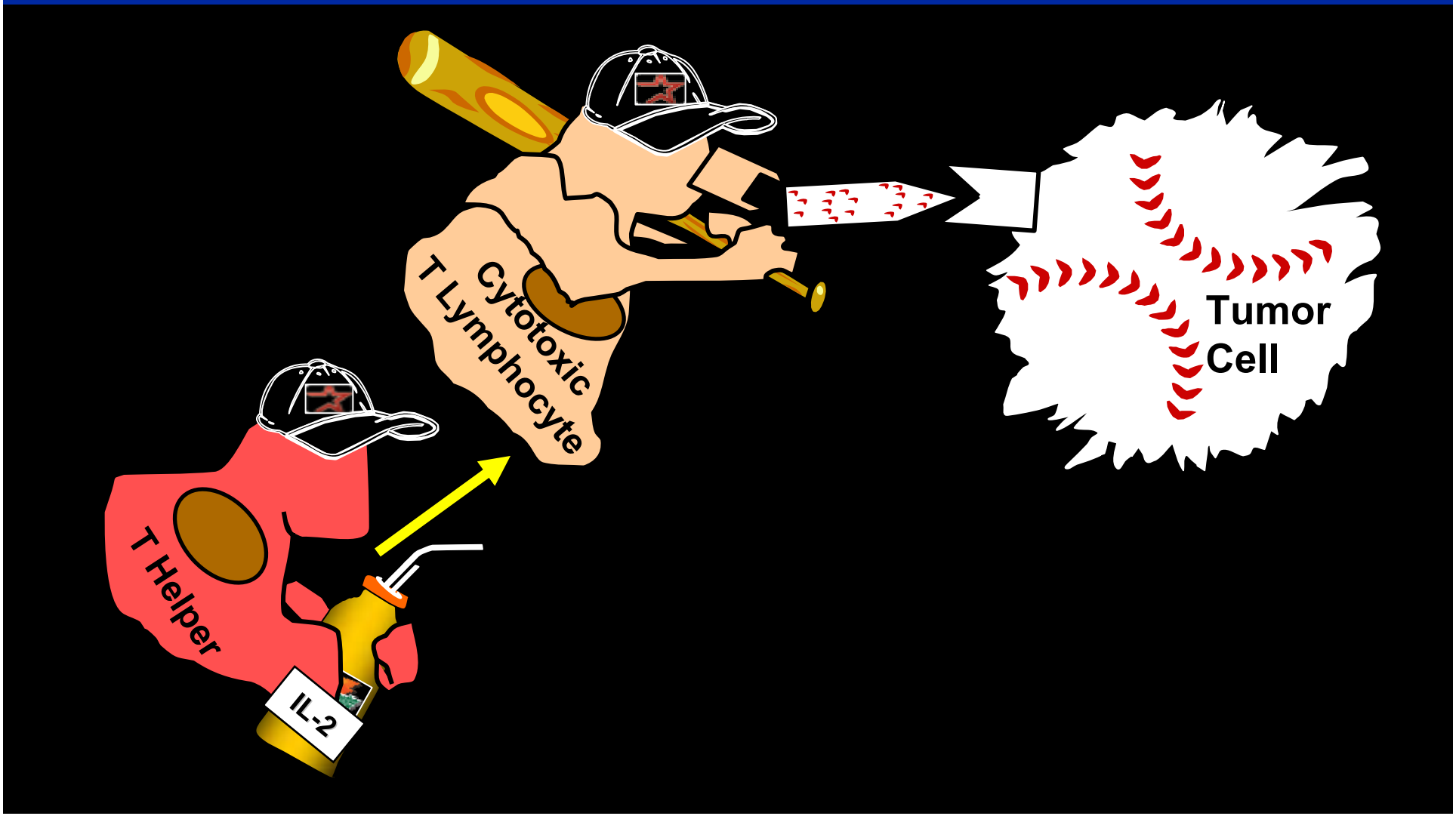


Cytotoxic T-lymphocytes Can Recognize and Kill Tumor Cells

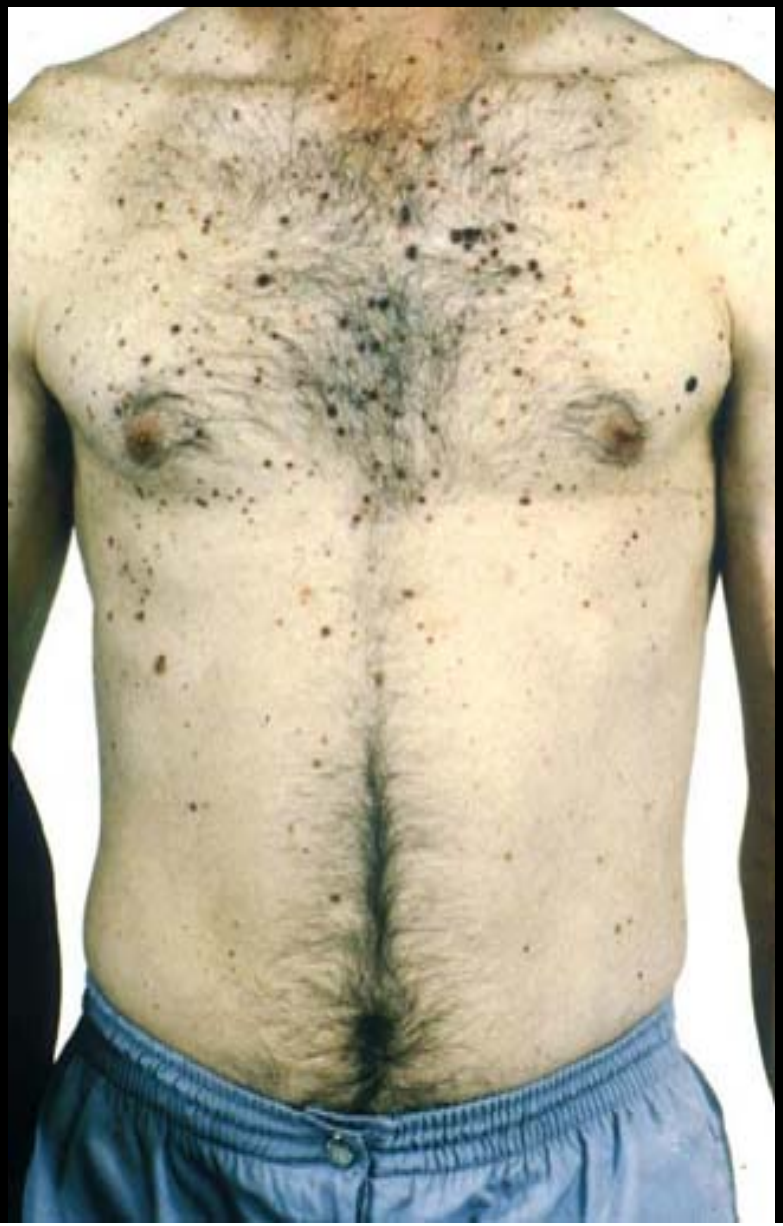


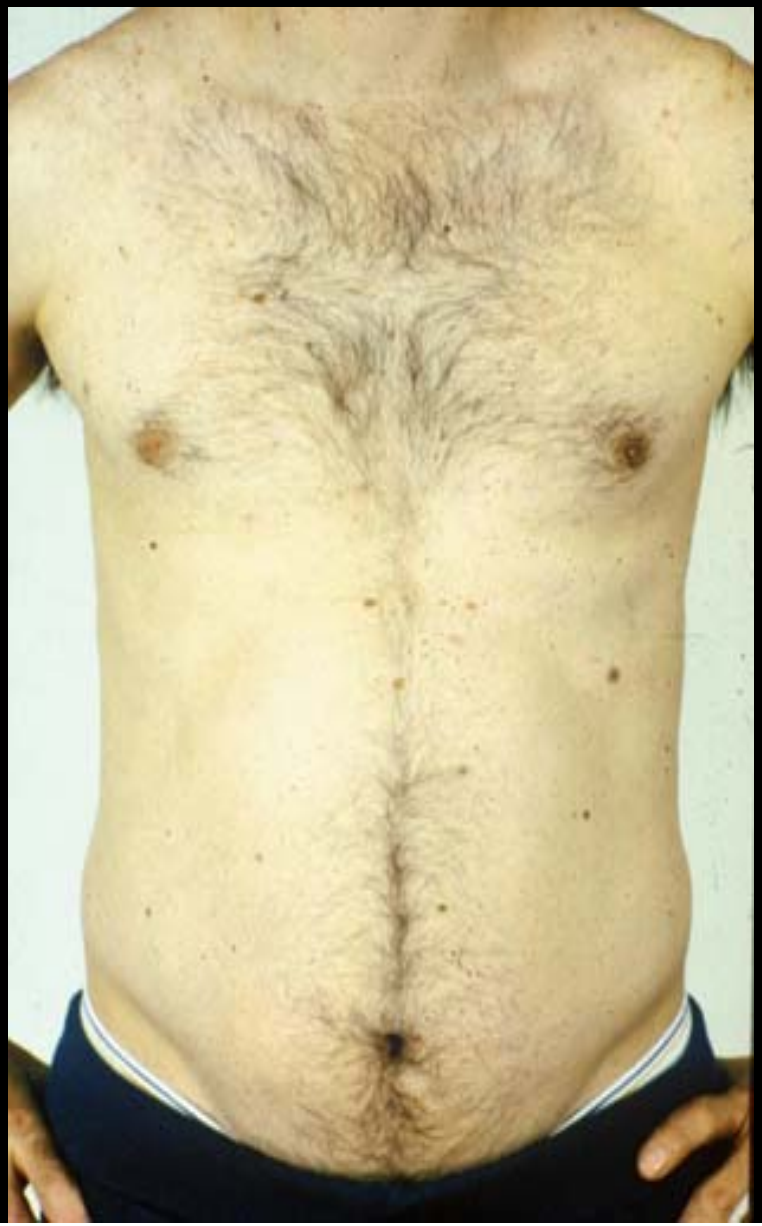
(From UVA)

Interleukin-2, a natural protein produced by T-helper cells, can stimulate cytotoxic T-cells to kill tumor cells

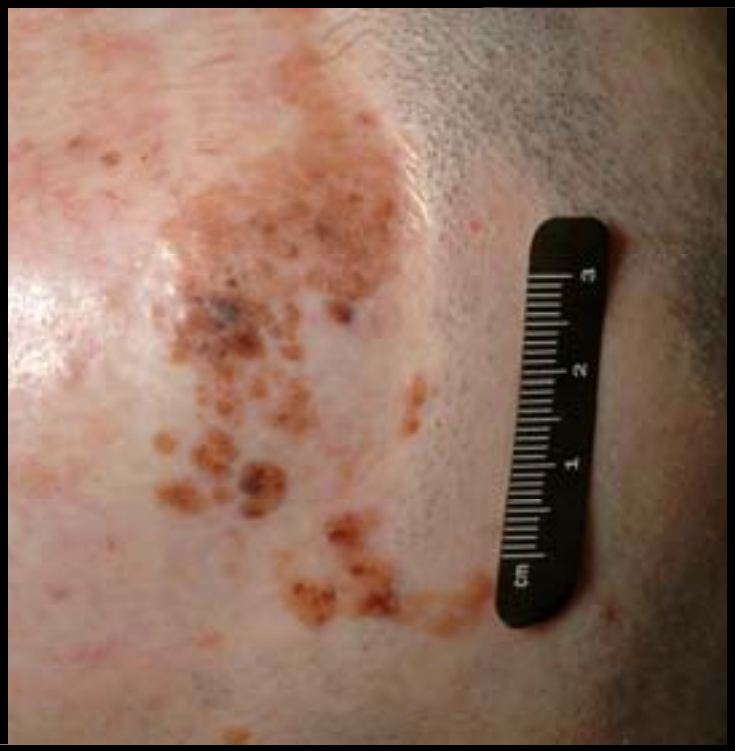


Metastatic melanoma treated with IL-2

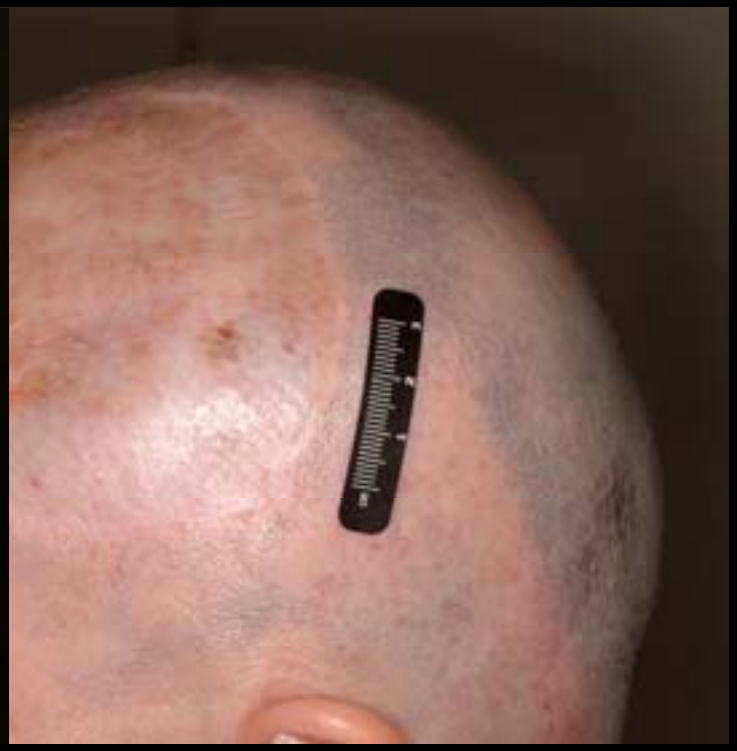




Response to high dose IL-2

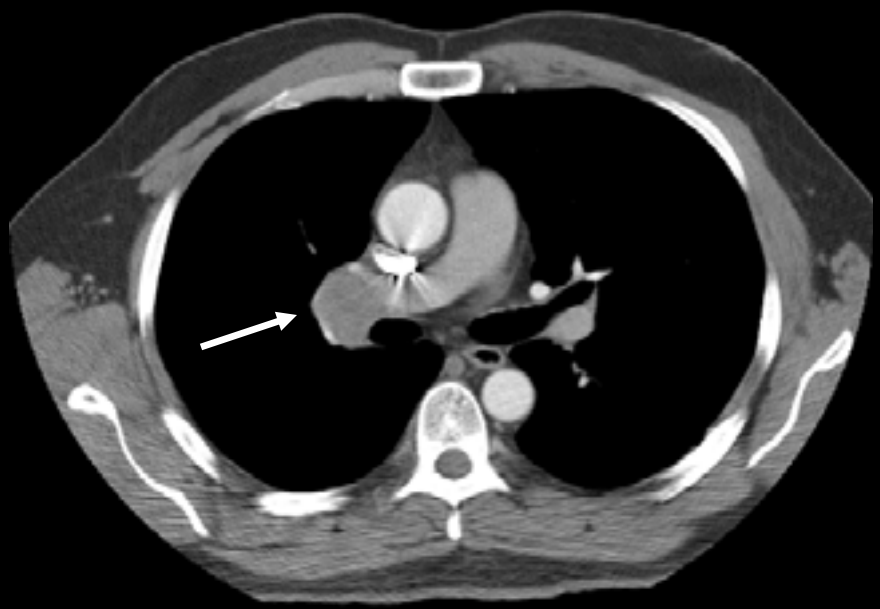


Pre IL-2

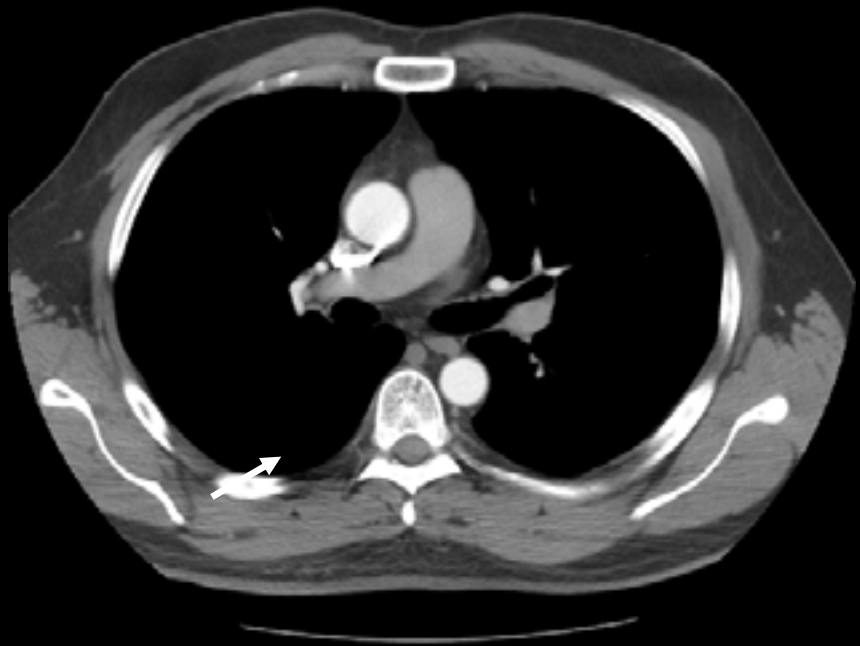


Post IL-2

Response to high dose IL-2



Pre IL-2

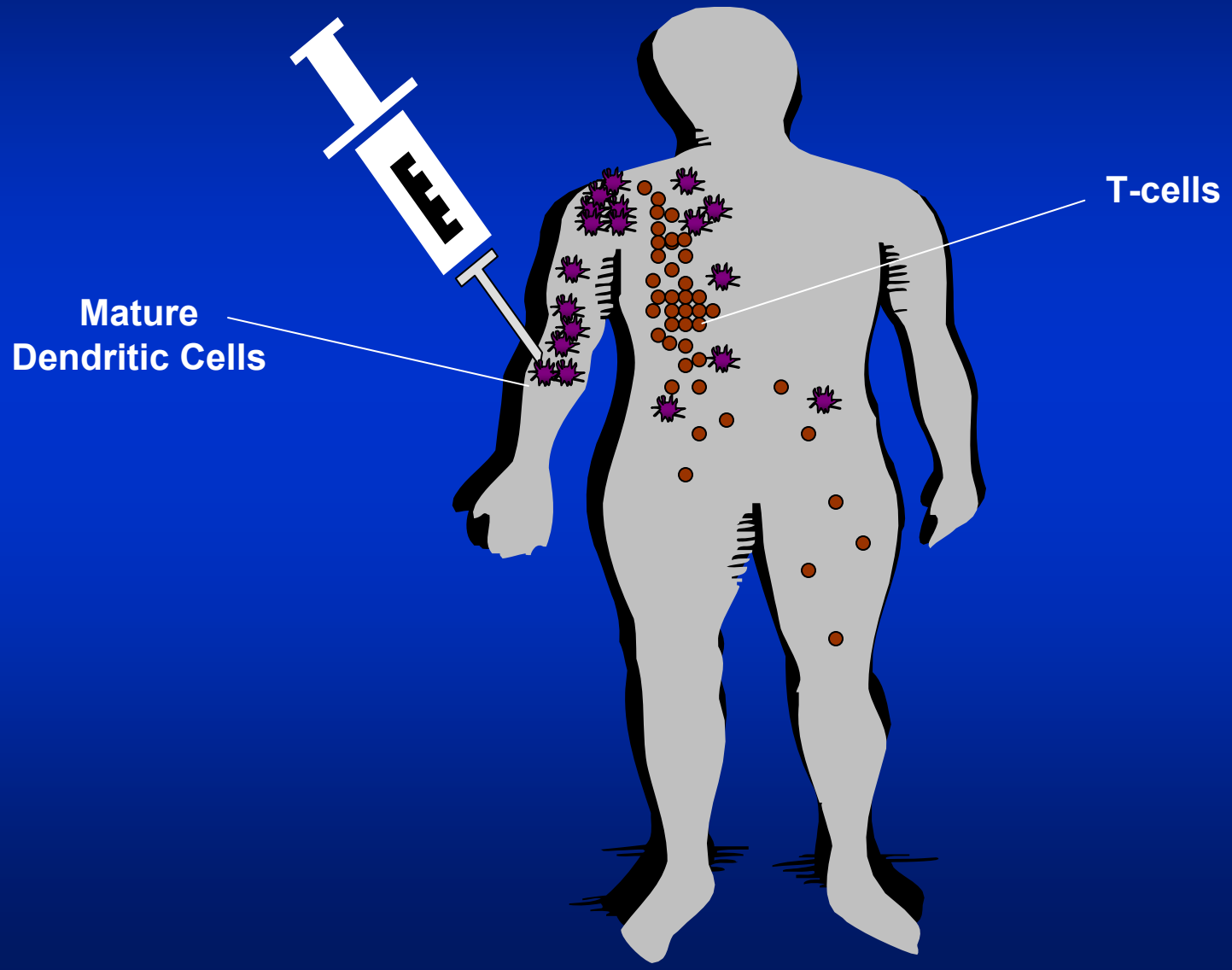


Post IL-2

IL-2 therapy is effective in some patients with metastatic melanoma

Total Number of Patients	Clinical Response
134	23 (17%)

Vaccines stimulate the proliferation of T-cells in vivo



Active Immunization of Patients with Metastatic Melanoma

Vaccine	Total	Objective response
Recombinant viruses	(number of patients)	
Adenovirus (MART-1 or gp100)	24	1
Vaccinia (MART-1 or gp100)	21	0
Fowlpox (MART-1 or gp100)	48	1
Fowlpox (ESgp100:209-2M)	36	0
Vaccinia + Fowlpox (tyrosinase)	13	0
Naked DNA	23	1
Dendritic cells (IV; peptide pulsed)	10	1
Peptides		
MART-1	23	1
gp100 (154, 209, 280)	28	1
gp100:209-2M*	79	0
Her-2/neu	7	0
gp100:ES-209-2M	9	0
Non A2 peptides (A1, A3, A24, A31, Cw7)	65	2
NY-ESO-1	33	0
Class I & II gp100	27	2
Telomerase	14	0
TRP-2	21	0
MART-1 + gp100 (multiple)	58	2
gp100 + MART + Flt3L	31	0
Total	570	12 (2.1%)

*alone or with GMCSF or IL-12

Potentially Targetable Immunoregulatory Molecules

	Molecule	Cellular Expression	Mechanism of Action
Membrane bound	CTLA-4	Helper T, Cytoxic T	Provides co-inhibitory signaling during naïve T-cell priming
		T-reg	Induces local tryptophan metabolism by DCs, inhibiting T-cell proliferation
	PD-1	Helper T, Cytoxic T	Inhibits T-cell proliferation, cytokine production and cytotoxicity
Soluble	IL-10	Tumor, TR1	Regulates growth and differentiation of a wide variety of immune cells
	IL-13	iNKT	Induces immature myeloid cells to produce TGF-β
	TGF-β	Tumor, TR1, Treg, Immature myeloid	Directly suppresses proliferation of antigen-activated T cells
	VEGF	Tumor	Blocks DC differentiation and maturation, leading to accumulation of iDC and iMC
	IDO	Tumor, Dendritic	Depletes local tryptophan, inhibiting T-cell proliferation
	ARG1	Tumor, Immature myeloid	Depletes local arginine, inhibiting CD3ζ expression and T-cell activation
	iNOS	Tumor, Immature myeloid	Generates nitric oxide, inhibiting T-cell priming, proliferation, and cytotoxicity

T-cell Therapy

Infusion of T-cells that are first manipulated in the laboratory.

- Activation
- Expansion
- Subset selection
- Gene transduction

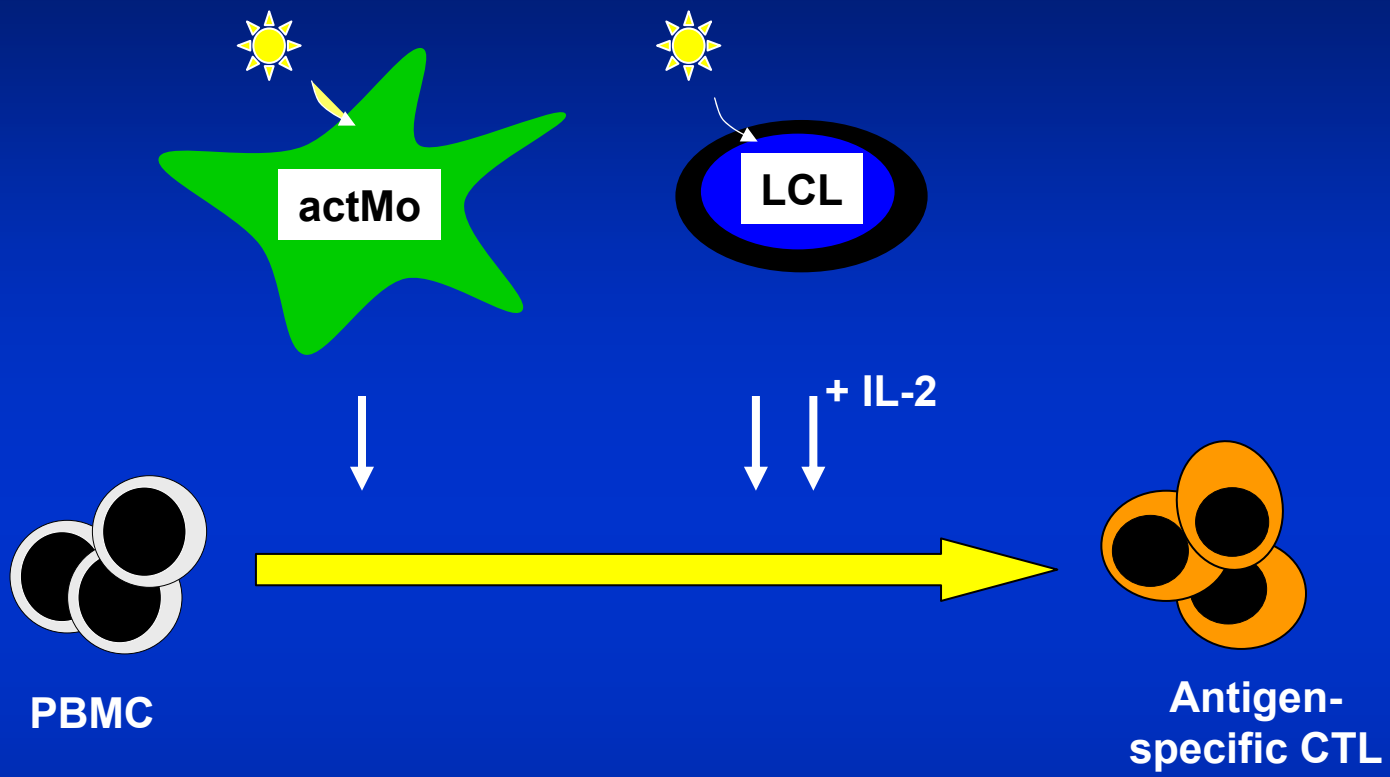
Advantages of T-cell Therapy

- Avoids immunoregulatory environment present in cancer patients
  - Use of T-cells from donor
  - T-cells manipulated ex-vivo
- Increases number of antigen-specific T-cells
  - Post transplant T-cell recovery can be slow
  - A high level of expansion is possible ex-vivo
- Allows control over phenotype of cells that are infused
  - Antigen specificity
  - Activation state

Evidence that T-cell therapy is effective

- Prevention of viral infection post transplant
- Donor Lymphocyte Infusion (DLI) to enhance graft vs tumor effect
- Treatment of melanoma with TIL therapy

Generation of virus-specific CTL



After 3rd or 4th stimulation analyze CTL lines ---> Freeze & QA/QC testing

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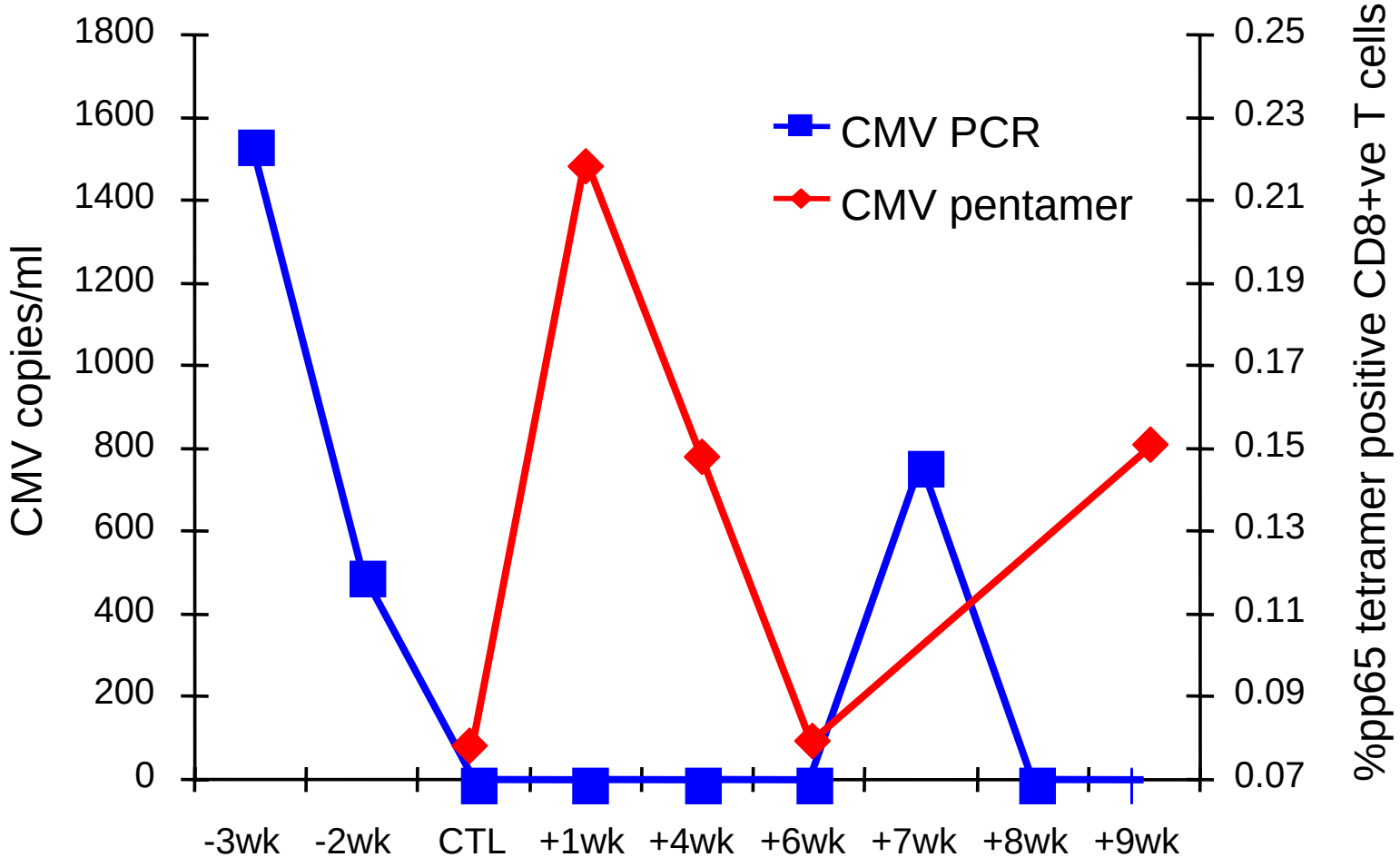
Baylor College of Medicine
Houston, Texas

Clinical Outcome - CMV



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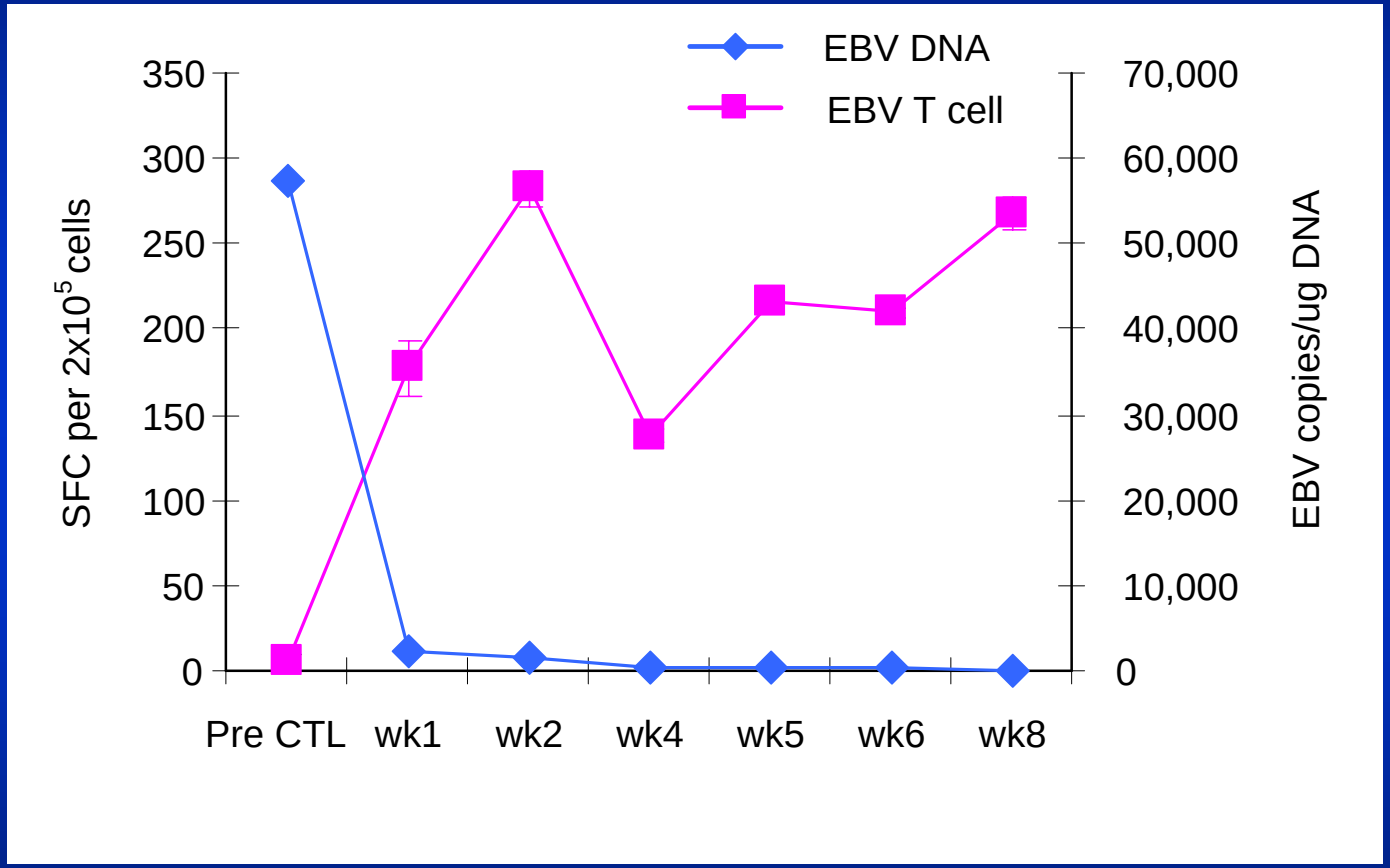
Reduction in EBV load post-CTL and rise in EBV CTLp



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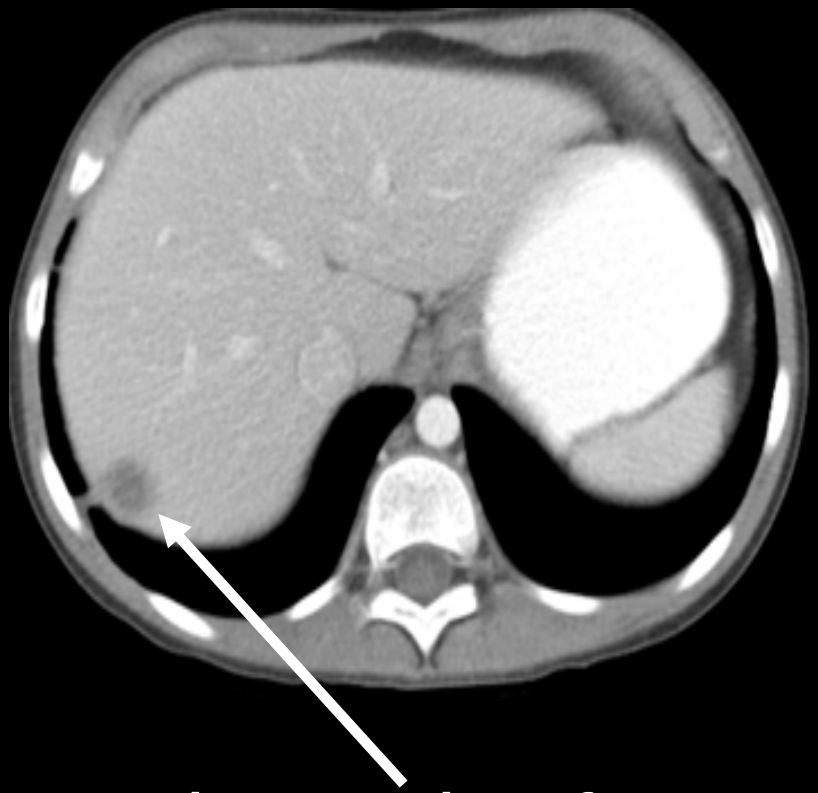
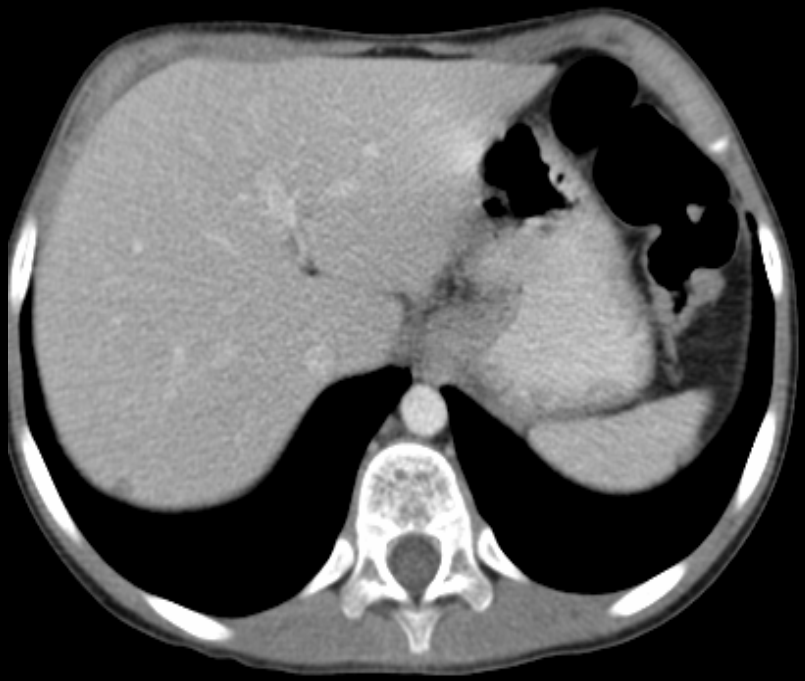
Resolution of liver lesion – no further therapy required



Diagnosis of PTLD



2 months later

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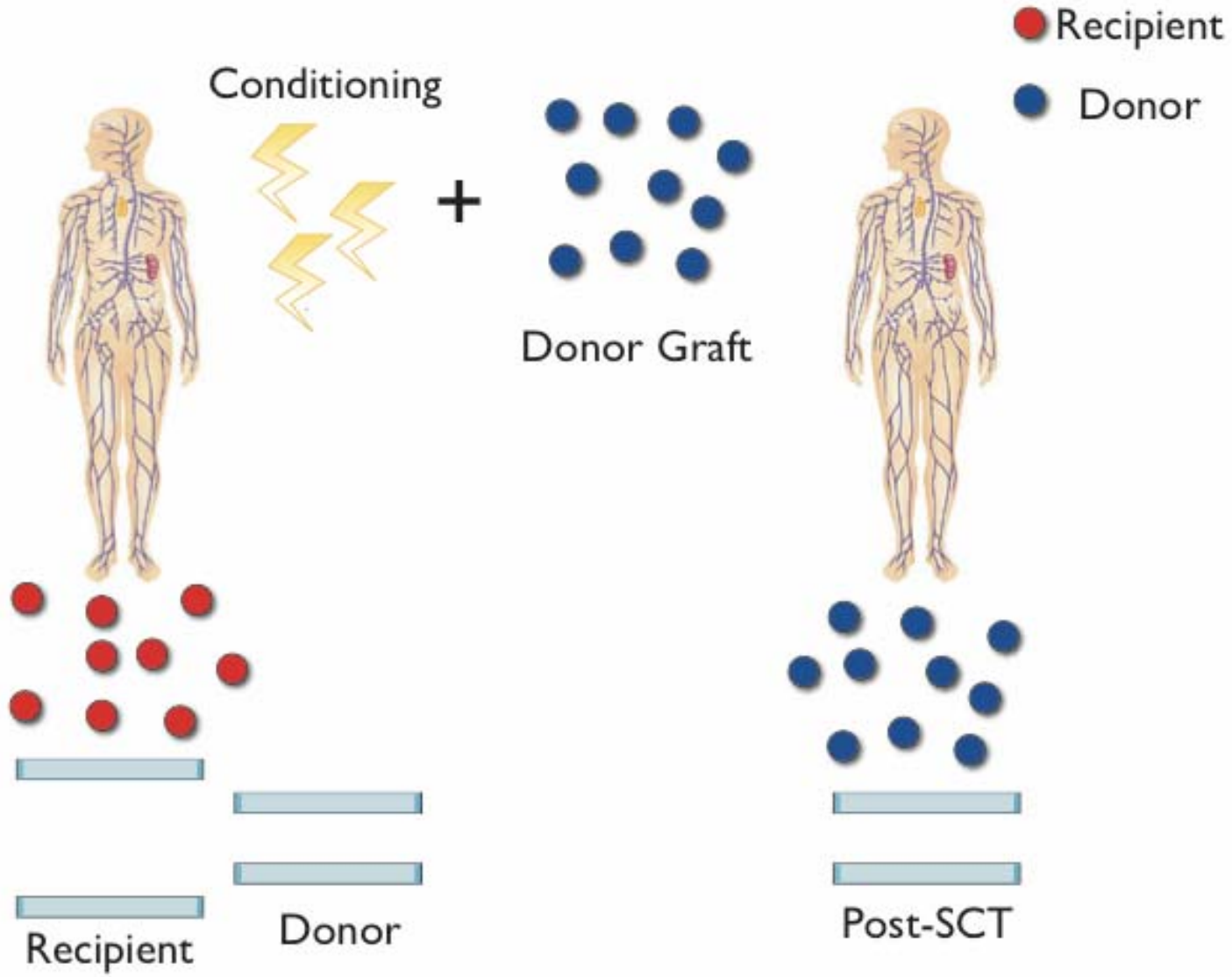
Evidence that T-cell therapy is effective

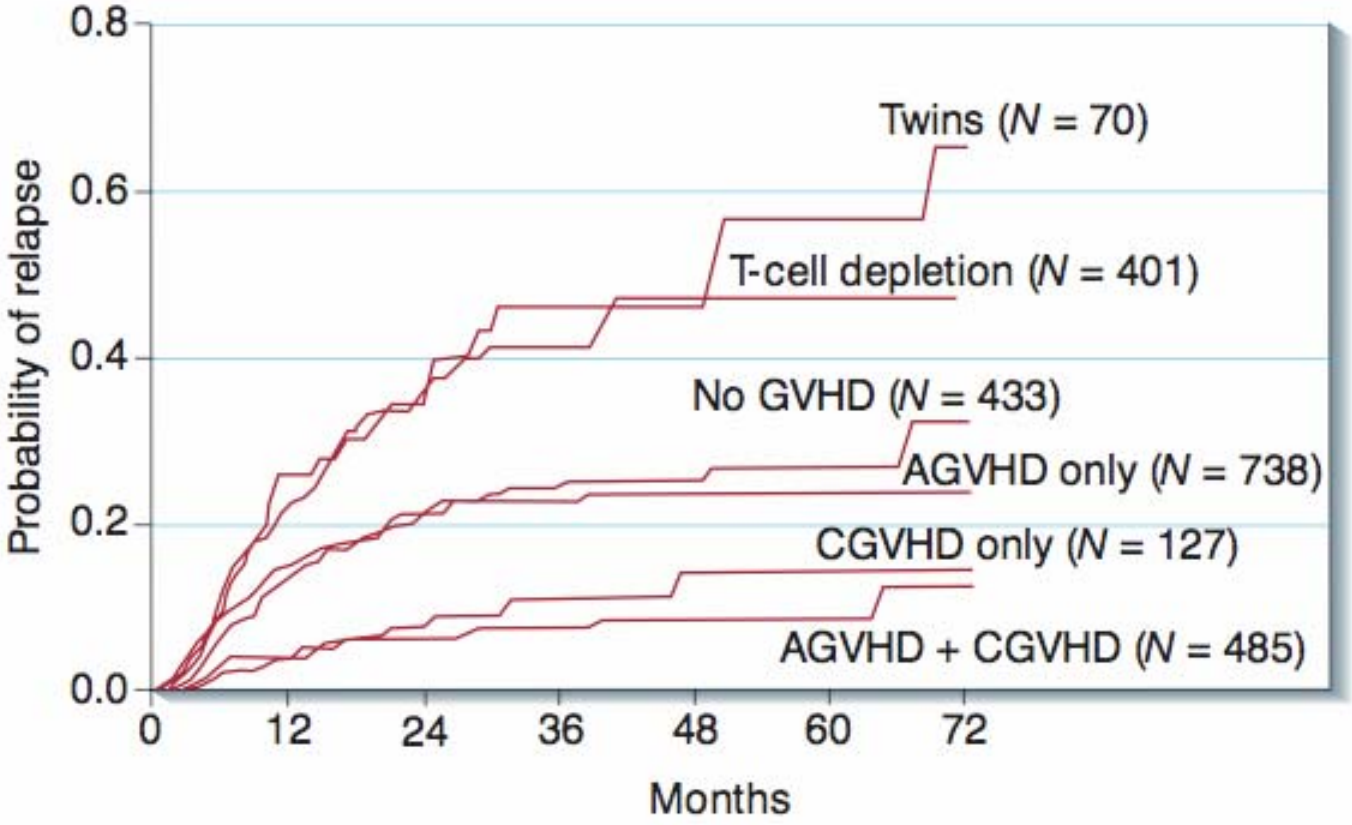
- Prevention of viral infection post transplant
- Donor Lymphocyte Infusion (DLI) to enhance graft vs tumor effect
- Treatment of melanoma with TIL therapy

Traditional Myeloablative Stem Cell Transplant



K. Komanduri

T cell depletion decreases GVHD incidence, but increases risk of relapse



Appelbaum FR. *Nature* 411: 385-389 (2001).

Response of Chronic Myeloid Leukemia to DLI

Disease Stage	Total	
Cytogenetic relapse	43/53	(81%)
Hematologic relapse	113/148	(76%)
Transformed phase	18/54	(33%)
All	174/255	(68%)

Luznik and Fuchs.
Cancer Control 9(2):123-137

Response of Acute Myeloid Leukemia, Acute Lymphocytic Leukemia, and Myelodysplasia to DLI Alone

Disease	Total	
Acute Myeloid Leukemia	18/81	(22%)
Acute Lymphocytic Leukemia	3/37	(8%)
Myelodysplasia	5/14	(36%)

Luznik and Fuchs.
Cancer Control 9(2):123-137

GVHD and response of chronic phase Chronic myeloid leukemia to DLI

Grade of GVHD	Studied	Responding	%
0	93	47	51
I	38	29	76
II	51	46	90
III	19	16	84
IV	8	6	75

$P \leq .0001$

Luznik and Fuchs.
Cancer Control 9(2):123-137

Strategies to Separate GVHD from GVL

- Infuse antigen-specific T-cells
- Deplete alloreactive T-cells from infused cells
- Insert suicide gene

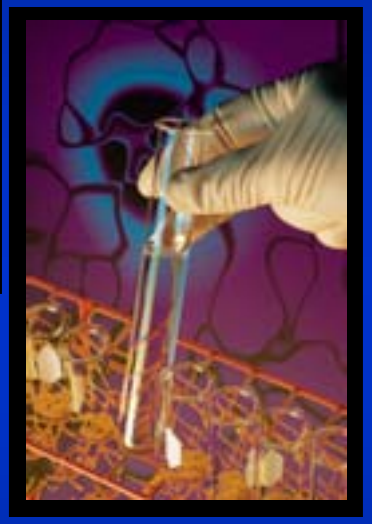
Evidence that T-cell therapy is effective

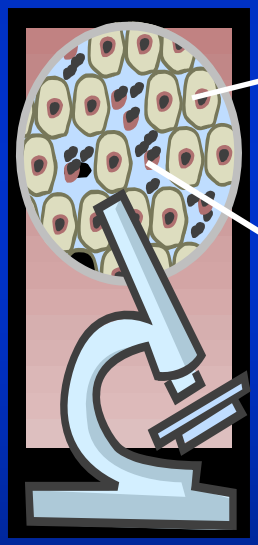
- Prevention of viral infection post transplant
- Donor Lymphocyte Infusion (DLI) to enhance graft vs tumor effect
- Treatment of melanoma with TIL therapy

Adoptive Cell Therapy (ACT) with antigen specific T-cells

Surgical Removal of Cancer Nodule

Single Cell Suspension Incubated with IL-2



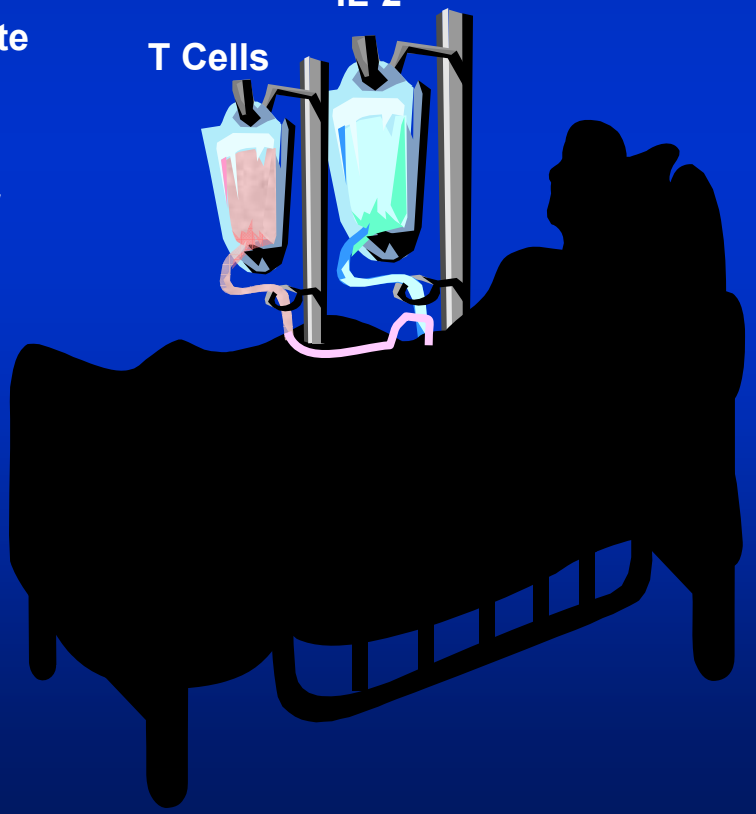


T Cells Proliferate

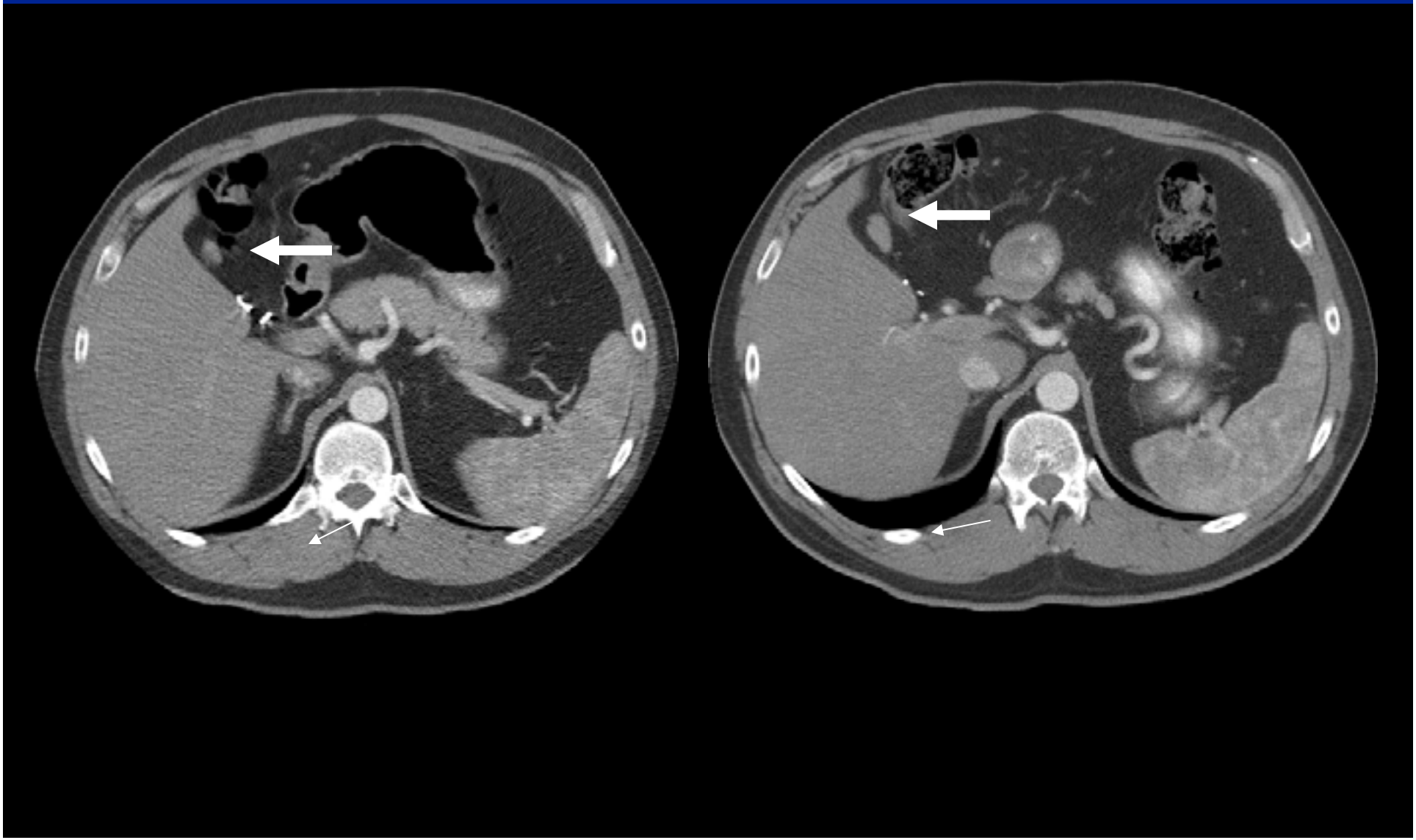
Cancer Cells Die

IL-2

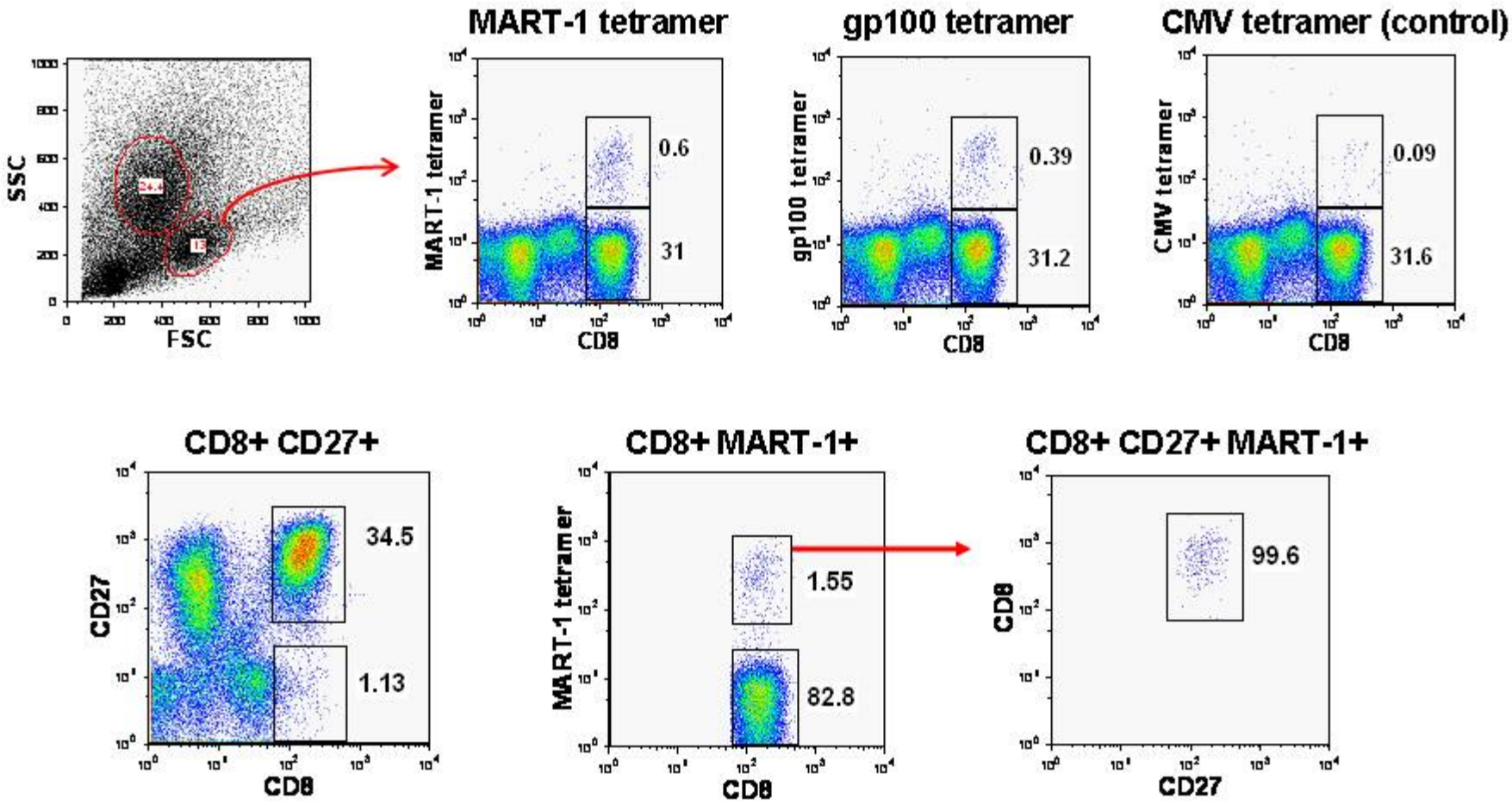
T Cells



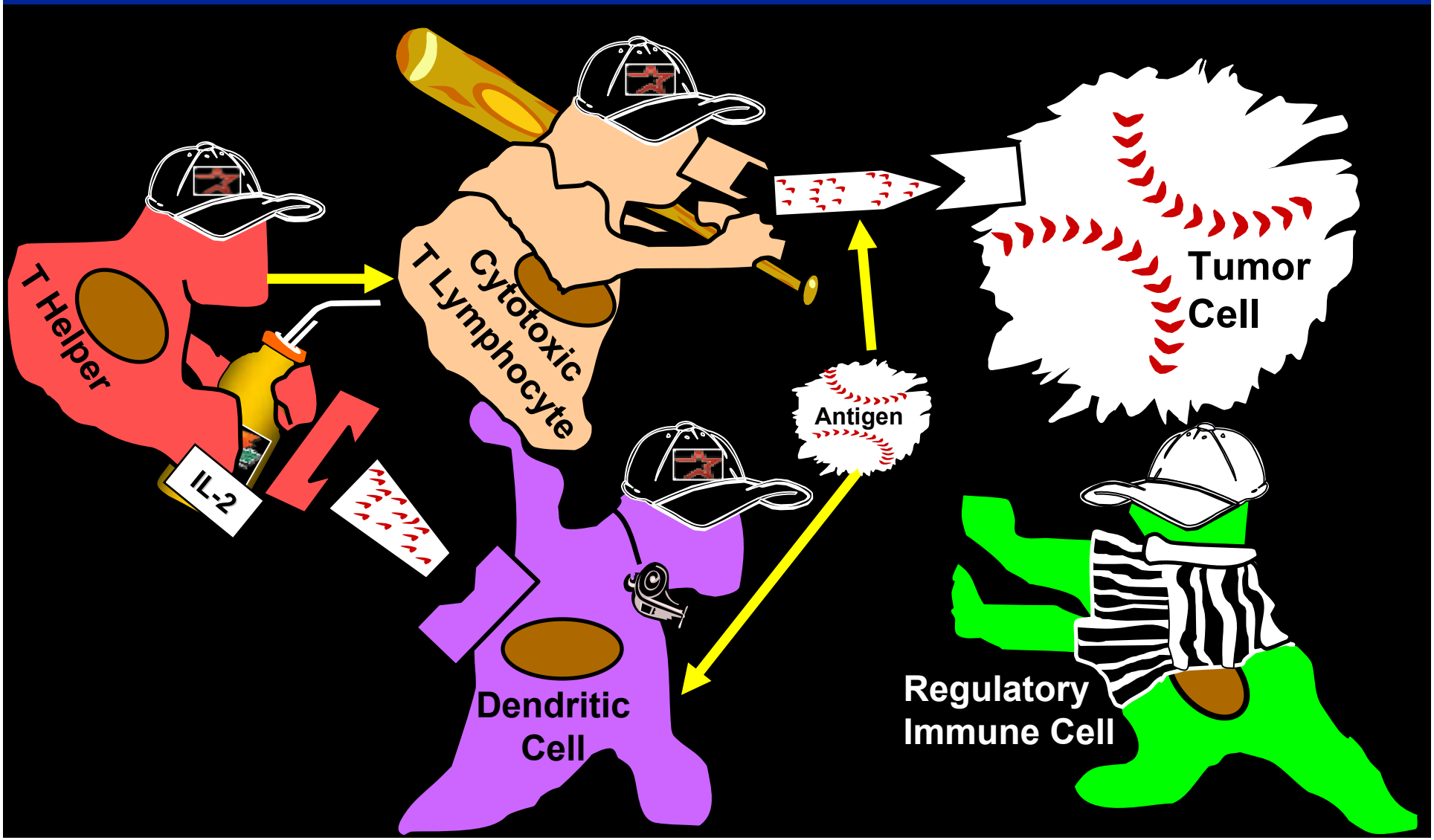
Growing melanoma metastasis in gall bladder fossa, resected for TIL



MART-1 and gp100 reactive TIL in fresh melanoma biopsy DE

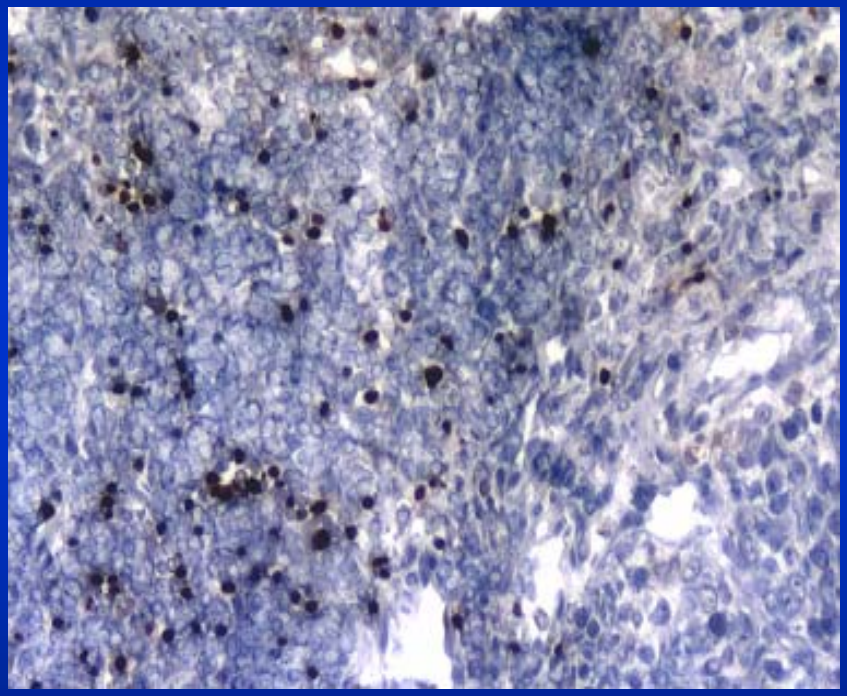


Producing an effective cancer vaccine will require a deep understanding of interactions between the "Players" that make up the immune system "Team"



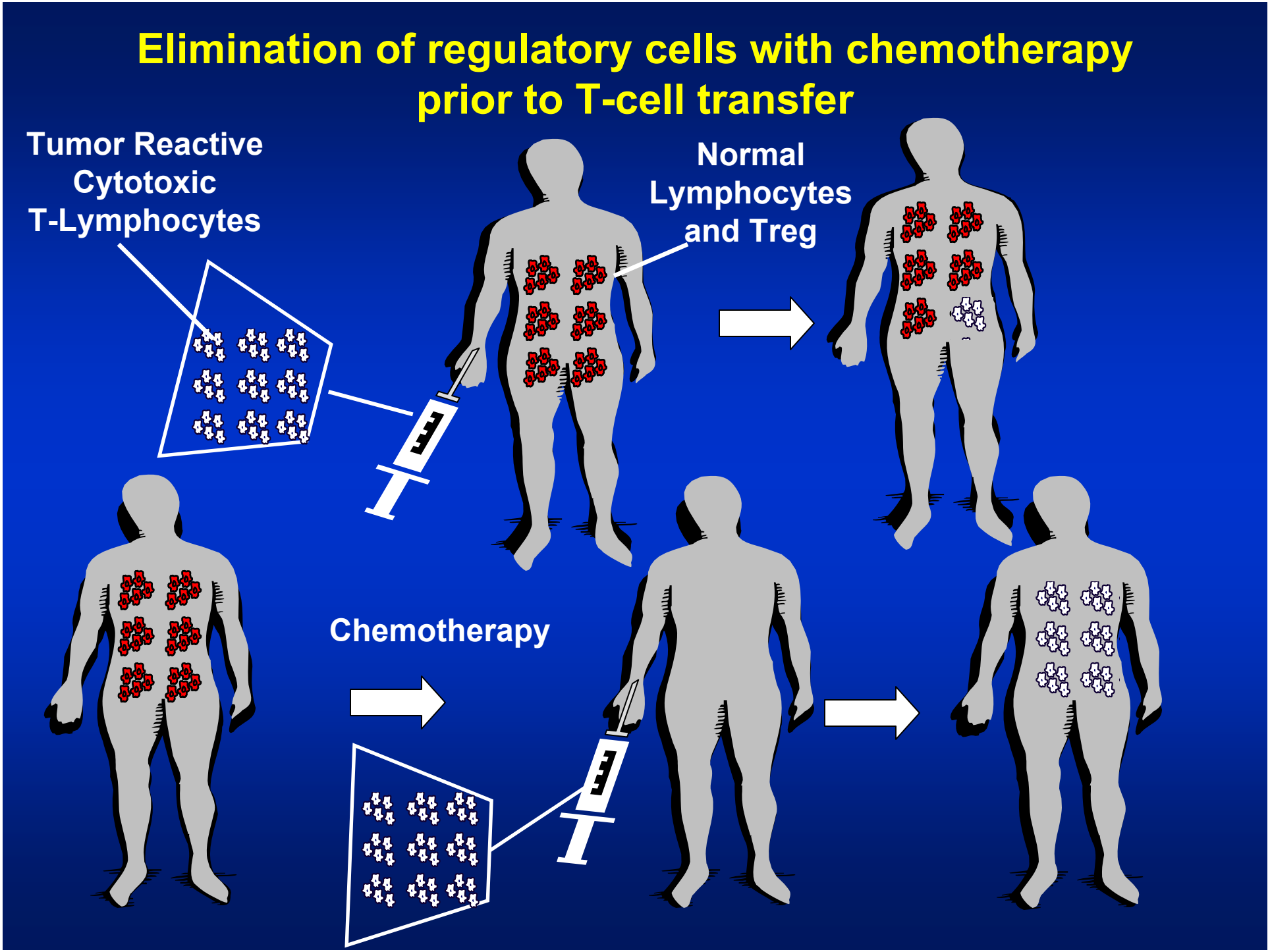
Melanoma tumor-infiltrating Foxp3+ cells

Foxp3 - Histology
(MT #712)

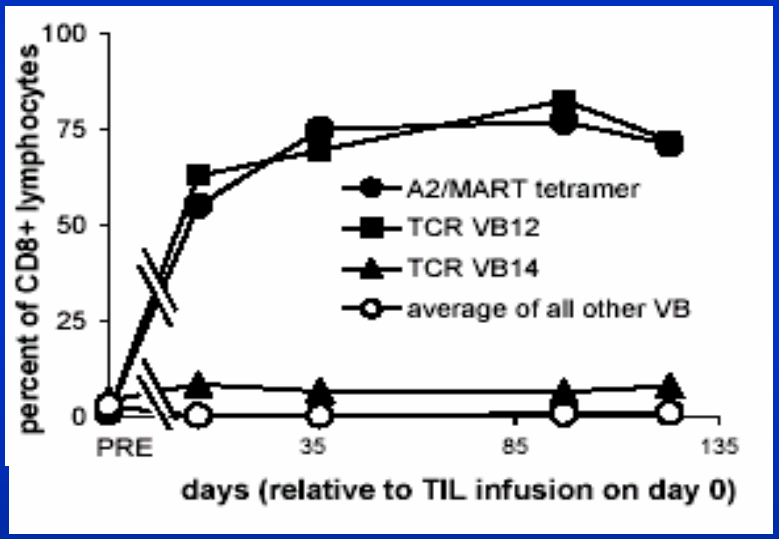


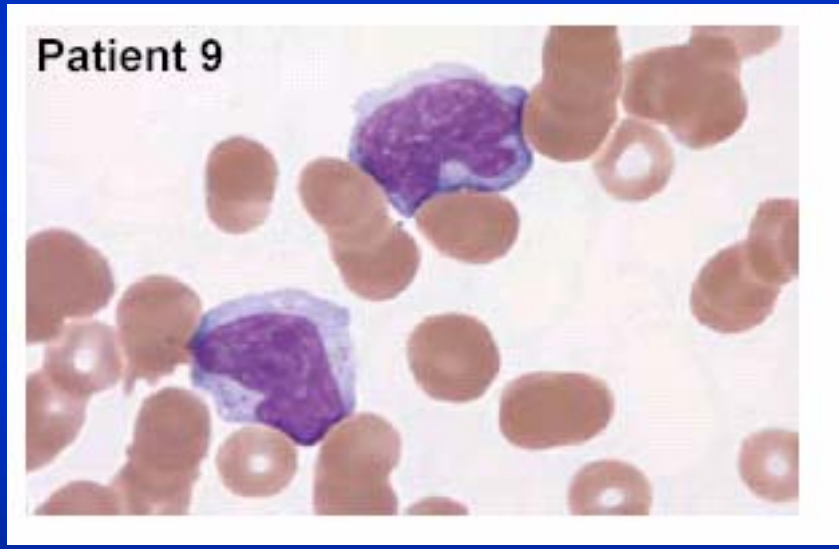
Multiple regulatory immune cell subsets have been shown to suppress antitumor immunity

Cell Type	Effector functions	Reference
T-reg (CD4+CD25+)	Inhibition of $CD4^+$ and $CD8^+$ T-cell proliferation via direct cell-to-cell interactions (involving CTLA-4, GITR?)	Sakaguchi, *Nature Immunology* 2005
Tr1 (CD4+CD25-)	Suppression of naïve and memory T-cell responses through production of high levels of IL-10 and TGF-β	Levings et al., *J Experimental Medicine* 2002
Immature myeloid	Inhibition of IFN-γ production by $CD8^+$ T cells mediated by reactive oxygen species (eg. H_2O_2)	Grabilovich, *Nature Rev Immunology* 2004
Invariant NKT	Cytokine release (diverse Th1 and Th2) *May prevent **or** activate antitumor immunity*	Wilson and Delovitch, *Nature Rev Immunology* 2003

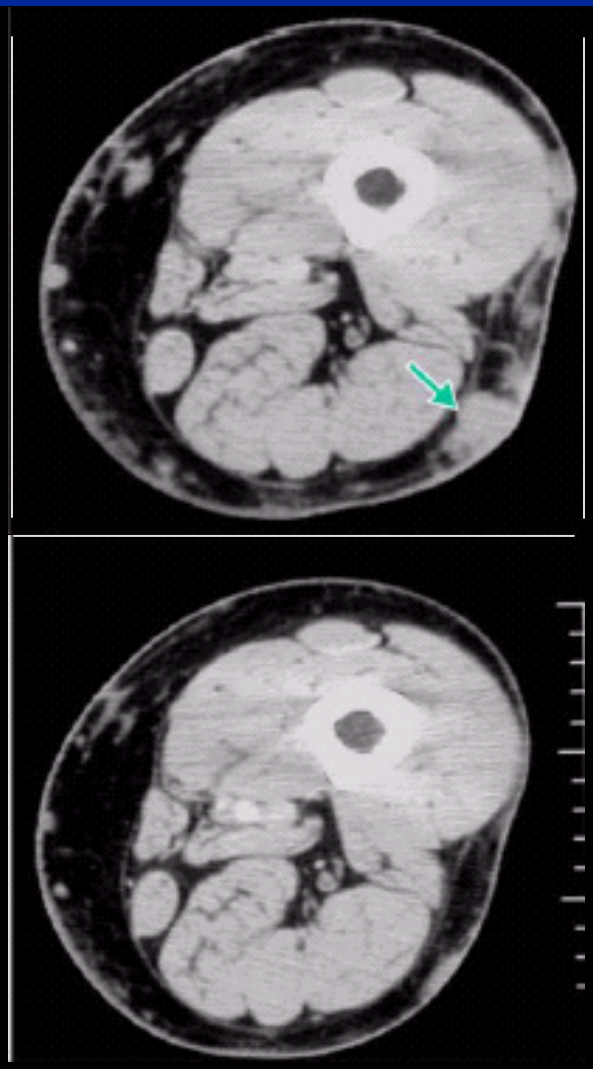

Elimination of regulatory cells with chemotherapy prior to T-cell transfer
Tumor Reactive Cytotoxic T-Lymphocytes
Normal Lymphocytes and Treg
Chemotherapy

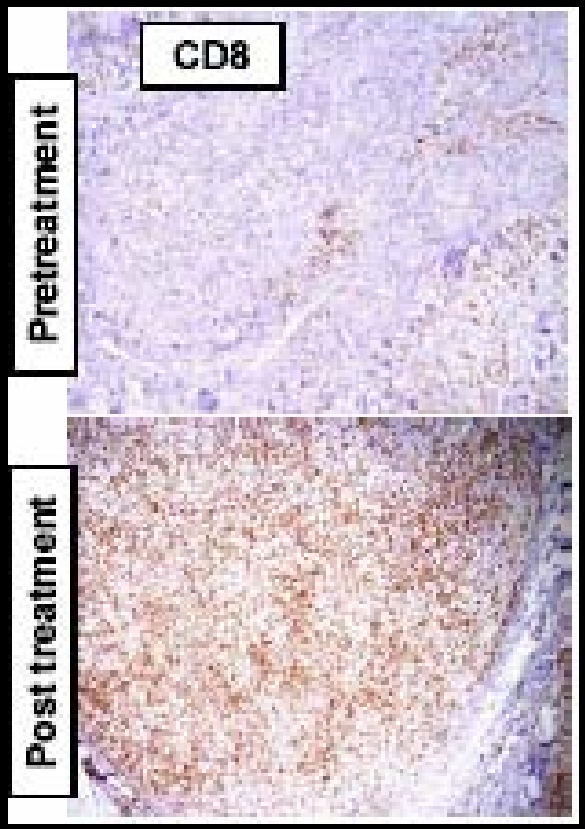
Infused T-lymphocytes persist when administered following lymphodepletion with chemotherapy



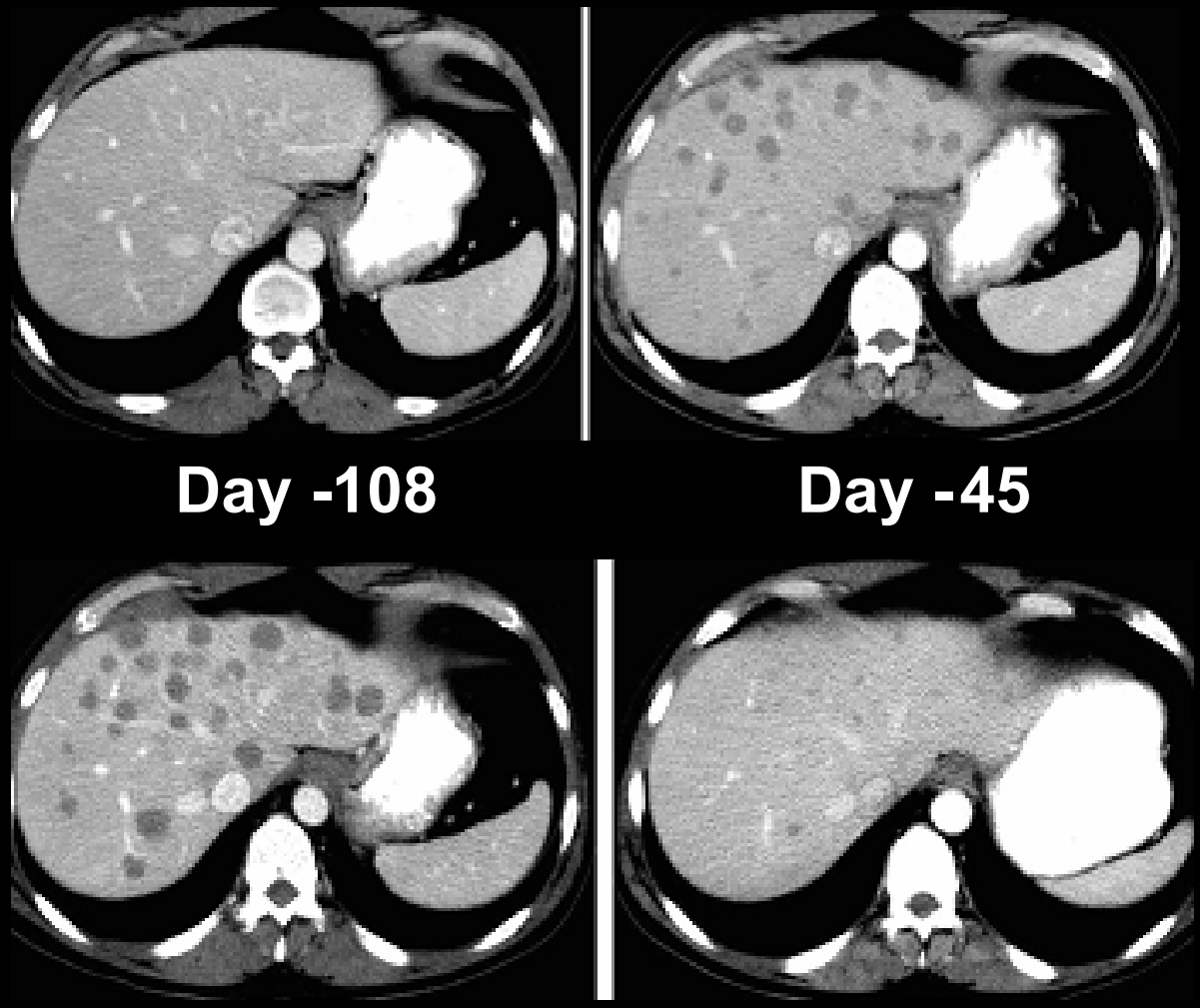


Clinical response following lymphodepletion + T-lymphocyte infusion





Clinical response following lymphodepletion + T-lymphocyte infusion



Day -108 Day -45

Day -25 Day +34

Clinical response following lymphodepletion + T-lymphocyte infusion

# Patients Enrolled	CR	PR	Total
35	4	14	18 (51%)

***Science*. 2002 Oct 25;298(5594); J Clin Oncol 2005 April; 23(10):2346-57**

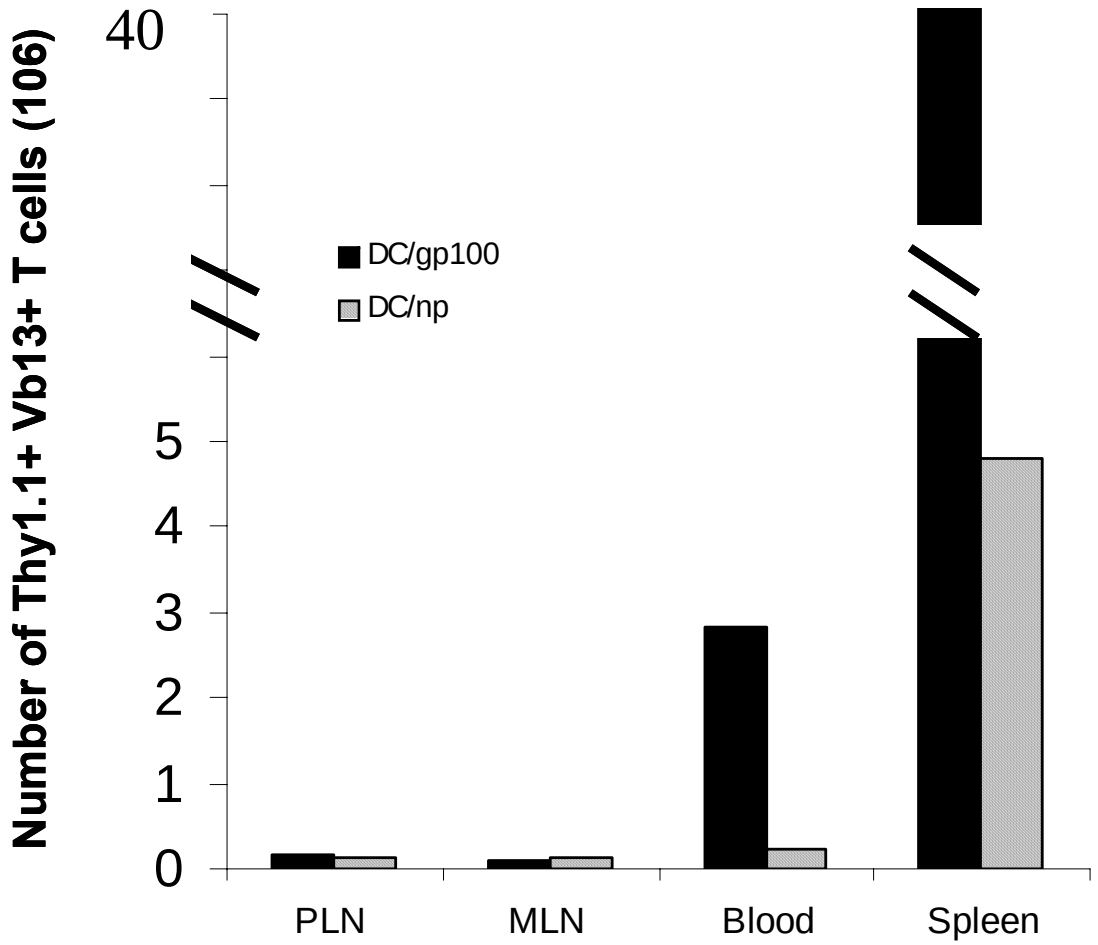
Challenges of adoptive cell therapy

- Rigorous therapy requiring excellent performance status
- Accessible tumor required to generate TIL
- Adequate numbers of tumor specific T-cells are only generated in approximately 40% of patients
- 4 – 6 weeks are required for the generation of T-cells
- Migration of T-cells to the tumor is suboptimal

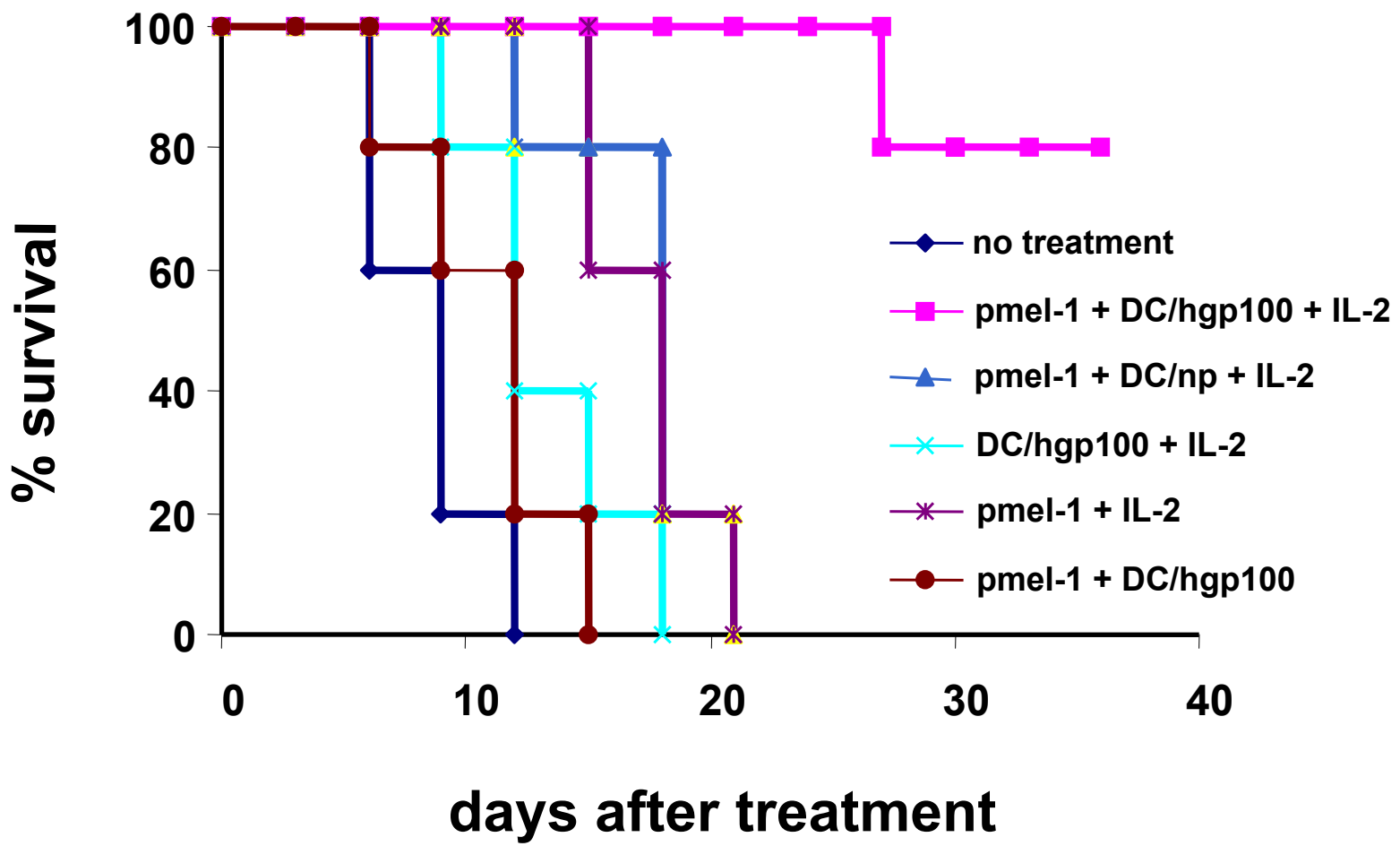
Improving adoptive immunotherapy

- **Enhance T-cell persistence**
- **Improve migration to tumor**
- **Improve recognition of the tumor**

DCs Increase the Numbers of Infused T-Cells in Blood and Spleen



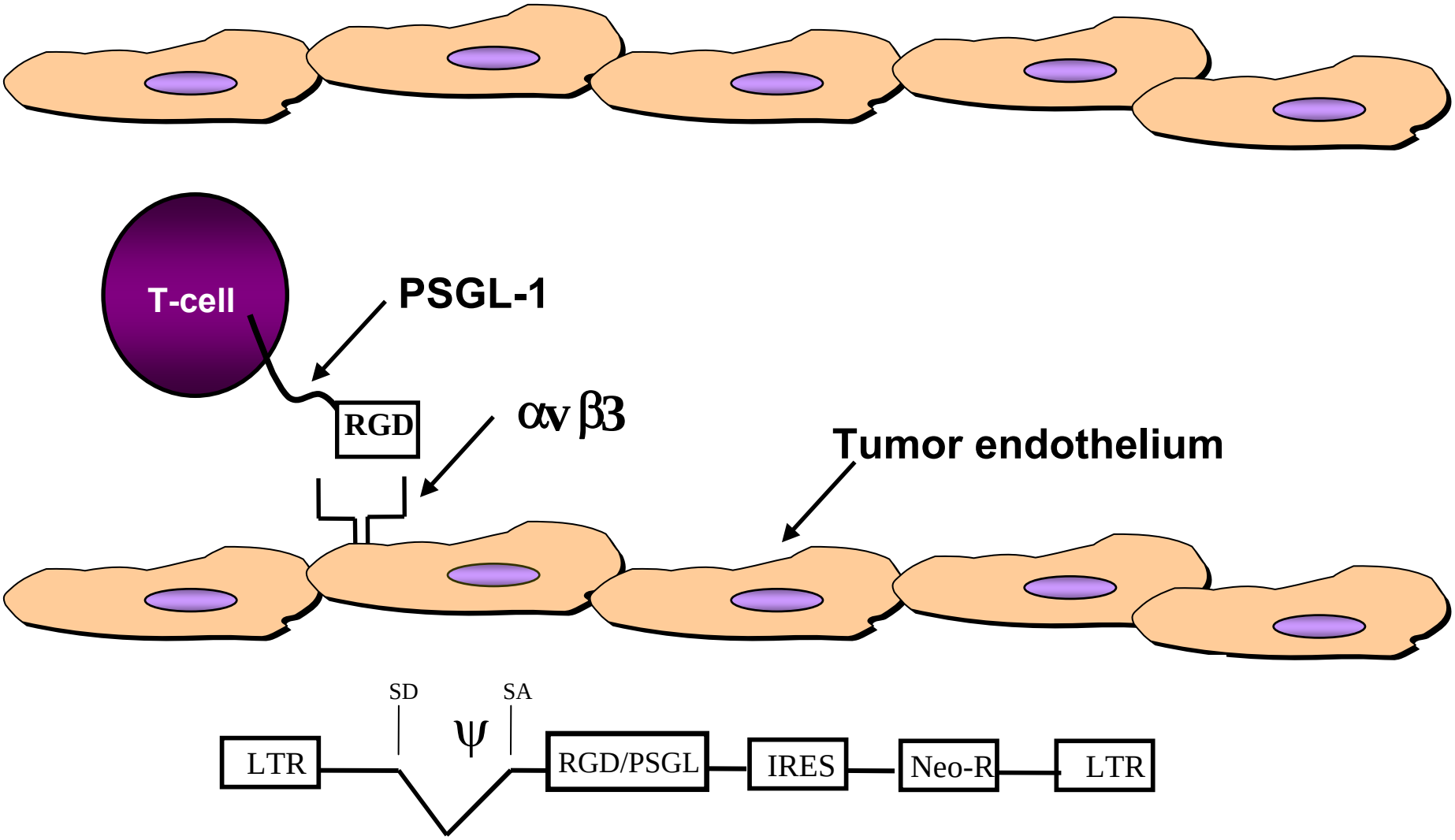
Survival is Increased in a Mouse Model by Combining Dendritic Cells & T-cells



Improving adoptive immunotherapy

- Enhance T-cell persistence
- Improve migration to tumor
- Improve recognition of the tumor

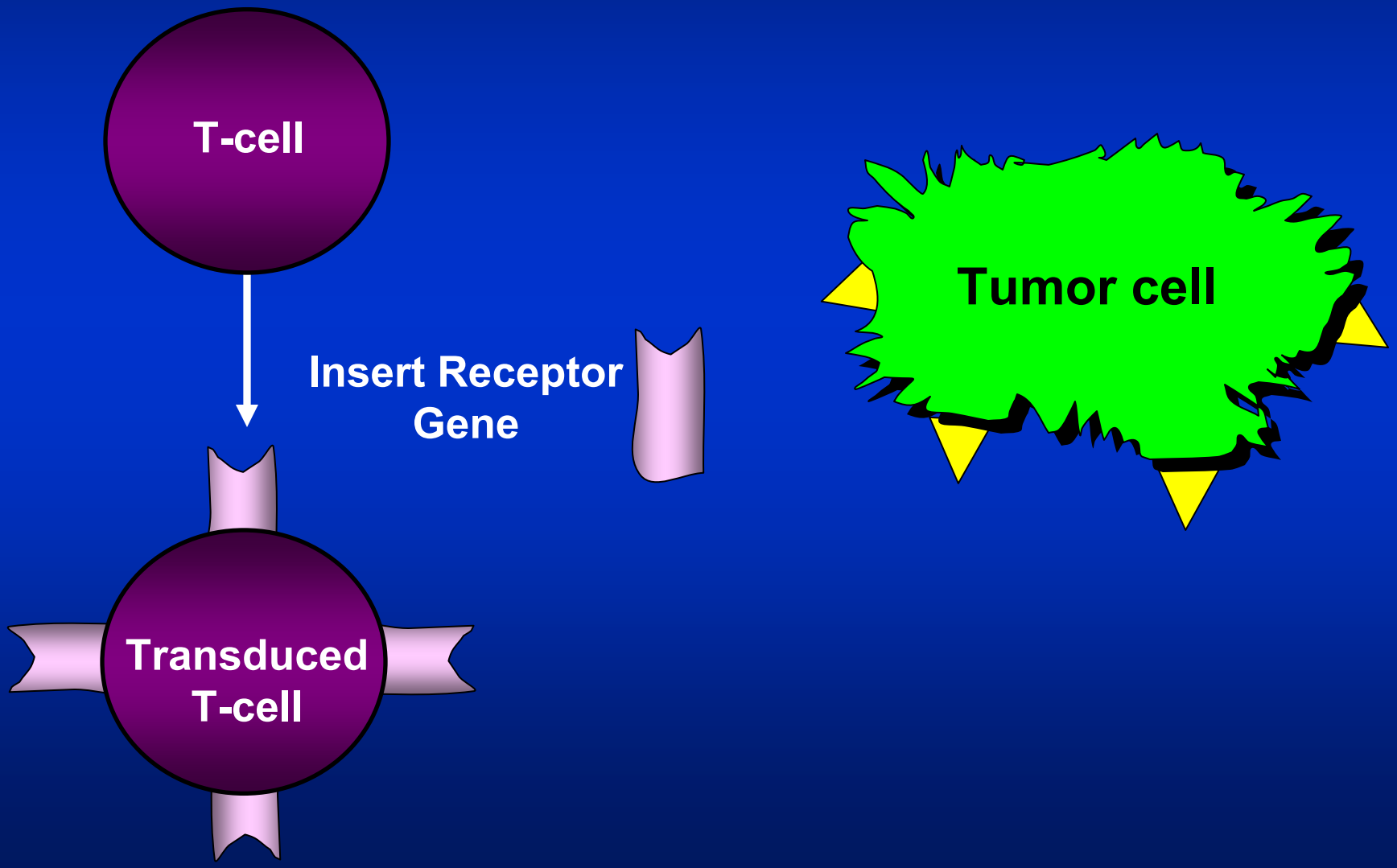
Transduction of T-cells with receptors to enable them to “See” tumor vasculature



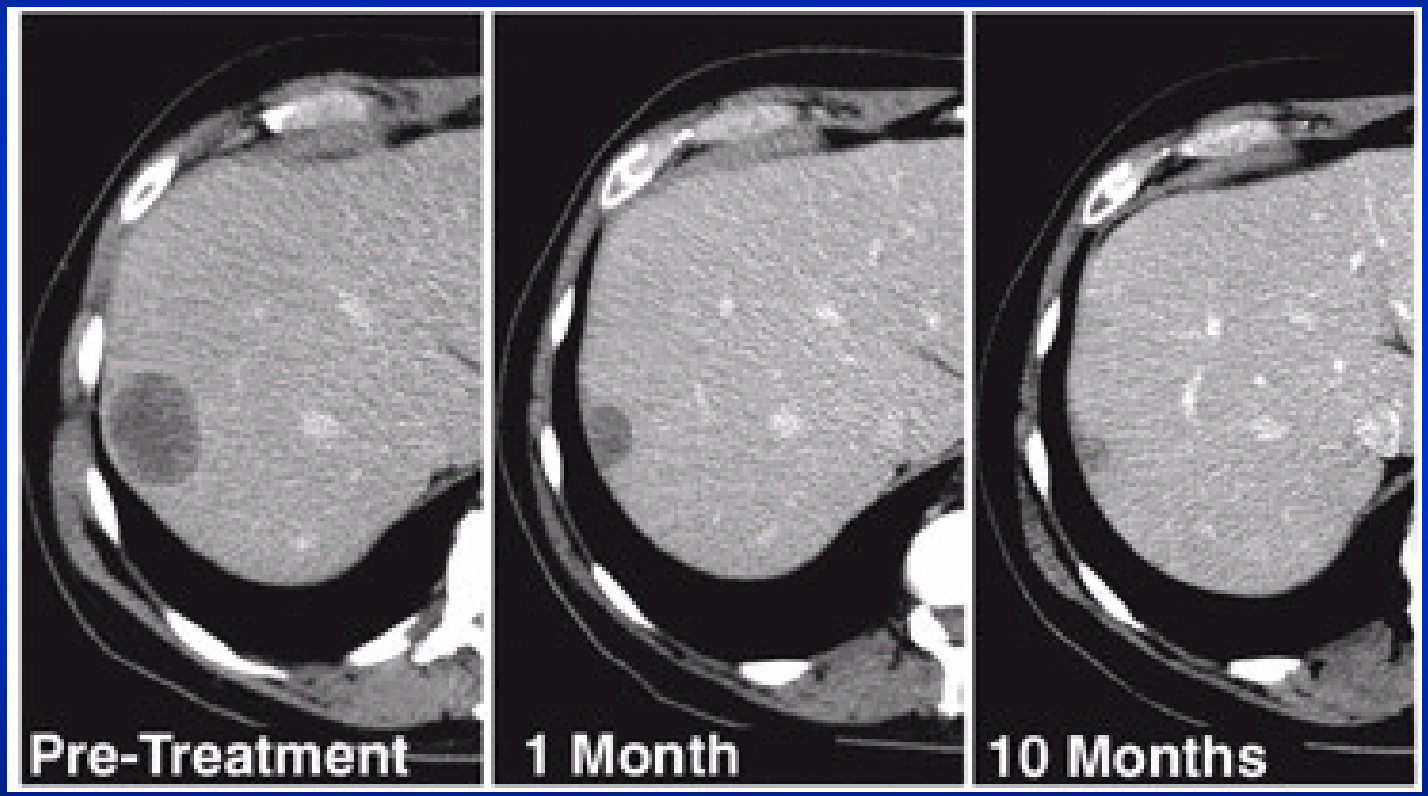
Improving adoptive immunotherapy

- Enhance T-cell persistence
- Improve migration to tumor
- Improve recognition of the tumor

Transduction of T-cells with receptor genes to direct T-cell specificity



Cancer regression in patients after transfer of genetically engineered lymphocytes



Morgan RA, et al.
Science 314:126-129

Summary

- The infusion of antigen specific T-cells can:
  - be effective in patients to induce tumor regression.
  - decrease viral infections post-transplant.

- T-cell therapy can be more potent than cytokine or vaccine therapy, possibly because expansion and activation of T-cells can be controlled in the laboratory in a non-immunosuppressive environment.

- Future studies will rely on rational combinations of adoptive therapy with active immunization, as well as with other immune adjuvants and targeted therapies.