20th Annual Scientific Meeting of the Society for Biological Therapy

Primer in Tumor Immunology Educational Course: November 10, 2005

Cancer Immunotherapy with T Cells: Vaccines and Adoptive Immunotherapy

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Outline: T Cell & Vaccine Therapy

- Cancers can be cured by immune T cells
  - Hematologic malignancy can be cured by allogeneic T cells
  - Solid tumors can also be treated with allogeneic T cells, but less effectively
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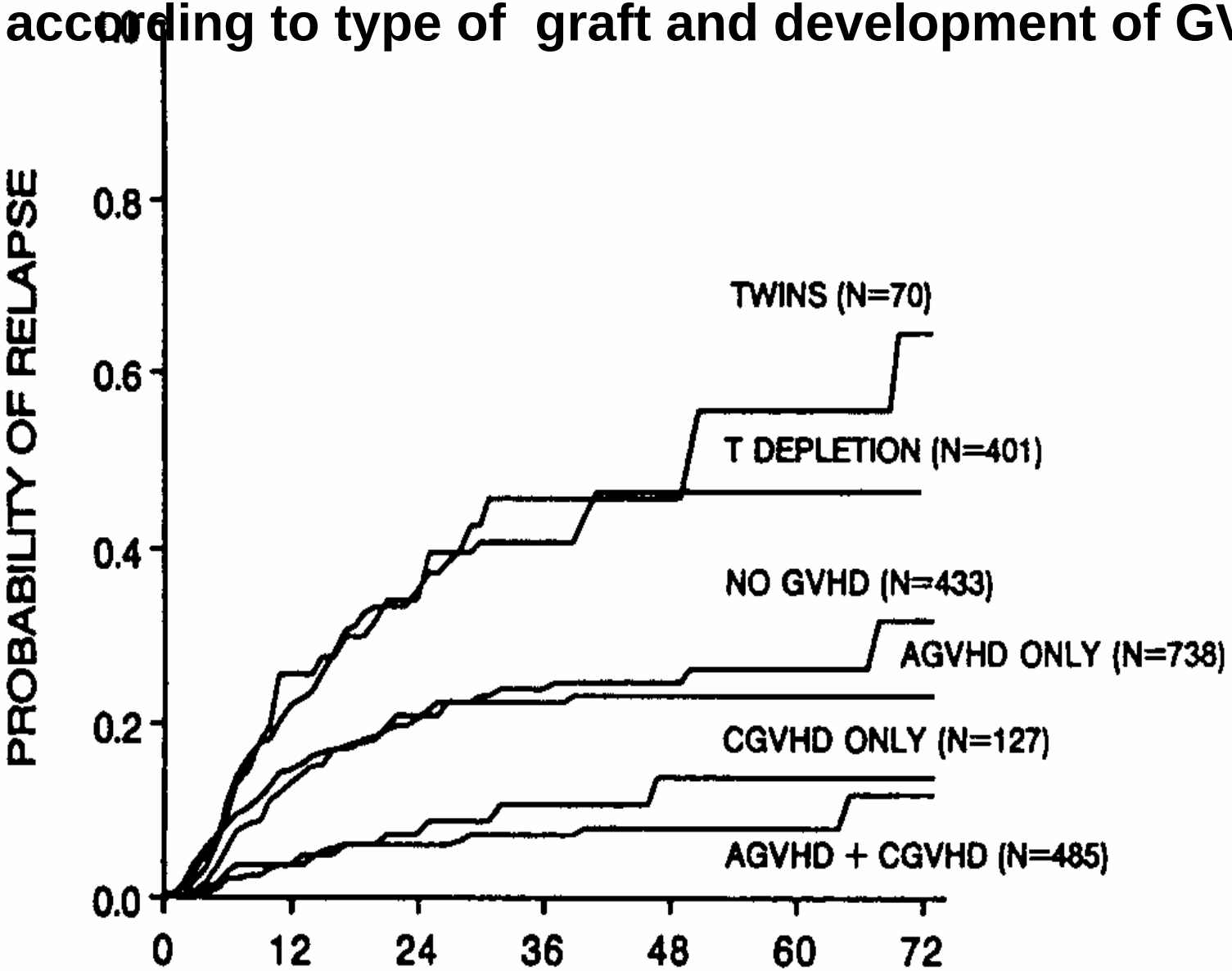
Probability of relapse after BMT for early leukemia varies according to type of graft and development of GVHD



(Horowitz et al. BLOOD 75:555, 1990)

Complete Response to Donor Lymphocyte Infusion as Therapy for Relapse after HLA-Matched Hematopoietic Cell Transplant

Chronic myeloid leukemia	
Cytogenetic/molecular relapse	40/50 (80)
Hematological relapse	88/114 (77)
Accelerated phase/blast crisis	13/36 (36)
Acute myeloid leukemia/myelodysplastic syndrome	15/58 (26)
Acute lymphoblastic leukemia	3/20 (15)
Multiple myeloma	5/17 (29)
Non Hodgkin lymphoma	–

(Baron & Storb, Semin Immun 26, 2004)

Major Problem of Allogeneic Transplant

- Donor T cells that mediate the graft vs. leukemia effect (GVL) commonly mediate severe and lethal GVHD

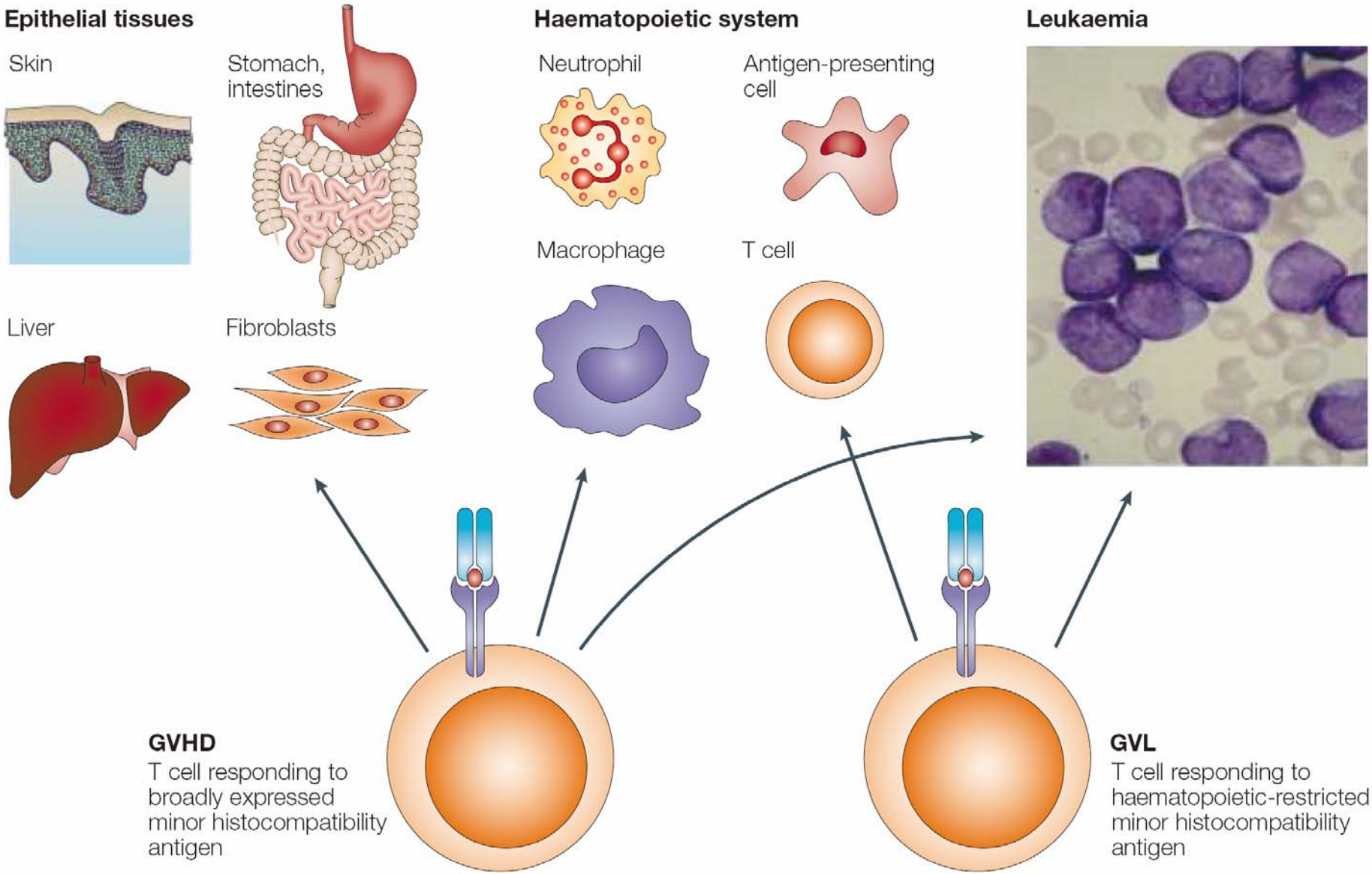
Tissue Targets of GVHD vs. GVL

- GVHD
  - Skin
  - Gut
  - Liver
  - Hematopoietic cells
    - Normal cells
    - Leukemia cells
- GVL
  - Hematopoietic cells
    - Leukemia cells
    - Normal cells

Molecular Targets of GVHD vs. GVL

- Peptides from segments of polymorphic proteins that differ between donor and host
  - AKA, minor histocompatibility Ag
- GVHD dominates, if dominant response is to polymorphic proteins expressed primarily by skin, liver and/or gut
- GVL dominates, if dominant response is to polymorphic proteins expressed primarily by hematopoietic cells
- Examples of potential dominant GVL targets
  - Polymorphic segments of hematopoietic differentiation Ag
  - Leukemia specific antigens
    - e.g. bcr-abl joining region segment
  - Aberrantly expressed leukocyte differentiation antigens
    - e.g., WT1, proteinase 3

Organ Targets of Graft vs. Host Disease & Graft vs. Leukemia



(Bleakley & Riddell,Nat Rev 4:2004)

Standard vs. Mini-Transplant

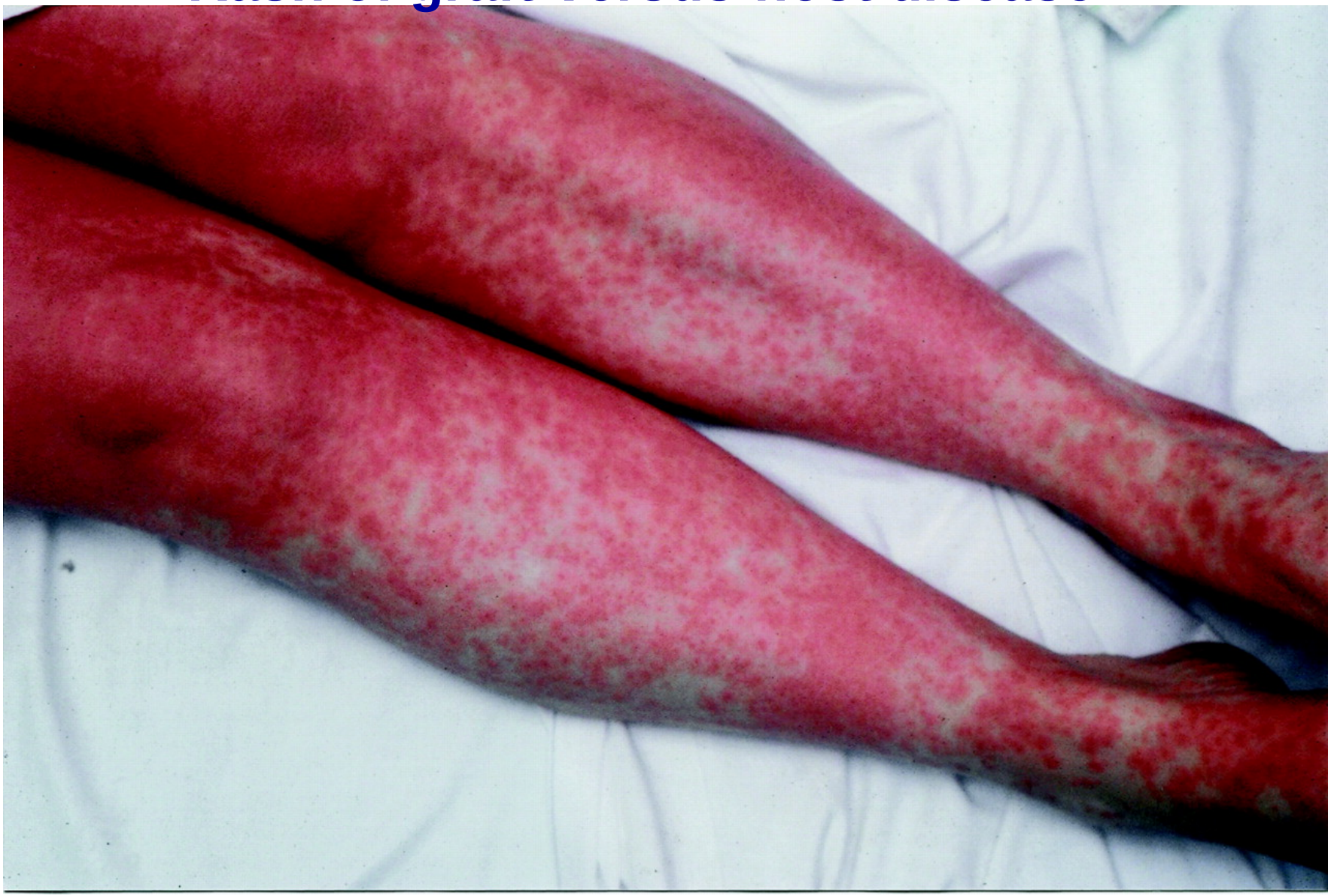
- Standard Transplant (myeloablative)
  - High dose chemotherapy/radiation therapy
    - Eliminates hematopoietic cells (normal & leukemic)
    - Prevents rejection of transplant
  - Leukemia eliminated by both chemotherapy/radiation and GVHD/GVL
- Mini-Transplant: low intensity (non-myeloablative)
  - High dose immunosuppression
    - Prevents rejection of transplant
  - Leukemia eliminated exclusively by GVHD/GVL
- Results
  - Less chemotherapy/radiation therapy related deaths
  - Common GVHD deaths
  - GVHD/GVL is therapeutic in some patients

Mini-Transplants for Leukemia

- 305 patients
  - 46% acute GVHD
    - 15% grade III/IV
  - 43% chronic GVHD
- 45% 2-year mortality
  - 23% Relapse
  - 22% Non-Relapse Mortality
- 40% 2-year relapse free survival

(Baron & Storb, Semin Immun 26, 2004)

Rash of graft-versus-host disease



Leger, C. S. et al. CMAJ 2004;170:1569-1577

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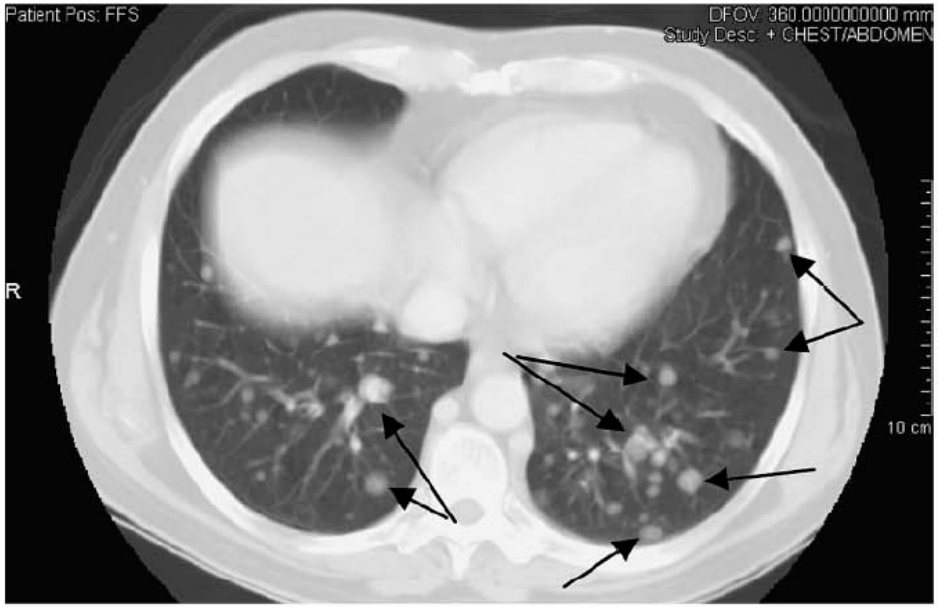
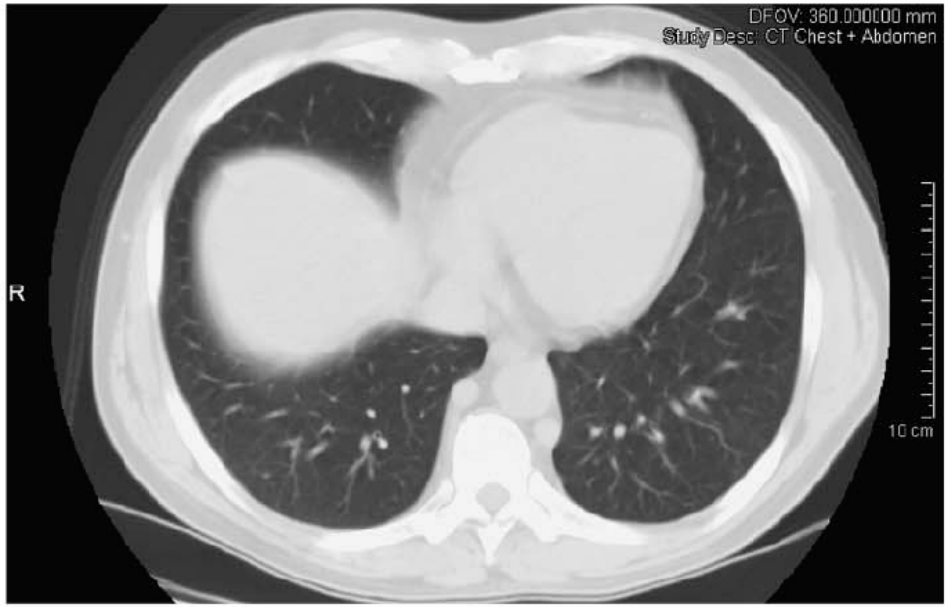
Mini-Transplants for Renal Cell Cancer

- Cumulative data - 6 studies
- 70 patients
  - 6% CR (4 pts)
  - 29% PR (20 pts)
  - 35% Total Response
  - 24% Regimen mortality (17 pts)

(Lundqvist & Childs, J Immunother 28:281, 2005)

(Durable GVT Effect: Metastatic Renal Cell Cancer



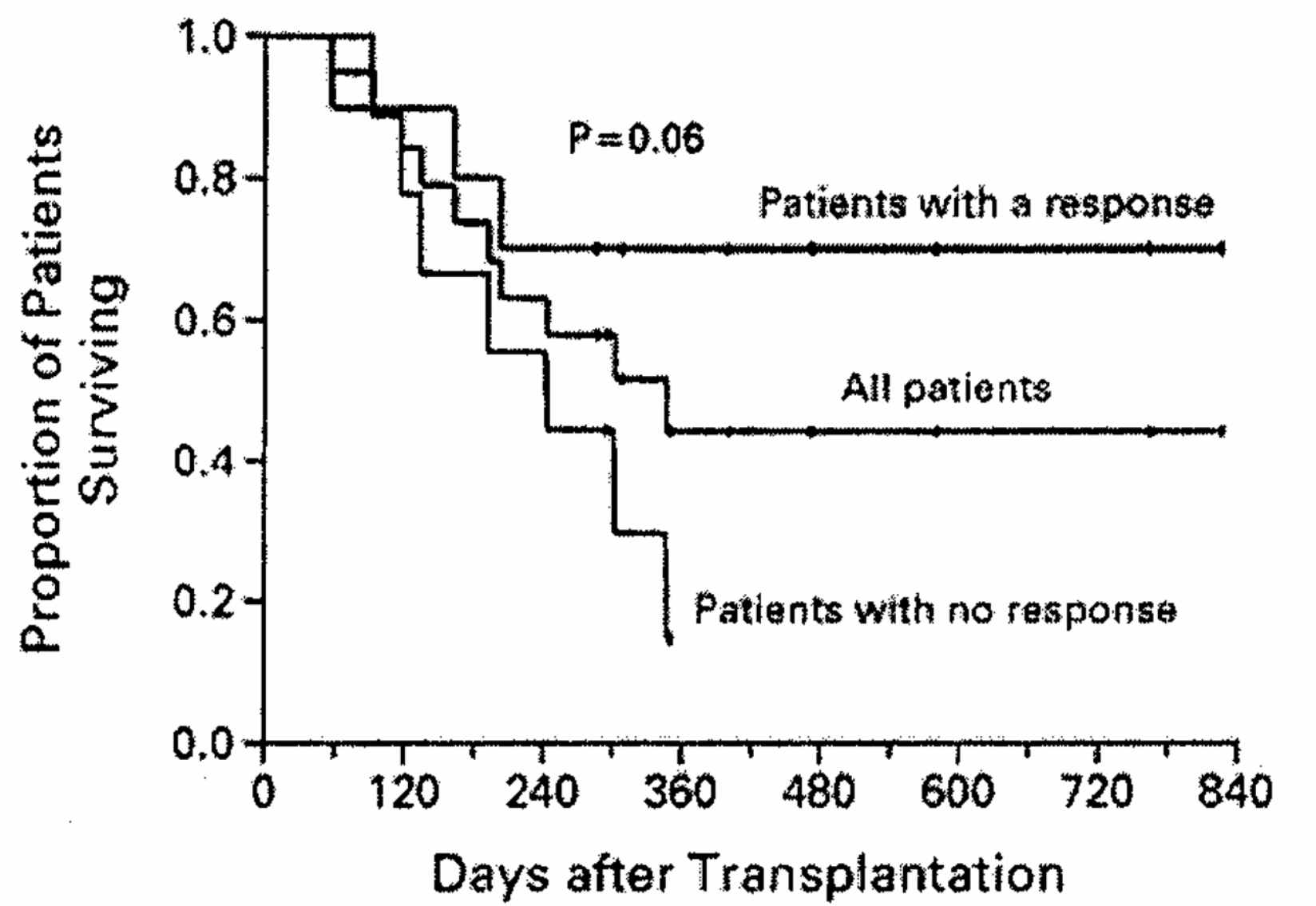


30 Days

7 Years

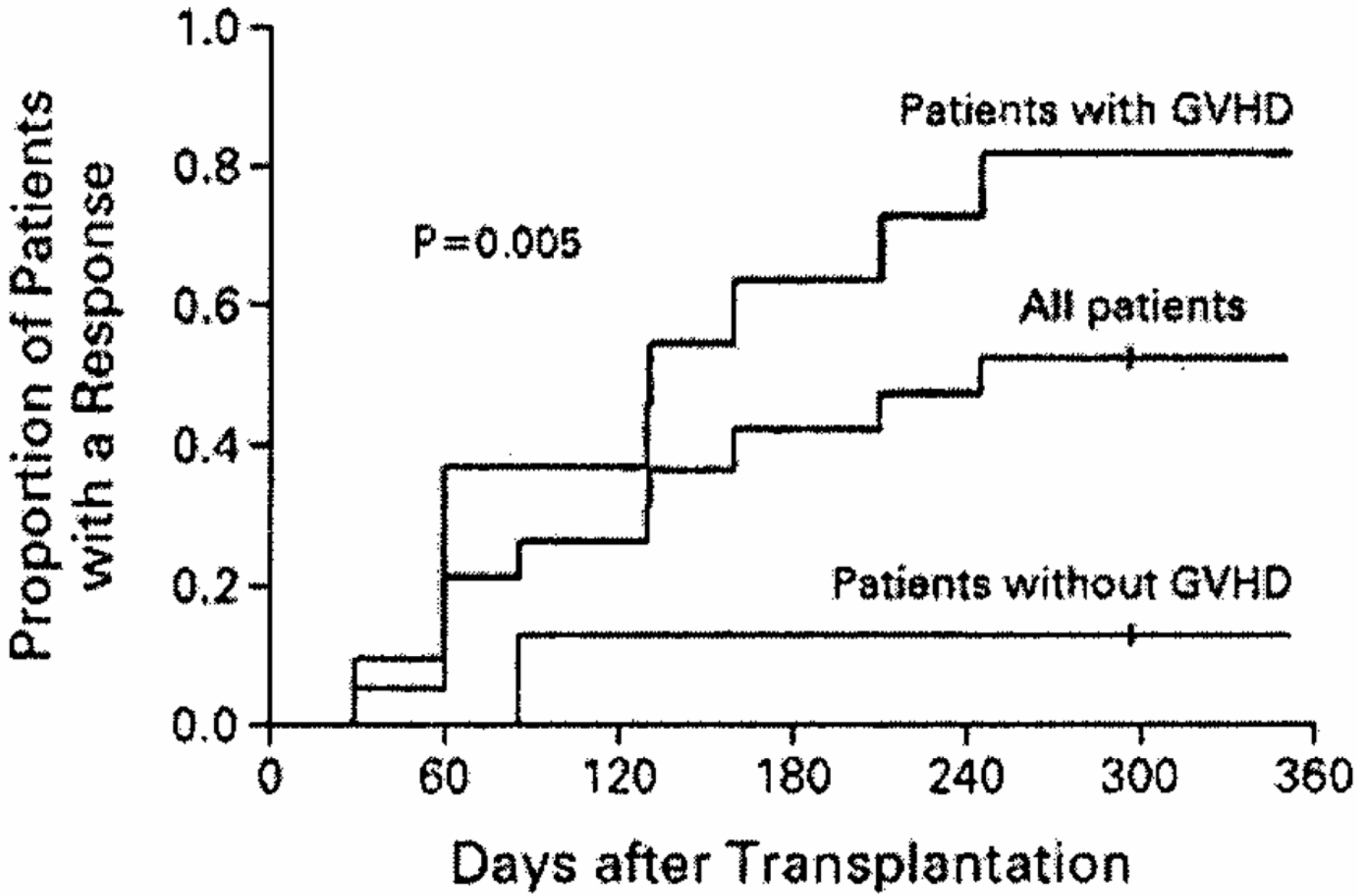
(Lundqvist & Childs, J Immunother 28:281, 2005)

Association of Response with Survival in RCC



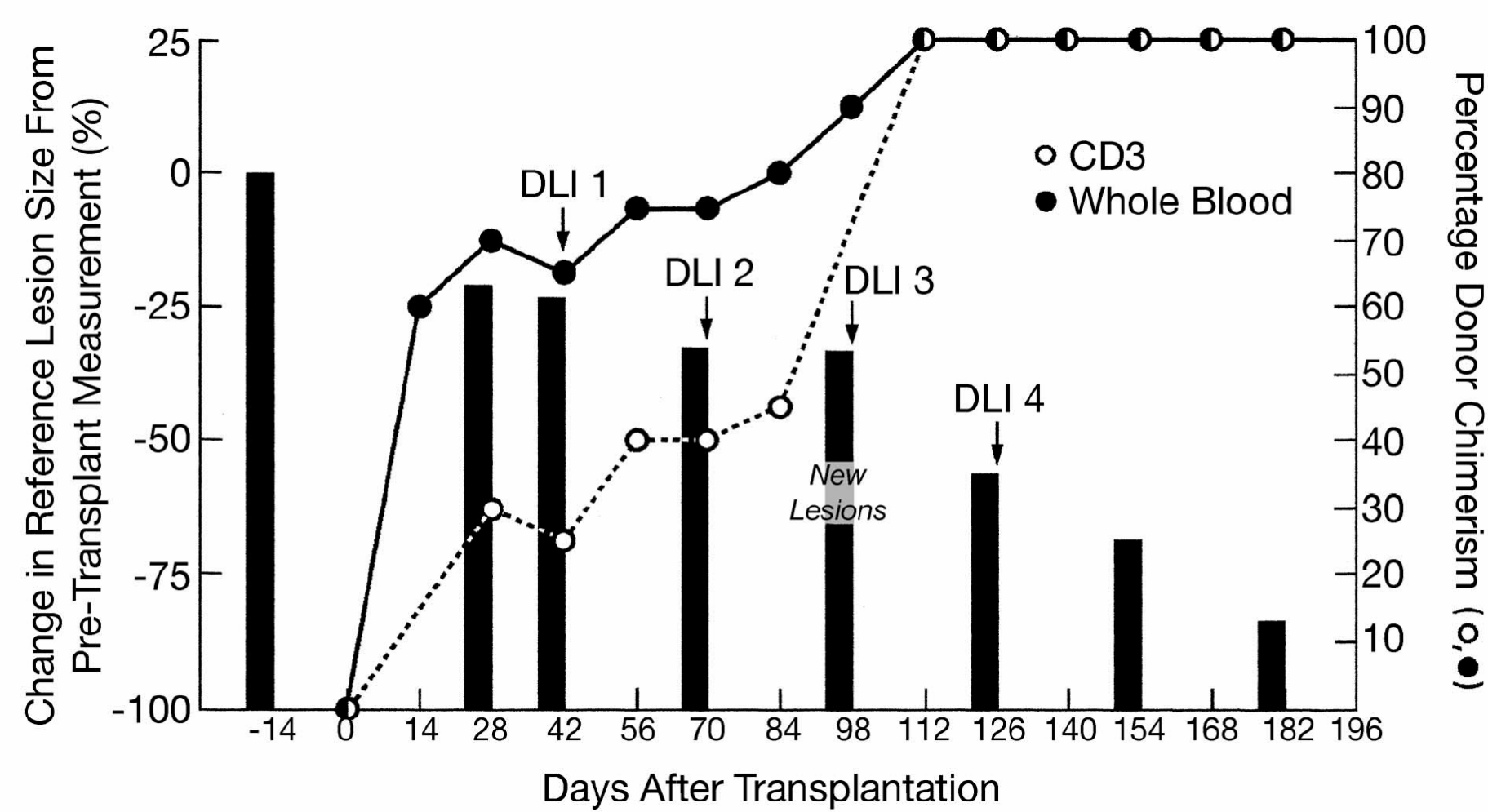
(Takahashi & Childs, ClinCaRes 10:6353s, 2004)

Association of GVHD with Response in RCC (n=19)



(Takahashi & Childs, ClinCaRes 10:6353s, 2004)

Course of Breast Cancer Response to Hematopoietic Cell Transplant + Donor Lymphocyte Infusion



(Bishop et al JCO 22:3886, 2004)

Allogeneic Transplant Conclusions

- Cancers can be cured by immune T cells
  - Hematologic malignancy can be cured by allogeneic T cells
  - Solid tumors can also be treated with allogeneic T cells, but less effectively
- Highly toxic with a high proportion of treatment related deaths

- Major question for tumor immunology:

  Can autologous tumor immune T cells reproduce the therapeutic efficacy of allogeneic transplant without the inordinate toxicity?

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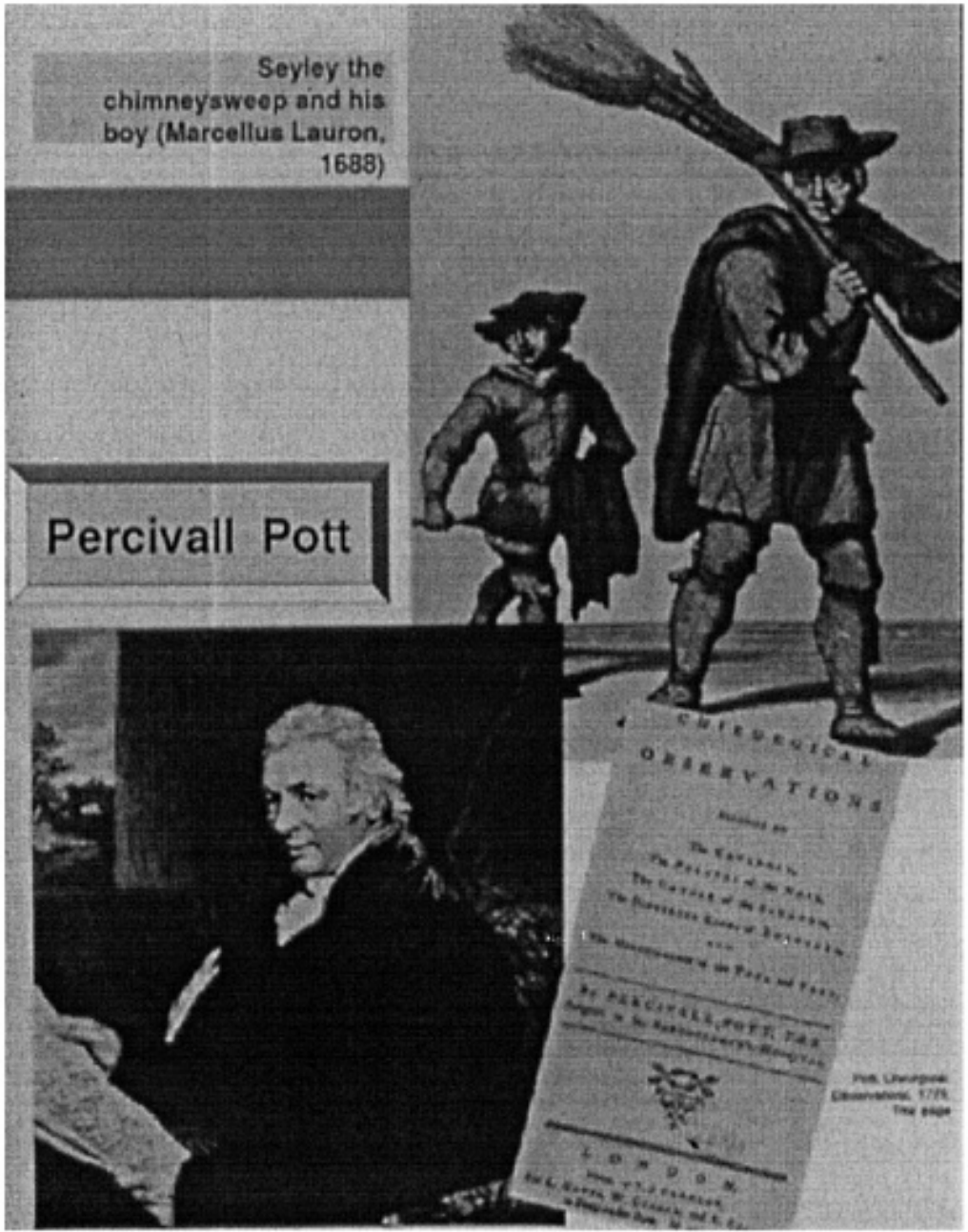
Questions

- Is cancer immunogenic?
- What are the immunogenic targets?

Cancer

- Uncontrolled growth
- Progeny of a single transformed cell
- Multi-step process
- Multiple genetic alterations occurring over many years
- Cumulative effect of genetic alterations on control of cell growth and differentiation

Carcinogenic Polycyclic Hydrocarbons



Animal Studies: Tumors Can Elicit Immunity and Immunity Can Protect

- Methylcholanthrene (MCA) induces sarcomas which are progressive and fatal in primary host
  - Resection yields cures
  - Implant into secondary host yields progressive tumor.
  - Reimplant into primary host yields rejection:
    - Specific
    - T cell-mediated
- Major challenge: To manipulate the primary host to augment the existent but ineffective host response to promote tumor eradication

Tumor Antigen Classification

- Tumor-specific antigens
  - Expressed only on tumors
    - Unique
    - Shared
- Tumor-associated antigens
  - Expressed on normal cells
  - Qualitative or quantitative different on tumor

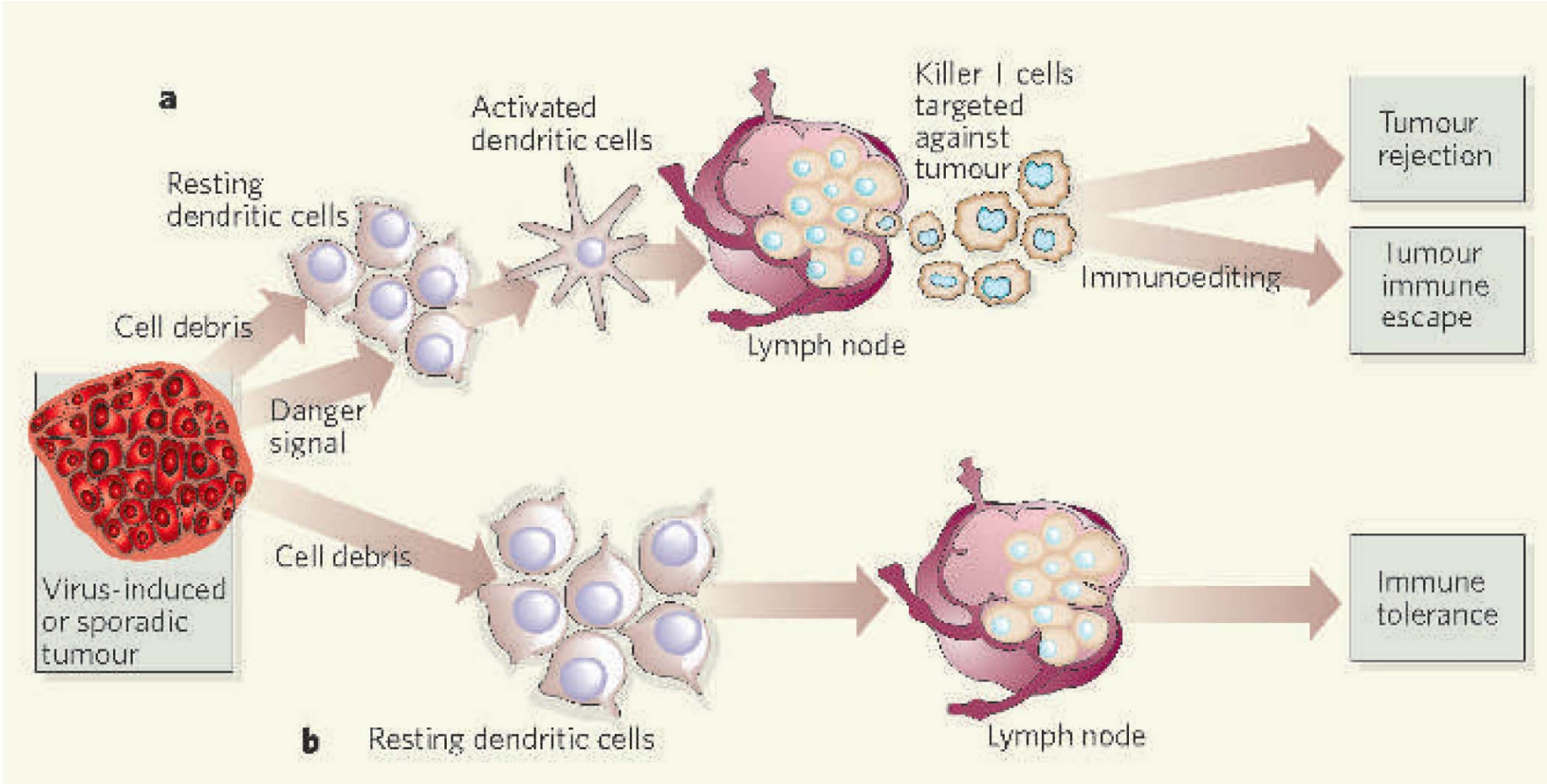
Tumor-Specific Antigens

- Products of genes mutated by chemical & physical carcinogens
  - Normal genes--random DNA mutations
  - Cancer-related genes--non-random DNA mutations
    - ras, p53, bcr-abl
- Antigen receptors
  - Surface immunoglobulin on B cell tumors
  - T cell receptor on T cell tumors
- Oncogenic viruses
  - MuLV, FeLV
  - HTLV, HPV, EBV

Tumor-Associated Antigens

- Normal cellular gene products
  - Oncofetal antigens
    - CEA, alpha-fetoprotein, p97
  - Cancer-testis antigens
    - MAGE-1,3
- Differentiation and lineage-specific antigens
  - MART-1, gp100, tryrosinase, TRP-2
  - PSA, PAP, PSCA, PSMA, Prostein
  - MUC1, EpCam, gangliosides, RBC antigens
  - Proteinase 3
- Overexpressed transformation related proteins
  - p53, HER-2/neu, WT1

Escaping the Immune System - a Model



(Melief, Nature 437:41, Comment on Willimsky & Blankenstein Nature 437:141 2005)

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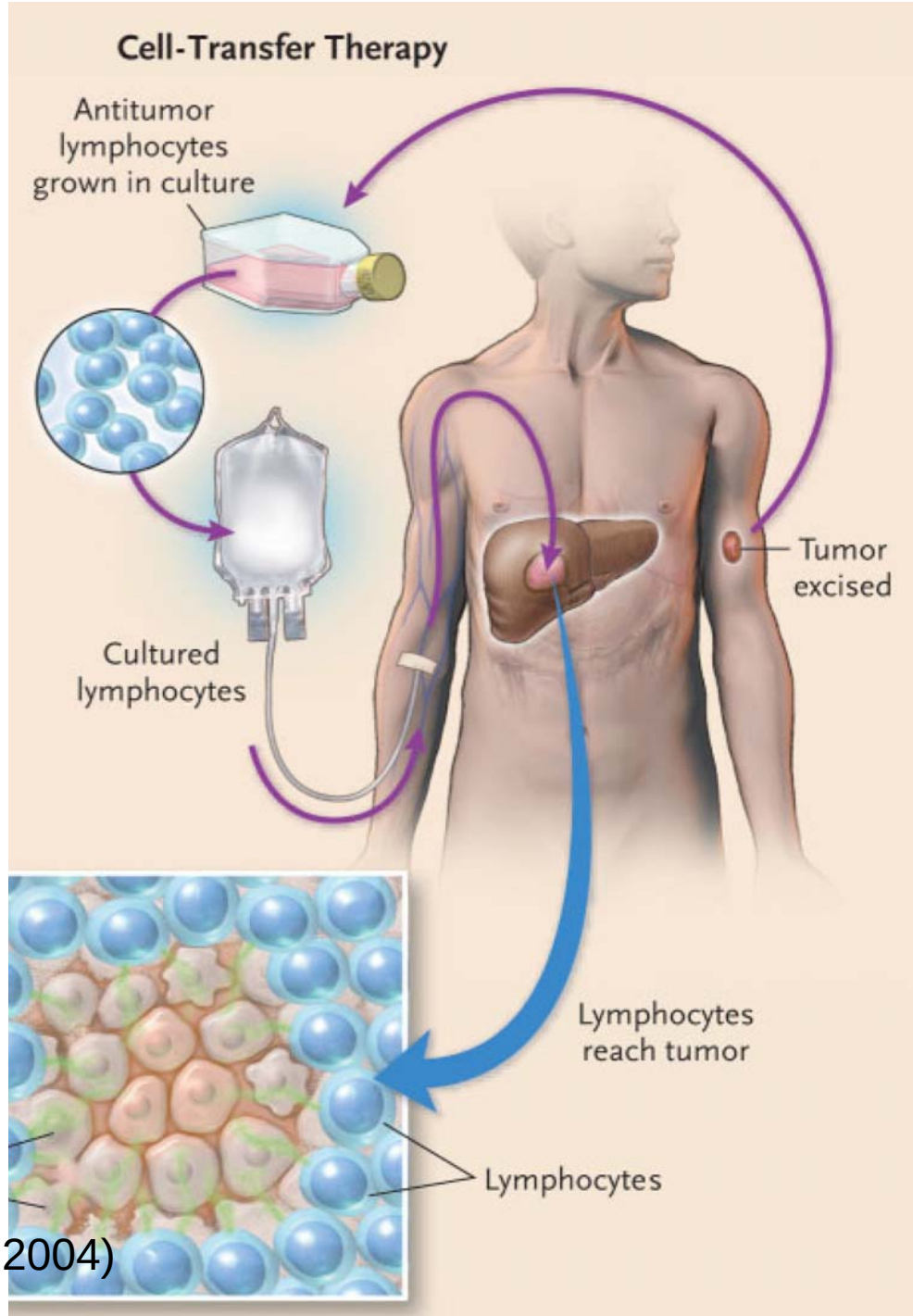


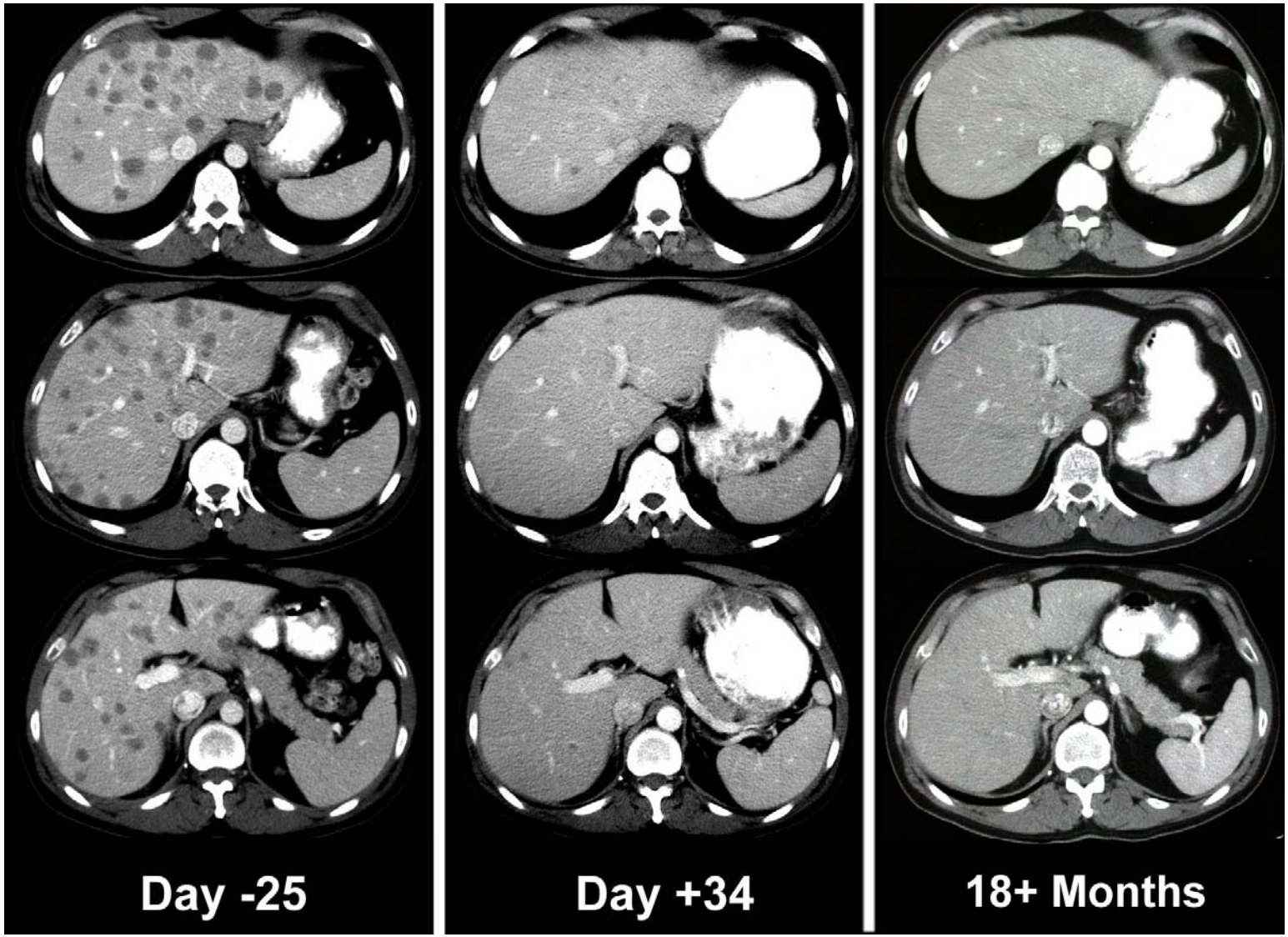
(Rosenberg NEJM 350:14, 2004)

"Adoptive Cell Transfer Therapy Following Non-Myeloablative but Lymphodepleting Chemotherapy for the Treatment of Patients With Refractory Metastatic Melanoma"

- 35 pts
- Refractory to high dose IL2
- Regimen
  - Lymphodepleting chemotherapy
  - Autologous tumor-reactive culture expanded T cells
- 18 of 35 (51%) Responders
- 3 (9%) CR – all ongoing (7+, 14+, 24+ months)
- 15 (43%) PR
  - Median duration 11.5 months
  - 3 ongoing (13+, 16+, 30+ months)
- **At least 50% of melanoma tumors cannot completely resist immune attack!**

(Dudley JCO 23:2346, 2005)

Patient 31: Mart-1 Reactive TIL



Dudley et al. JCO (2005)

"Adoptive Cell Transfer Therapy Following Non-Myeloablative but Lymphodepleting Chemotherapy for the Treatment of Patients With Refractory Metastatic Melanoma"

- Requires
  - Evident tumor
  - Multiple cultures/patient
  - 6-8 weeks of culture
- Most effective with high-dose toxic chemotherapy
  - 2 with Pneumocystis pneumonia
  - 1 with EBV lymphoma
  - 1 cortical blindness, progressive multifocal neuropathy
- TIL not uniformly available
  - Obtainable in 81% of patients attempted
  - Fewer than 81% treatable
- Effect on overall survival unknown

(Dudley JCO 23:2346, 2005)

Melanoma T Cell Therapy Lessons

- Antigens expressed by tumors can elicit immune responses.
  - Immune T cells can existent in cancer patients and co-exist with cancer cells
  - Cancers can grow despite existent immune T cells
- Antigen-specific T cells can treat established malignancy.
  - Ineffective T cells can be rendered effective by in vitro growth and treatment with increased numbers
- Tumor antigens need not be tumor specific
  - T cell targets can be tissue-specific differentiation antigens

Can Vaccines Increase the Number of Immune T Cells In Vivo and Thereby Reproduce the Therapeutic Effects of T Cell Therapy?

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Cumulative Results: NCI Trials of Solid Tumor Vaccines for Metastatic Disease

- Background
  - 440 patients
  - 96% had melanoma
  - All metastatic
  - Variety of vaccines- peptide, virus-vector, tumor cell, dendritic cell, heat shock protein
- Outcome
  - 1% CR - 4 pts
  - 2% PR - 9 pts
  - 97% NR - 428 pts
  - 2.6% Overall response - 13 pts

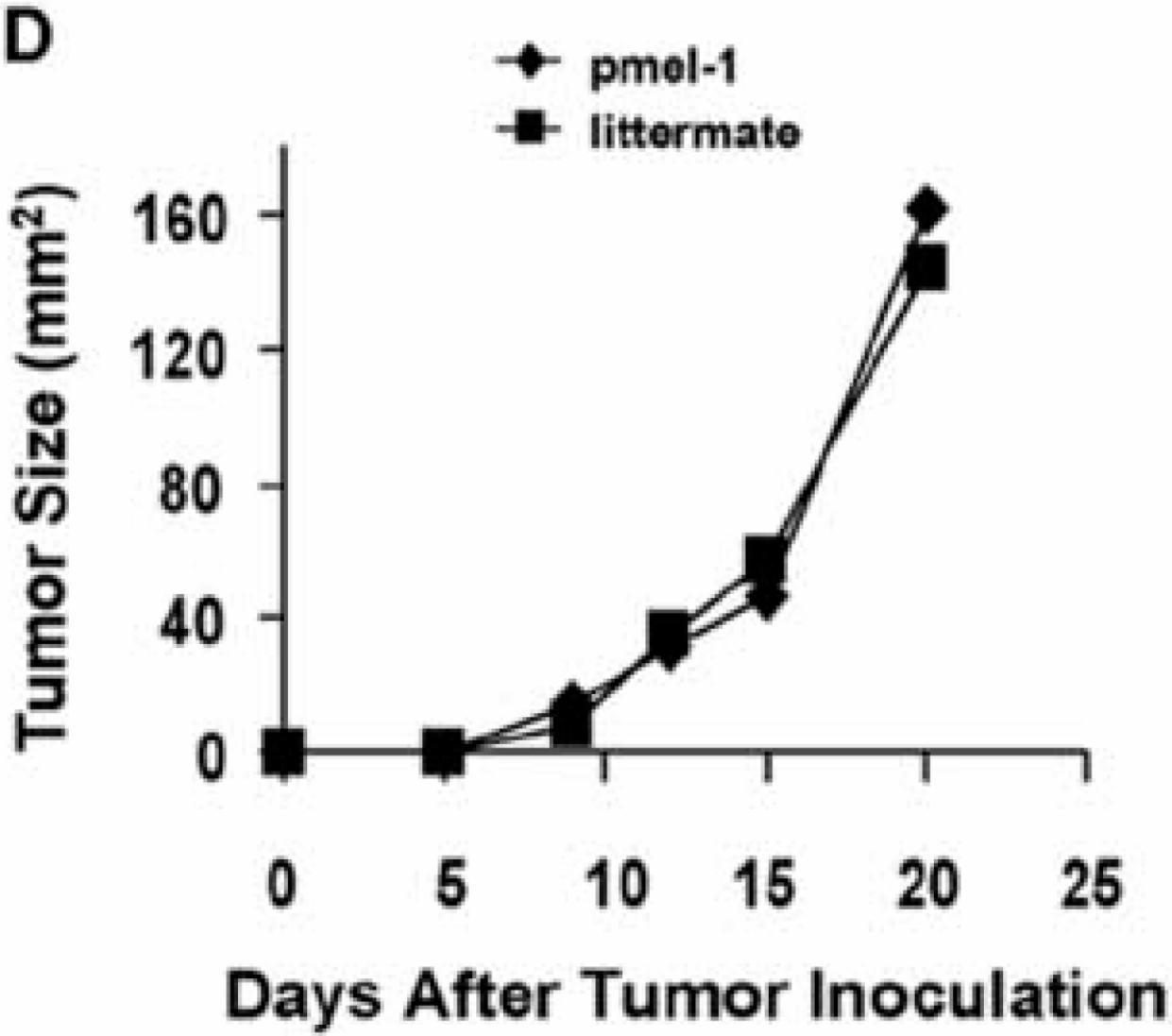
(Rosenberg et al; Nature Med,10:2004)

“Tumor Regression and Autoimmunity after Removal of a Functionally Tolerant State of Self-Reactive CD8+ T Cells”

- Pmel-1(gp100) TCR transgenic mice
- B16 melanoma grew normally in pmel-1 TCR TG mice
- Peptide vaccine resulted in only modest delay in subcut tumor growth
- Adoptive transfer of T cells plus vaccine induced T cell infiltration into tumors, but no marked tumor cell death
- Plus IL-2 - extensive tumor cell death and loss of tissue integrity

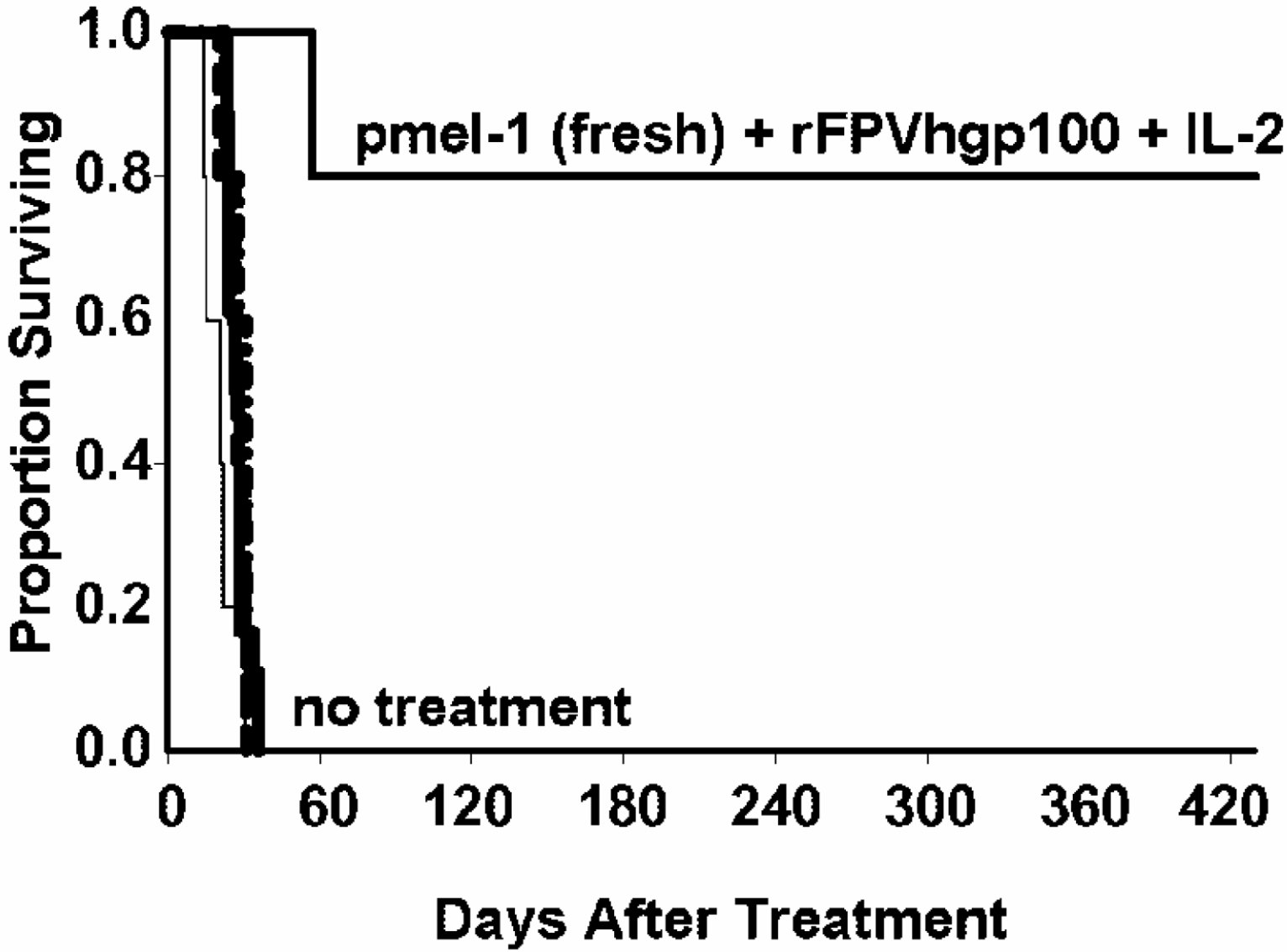
Overwijk (Restifo) JEM 189:569, 2003

Unimpeded Growth of Antigenic Tumor in TCR TG Mice



Overwijk (Restifo) JEM 189:569, 2003

Therapy with T Cells + Vaccine + IL-2



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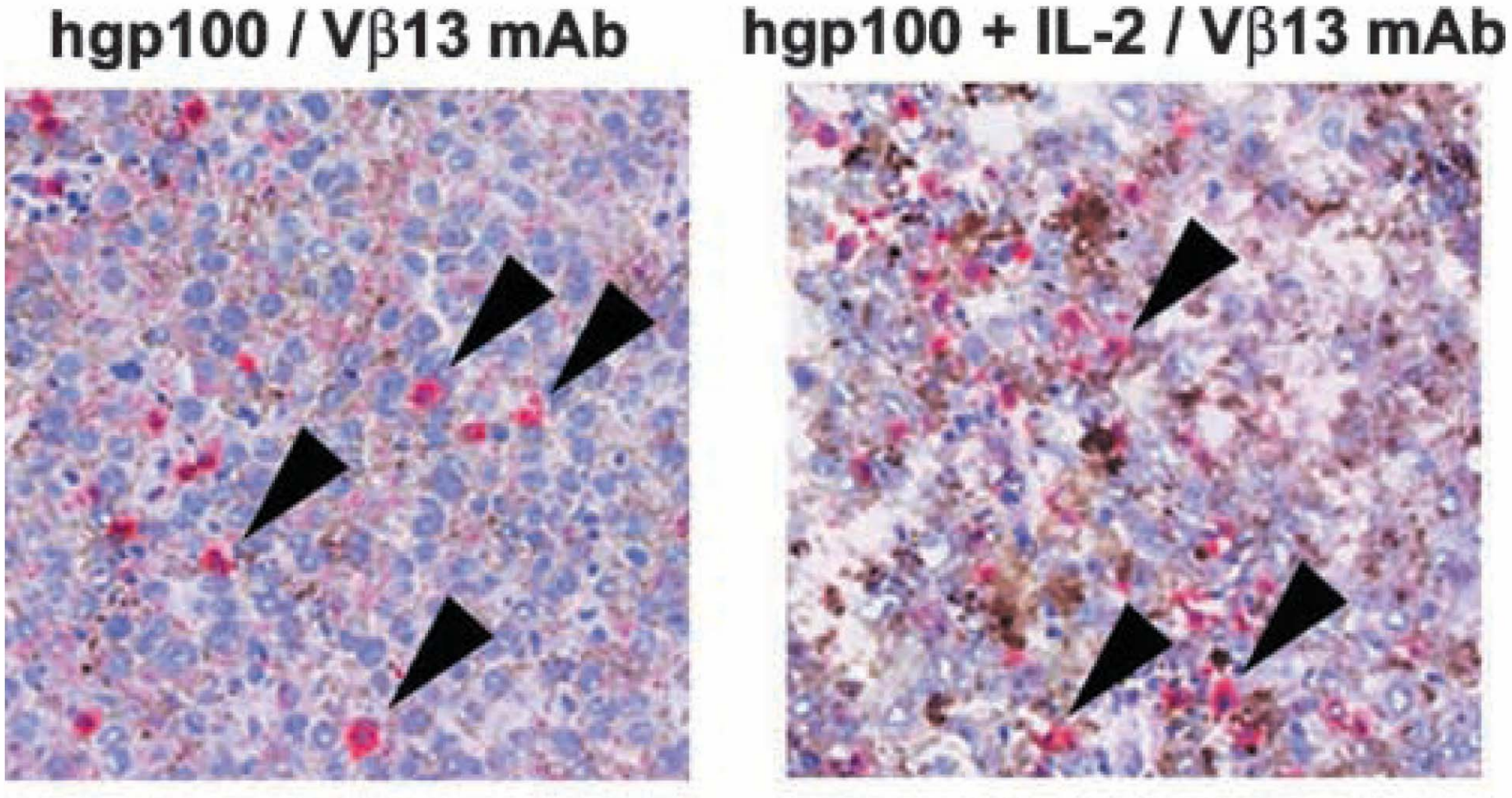
T Cells + Vaccine

T Cells + Vaccine + IL-2



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- The presence of overwhelming numbers of Pmel specific T cells (>95% of CD8+ T cells) did not impact on tumor growth
- Large numbers of antigen specific T cells are necessary, but not sufficient
- One effective regimen employed T cell transfer + vaccine + IL-2
- Other regimens should be as or more effective

Overwijk (Restifo) JEM 189:569, 2003

“Human Tumor-Specific T Lymphocytes: Does Function Matter More Than Number?”

- Not a tight correlation between vaccine induced T cell response and detectable clinical benefit
- Some pts have a strong response without clinical benefit
- Some pts respond with few detectable anti-tumor T cells
  - Plausible model: anti-vaccine T cells, even at very low frequencies, modify an immunosuppressive environment within a tumor, opening a permissive window for the priming or restimulation of other anti-tumor T cells

(Coulie & Connerotte Curr Opin Imm 17:320, 2005)

Possible reasons for the coexistence of tumor cells with primed tumor-specific T cells

- Tumor resistance
- Lymphocyte quiescence
- Too low lymphocyte: tumor ratio

(Coulie & Connerotte Curr Opin Imm 17:320, 2005)

Possible reasons for the coexistence of tumor cells with primed tumor-specific T cells

- Tumor resistance
  - Environment not permissive to T cell infiltration
  - Decrease of loss or antigen expression
  - Resistance to lysis or to TRAIL- or Fas-induced apoptosis
  - Contact inhibition of T cells (NK inhibitory receptors)

(Coulie & Connerotte Curr Opin Imm 17:320, 2005)

Possible reasons for the coexistence of tumor cells with primed tumor-specific T cells

- Lymphocyte quiescence
  - Shortage of soluble factors (tryptophan, arginine, IL-2, etc.)
  - Inappropriate co-stimulation
  - Immunosuppressive soluble factors (TGF-beta, galectin-1, IL-10, prostoglandins, etc.)
  - Regulatory T cells (Tregs)

(Coulie & Connerotte Curr Opin Imm 17:320, 2005)

Possible reasons for the coexistence of tumor cells with primed tumor-specific T cells

- Too low lymphocyte: tumor ratio
  - Insufficient expansion of anti-tumor T cell clones
  - T cell apoptosis within tumor

(Coulie & Connerotte Curr Opin Imm 17:320, 2005)

Methods to Increase Efficacy of Cancer Vaccines

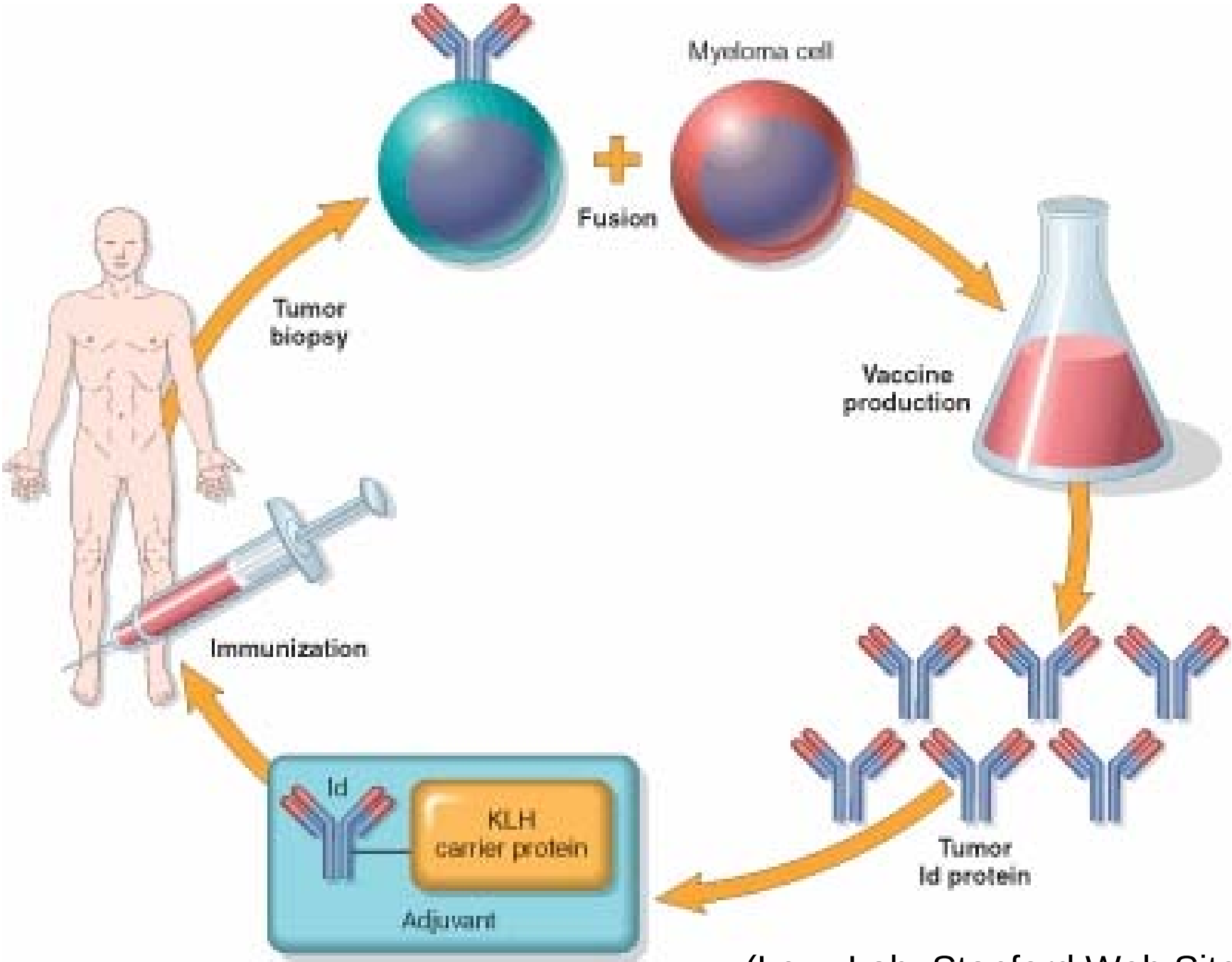
- Increase the number and/or function of effector T cells
- Treat smaller amounts of tumor

Vaccine Therapy of Minimal Residual Disease vs. Evident Disease

- Minimal residual disease
  - Increased effector/tumor ratio
  - Less tumor induced immunosuppression
  - Less chemotherapy/radiation therapy induced suppression
  - Increased time for immune response to function
  - Possibly less protection from established tumor stroma
- Proof of efficacy requires large randomized trials

Vaccine Therapy of Heme Malignancy vs. Solid Tumors

- Trials in hematologic malignancy might offer greater likelihood to develop effective vaccines
  - Lymphoma - anti-idiotype
  - Leukemia - proteinase 3 and WT1
- Possible reasons for better efficacy for heme malignancy
  - Susceptible Targets
    - Leukemia/lymphoma susceptibility to CTL
    - Leukemia/lymphoma susceptibility to Th cytokines
  - Compartment accessibility to T cells



(Levy Lab: Stanford Web Site)

"Complete molecular remissions induced by patient-specific vaccination (Idiotype protein) plus GM-CSF against lymphoma"

- B cell lymphoma
- Immunized to "self" Ig (idiotype determinants)
  - Chemotherapy induced remission
  - Vaccination beginning at 6 months
- Tumor-specific T cells elicited in 19 of 20 patients
- Lymphoma detectable by PCR in 11 patients
- Lymphoma cleared in 8 of 11 patients

(Bendandi et al: Nature Med. 5:1171, 1999)

Proteinase 3 Leukemia Vaccine

- Proteinase 3
  - Normal granulocyte protein; increased in leukemia
  - Peptide-base vaccine (PR1)
- 42 patients were enrolled,
  - 25 AML, 10 CML, 7 MDS
- 22 patients (49%) had an immune response
  - 4 CR
    - 3 AML
    - 1 CML
  - 2 partial remissions
    - 1 MDS
    - 1 CML

(Molldrem ASH Abstract 259. Presented Dec. 6, 2004: Medscape)

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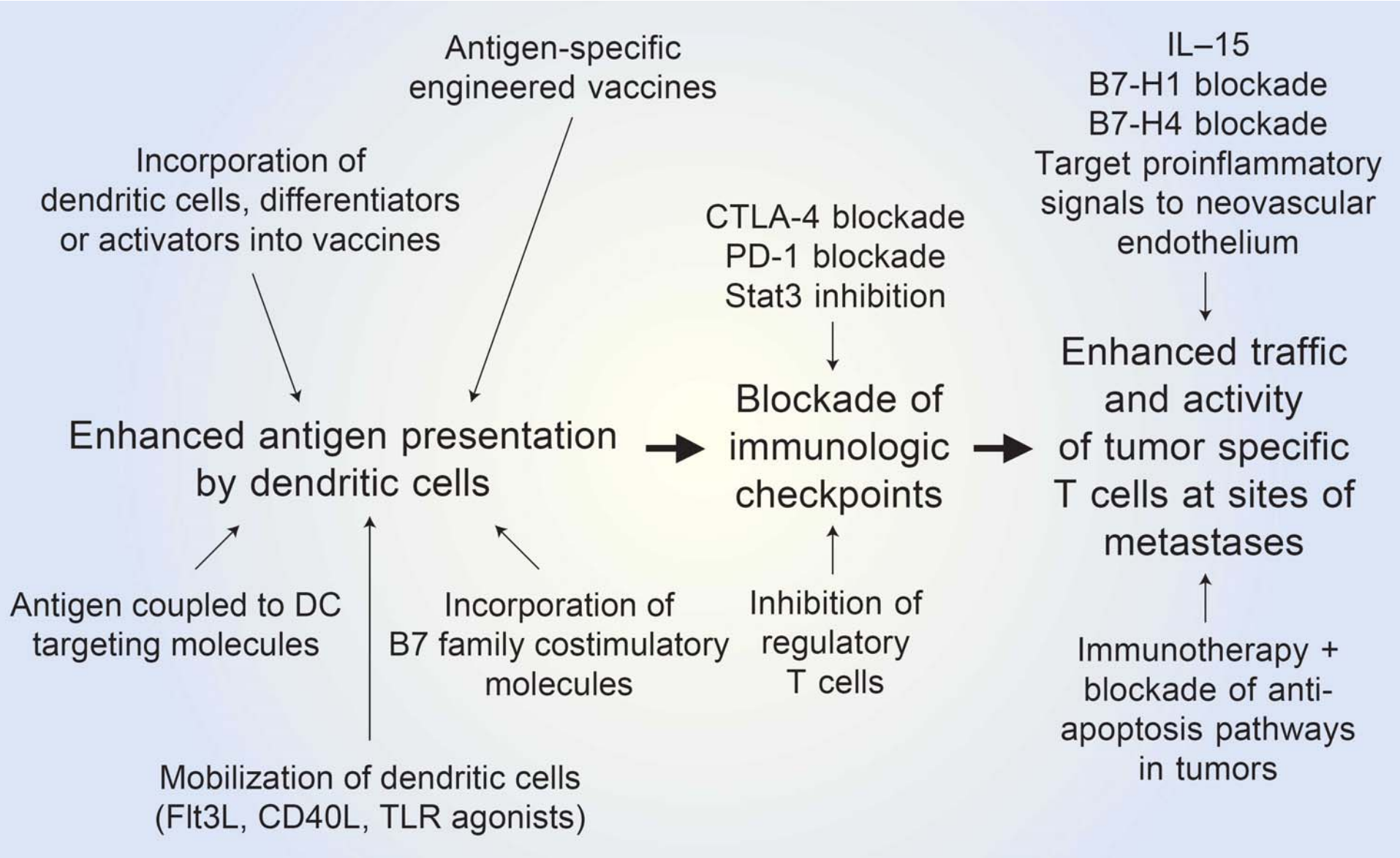
Multiple Points of Intervention to Engender Successful Cancer Immunotherapy



(Pardoll &Allison Nature Med,10:2004)

Examples of potential points of intervention and potential immunotherapeutic drugs to increase the number & therapeutic function of immune T cells in vivo

- Co-stimulatory molecules
  - CD28 & CTLA4
  - Extended B7 family
- Regulatory T cells (CD4+CD25+ Treg)
- T cell growth factors
  - IL-7
  - IL-15

CD28 and CTLA4: Positive & Negative Co-stimulatory Molecules

- Two receptors are necessary for T cell activation
  - TCR
    - Binds to peptide/MHC complex
  - CD28
    - Expressed constitutively on T cells
    - Binds to B7-1 and B7-2 on APC
- TCR + CD28 engagement promotes T cell activation, proliferation, IL2 production
- Subsequent CTLA4 up-regulation and engagement dampens T cell activation

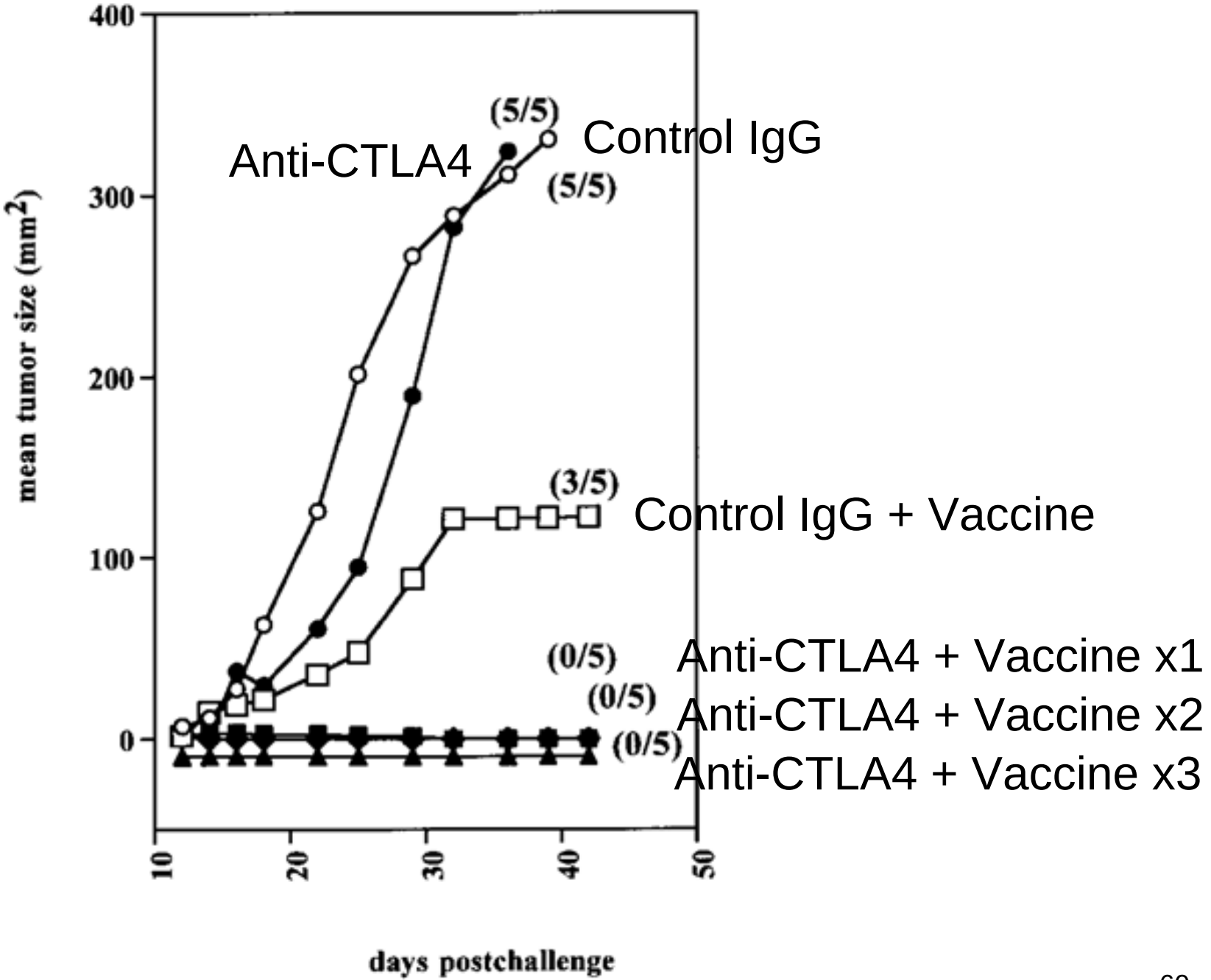
CD28 and CTLA4: Positive & Negative Co-stimulatory Molecules

- CTLA4
  - Not expressed on resting T cells
  - Up-regulated following T cell activation
  - Binds to B7-1 and B7-2 on APC
    - Higher affinity than CD28
  - Antagonizes T cell activation
    - Interferes with IL2 production, IL2 receptor expression and T cell cycle progression

"Combination Immunotherapy of B16 Melanoma Using CTLA-4 and GM-CSF-producing Vaccines Induces Rejection of Subcutaneous and Metastatic Tumors Accompanied by Autoimmune Depigmentation"

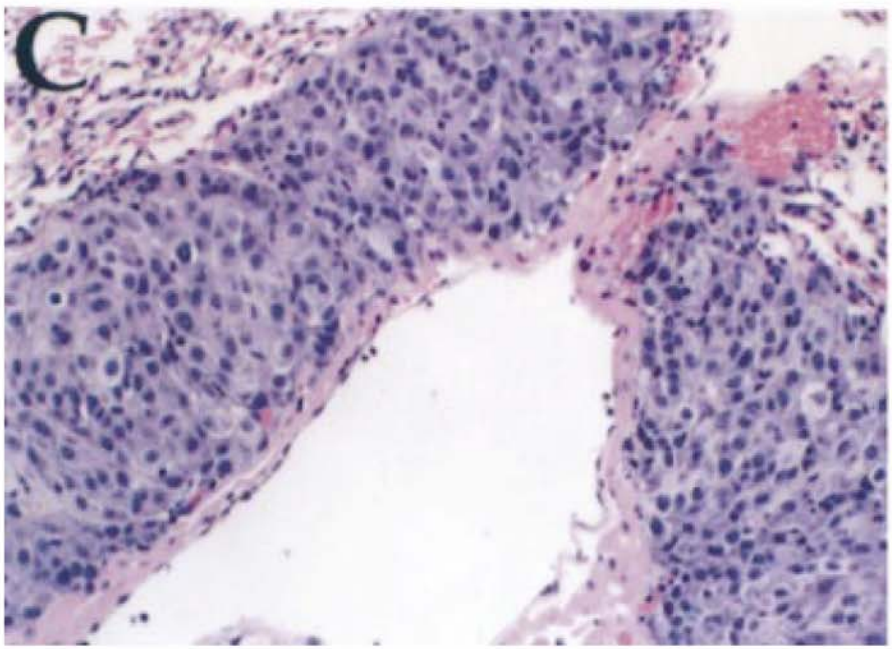
- Highly tumorigenic, poorly immunogenic murine melanoma B16-BL6
- Anti-CTLA-4 blockade and vaccination
  - Eradicated established tumors 80% (68/85)
  - Each treatment alone showed little or no effect
- Tumor rejection was dependent on CD8+ T cells
  - Depigmentation occurred in CD4-depleted mice

(van Elsas, Hurwitz, Allison, JEM 190:355, 1999)

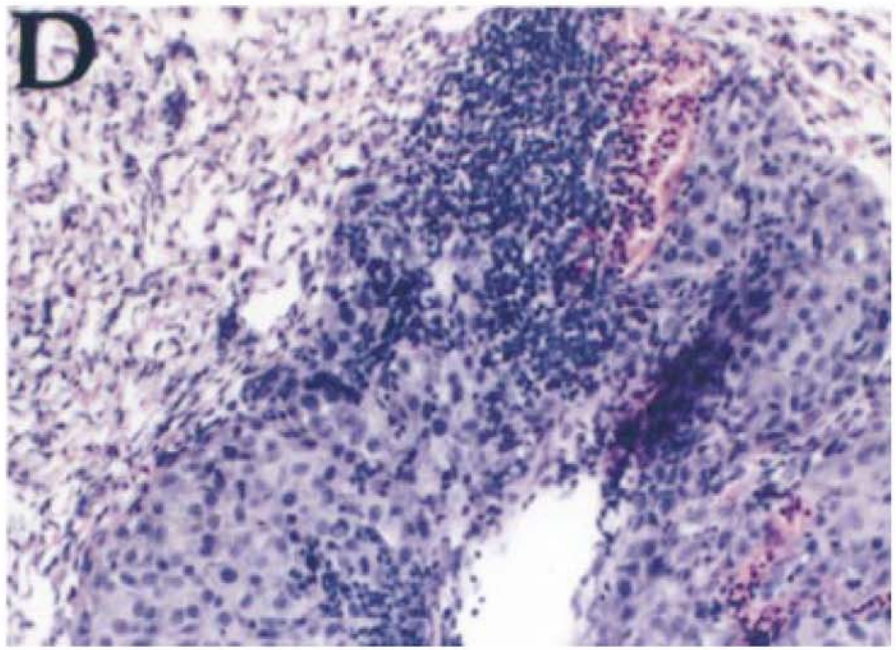


(van Elsas, Hurwitz, Allison, JEM 190:355, 1999)

T cell infiltration of pulmonary metastasis

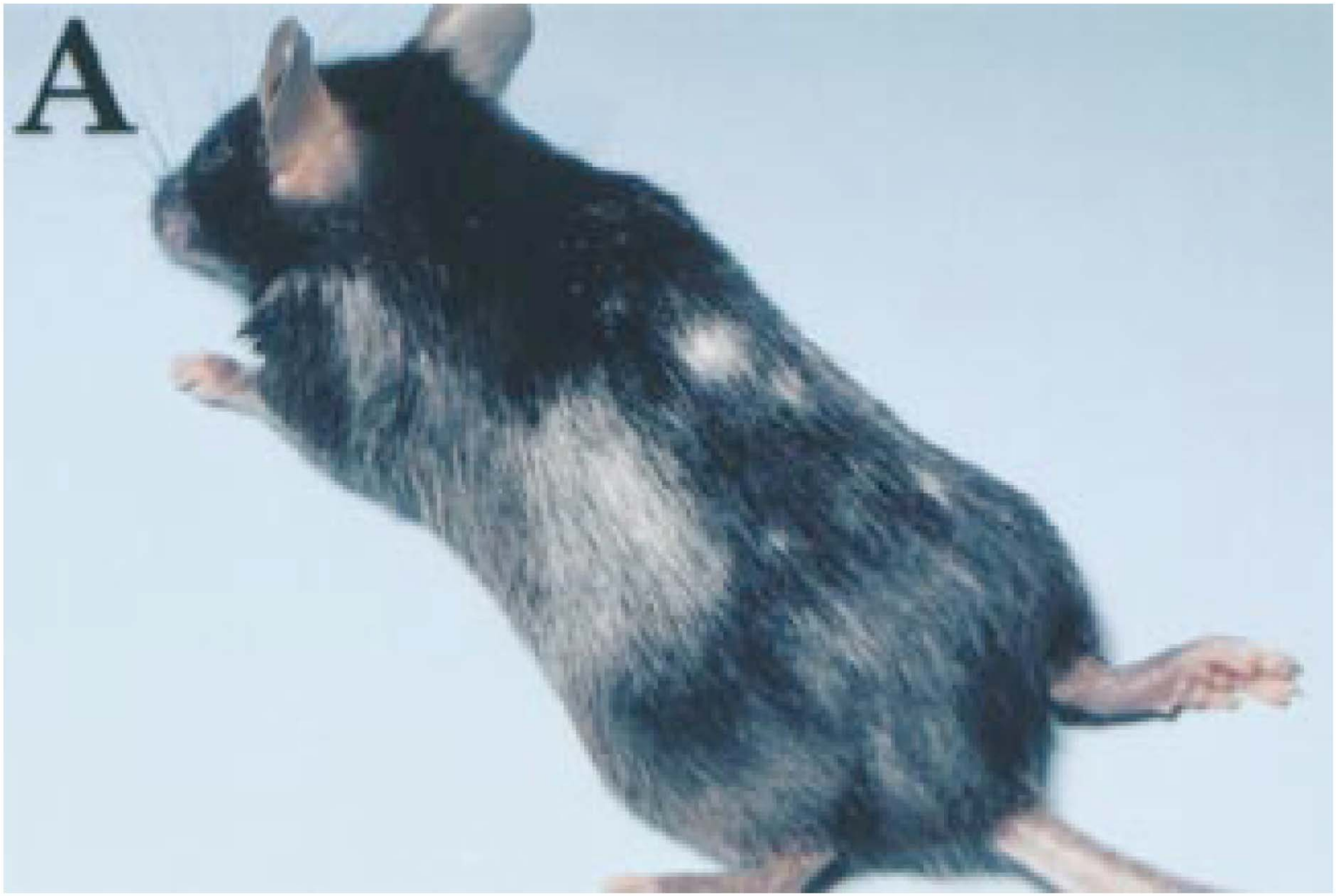


Vaccine alone



Vaccine + anti-CTLA4

(van Elsas, Hurwitz, Allison, JEM 190:355, 1999)



(van Elsas, Hurwitz, Allison, JEM 190:355, 1999)

“Autoimmunity Correlates With Tumor Regression in Patients With Metastatic Melanoma Treated With Anti–Cytotoxic T-Lymphocyte Antigen-4”

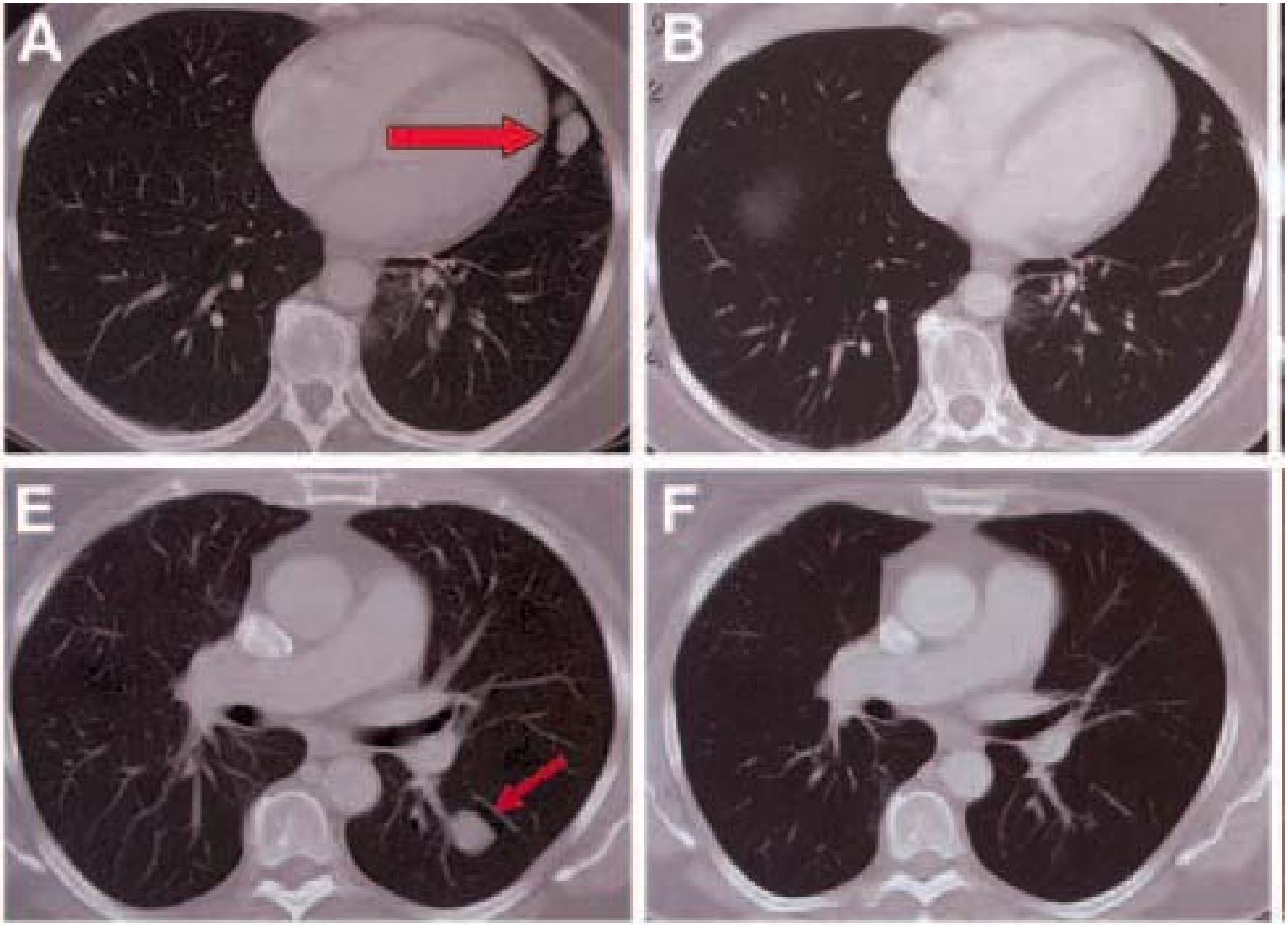
- 56 patients with progressive stage IV melanoma
  - Anti–CTLA-4 every 3 weeks,
  - Concomitant vaccination with gp100 HLA-A*0201-restricted peptides
- 2 CR (30+ 31+ months)
- 5 PR (4, 6, 25 , 26 , & 34 months,
- 13% overall objective response
  - Tumor regression seen in lung, liver, brain, lymph nodes, & subcutaneous sites

(Attia et al (Rosenberg) J Clin Oncol 23:6043-6053 2005)

"Autoimmunity Correlates With Tumor Regression in Patients With Metastatic Melanoma Treated With Anti–Cytotoxic T-Lymphocyte Antigen-4"

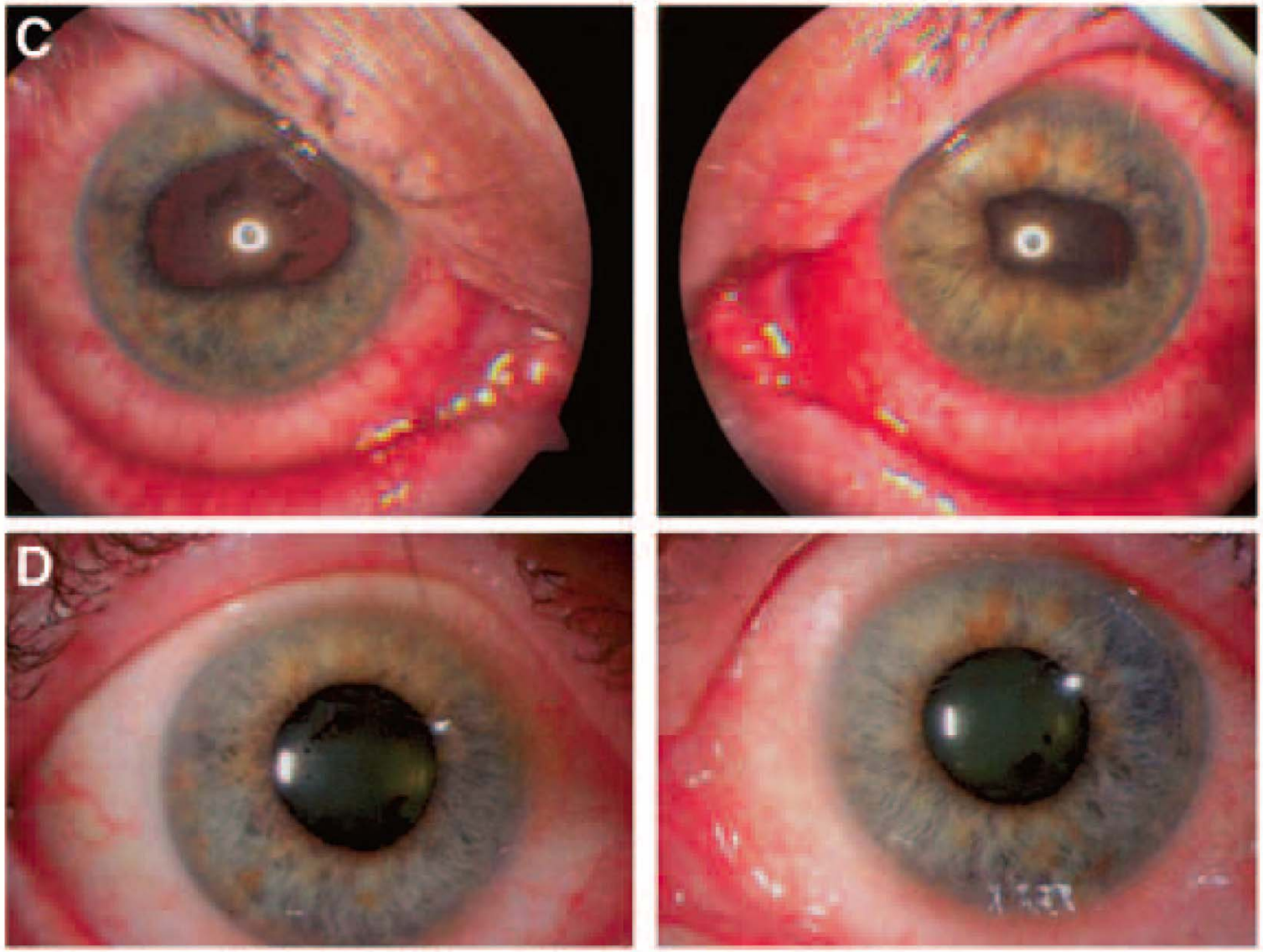
- 14 of 56 (25%) experienced grade 3/4 autoimmune toxicity
  - 7 colitis
  - 4 dermatitis
  - 1 uveitis
  - 1 enterocolitis
  - 1 hepatitis
  - 1 hypophysitis
- 5 of 56 experienced grade 1/2 autoimmune toxicity (vitiligo, antinuclear antibodies and pulmonary infiltrates)
- Correlation of autoimmunity with anti-tumor response
  - 36% with autoimmunity had clinical response
  - 5% without autoimmunity had clinical response

(Attia et al (Rosenberg) J Clin Oncol 23:6043-6053 2005)



(Attia et al (Rosenberg) J Clin Oncol 23:6043-6053 2005)

C: Uveitis with posterior synechiae (iris adhesions to the lens) causing irregular pupils
D: The same patient, 4 days later, after treatment with topical corticosteroids.

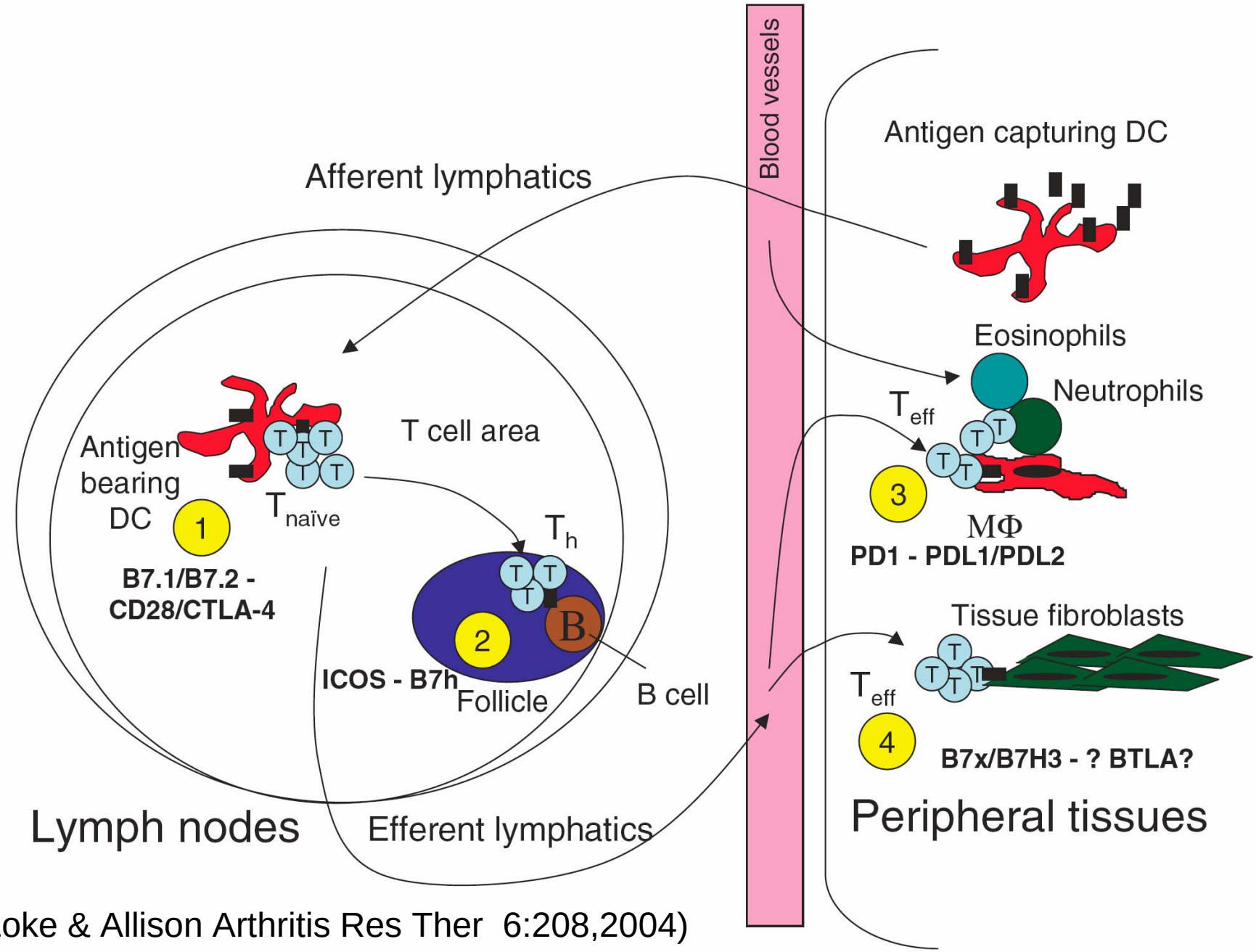


(Attia et al (Rosenberg) J Clin Oncol 23:6043-6053 2005)

Extended B7 Family and Regulatory T cells

- B7-1/B7-*2* & CD28/CTLA-4 regulate clonal composition of naive T cells that become activated by antigen-bearing DCs migrating into lymphoid organs from peripheral tissues
- B7h & inducible costimulatory molecule (ICOS) promotes T-dependent antibody isotype switching and expansion of effector T cells after clonal expansion of naive T cells, when the differentiated T helper cells (Th) migrate into the follicles
- Programmed death ligands (PDLs) & (PD)-1 regulate effector T cells trafficking into inflamed tissues
- B7-H3 & B7x and BTLA (B and T lymphocyte attenuator) could be last-ditch regulators and control the interaction between effector T cells and the peripheral tissues

(Loke & Allison Arthritis Res Ther 6:208,2004)



(Loke & Allison Arthritis Res Ther 6:208,2004)

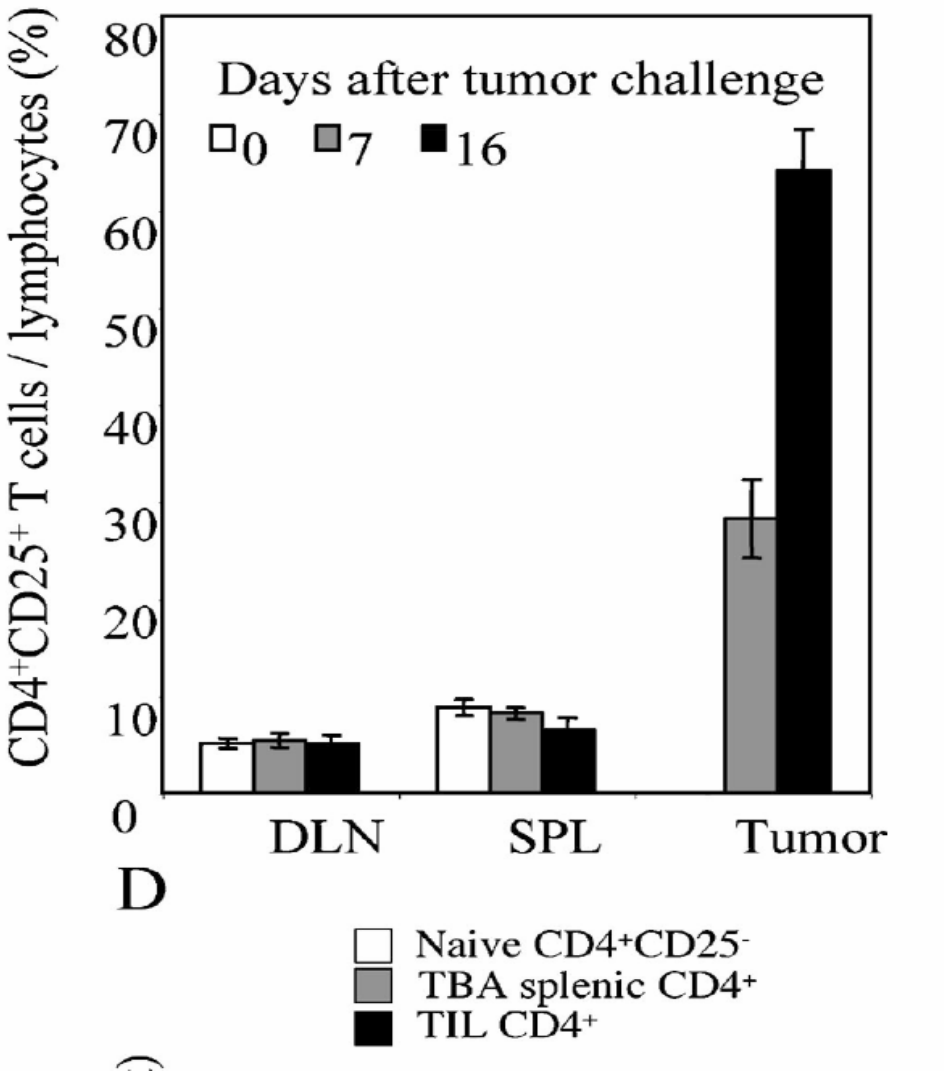
Regulatory T cells: (CD4+CD25+ Treg)

- Naturally occurring
- Control immunologic tolerance to self antigens
- Approximately 5-15% of normal CD4+ T cells
- Constitutively express high levels of cell surface
  - CD25 (IL-2Ra)
  - GITR (glucocorticoid-induced THF receptor
  - CTLA-4
- Absence is associated with severe autoimmunity

Regulatory T cells: (CD4+CD25+ Treg)

- Functionally competent when isolated ex vivo
- Upon TCR cross-linking
  - Suppress proliferation and IL2 production of responder CD25-CD4+ or CD8+ T cells
    - Contact-dependent manner
- Suppress autoimmunity, tumor immunity, allergy and immunity to chronic infection
  - Carefully timed depletion of CD25+ T cells enhances tumor immunity and autoimmunity

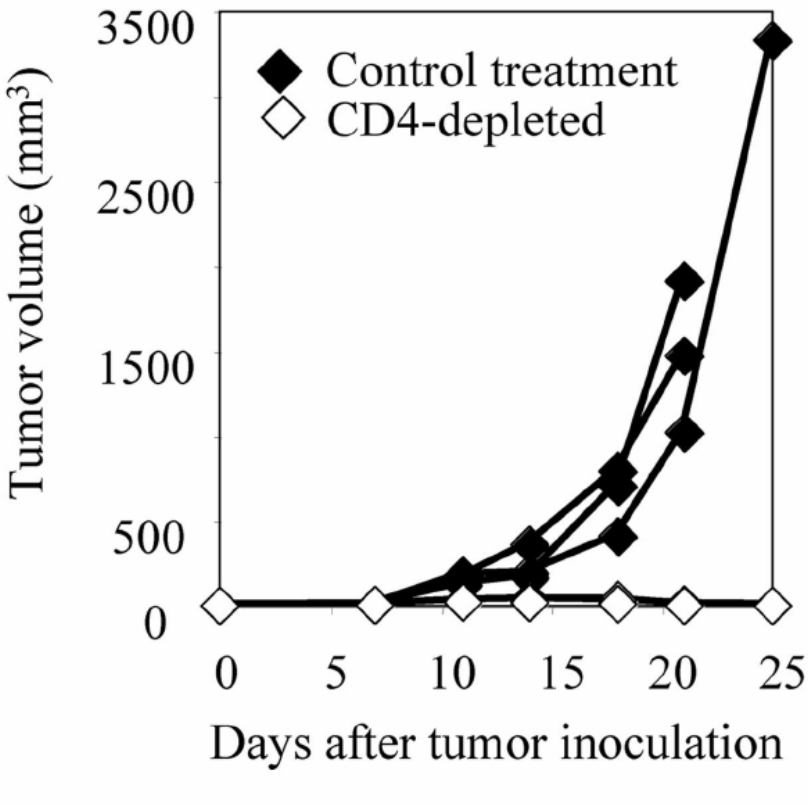
“Intratumor depletion of CD4+ cells unmasks tumor immunogenicity leading to the rejection of late-stage tumors”

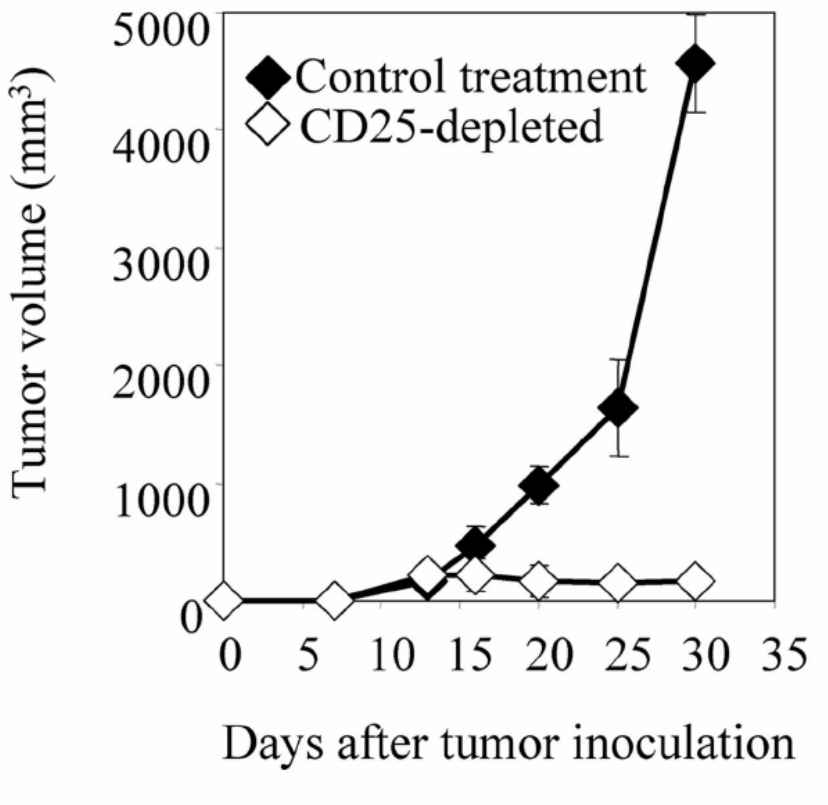


- C3B6F1 mice Inoculated s.c. with fibrosarcoma cells
- Identified intratumor growth of CD4+CD25+ T cells

(Yu, et al (Schreiber, Fu) JEM 201 779–791 2005)

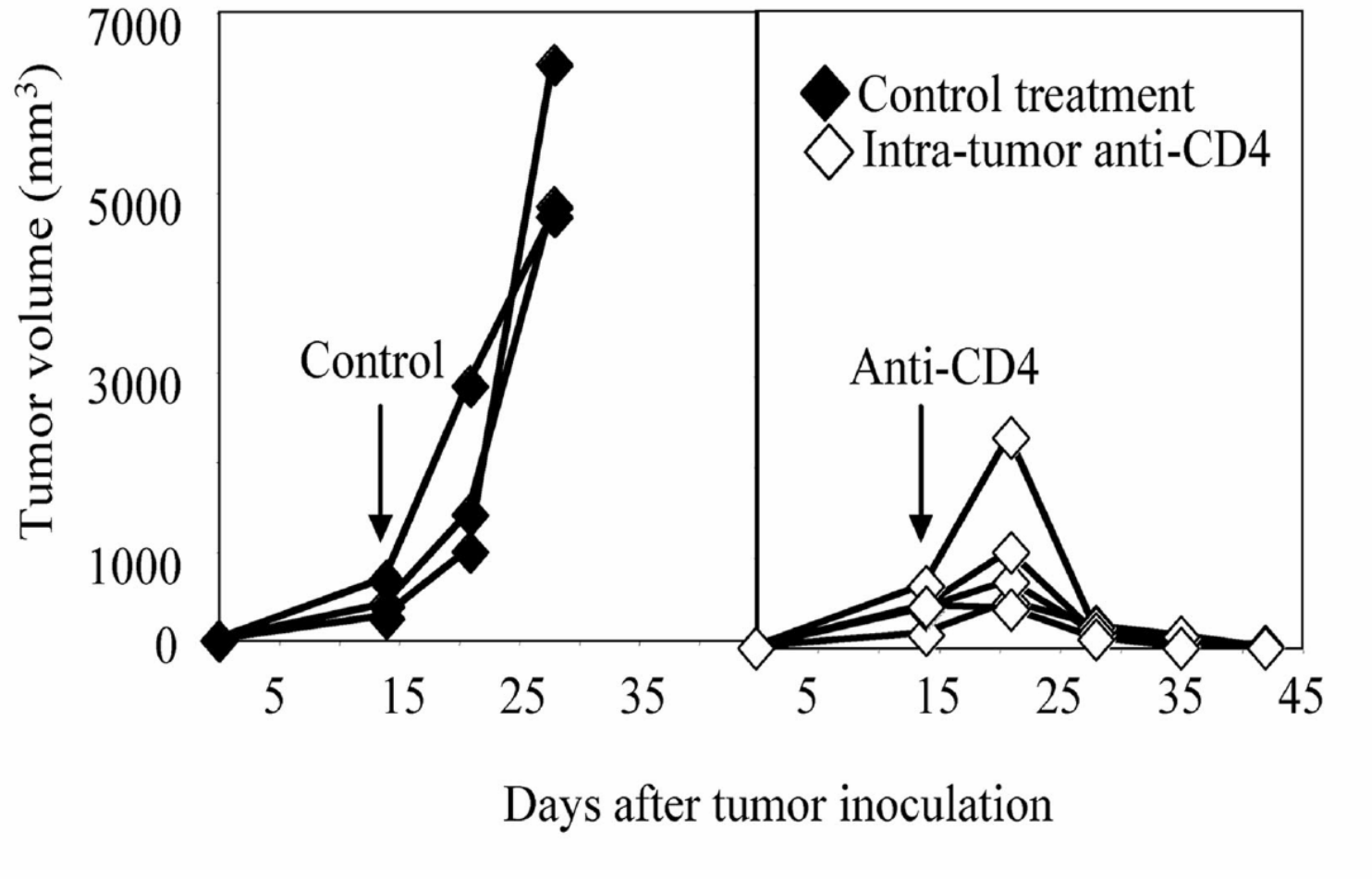
In vivo Deletion of CD4+ or CD25+ T cells Unmasks Tumor Immunogenicity Leading to the Rejection of Late-stage Tumors





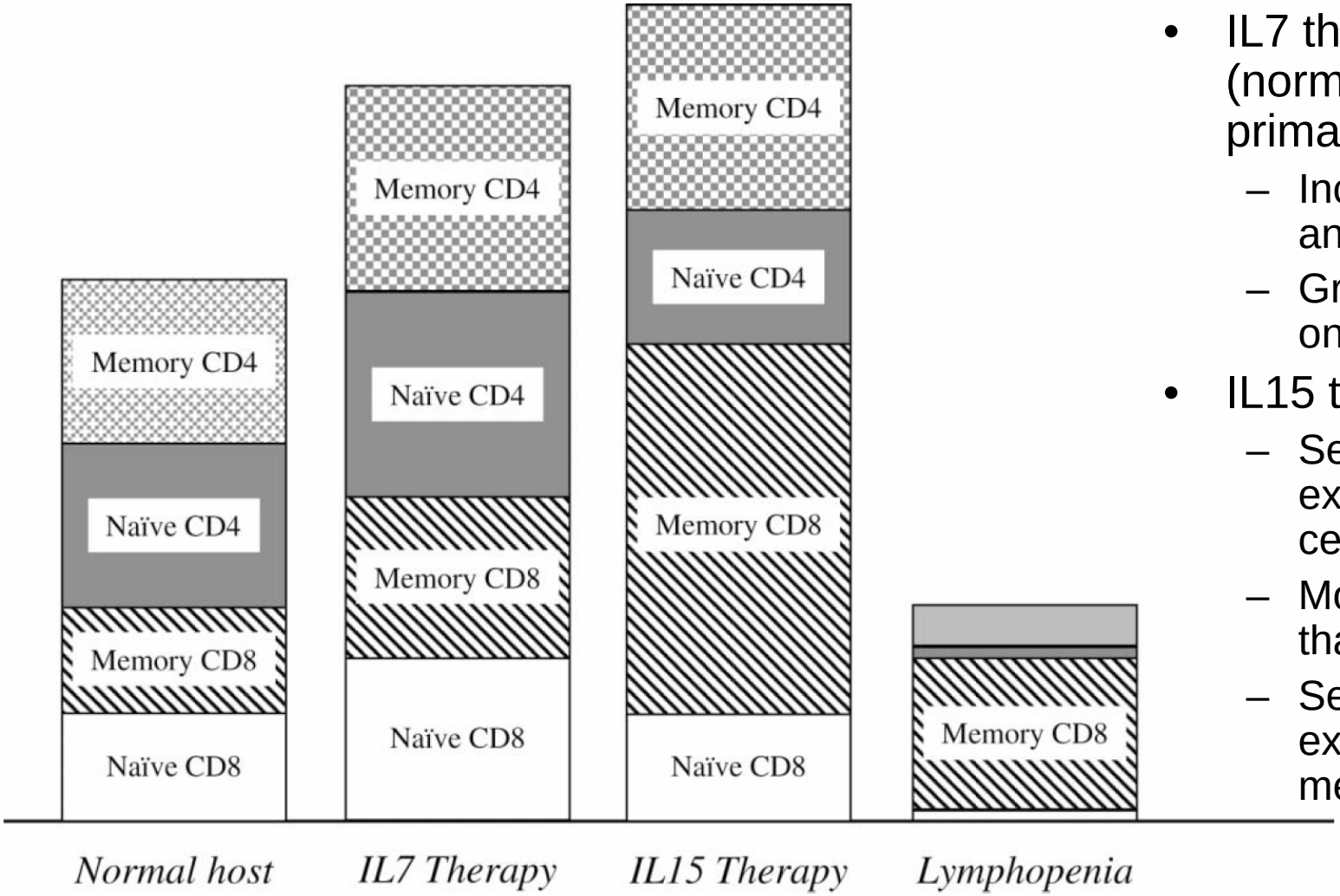
(Yu, et al (Schreiber, Fu) JEM 201 779–791 2005)

Intra-Tumor Deletion of CD4+ or CD25+ T cells Unmasks Tumor Immunogenicity Leading to the Rejection of Late-stage Tumors



(Yu, et al (Schreiber, Fu) JEM 201 779–791 2005)

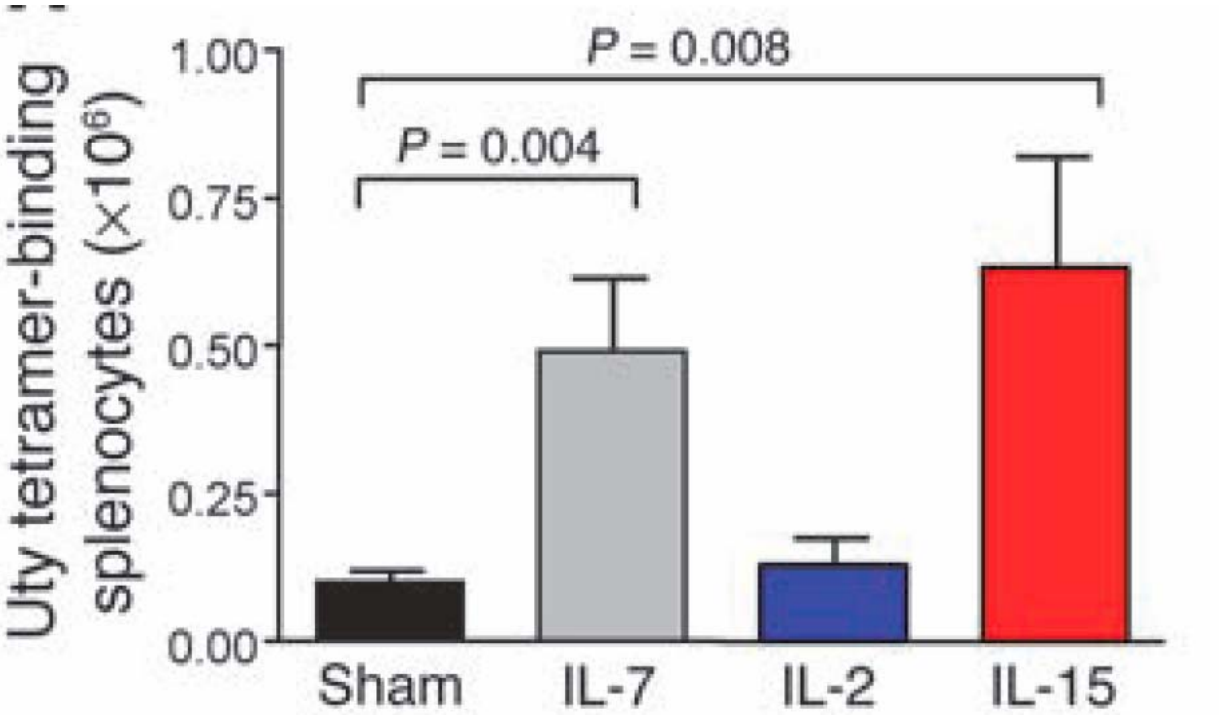
“Cytokine Signals in T-Cell Homeostasis”



- IL7 therapy (normal mice & primates)
  - Increases CD4+ and CD8+ cells
  - Greater effect on the CD8+
- IL15 therapy
  - Selectively expands CD8+ cells
  - More potent than IL7
  - Selectively expands CD8+ memory cells

(Guimond, Fry & Mackall J Immunother 28, 2005)

“Adjuvant IL-7 or IL-15 Overcomes Immunodominance and Improves survival of the CD8+ Memory Cell Pool”



- Day 0: female mice immunized against male minor histocompatibility antigen complex (HY)
- Days 0-27: rhIL-7 rhIL-15
- Day 28: Quantified male antigen (Uty) tetramer binding T cells

(Melchionda et al (Mackall) JCI 115 2005)

Conclusions

- Cancers can be cured by immune T cells
  - Hematologic malignancy can be cured by allogeneic T cells
  - Solid tumors can also be treated with allogeneic T cells, but less effectively
- Cancer cells are immunogenic and can be recognized and killed by autologous T cells
- Autologous immune T cells can be used effectively in therapy
  - Transferred immune T cells are most effective
  - Vaccines that induce immune T cell responses can be effective, but less so
- Many new biological reagents are available as potential immunotherapeutic drugs to substantially increase the number and therapeutic function of immune T cells in vivo