Cancer Immunotherapy with T Cells: Vaccines and Adoptive T Cell Therapy

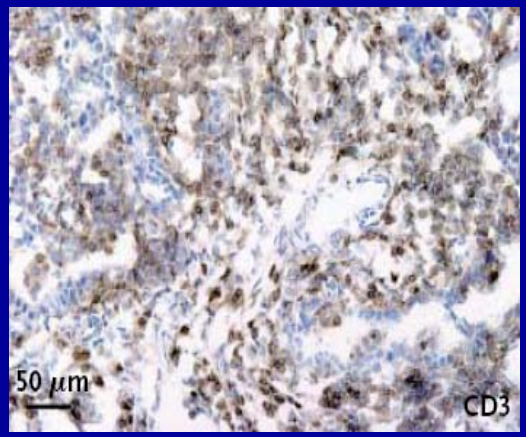
I. T cells and tumor immunity

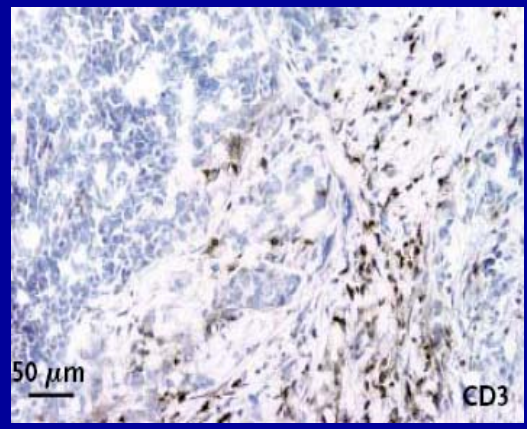
II. Vaccines: generate T cell response

III. T cell therapy: augment T cell response

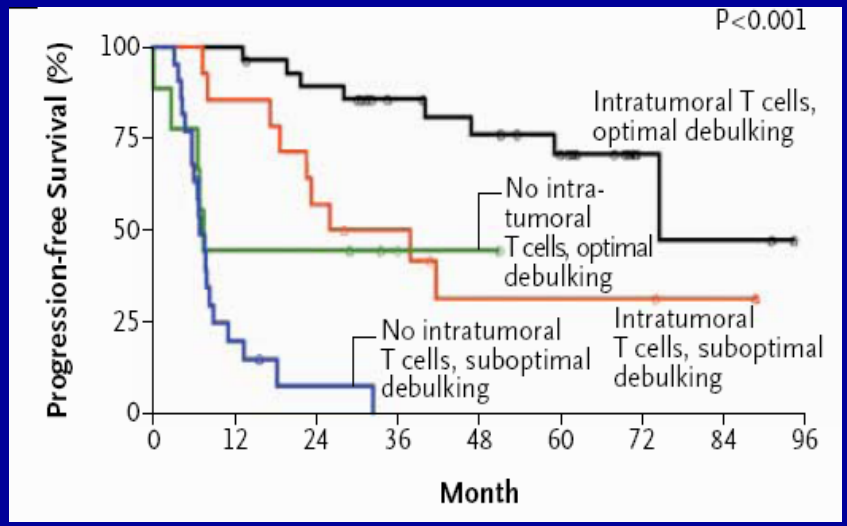
T Cell Infiltration Predicts Survival in Ovarian Cancer

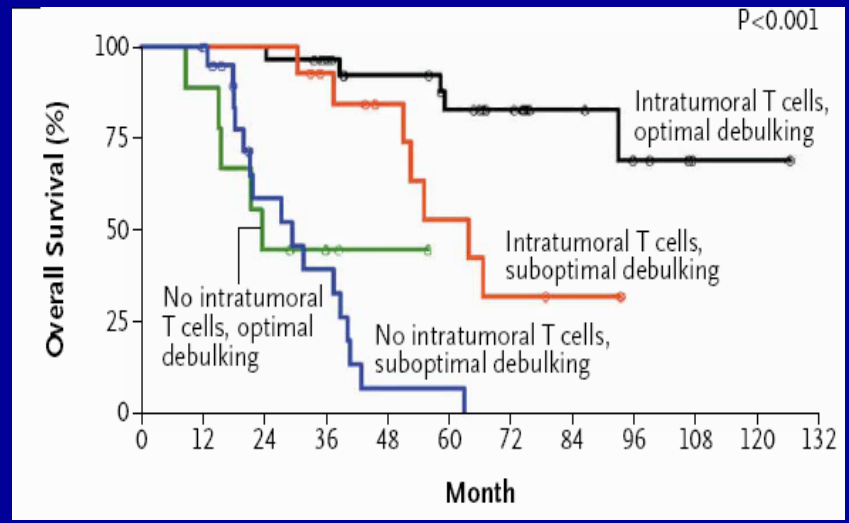
Intratumoral





Stromal

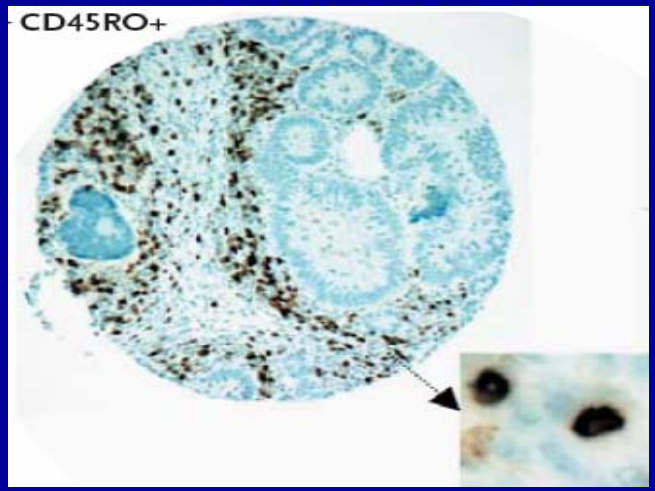


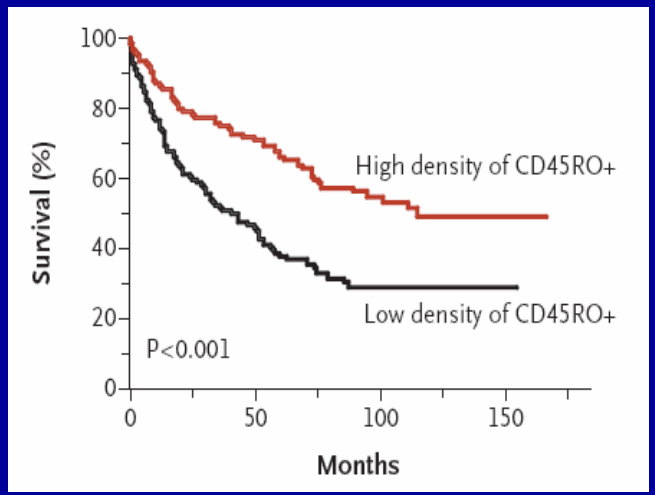


74 advanced stage ovarian

Zhang et al, NEJM, 2003

Infiltrating Memory T Cells Predict Outcome in Colorectal Cancer





>400 samples

Pages F et al, NEJM, 2005

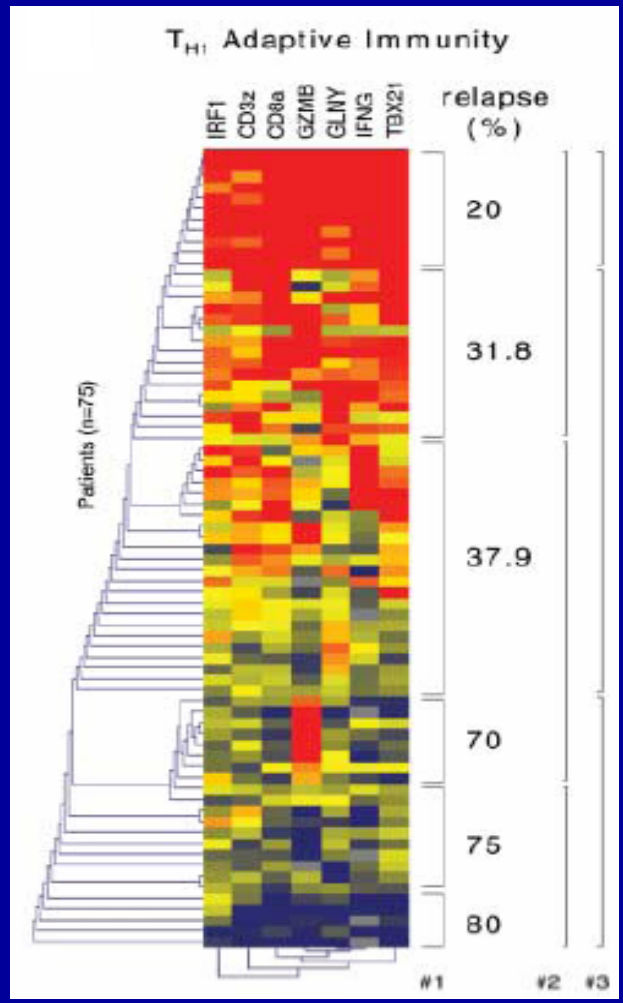
Factors Predicting Outcome:

Th1

T_{EM}

Central

Dense



75 samples

Galon, J. et al, Science, 2006

Cancer Antigens Recognized by the Immune System

Self Antigens

Unique

Differentiation

Shared

Overexpressed

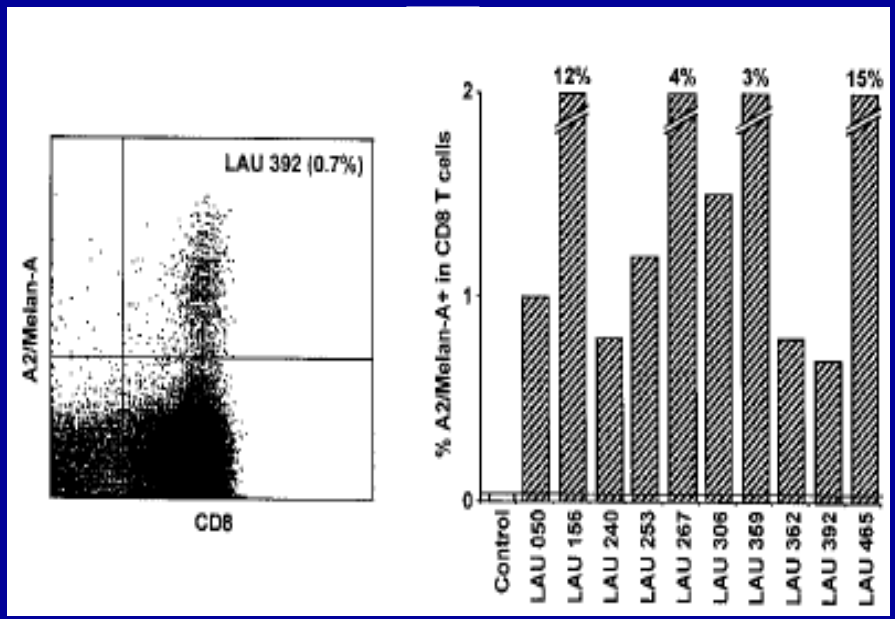
Foreign

Tumour-associated antigen	Tumour
P53	Several carcinomas
KRAS2	Several carcinomas
APC	Colorectal carcinoma
TGFβ receptor II	Colorectal carcinoma
Caspase 8	Head and neck tumours
β catenin	Melanoma
CDK4	Melanoma
GnTV	Melanoma
SYT-SSX fusion protein	Soft-tissue sarcoma
GP100	Melanoma
MART1	Melanoma
Tyrosinase	Melanoma
TRP1	Melanoma
TRP2	Melanoma
PSA, PAP, PSMA	Prostate carcinoma
Melanoma antigen family (MAGE)	Several types
G antigen family (GAGE)	Several types
B melanoma antigen (BAGE)	Several types
SSX2	Several types
SAGE1	Several types
LAGE1	Several types
Cancer/testis antigen NY-ESO1	Several types
CEA	Several carcinomas
ERBB2	Several carcinomas
GA733-1	Several carcinomas
Mucin 1	Several carcinomas
Survivin	Several types
Telomerase	Several types
CD55	Several carcinomas
PRAME	Several types
Chorionic gonadotrophin β	Several types
α fetoprotein	Hepatocellular carcinoma
GloboH, transcription factor α, and sialyl-Tn	Several carcinomas
Gangliosides	Melanoma
SART1, SART2	Some carcinomas
E6, E7 (human papillomavirus)	Cervical carcinoma
LMP2, EBNA1 (Epstein-Barr virus)	Nasopharyngeal carcinoma

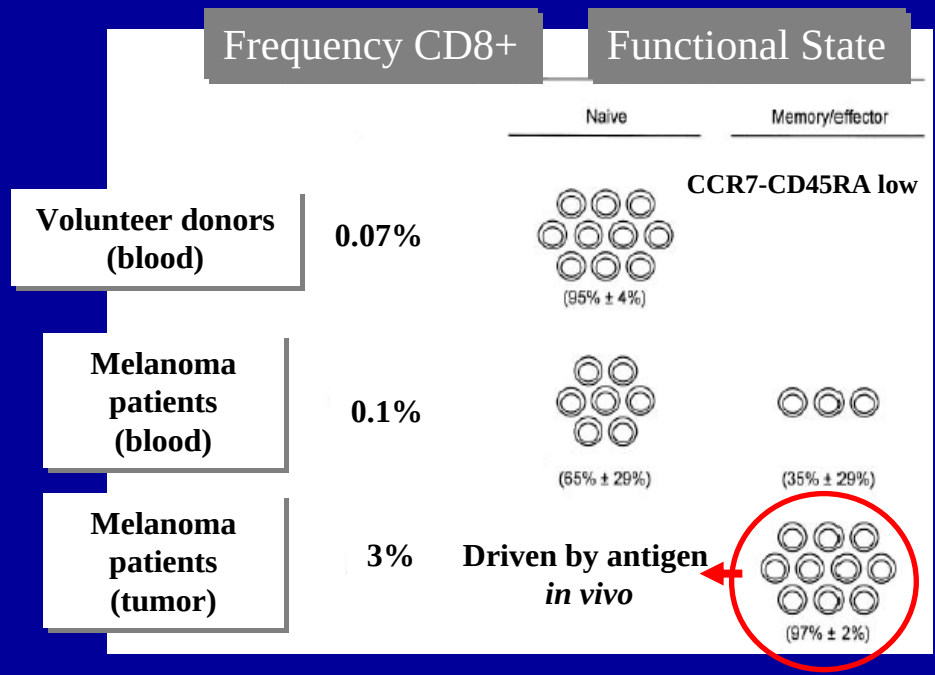
adapted from Mocellin S et al, Lancet Oncol, 2004

Pre-Existent Tumor T Cell Immunity is Low Level

Minority of the inflammatory infiltrate in tumors



Effector cells at the site of the tumor



Adapted from Romero et al, Immunol Rev, 2002

Cancer Immunotherapy with T Cells: Vaccines and Adoptive T Cell Therapy

I. T cells and tumor immunity

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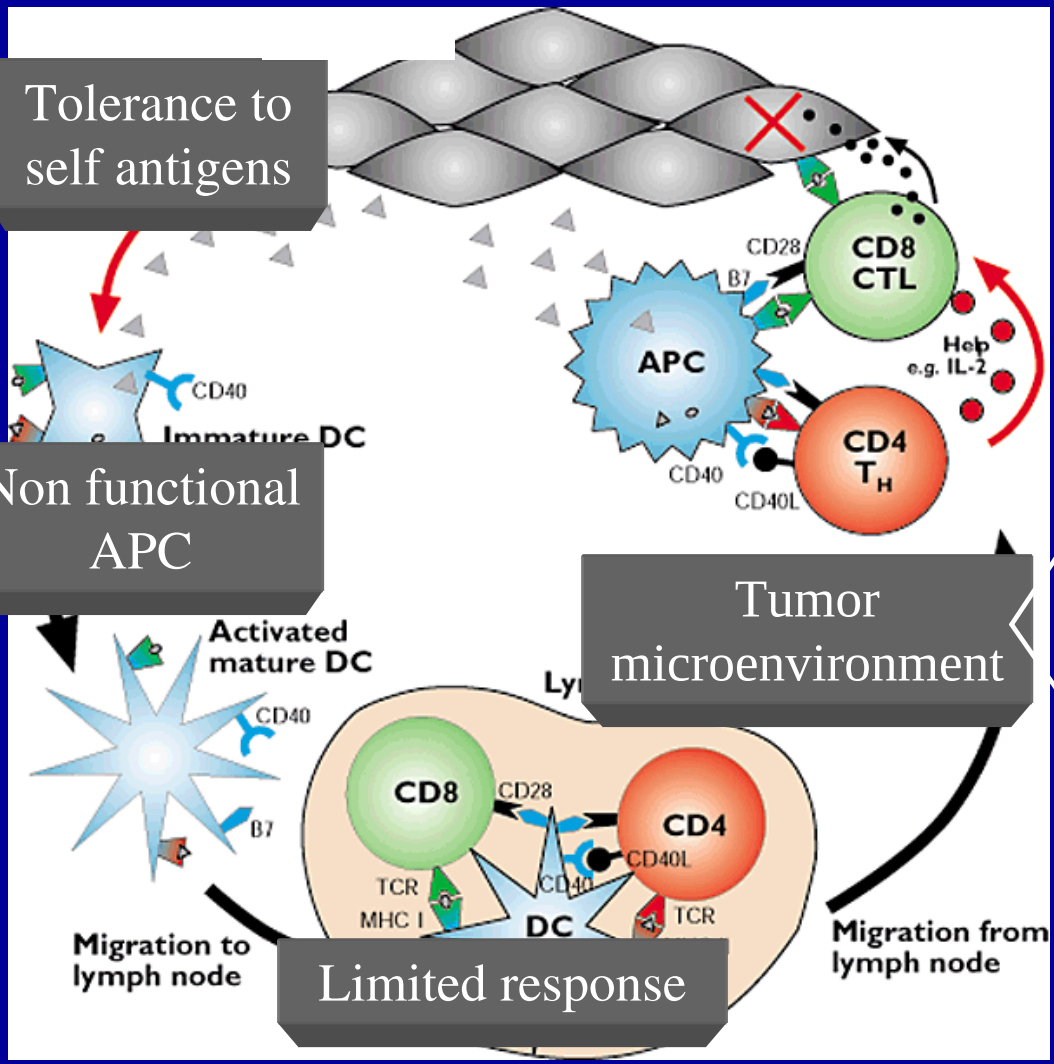
Mechanisms of Ineffective Tumor Immunity

T regulatory cells

Tolerance to self antigens

Macrophage
APC w/o co-stim
Suppressive DC
Lack of DC

Non functional APC

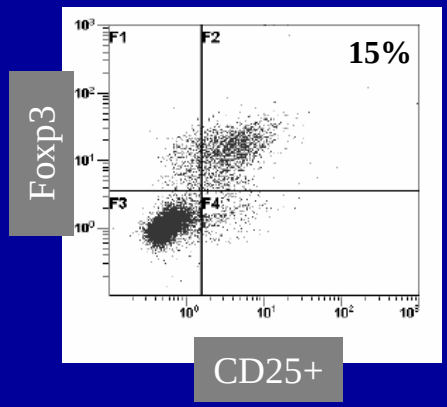


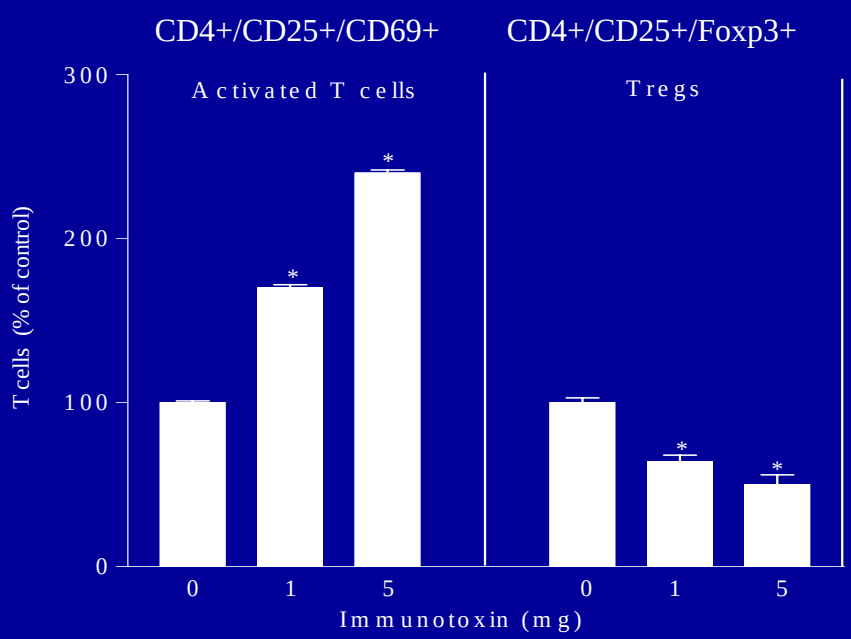
Tumor microenvironment

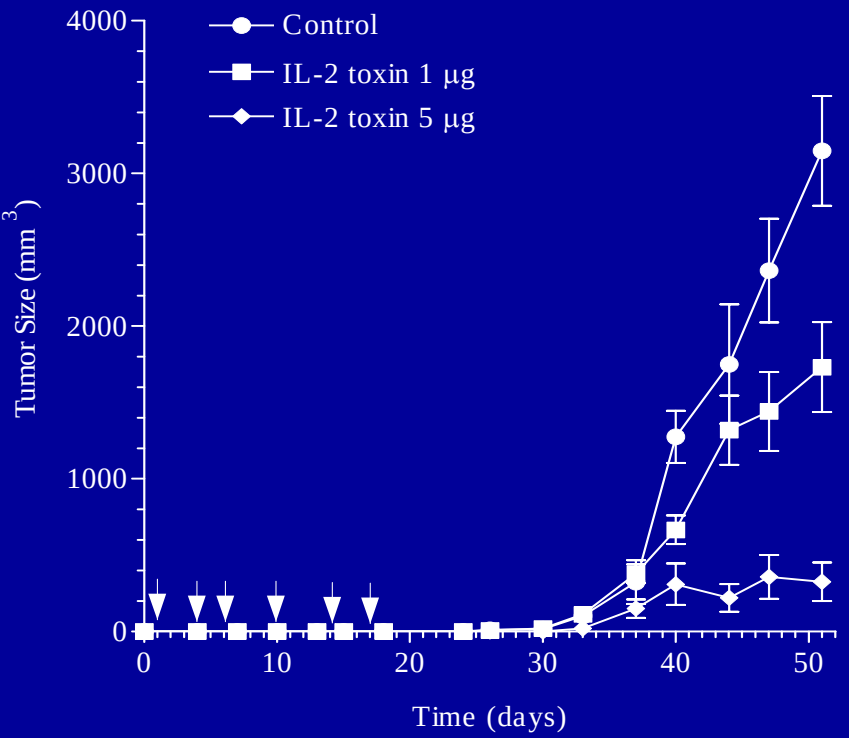
Chronic inflammation
Inhibitory cytokines

adapted from Smyth et al, Nat Immunol, 2001

Circumventing Tolerance via Treg Depletion





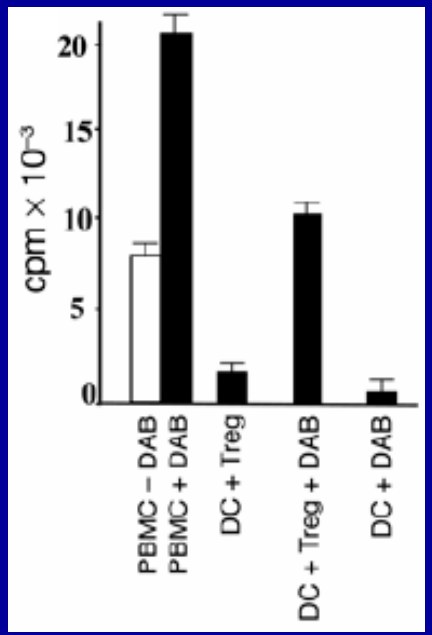


Increased tumor antigen specific immunity
T cell and antibodies

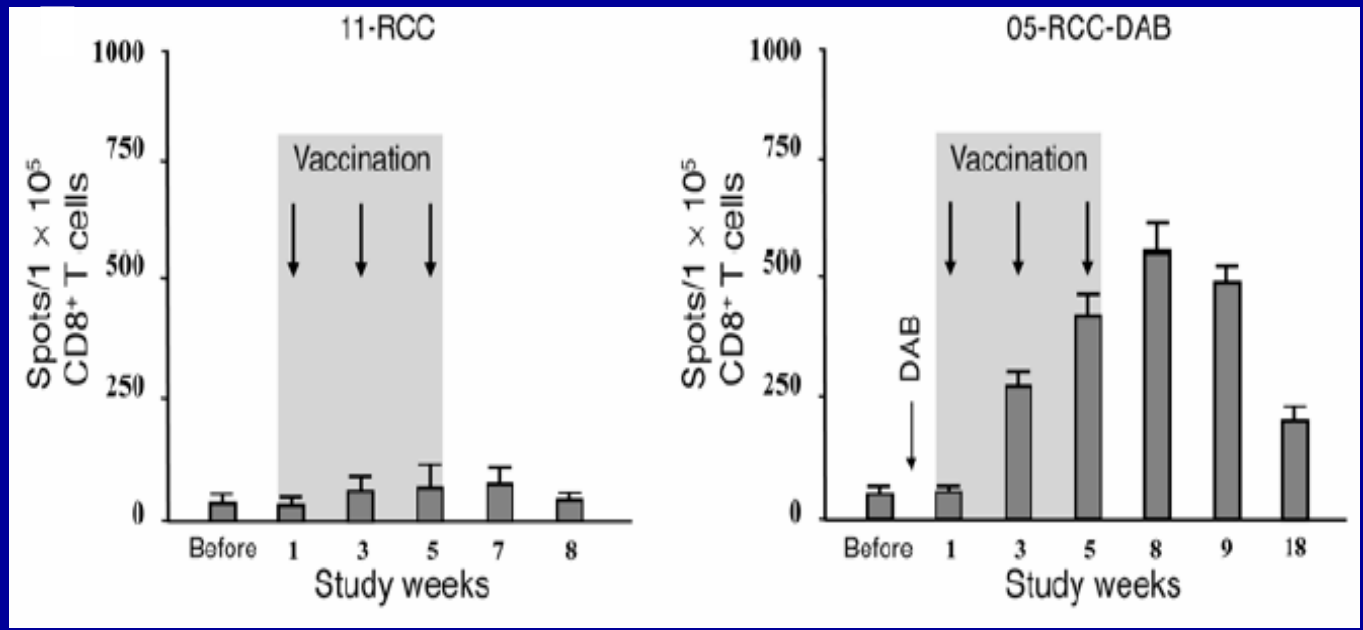
Knutson et al, JI, 2006

Depletion of Tregs Prior to Vaccination Enhances Immunity

XCD25-Immunotoxin enhances MR



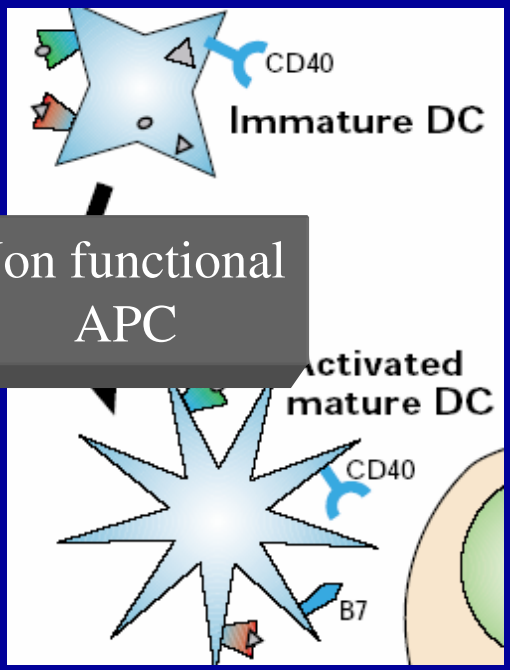
3 id injections of tumor RNA transfected DC +/- XCD25 Immunotoxin



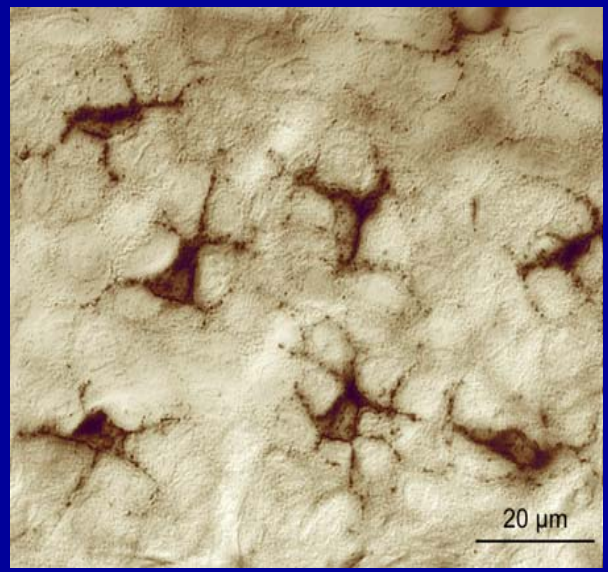
RENAL CELL CA

Dannull, J et al, JCI, 2005

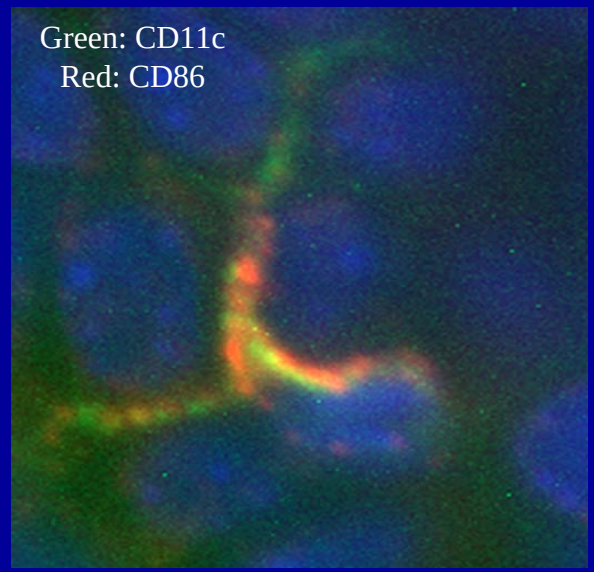
Activating APC for Vaccination



Resting

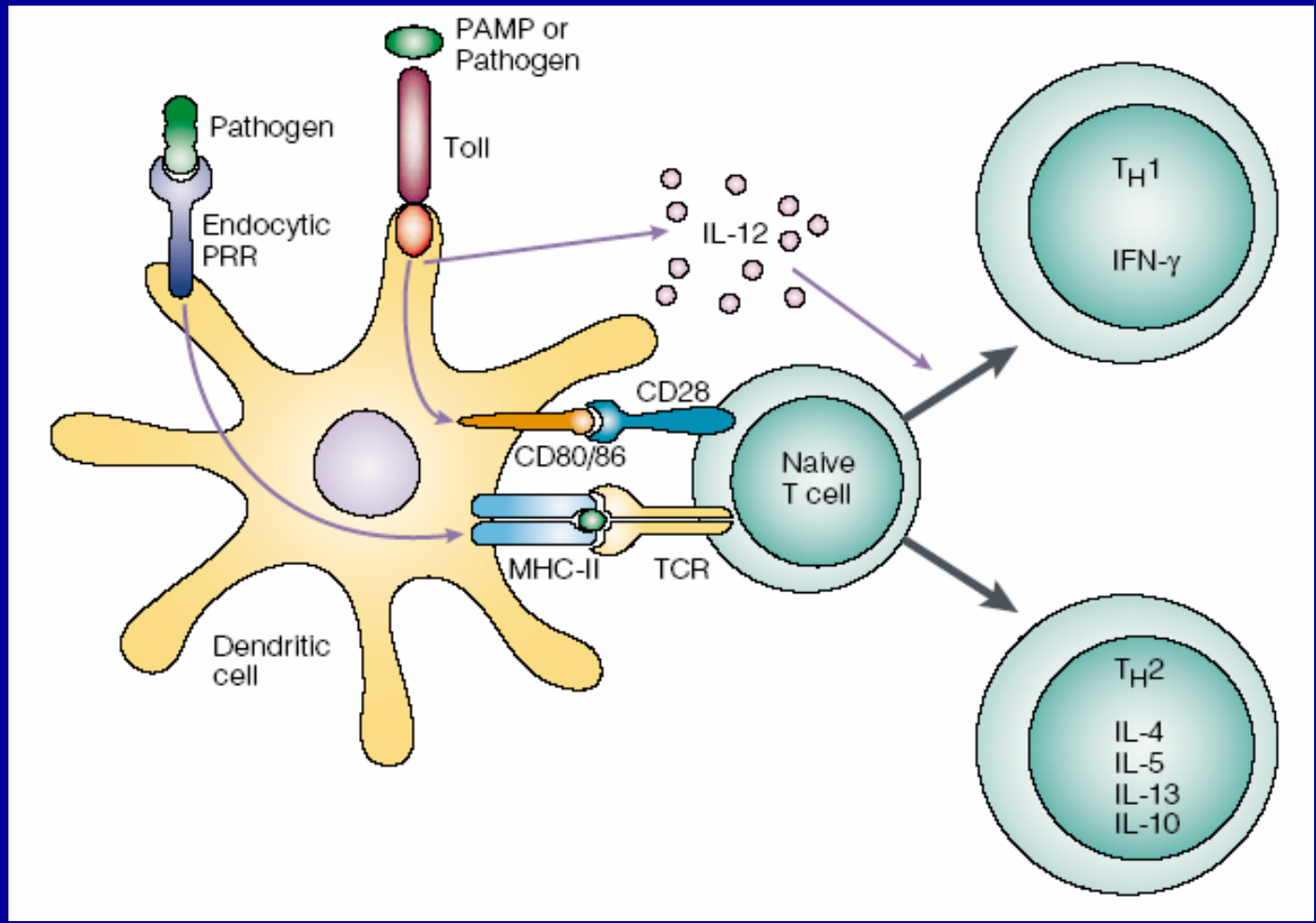


Activated



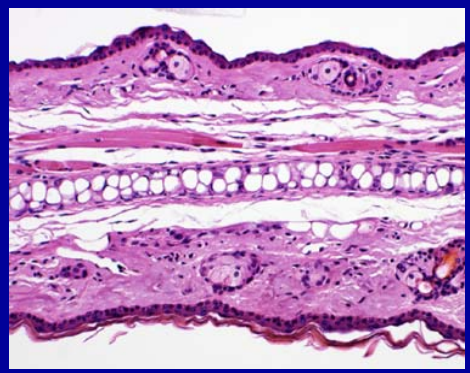
Intradermal injection of cytokines:
trafficking to dermis/activation

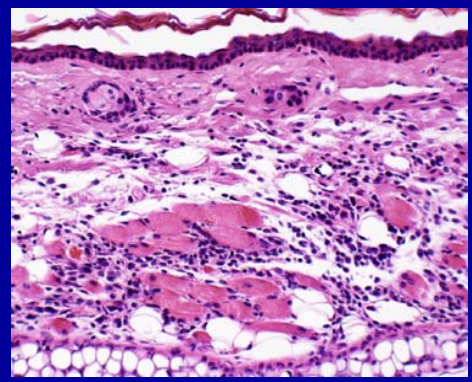
Toll-Like Receptor Ligands

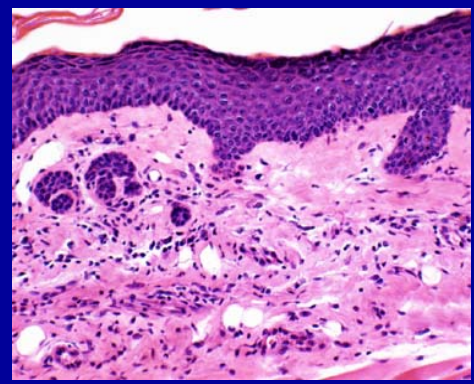


Medzhitov, R. Nat Rev Immunol, 2001

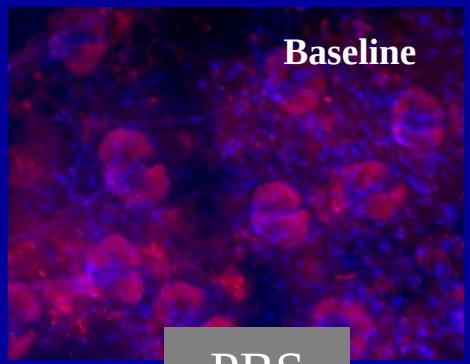
Activation of Skin APC



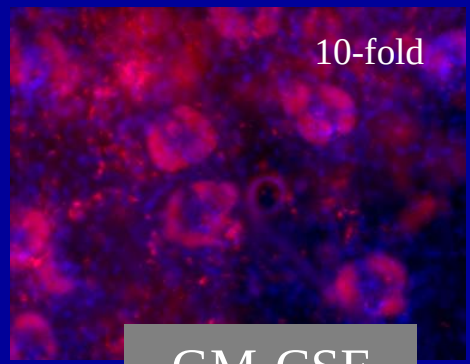




H&E



PBS



GM-CSF

Imiquimod

Dermis

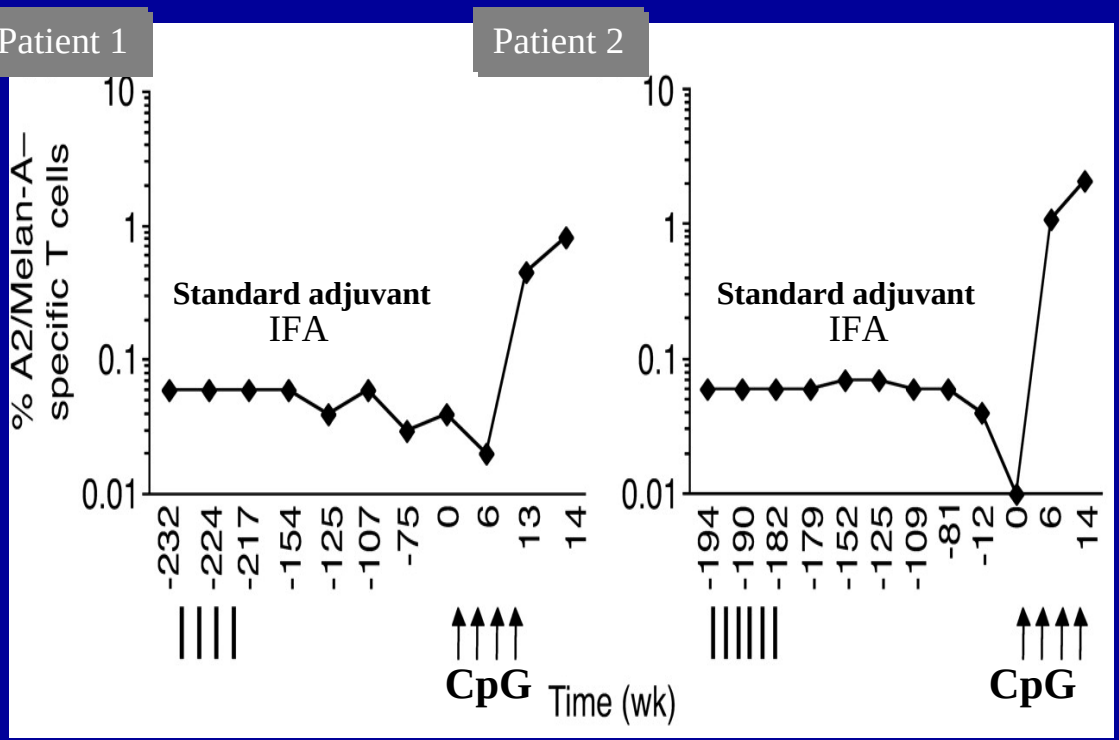
TLR-7 Agonist

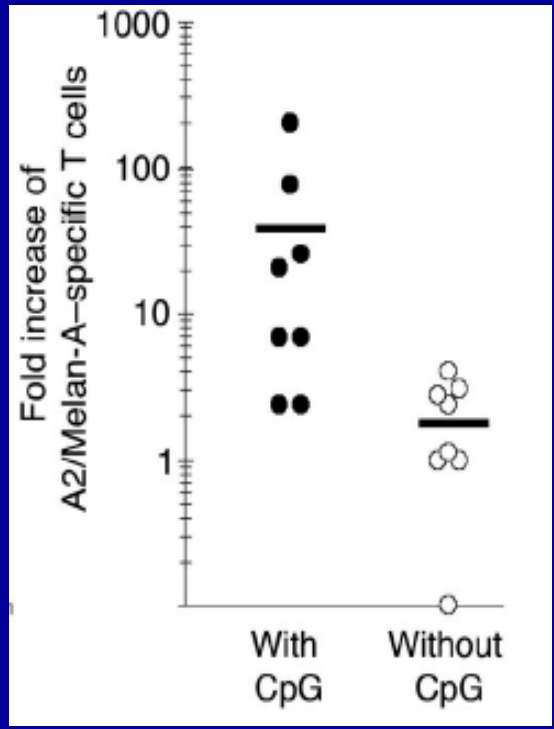
Class II

Wagner et al, 2006

Stimulating Dendritic Cells *in situ* with CpG via TLR-9

T_{EM} with lytic activity

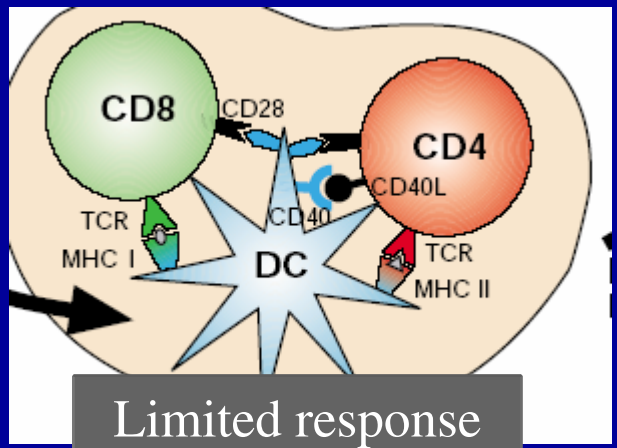


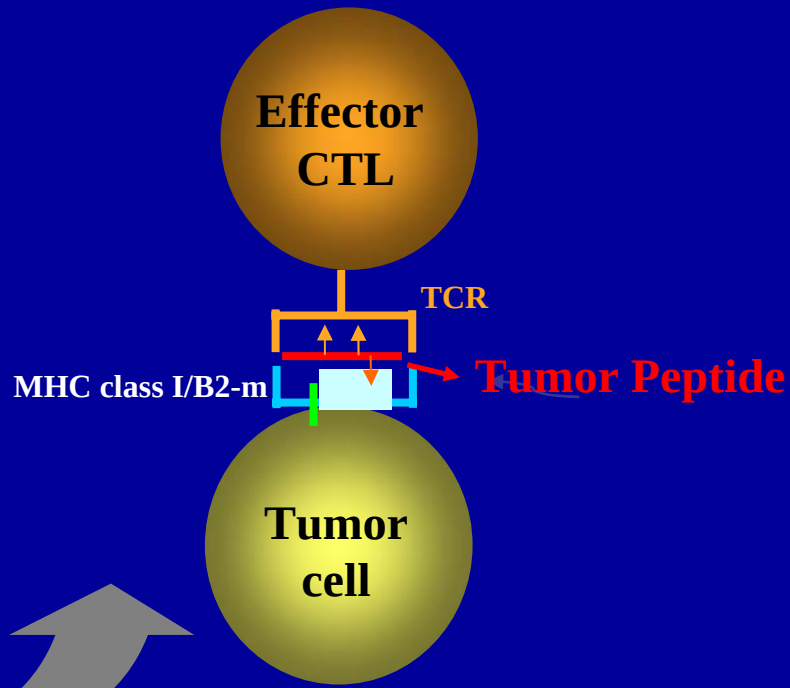


8 melanoma patients

Speiser et al, JCI, 2005

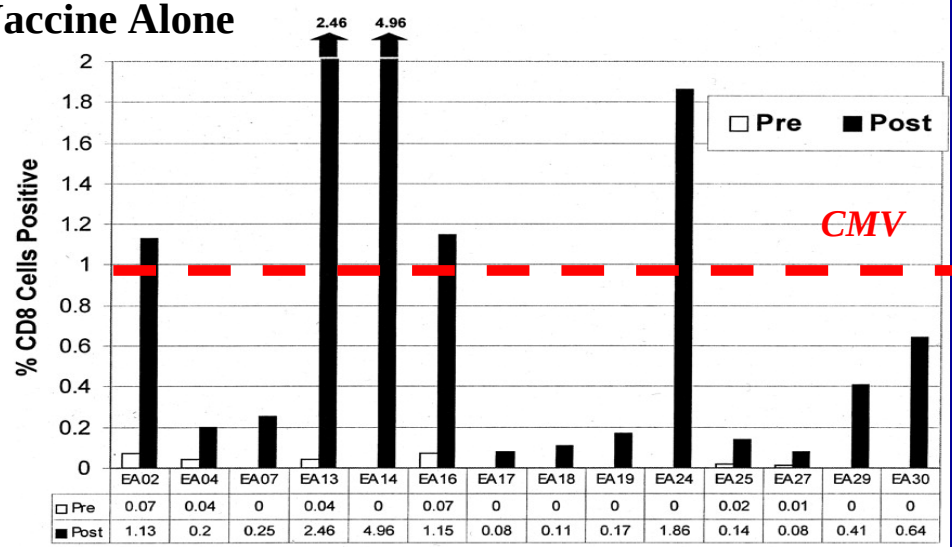
Manipulating the Antigen for Vaccination





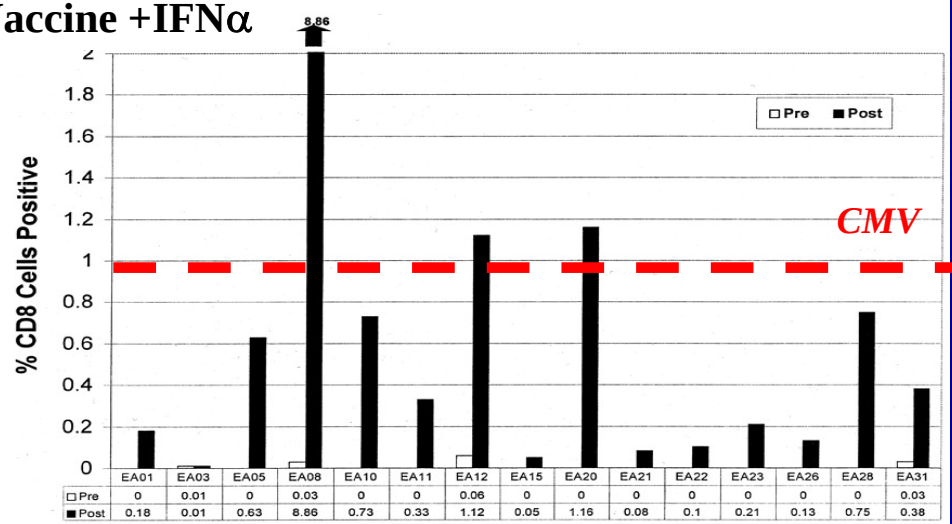
Peptide Modified to Increase Class I Binding

Vaccine Alone



	EA02	EA04	EA07	EA13	EA14	EA16	EA17	EA18	EA19	EA24	EA25	EA27	EA29	EA30
Pre	0.07	0.04	0	0.04	0	0.07	0	0	0	0	0.02	0.01	0	0
Post	1.13	0.2	0.25	2.46	4.96	1.15	0.08	0.11	0.17	1.86	0.14	0.08	0.41	0.64

Vaccine +IFNα



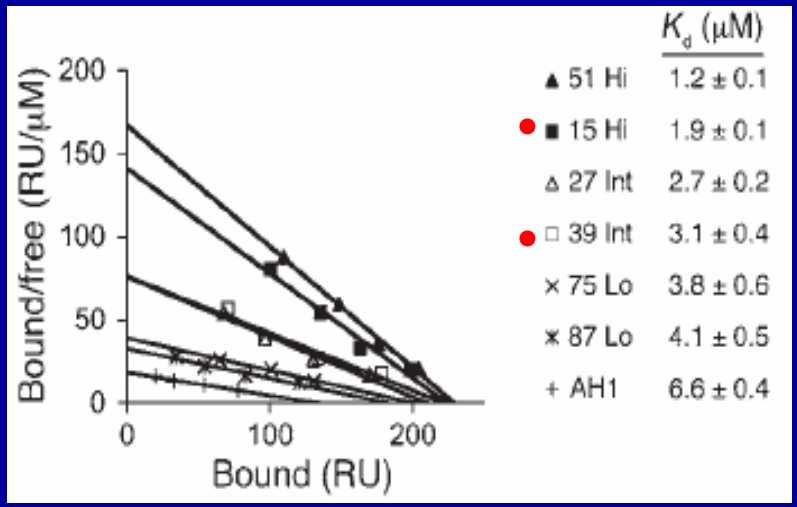
	EA01	EA03	EA05	EA08	EA10	EA11	EA12	EA15	EA20	EA21	EA22	EA23	EA26	EA28	EA31
Pre	0	0.01	0	0.03	0	0	0.06	0	0	0	0	0	0	0	0.03
Post	0.18	0.01	0.63	8.86	0.73	0.33	1.12	0.05	1.16	0.08	0.1	0.21	0.13	0.75	0.38

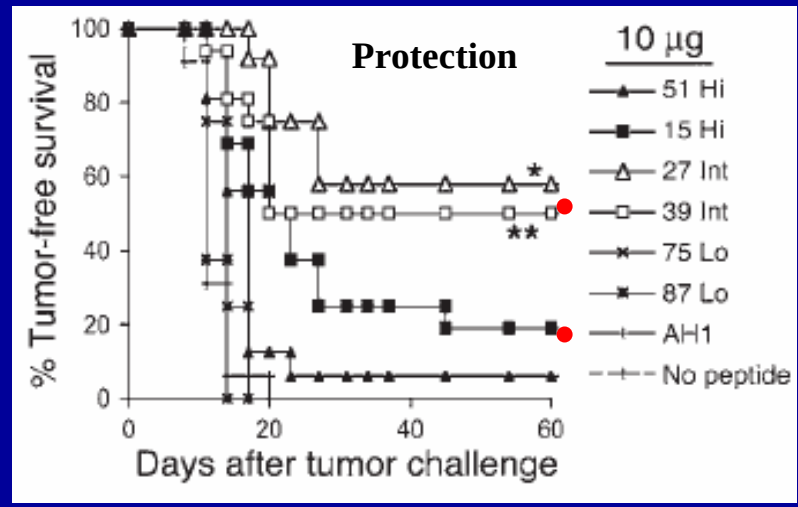
Modified gp100 Peptide

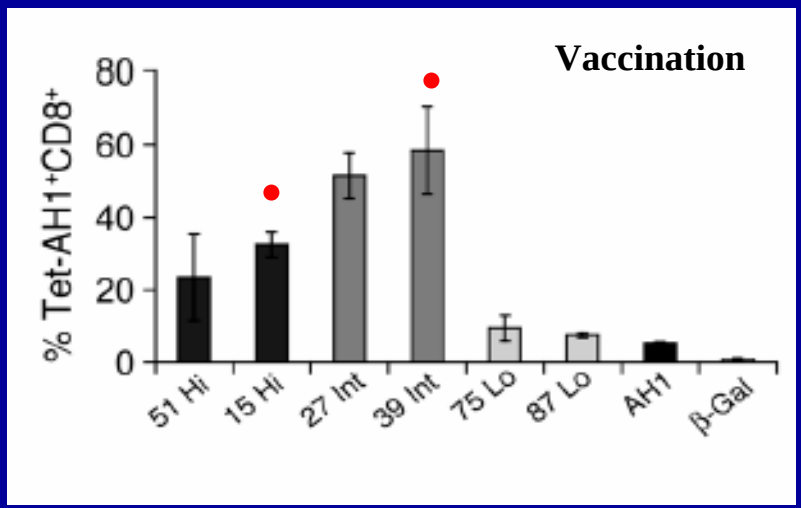
- Stage I-III melanoma: adjuvant setting
- Modified gp100 peptide
  - HLA-A2
  - p209-2M
- Given sq in IFA q 2 or 3 weeks
- HLA-tetramer to assess immunity
- Increased peptide specific CD8+ in 28/29
- 28% of patients >1%

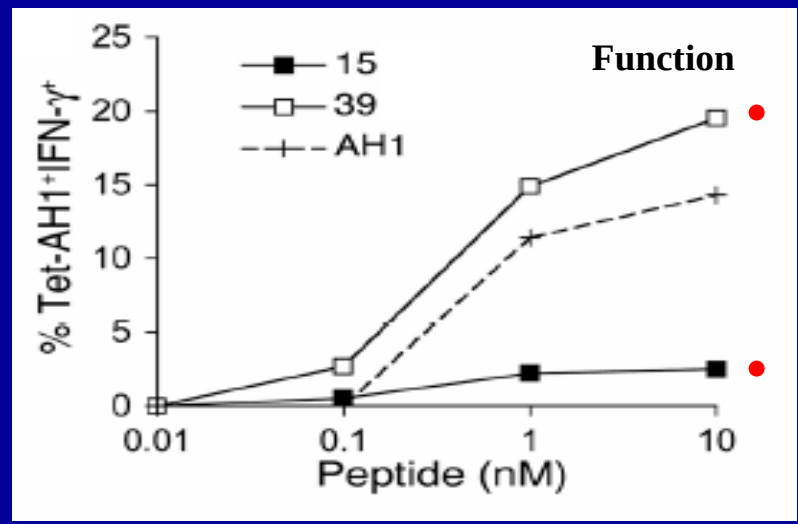
Smith et al, JCO, 2003

Intermediate Binding Altered Peptides are Optimal Vaccine Candidates





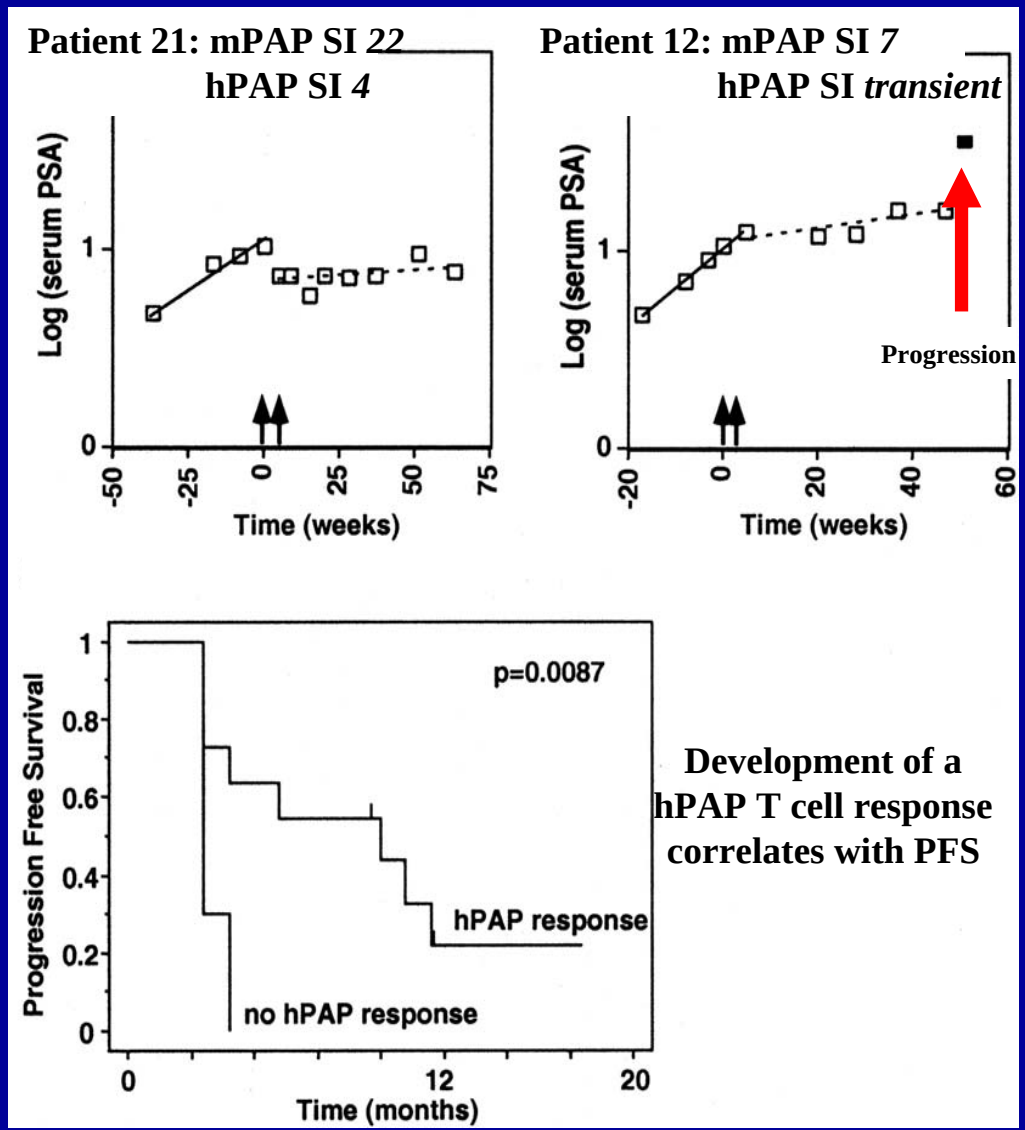




AH1 epitope/CT26 tumor/BLAB/c: libraries screened by T cell clone

McMahan, R et al JCI, 2006

Xenoantigen Immunization



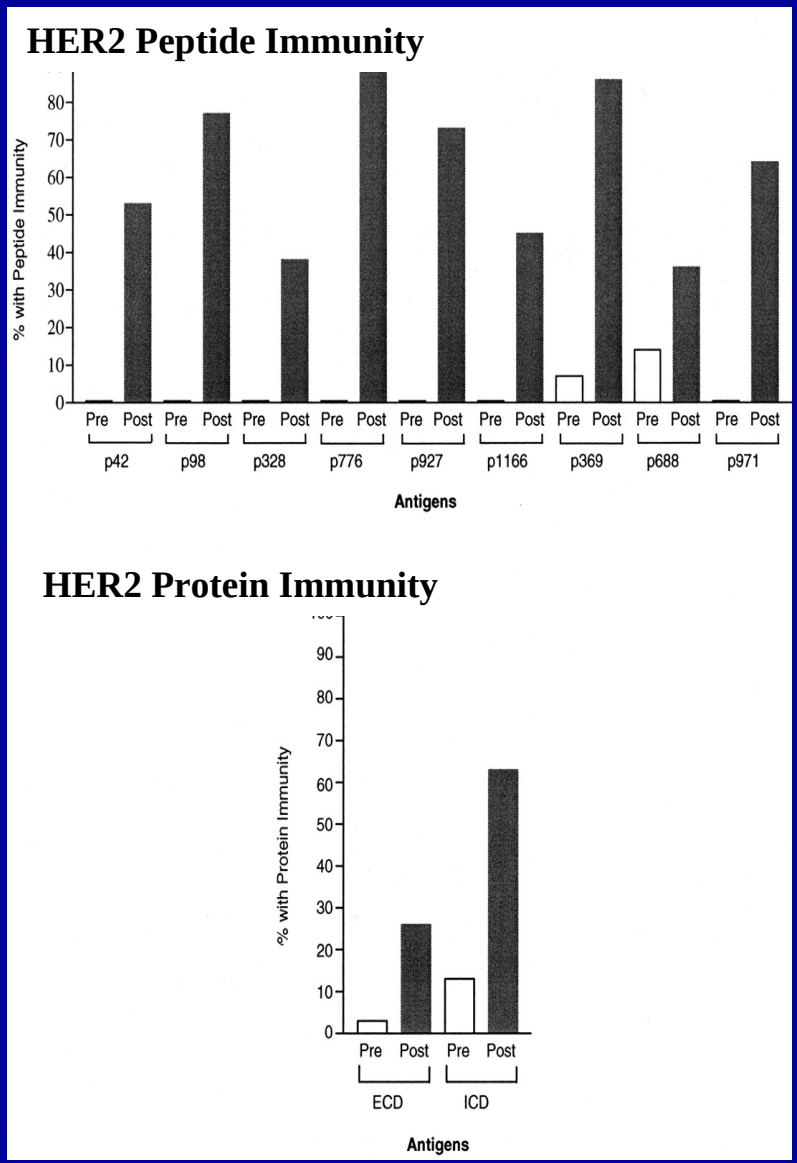
Development of a hPAP T cell response correlates with PFS

Mouse PAP in Man

- DC pulsed with mouse PAP protein
- Highly homologous foreign protein
- 21 patients with metastatic prostate cancer
- 2 monthly vaccinations
- All patients=immunity to mouse PAP
- 50% immunity to human PAP
- 6/21 with clinical stabilization
- Stabilization associated with human PAP immunity

Fong et al, JI, 2001

Vaccinating to Induce CD4$^+$ T Cell Immunity



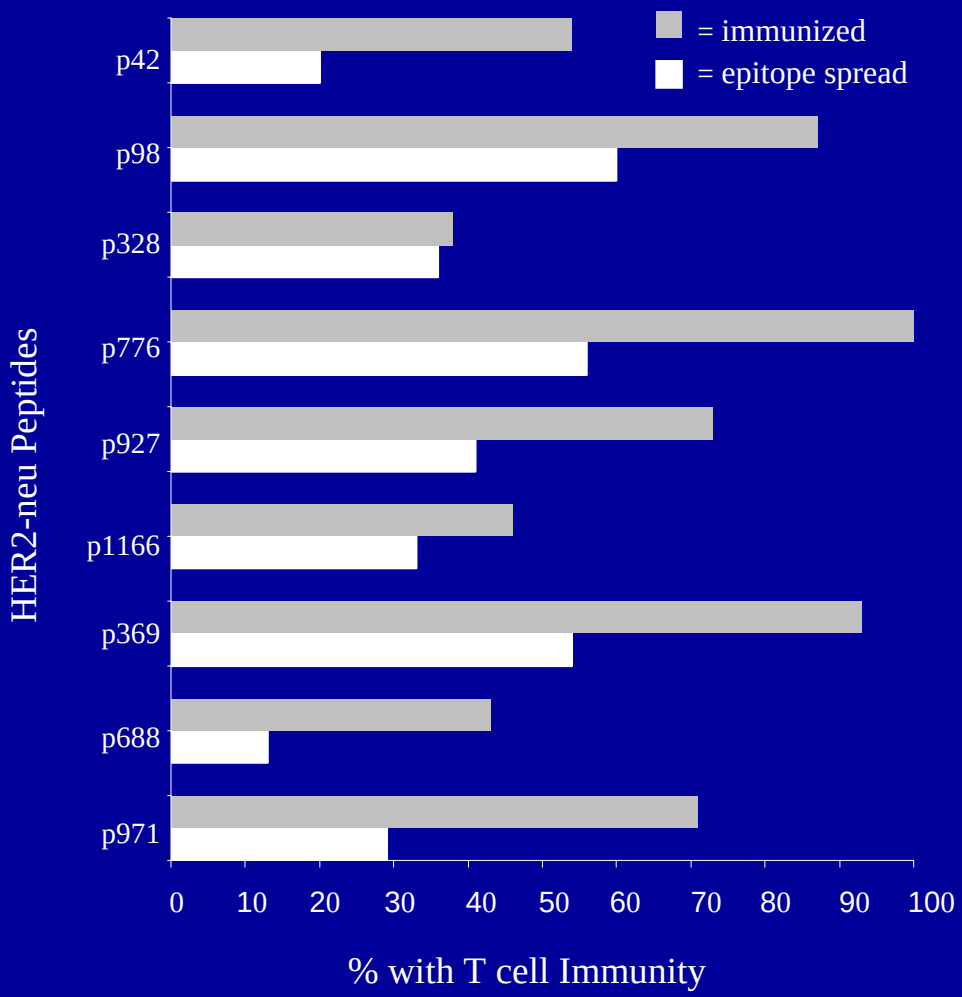
Definition of Class II Epitopes

- HER2 Th peptides in GM-CSF given i.d.
- 3 peptides/vaccine
- Stage III/IV breast, ovarian, or NSCLC
- 38 patients completed all 6 immunizations
- >90% developed immunity to HER2 peptides
- >60% developed immunity to HER2 protein
- Immunity could persist>1 year
- Epitope spreading in majority=protein response

Disis et al, JCO, 2002

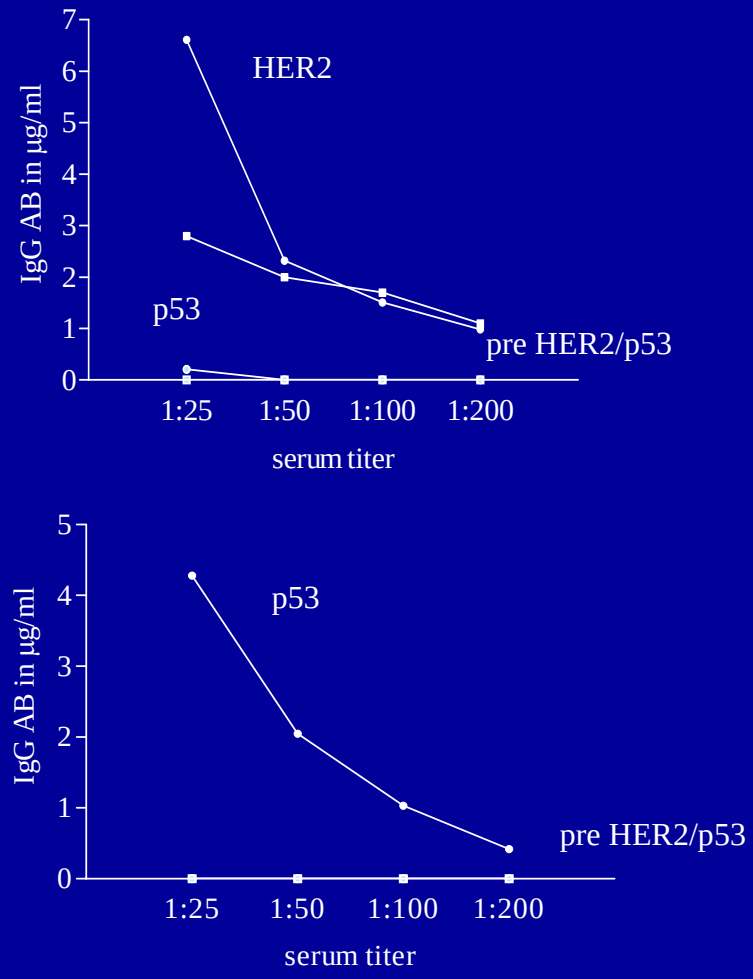
Evolving Immunity with Immunization

Intramolecular epitope spreading



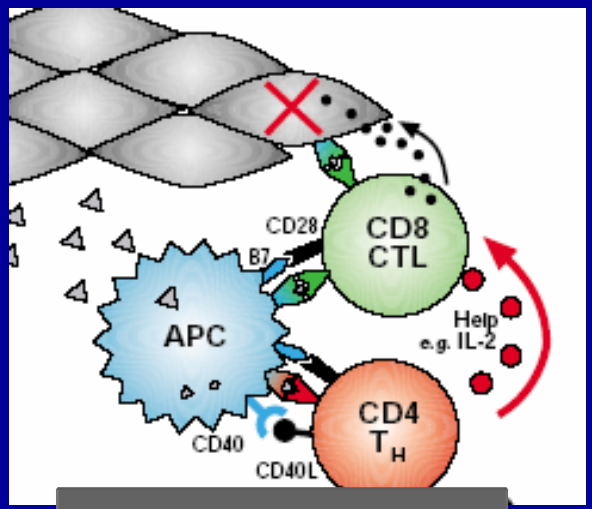
Disis et al, JCO, 2002

Intermolecular epitope spreading

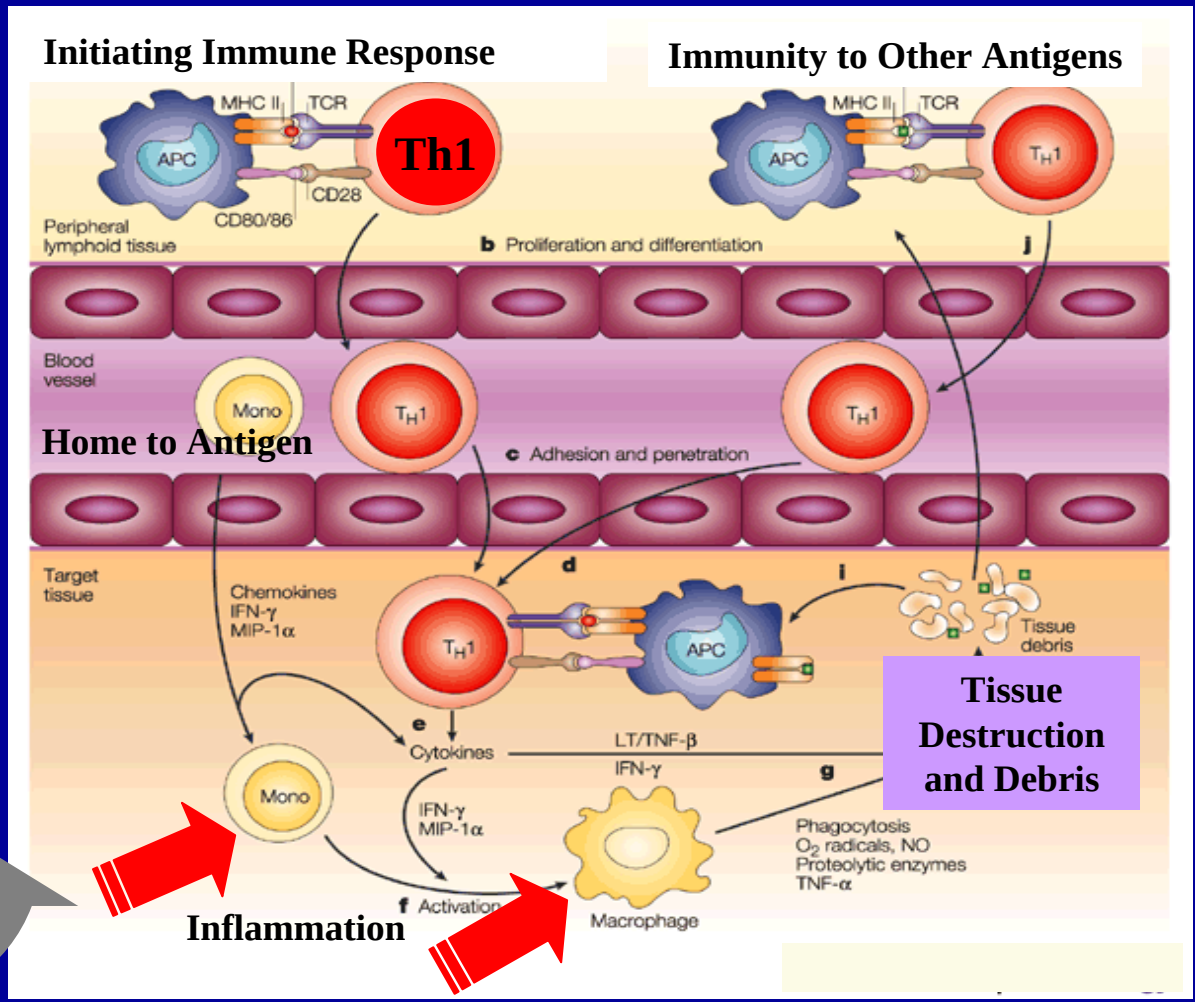


Disis et al, J Clin Immunol, 2004

Productive Immunity Modulating the Microenvironment

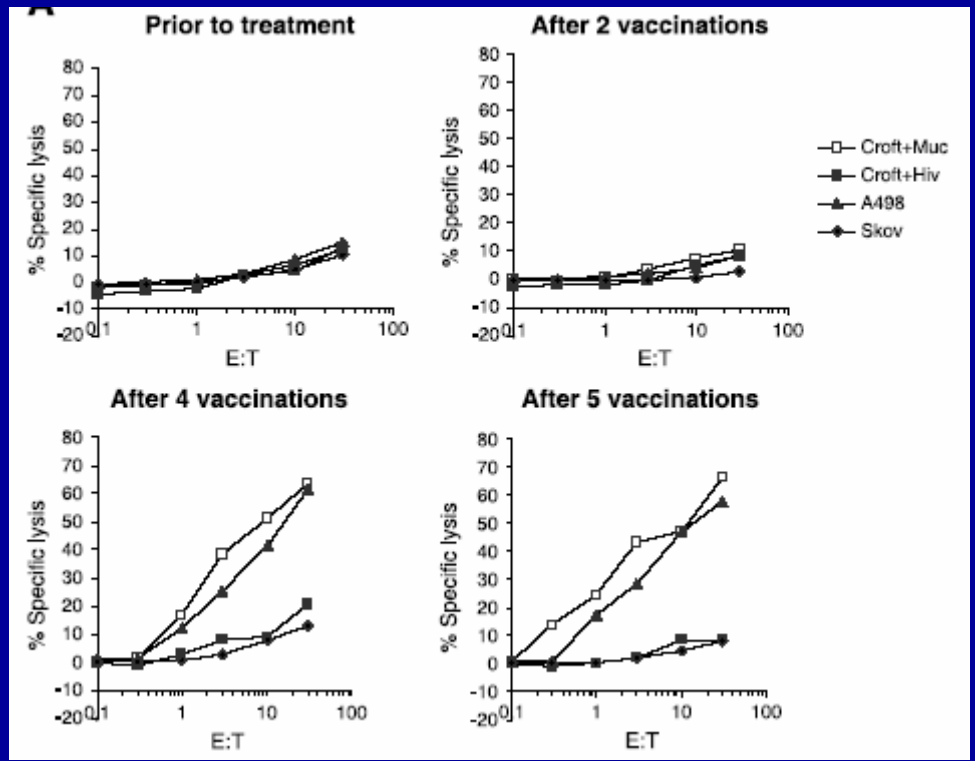


Tumor microenvironment

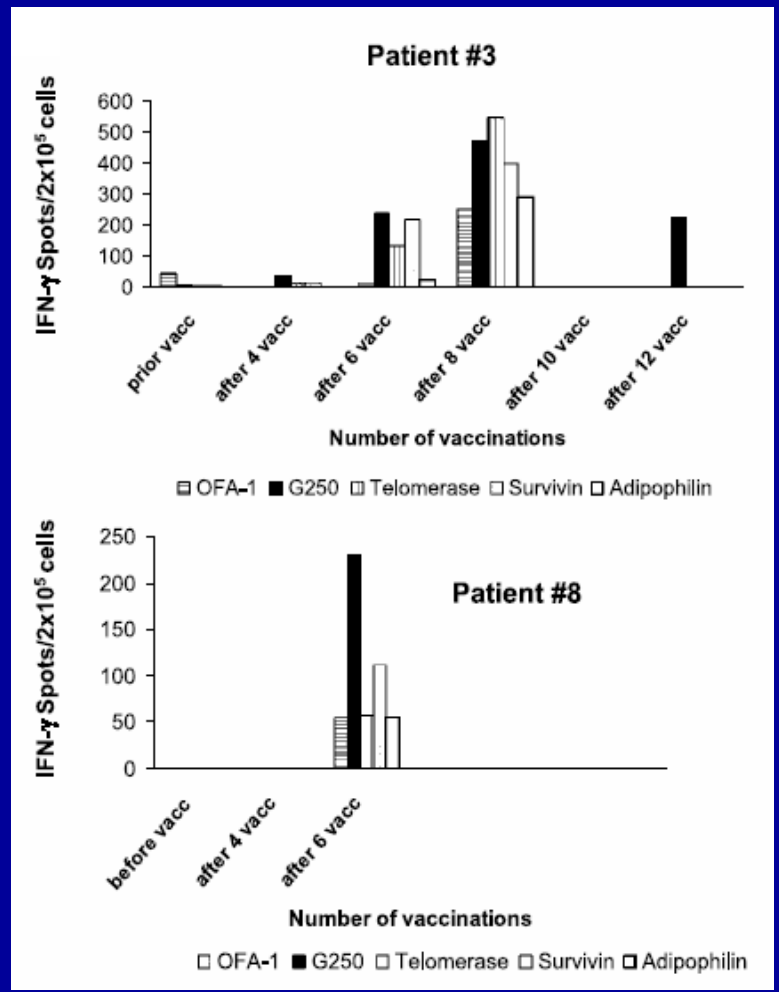


Vanderlught et al, Nat Rev Immunol, 2002

DC-MUC-1 Vaccine + LD IL-2 in RCC Elicits Epitope Spreading



15% RR (PR+CR), 1 CR
Induced immunity associated with response (r=0.79)
(n=20)



Wierecky J et al, Ca Res, 2006

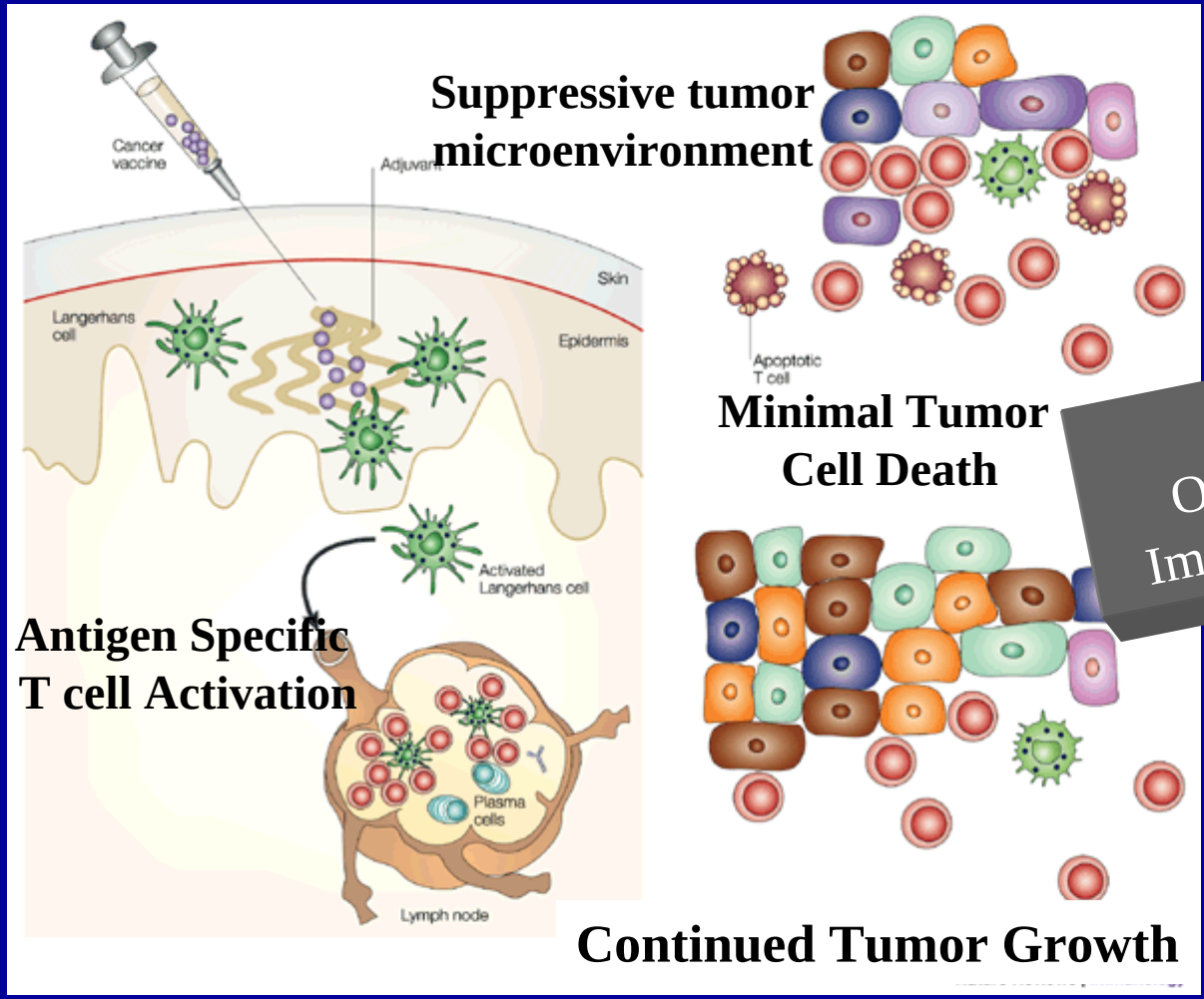
Vaccinating Established Disease

Clinical Outcomes: Cancer Vaccines in Melanoma Patients

Vaccine	Total Patients	Responding Patients	RR%
Peptide	410	11	2.7
Viral Vector	160	3	1.9
Tumor Cells	43	2	4.6
Dendritic Cells	116	11	9.5

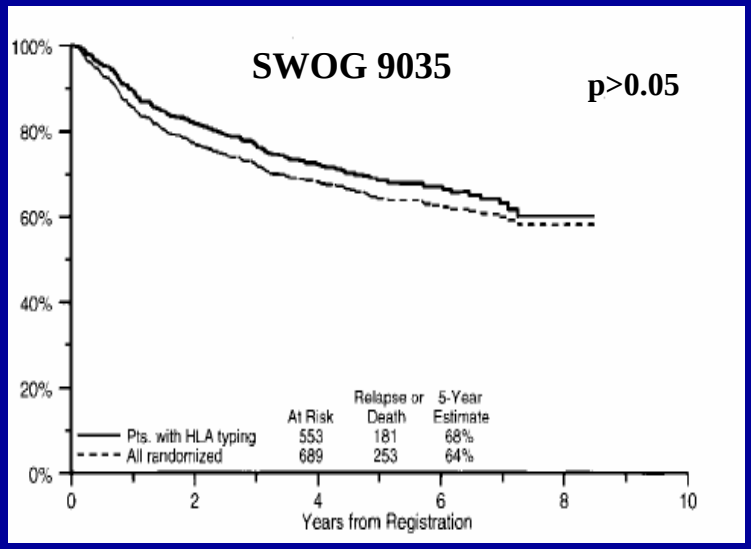
adapted from Banchereau et al, Nat Rev Immunol, 2005

Therapeutic Immunization



Adapted from Finn, Nat Rev Immunol, 2003

Cancer Vaccines in the Adjuvant Setting



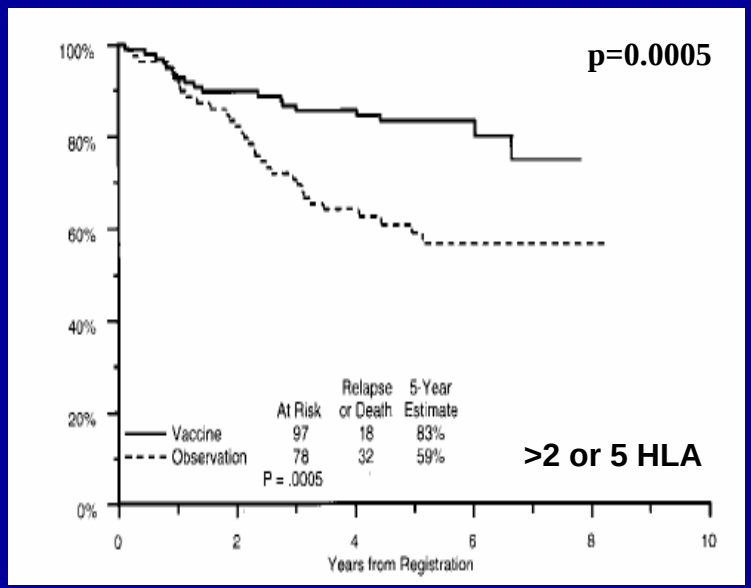
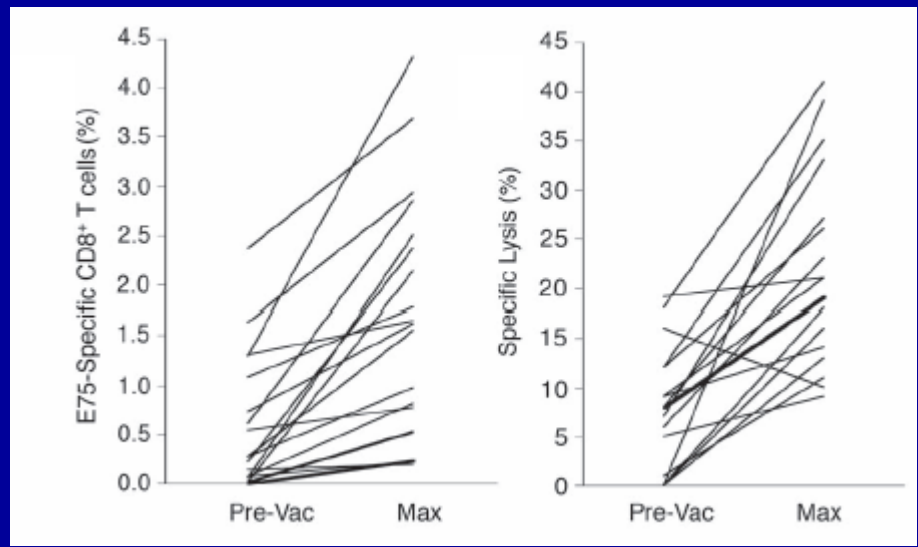


Table 4. Survival and Recurrence Rates for the Vaccinated and Prospectively Observed Control Groups of Patients With Node-Positive Breast Cancer

Median Follow-Up*	Vaccinated, HLA-A2+ (n = 24) (%)	Observed, HLA-A2− (n = 29) (%)
Overall survival	100	93
Disease-free survival	85.7	59.5
Recurrence rate	8.3	20.7

* Median follow-up was 22 months (range, 6 to 48 months).



Sosman et al, JCO, 2002

Peoples G. et al, JCO, 2005

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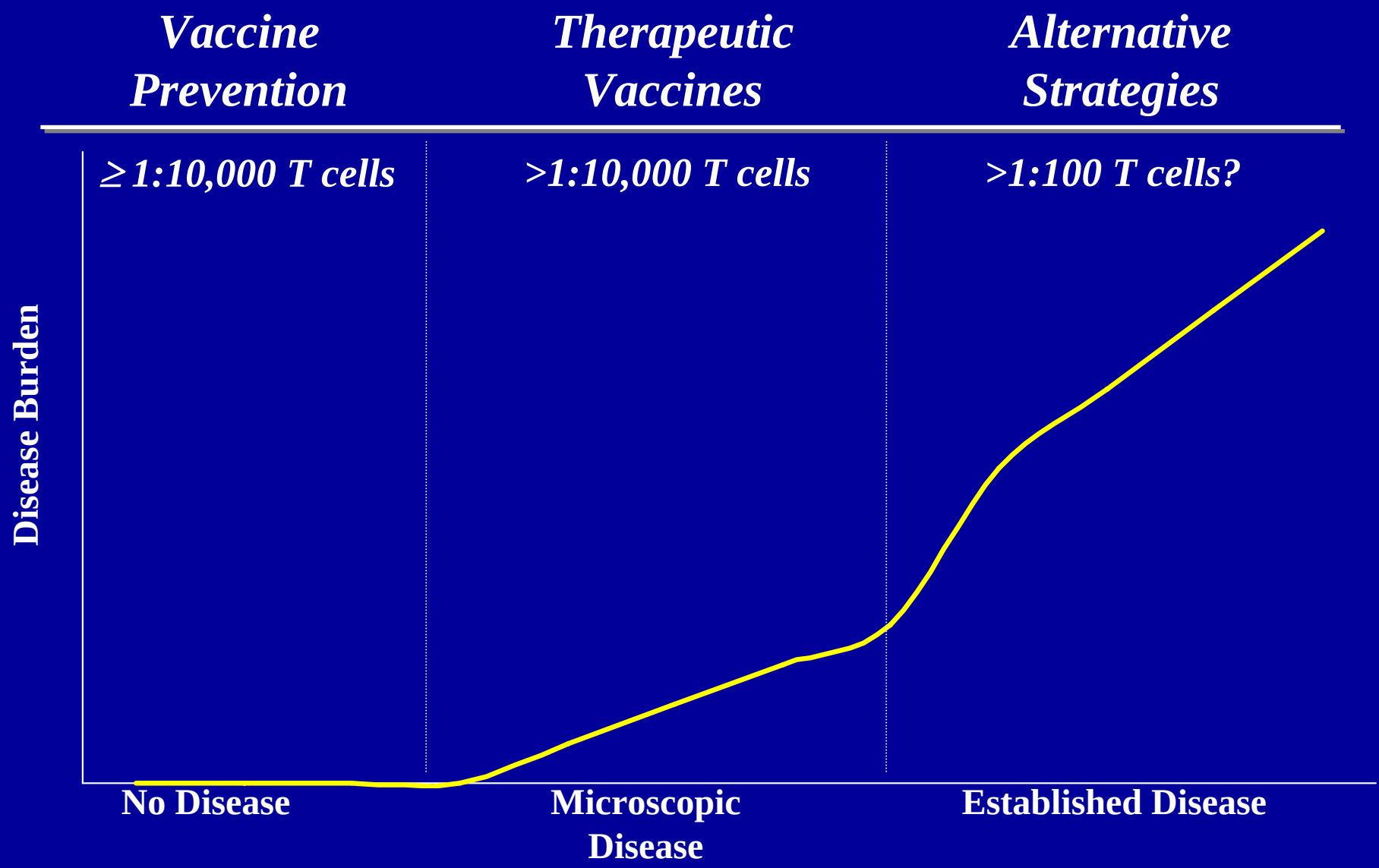
I. T cells and tumor immunity

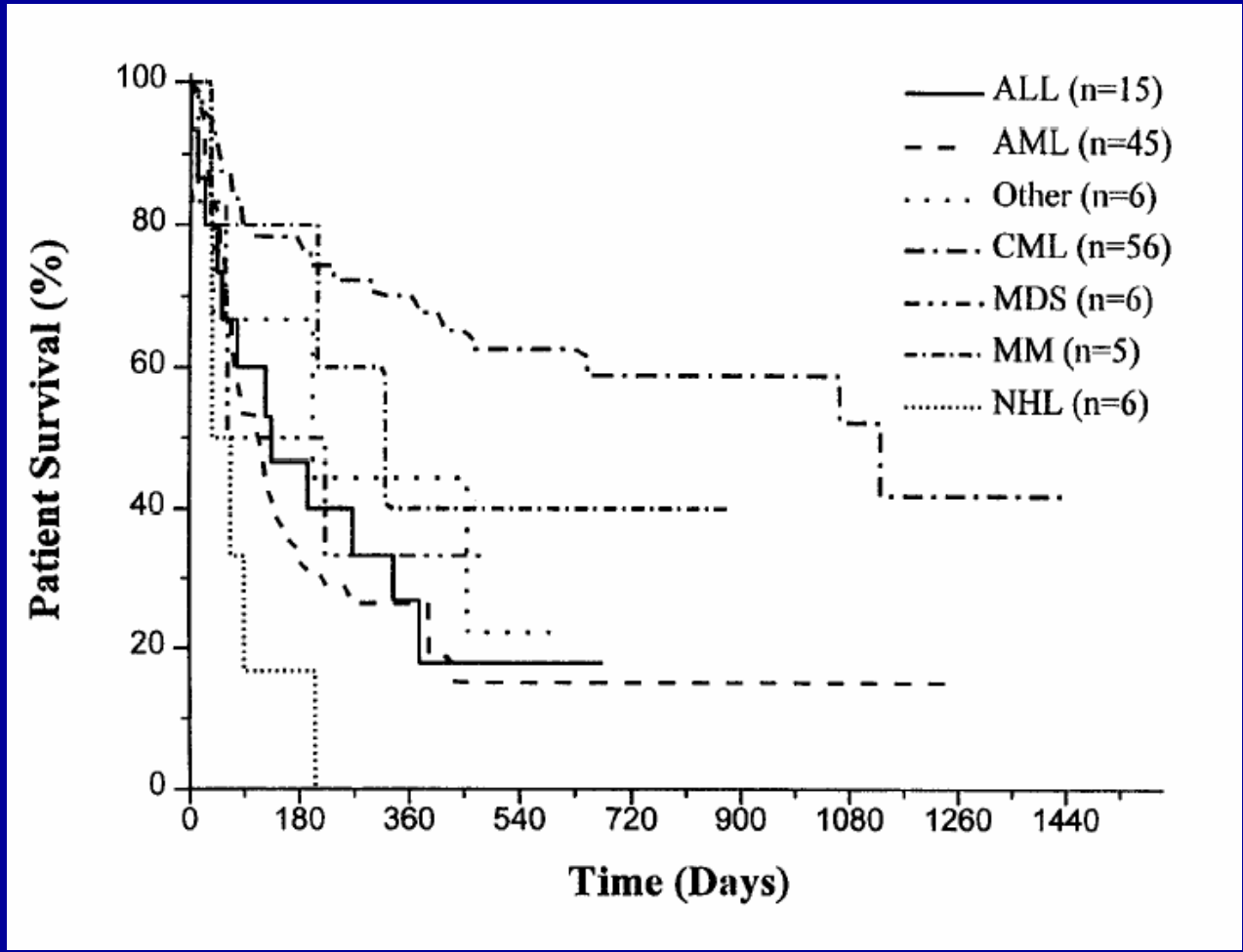
II. Vaccines: generate T cell response

III. T cell therapy: augment T cell response

Intervention Based on Tumor Burden



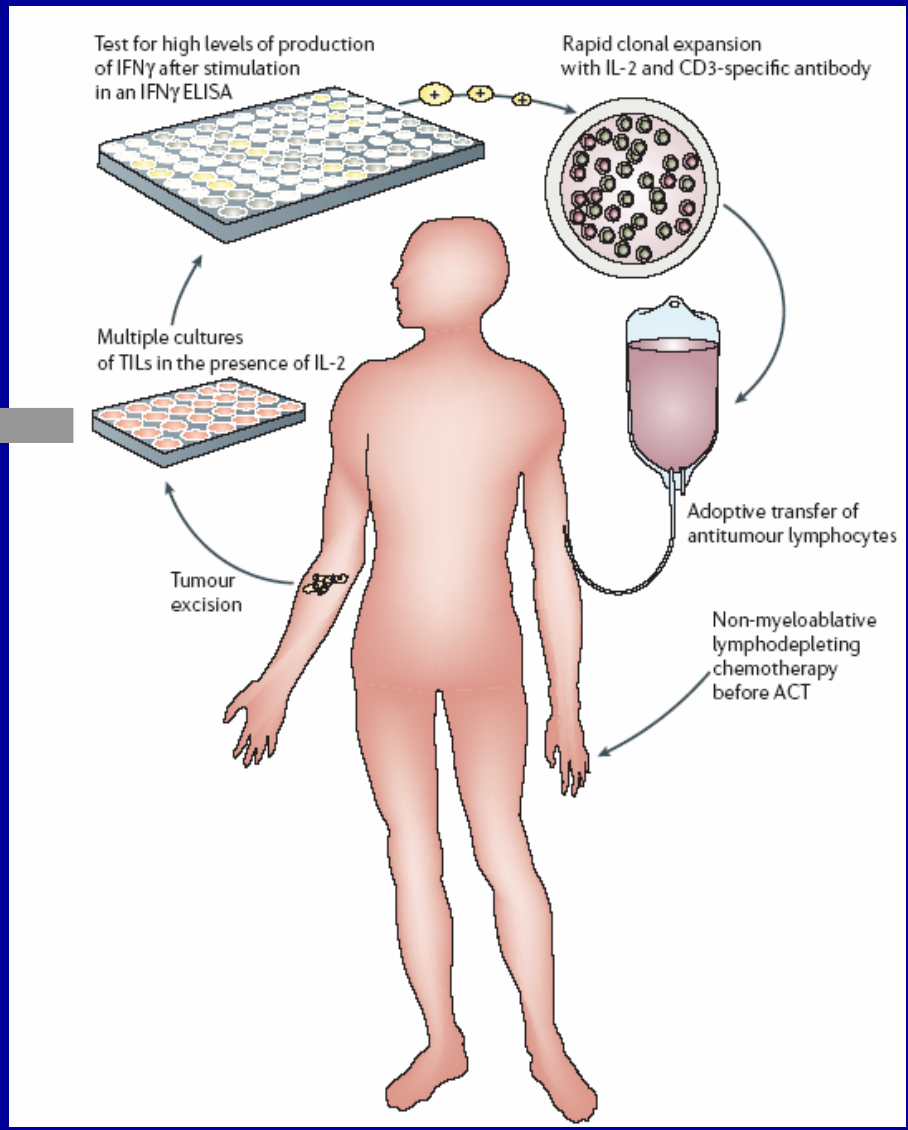
Long Term Survival after Transplant Relapse with DLI



Collins et al, JCO, 1997

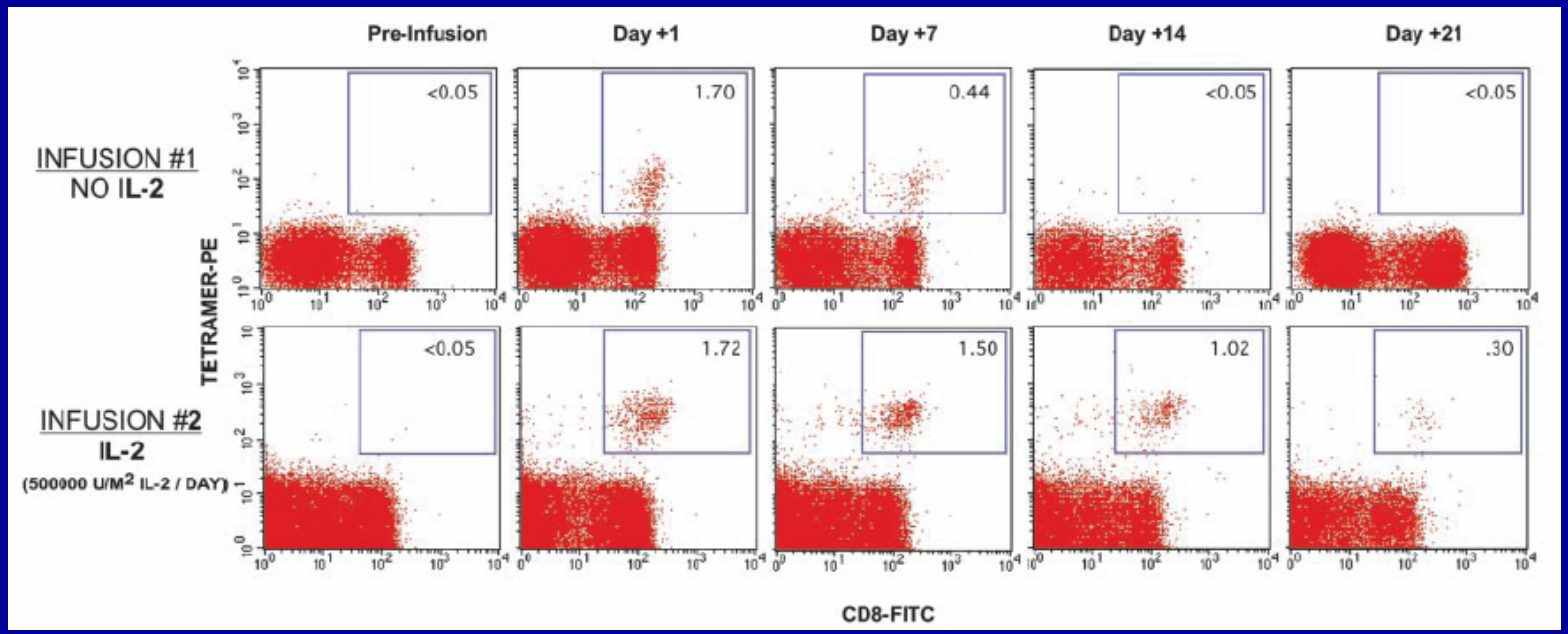
Transfer of Tumor Competent T Cells

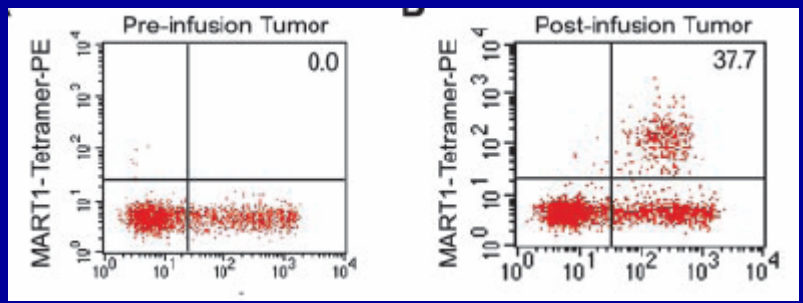
Clones
Enriched PBMC
TIL
Gene Modified Cells



Gattinoni L et al Nat Rev Immunol, 2006

Adoptive T Cell Therapy with CD8+ T Cell Clones



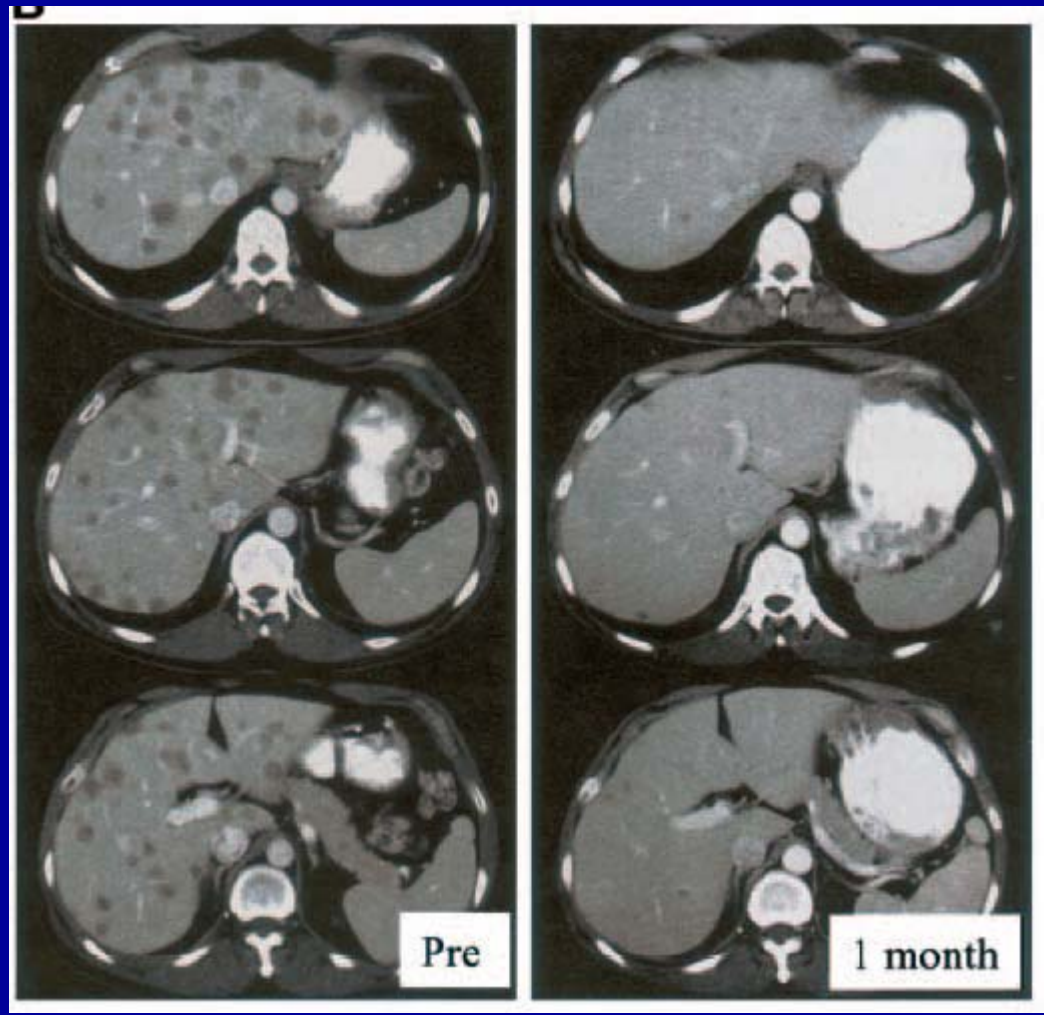


Infusion of MART-1 CD8+ T Cell Clones

Yee, C et al, PNAS, 2002

Adoptive Transfer of Expanded TIL After Induction of Lymphopenia

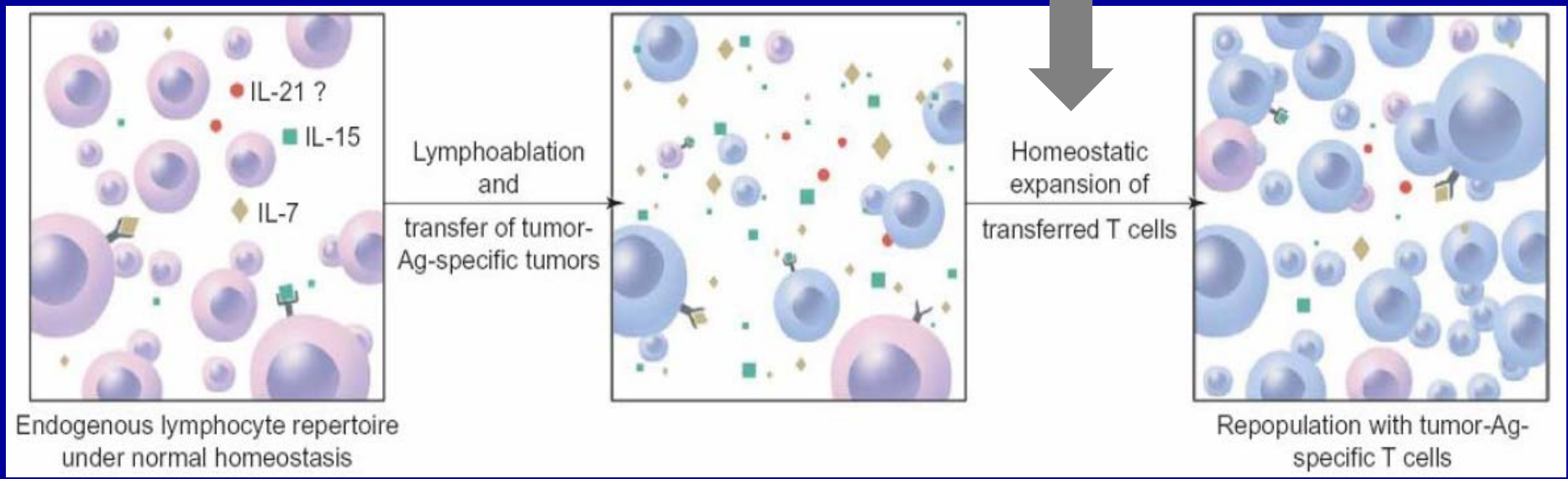
- 35 patients with MM
- Cytoxan/Fludarabine
- TIL + HD IL-2
- 18/35 (51%) had objective clinical response
  - 3 CR
  - 15 PR
- 1 patient: EBV lymphoma



Dudley M et al, JCO, 2005

Lymphodepletion Will Enhance T Cell Expansion *in vivo*

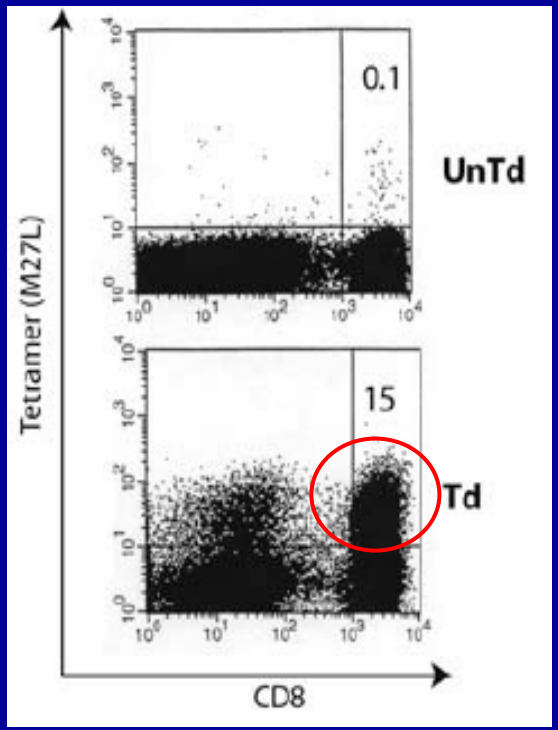
- Removal of cells (e.g. NK) that consume critical cytokines, IL-7, IL-15
- Preferential depletion of T regulatory cells
- Homeostatic proliferation



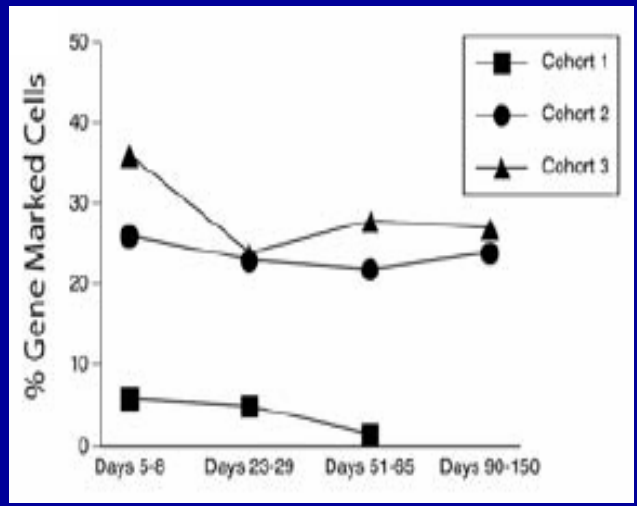
Klebanoff CA et al, Trend Immunol, 2006

T Cells Genetically Engineered to Express Functional MART-1 TCR

MART-1 TCR from CR TIL

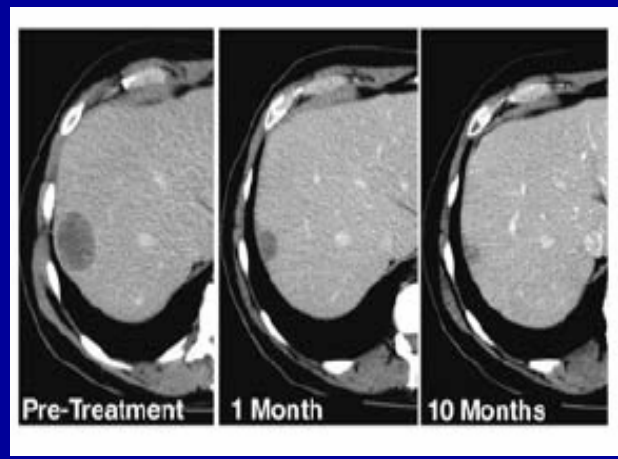


Transduced PBMC



Cohorts based on cell doubling time
Infused when actively dividing

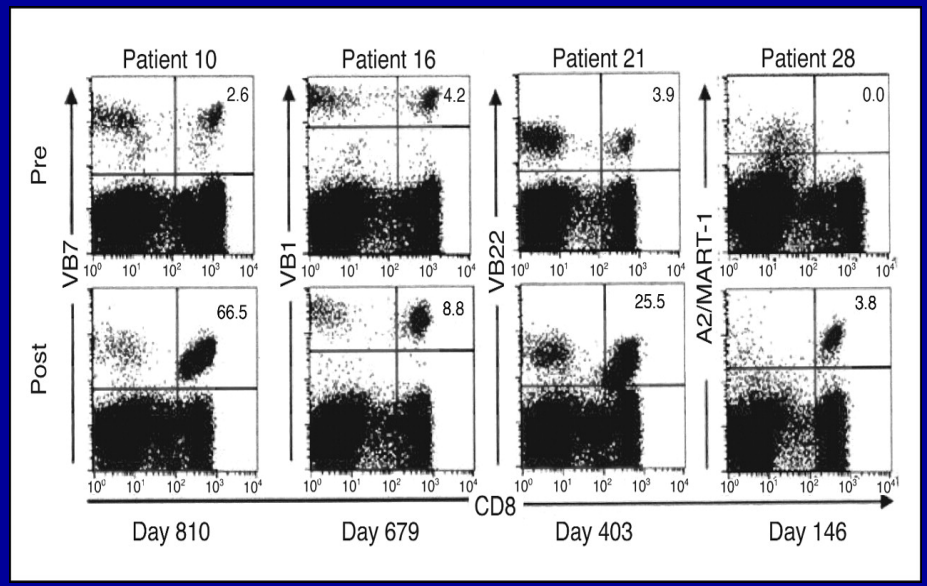
12% Partial Response Rate



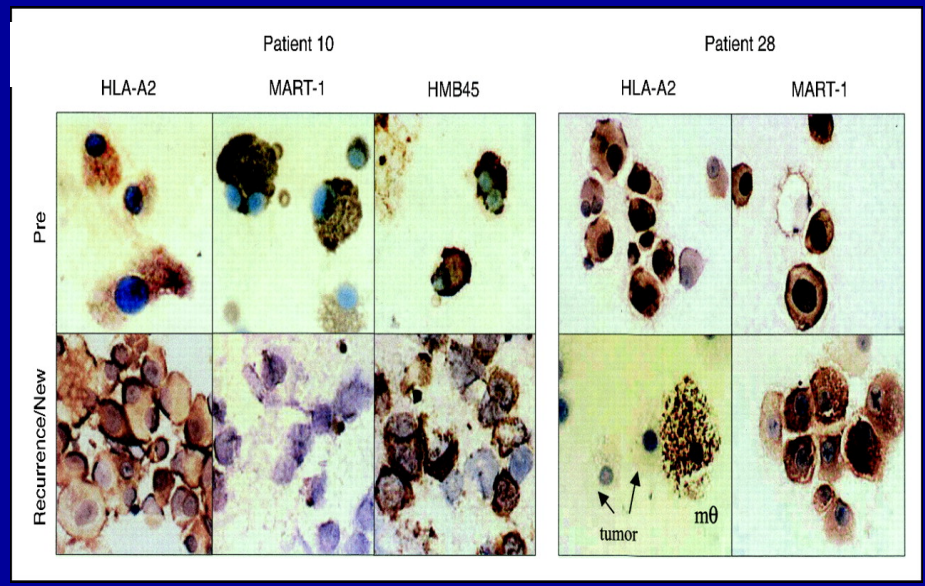
Tumor regression

Morgan RA et al, Science, 2006

Effect of Adoptively Transferred T Cells *in vivo*



Persistence



Immune Escape

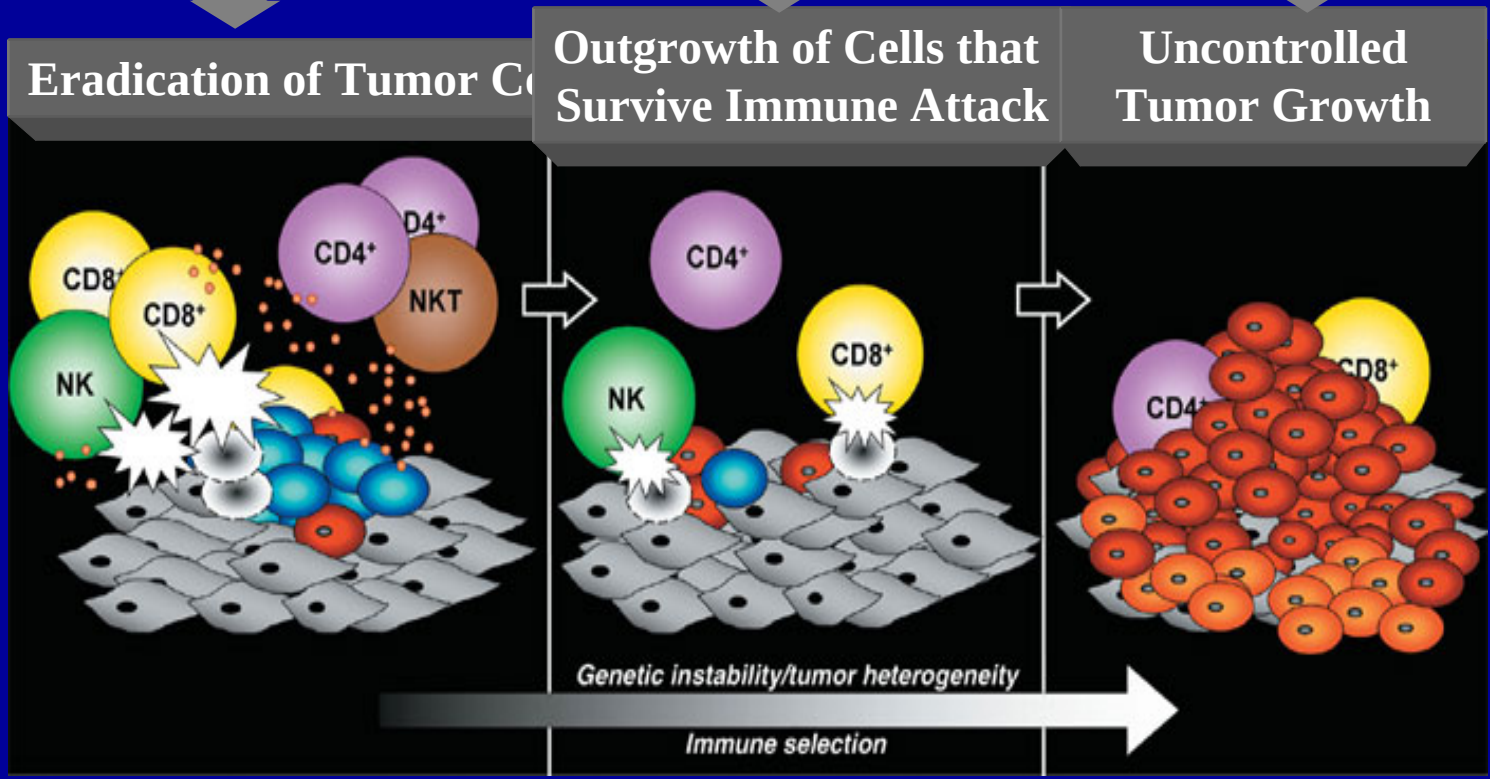
Dudley M et al, JCO 2005

Successful Immunity Leads to Immunoediting

Functional and Effective Immunity

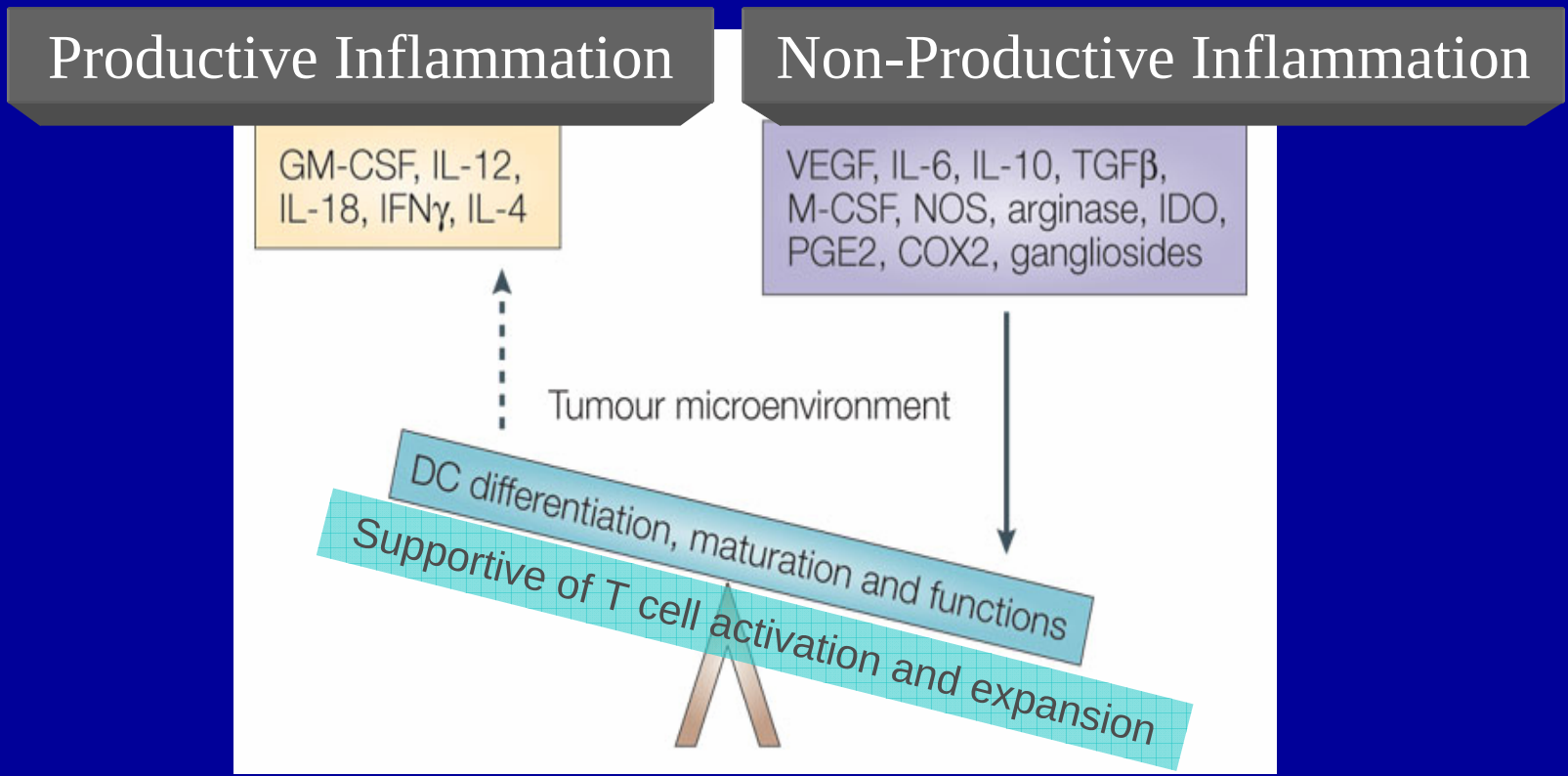
Persistent and Ongoing Immune Response: Selective Pressure

Tumor that has been "Immunologically Sculpted"



Dunn et al, Nature Immunol, 2002

Generating Anti-Tumor T Cell Immunity: Effectors and the Environment



adapted from Zou, Nat Rev Ca, 2005