TUMOR ANTIGENS AND VACCINES

Leisha A. Emens MD, PhD
Associate Professor of Oncology
Cancer Immunology/Breast Cancer Research Programs
Johns Hopkins University School of Medicine

CONFLICT OF INTEREST

Biosante: Under a licensing agreement between Biosante and Johns Hopkins University, the University is entitled to milestone payments and royalty on sales of the GM-CSF-secreting cell-based vaccine product described in this presenation. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

Roche/Genentech: Xeloda Advisory Board, Breast Cancer Advisory Board, Research Funding

Bristol Myers Squibb: Breast Cancer PD-1 Advisory Board

"It is by no means inconceivable that small accumulations of tumour cells may develop, and because of their possession of new antigenic potentialities, provoke an effective immunological reaction with regression of the tumour and no clinical hint of its existence."

--Macfarlane Burnet

Immunologist, 1957

CANCER IMMUNOSURVEILLANCE IN HUMANS

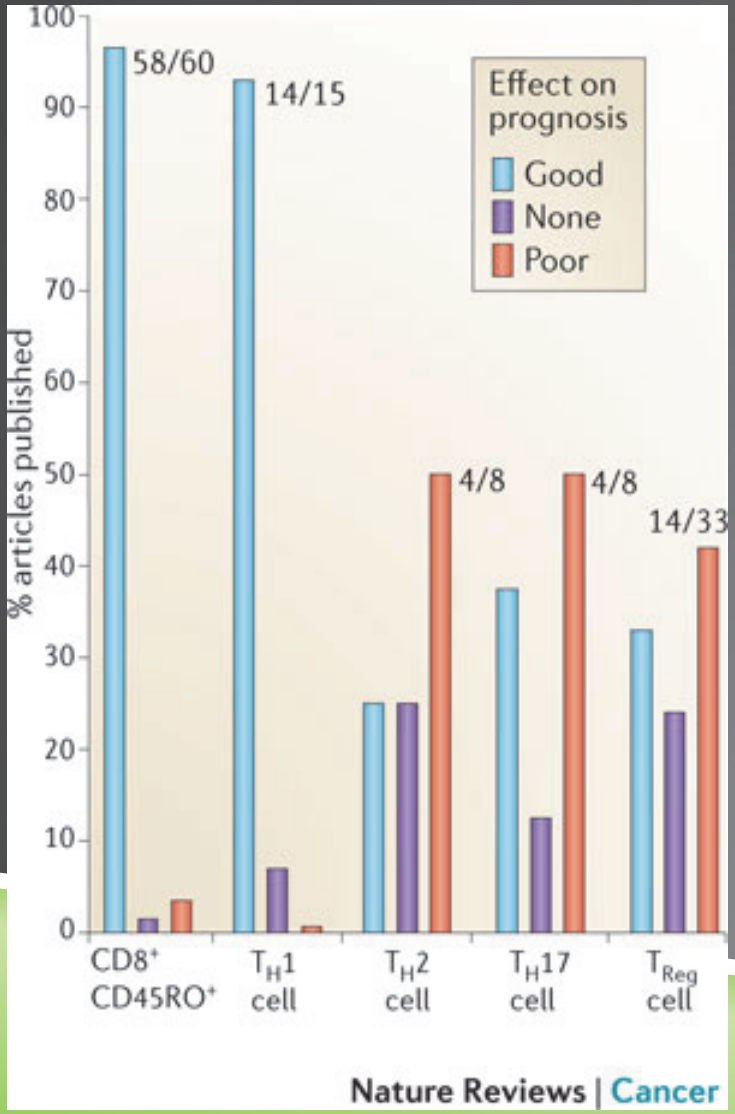
Site of Cancer*	Ratio of Cases Observed/Expected
Non-melanoma skin	24.7
Thyroid/Endocrine	14.3
Head and Neck	13.8
Cervix/Vulva/Vagina	10.8
Non-Hodgkn's lymphoma	10.3
Kidney/Ureter	9.1
Bladder	5.5
Colorectal	3.6
Lung	2.4
Brain	2.4
Prostate	2.1
Melanoma	1.7
Breast	1.1

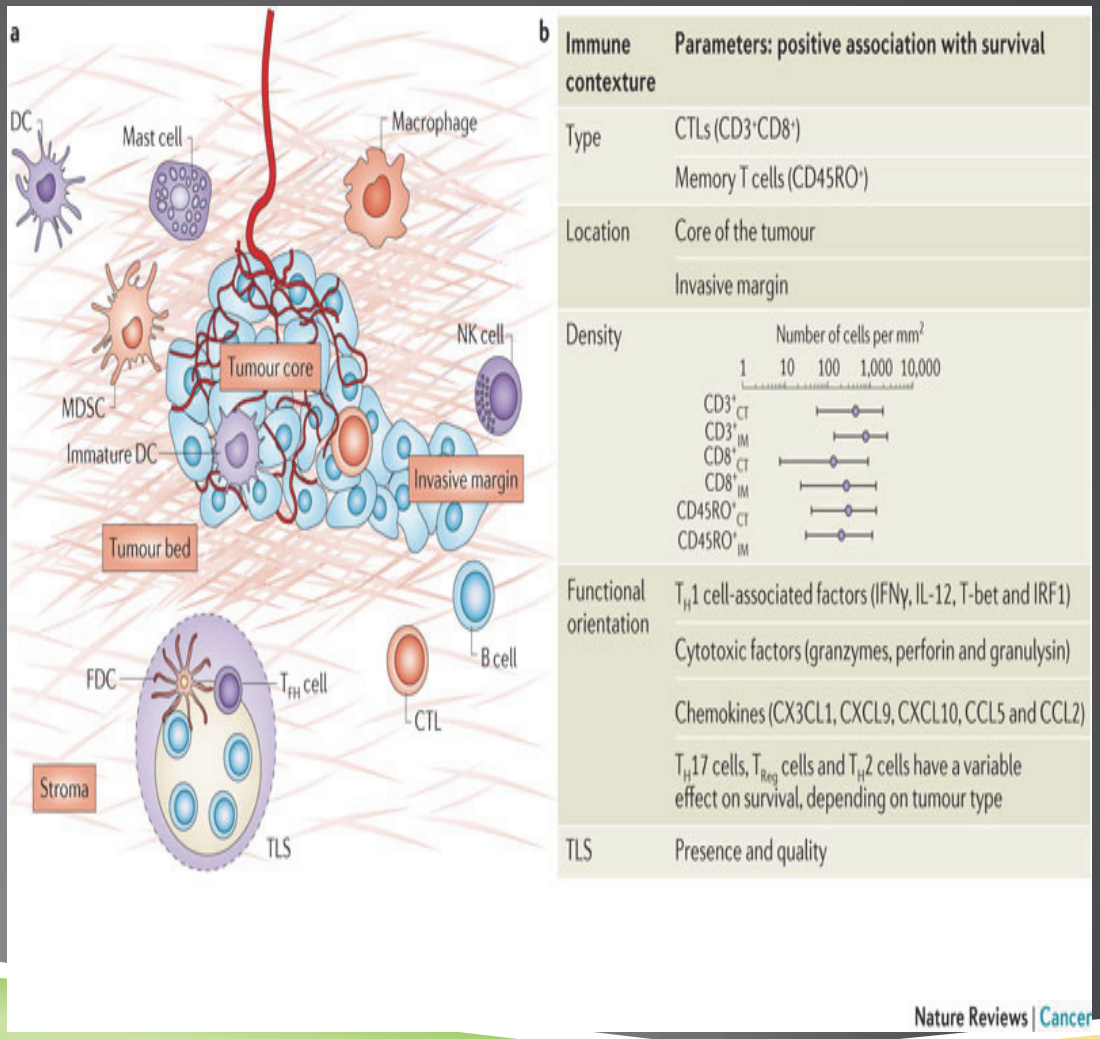
Cancer incidence in immunosuppressed transplant patients
Adapted from Peto 2001 Nature 411: 390.

CANCER IMMUNOSURVEILLANCE IN IMMUNOCOMPROMISED HUMANS

- 400-500X increase in Kaposi's sarcoma (HHV-8)
- 28-49X increased in lymphoproliferative disease, inlcuding Hodgkin's disease (EBV)
- 100X increase in squamous cell vulvar and anal carcinomas (HPV)
- 20-38X increase in hepatocellular carcinoma (HBV and HCV)
- 14-16X increase in cervical cancer (HPV)

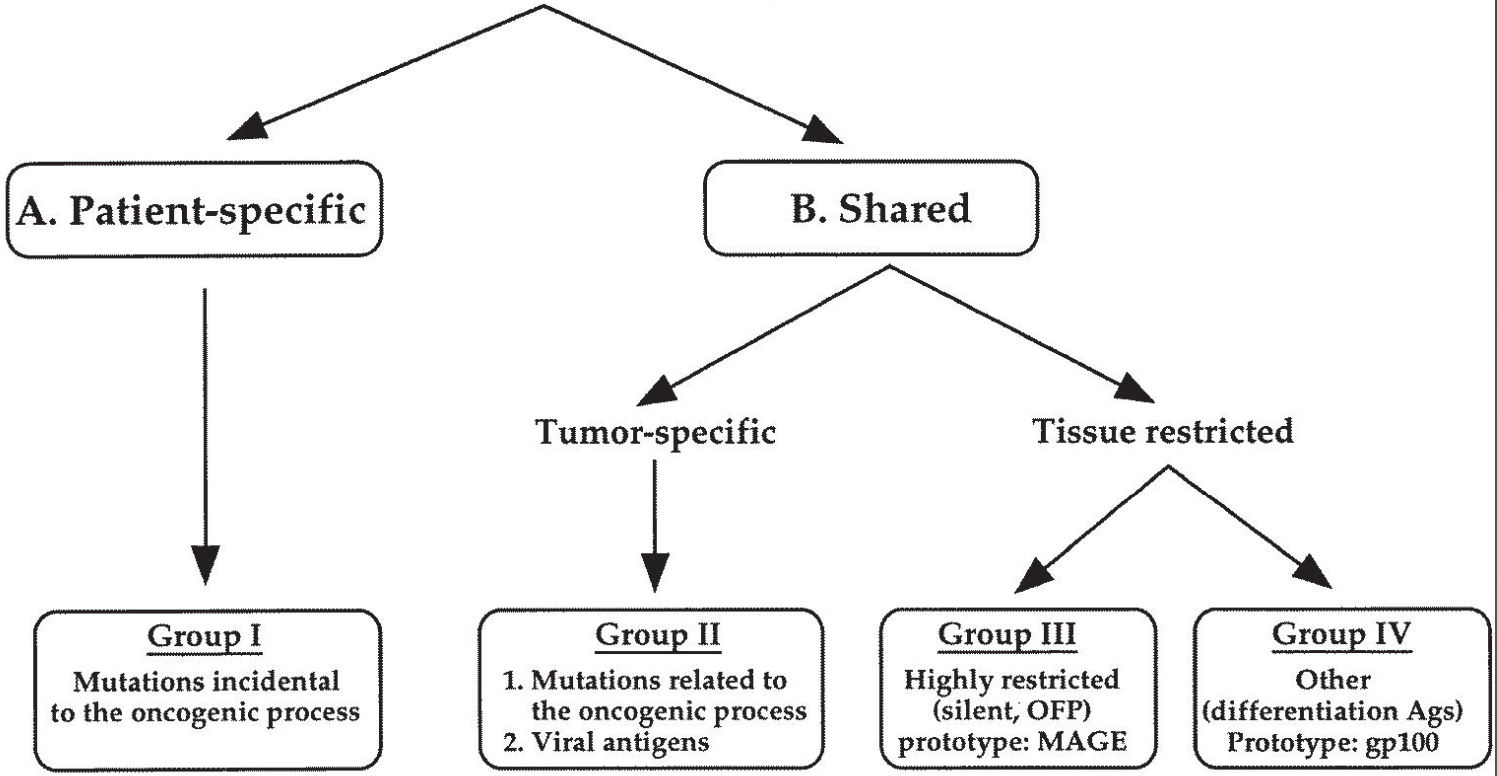
THE IMMUNE SYSTEM RECOGNIZES TUMORS





Fridman 2012 Nature Rev Cancer 12: 298.

Human Tumor Antigens



Tolerance	Non	Non	Non-partial	Partial
T cell affinity	High	High	High-Interm.	Interm.-low
Tumor rejection antigen	Strong	Strong	Strong-interm.	Interm.-poor

Gilboa 1999 Immunity 11: 263.

EXAMPLES OF TUMOR ANTIGENS

Type of Cancer Antigen	Examples
Viral antigens	HPV E6/E7, EBV LMP, HBV, HCV
Novel cancer antigens	mutated k-ras (pancreas, lung cancers) p53 (many cancers) fusion proteins (bcr-abl in CML) many others
Overexpressed, nonmutated self proteins	HER-2 (breast and gastric cancers) hTERT (many cancers) Ganglioside GD3 (melanomas)
Embryonic/oncofetal proteins	NY-ESO-1, MAGE/BAGE/GAGE
Expression outside immunologically privileged site	Hu, Yo, GAD
Tissue-specific differentiation antigens	MART-1/melan-A, gp-100, tyrosinase, PSA

PREVENTIVE CANCER VACCINES

- Gardasil for the prevention of HPV-related cervical cancer
  - 2nd most common cause of cancer in women worldwide
  - HPV types 6, 11, 16, 18, quadrivalent vaccine of VLPs
  - Prevents 75% of cervical cancers, 70% of vaginal cancers, and 50% of vulvar cancers in girls and young women, and 90% of genital warts in young people
  - HPV-related head and neck cancer?
- HBV vaccines for the prevention of HBV-related liver cancer
  - 5th and 8th most common cancer in men and women respectively worldwide
  - Decreased incidence of HCC in children ages 6-9 years from 0.52-0.13 per 100,000

THERAPEUTIC CANCER VACCINE

Siipuleucel-T (Provenge^{R}) : First FDA-approved therapeutic cancer vaccine

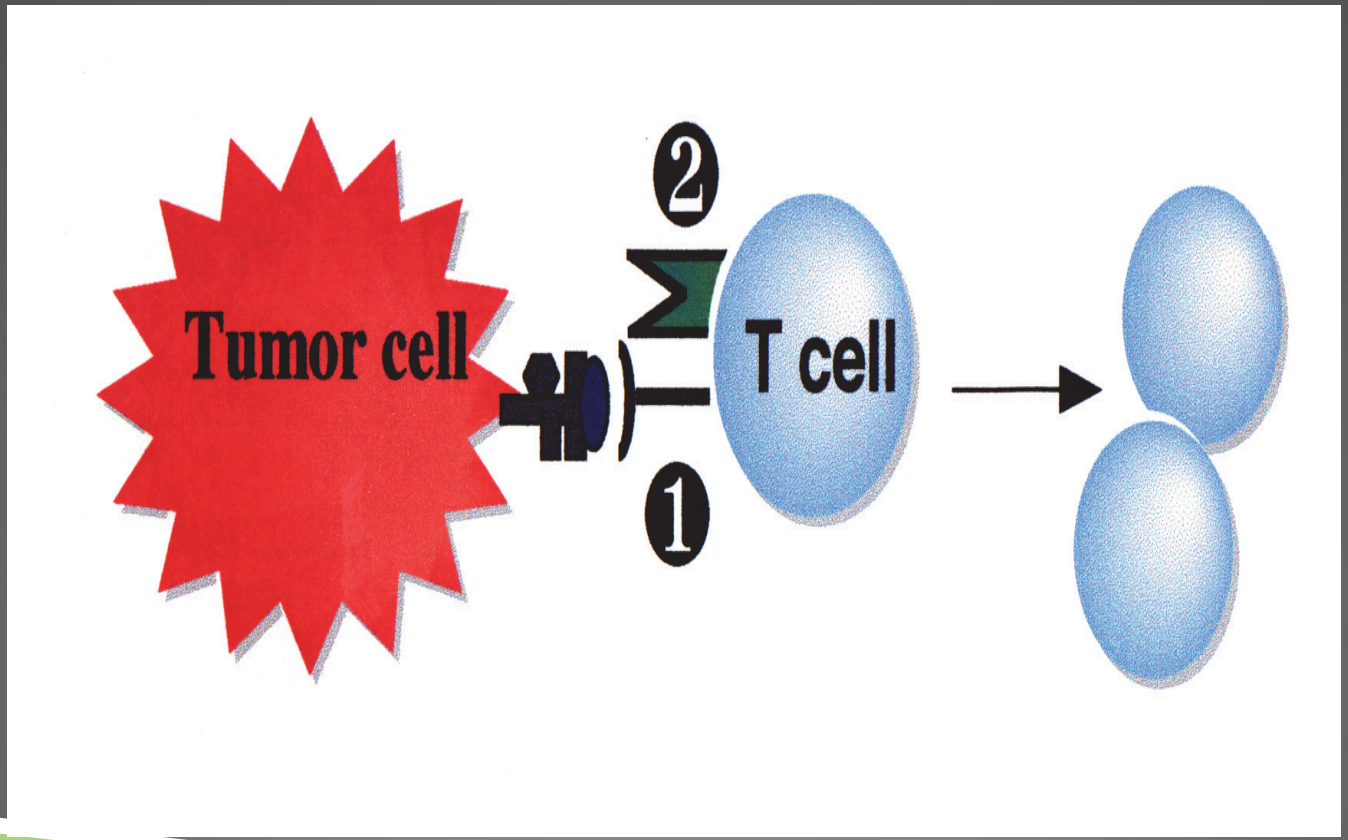
1. Composed of autologous dendritic cells loaded with prostatic acid phosphatase fused with granulocyte-macrophage colony-stimulating factor (PAP-GM-CSF)
2. Given as 3 treatments 2 weeks apart
3. Prolongs survival of men with metastatic hormone-refractory prostate cancer by 4.1 months
4. Retrospective data show that this is the greatest survival benefit demonstrated for this patient population to date
5. Minimal toxicity
6. Expensive ($100, 000)

SIPULEUCEL-T (PROVENGE[R]): PHASE III IMPACT TRIAL

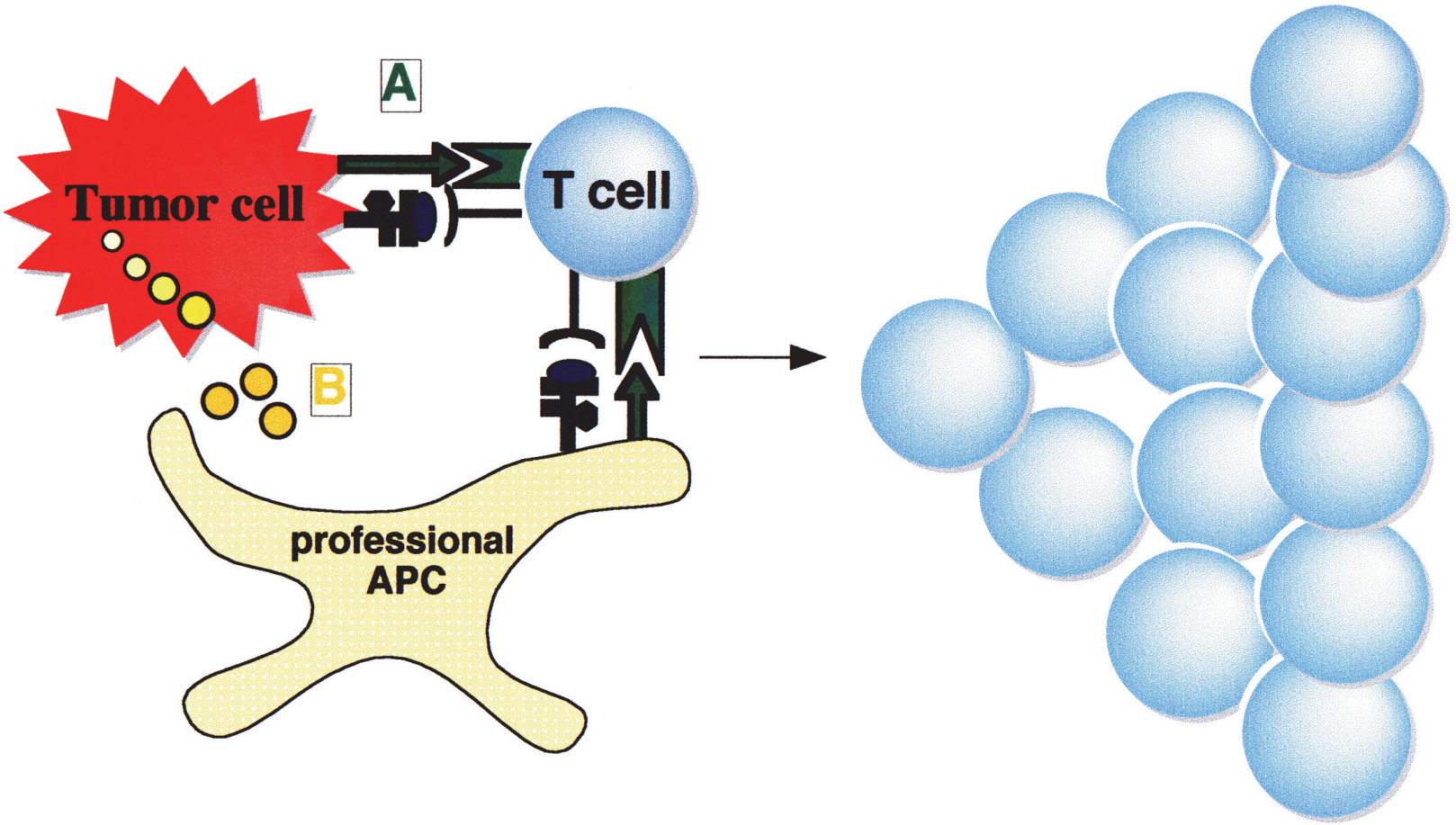
	Placebo (n=171)	Sipuleucel-T (n=341)	Delta or p-value
Overall survival	21.7 months	25.8 months	4.1 months
36-month survival	23.0%	31.7%	+8.7%
TTP	14.4 weeks	14.6 weeks	p=0.63
Relative reduction in risk of death	-------	22%	P=0.03
Relative reduction in risk of death from prostate cancer	-------	23%	P=0.04

Kantoff 2010 NEJM 363: 411.

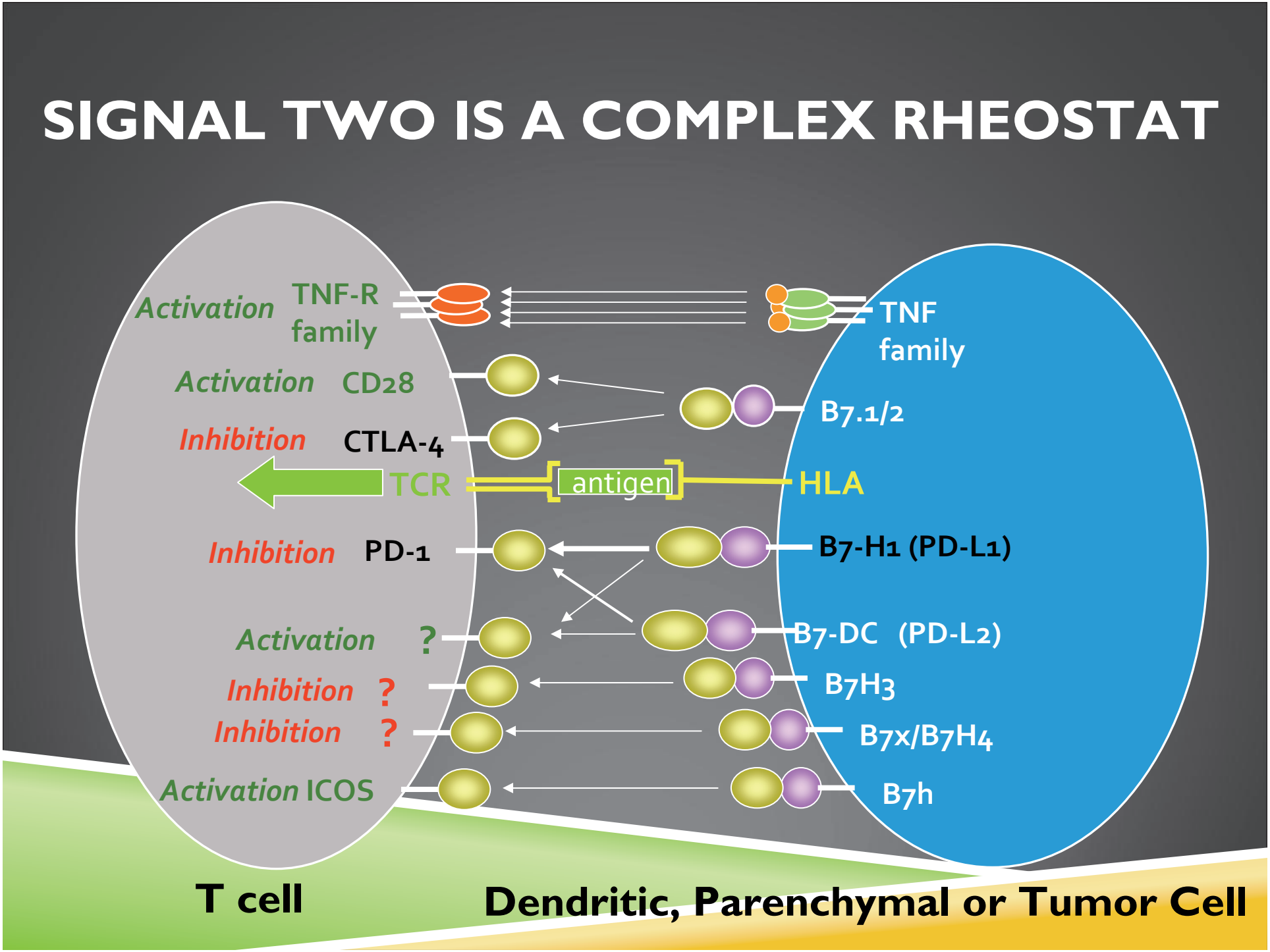
HOW ENDOGENOUS TUMOR ANTIGENS ARE RECOGNIZED



Two Signals Lead To Activation Rather Than Ignorance



SIGNAL TWO IS A COMPLEX RHEOSTAT



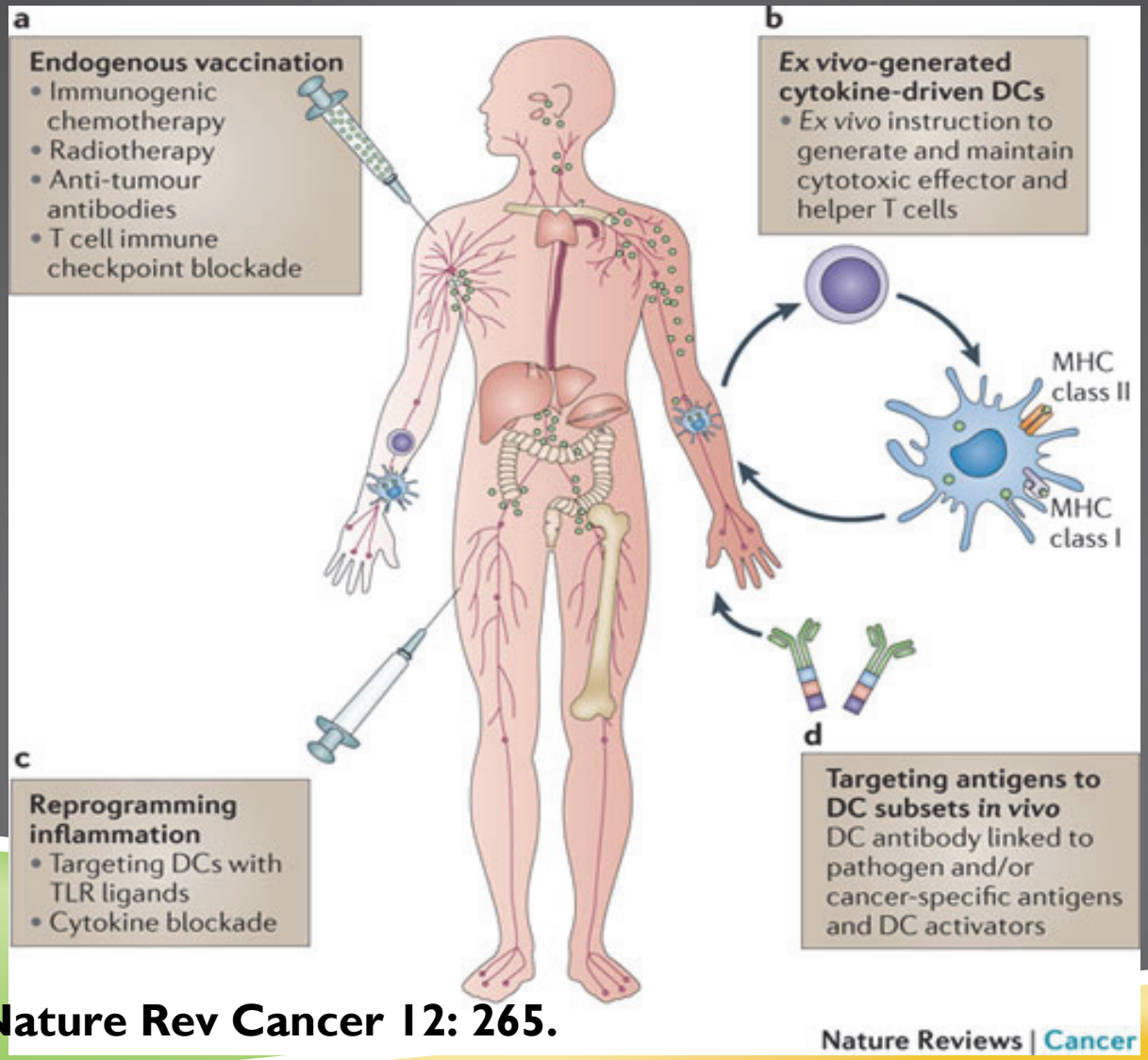
CANCER VACCINE PLATFORMS

Vaccine Platform	Rationale
Peptide	Sub-dominant/cryptic epitopes elicit immunity to self Ags, given with potent adjuvants to enhance immunogenicity
Protein	Given with potent adjuvants to enhance immunogenicity
Plasmid DNA	Stable transfection of skin/muscle allows Ag presentation
Dendritic cells	Potent antigen-presenting cells present tumor Ags
Viral or Bacterial Vectors	Initiate presentation through MHC Class I to stimulate T cells in the presence of a foreign stimulus/adjuvant
Whole Tumor Cells	Deliver multiple relevant tumor Ags
Engineered scaffold	Deliver optimal tumor Ags and co-stimuli

CANCER VACCINE PLATFORMS

Vaccine Platform	Immunogenicity	Toxicity	HLA Match Required
Dendritic cells	High	Low	yes
Peptide	Low	Low	yes
Protein	Moderate	Low	no
Plasmid DNA	Low	Low	no
Viral or Bacterial Vectors	High	High	no
Whole Tumor Cells	Moderate	Low	no
Heat Shock Proteins	High	Low	no
Engineered scaffold	High	Low	variable

DENDRITIC CELL VACCINES FOR CANCER TREATMENT



Palucka 2012 Nature Rev Cancer 12: 265.

PEPTIDE VACCINES FOR CANCER TREATMENT

Issues:

1. Typically weak immunogens and require adjuvants
2. Require MHC matching to the patient
3. Low toxicity
4. Ease and low cost of manufacture
5. Typically induce antigen-specific immunity, clinical responses rare
6. Need to activate $CD4^+$ and $CD8^+$ T cells—nested MHC Class I and II epitopes, add PADRE to mixture
7. Single or multiple, long or short, alone or in combination, best adjuvant

CANCER VACCINE ADJUVANTS

TLR Agonists	Non-specific Immunomodulators
microbial products	mineral salts, emulsions, microparticles, liposomes
BCG (TLR2, TLR4, NLR2)	Incomplete Freund's adjuvant
Poly I:C and Poly I:C12U (TLR3)	Montanide ISA 51 and 720
LPS (TLR2, TLR4)	Alum, MF59, QS21
Monophosphoryl lipid A (MPLA) (TLR4)	Keyhole Limpet Hemocyanin (KLH) protein
Imiquimod (TLR7, TLR8)	
CpG ODNs (TLR9)	

PHASE III MELANOMA PEPTIDE VACCINE TRIAL

- Stage IV or locally advanced Stage III cutaneous melanoma
- HLA-A2-positive
- suitability for IL-2 therapy

	IL-2 Alone (720KIU/kg) (n=94)	gp100 (210M)+ montanide ISA 51 followed by IL-2 (n=91)	p value
Clinical response	6%	16%	p=0.03
Progression-free survival	1.6 months	2.2 months	p=0.008
Overall survival	11.2 months	17.8 months	p=0.06

Schwartzentruber 2011 NEJM 364: 2119.

PHASE III PATIENT-SPECIFIC IDIOTYPE VACCINE TRIAL FOR FOLLICULAR LYMPHOMA

- chemotherapy-naïve follicular lymphoma in CR after primary chemotherapy
- bulky (>5 cm) Stage II, III, IV disease
- lymph node with surface IgG or IgM accessible for biopsy

	KLH+GM-CSF (n=41)	Id-KLH+GM-CSF (n=76)	p value
Progression-free survival	30.6 months	44.2 months	p=0.045
Overall survival	Not reached	Not reached	p=0.696

Schuster 2011 JCO 29: 2787.

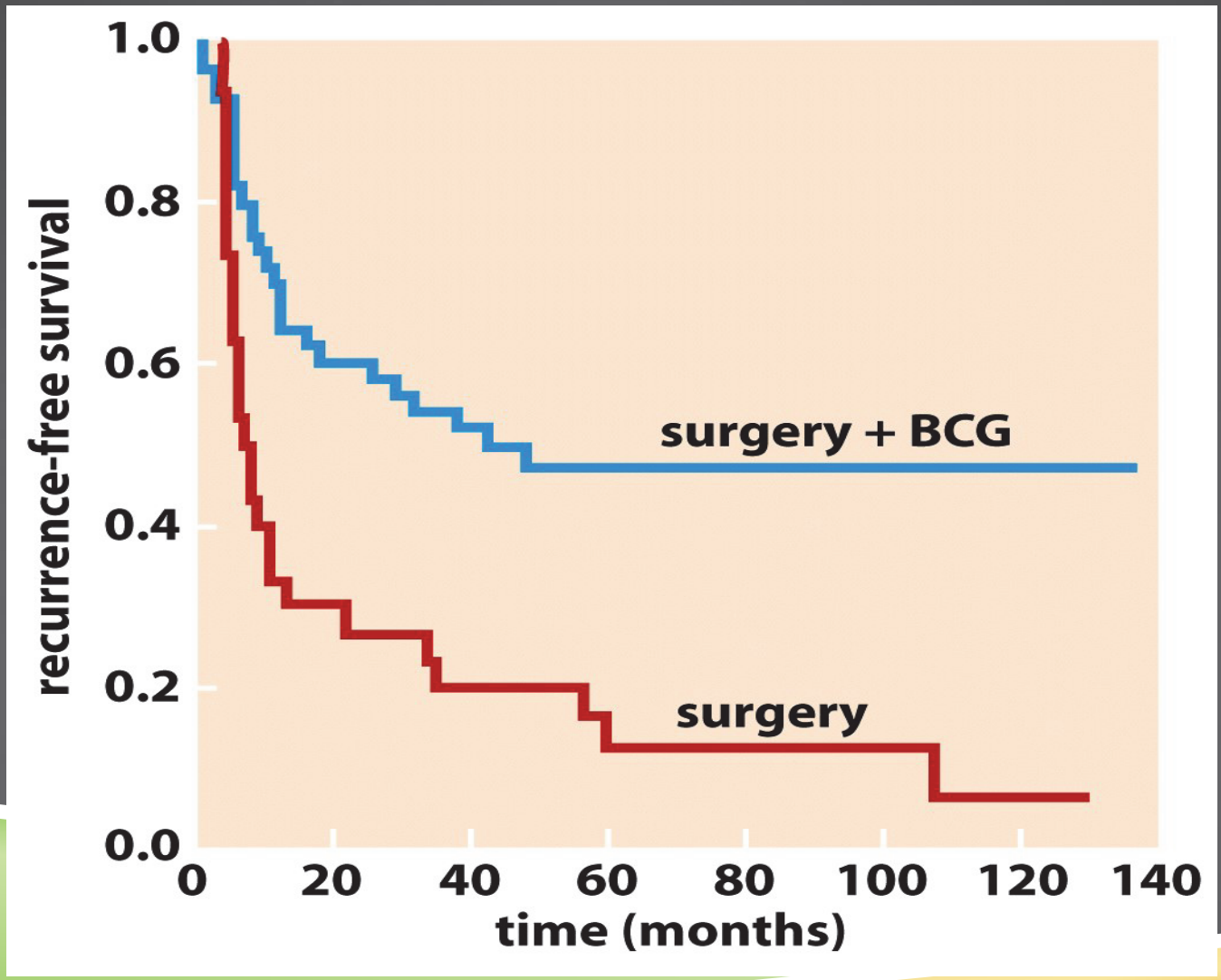
PHASE II POX VIRUS-PSA VACCINE TRIAL

- min symptomatic hormone-refractory metastatic prostate cancer
- vaccinia virus prime, followed by 6 fowlpox virus boosts
- PSA antigen+three immune costimulatory molecules (B7.1/ICAM-1/LFA-3)

	Empty vector+ saline (n=40)	PROSTVAC-VF+ GM-CSF (n=82)	p value
Progression-free survival	3.7 months	3.8 months	p=0.6
Median overall survival	16.6 months	25.1 months	p=0.0061

Kantoff 2010 JCO 28: 1099.

BACTERIA CAN TREAT SUPERFICIAL BLADDER CANCER

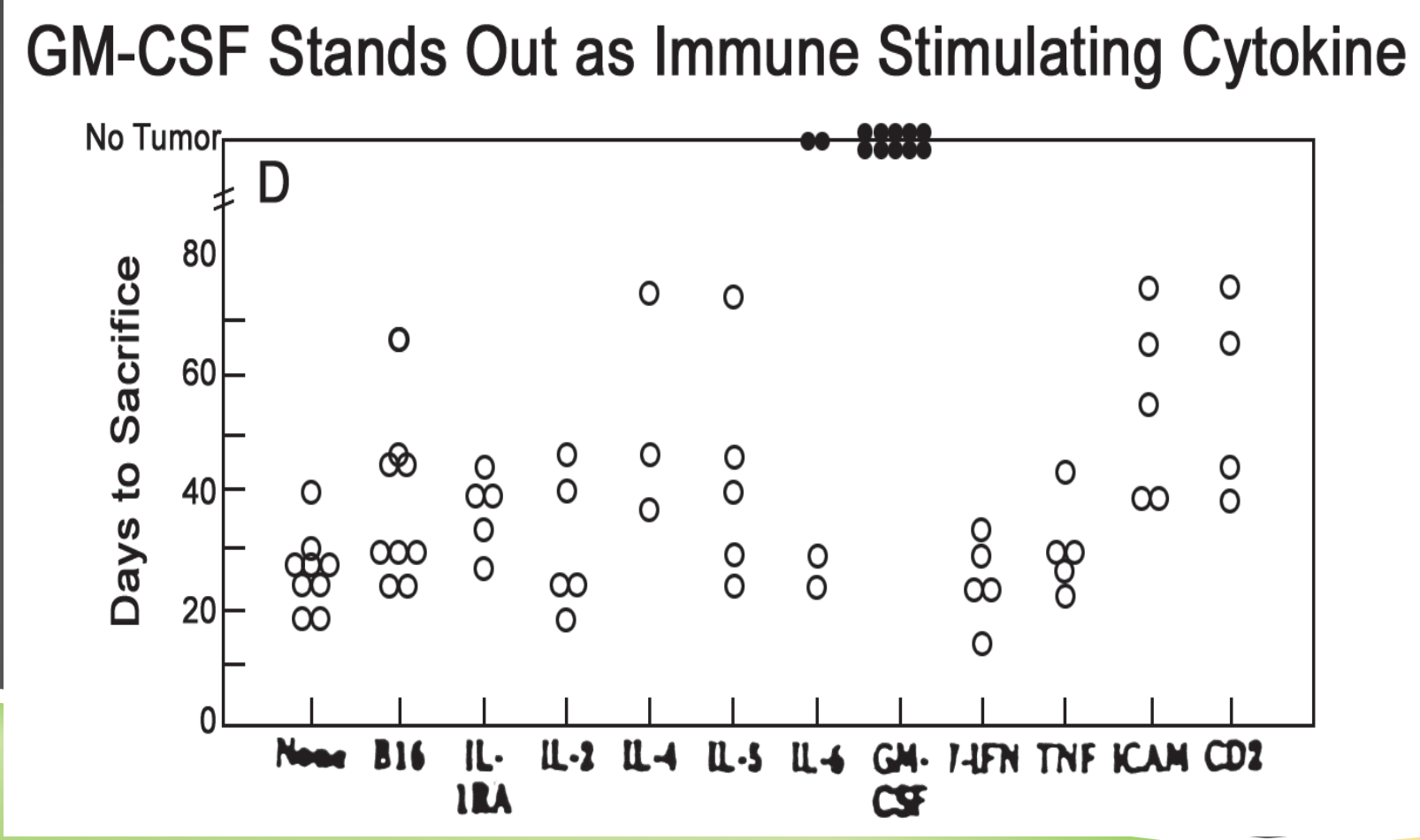


WHOLE TUMOR CELLS

Issues:

1. autologous vs. allogeneic vs. dendritic cell fusion
2. unmodified vs. modified
3. deliver multiple tumor antigens, both known and unknown
4. no requirement for HLA match
5. expensive, allogeneic not as expensive as patient-specific product
6. allogeneic vaccines are generalizable

SYSTEMATIC ANALYSIS OF MODIFIED TUMOR CELL VACCINES IN PRECLINICAL MODELS



Dranoff 1993 PNAS 90: 3539.

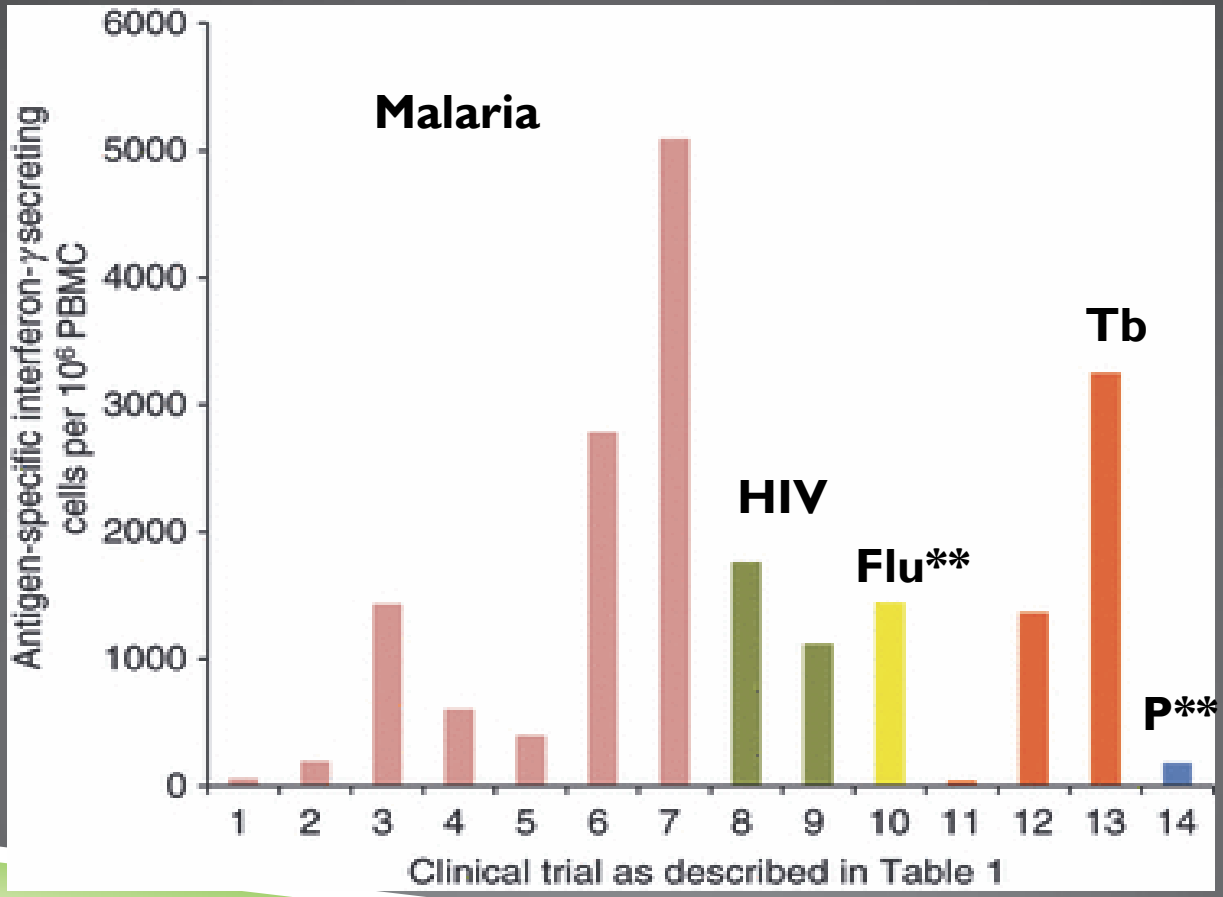
PHASE III TRIAL OF PROSTATE GVAX

- Taxane-naïve, symptomatic hormone-refractory prostate cancer
- Docetaxel 75 mg/m^2 every 3 weeks plus prednisone 10 mg/day vs. Docetaxel 75 mg/m^2 every 3 weeks plus GVAX 2 days later, then GVAX every 4 weeks (10 cycles chemotherapy given in each arm)

	Docetaxel 75 mg/m^2+Prednisone (n=204)	GVAX+Docetaxel 75 mg/m^2 (n=204)	p value
Deaths	47	67	p=0.03
Overall survival	14.1 months	12.2 months	p=0.0076

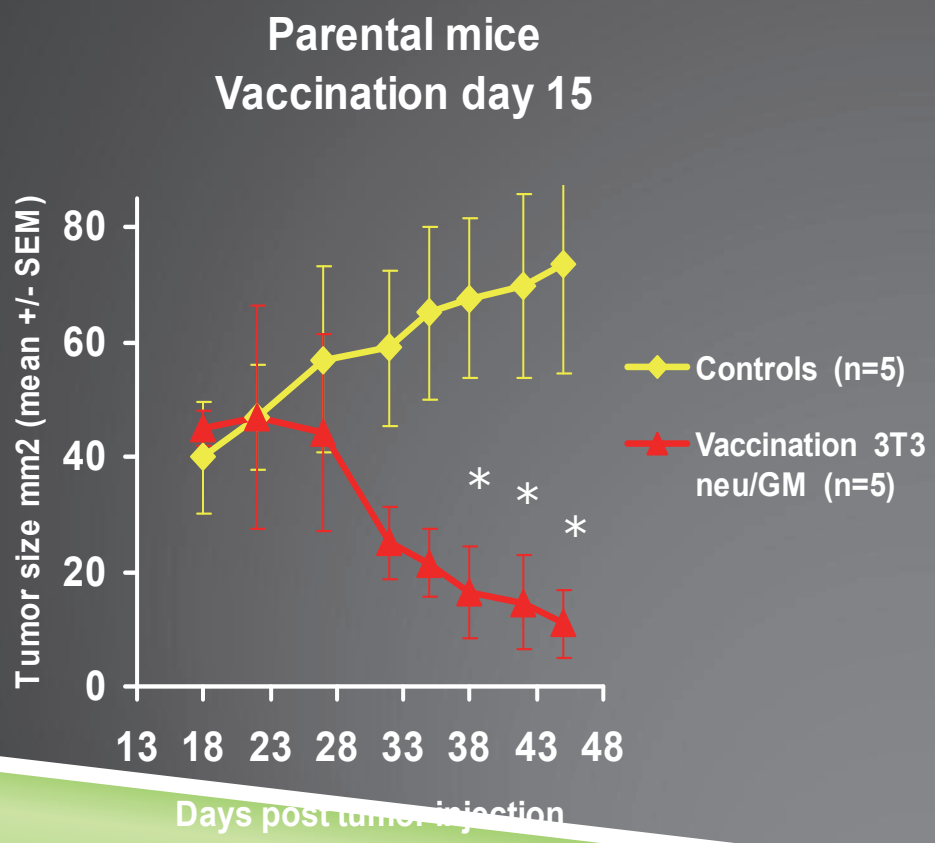
Small 2009 GU ASCO

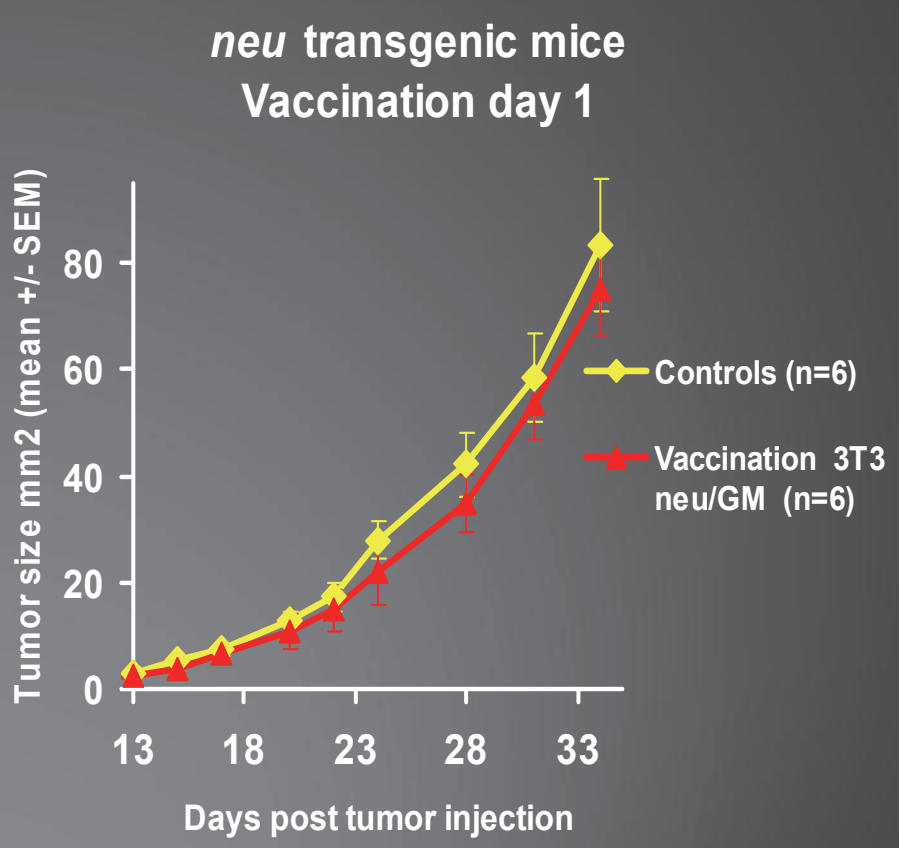
AMPLITUDE OF T CELL IMMUNITY INDUCED BY VARIOUS VACCINES



Gilbert 2011 Immunology 135: 19.

IMMUNE TOLERANCE TO HER2 IN *NEU* TRANSGENIC MICE





* $p < .05$

Machiels 2001 Cancer Res 6: 3689.

IMMUNE TOLERANCE: A MAJOR BARRIER TO TUMOR IMMUNITY

- $CD4^+CD25^+$ regulatory T cells
- Myeloid-derived suppressor T cells
- Suboptimal T cell repertoire
- Inadequate positive co-stimulation
- Excessive negative counter-stimulation
- Ineffective T cell trafficking
- Suppressive tumor microenvironment

WHAT TO COMBINE WITH IMMUNOTHERAPY?

- Endocrine therapy
- Chemotherapy—dose and schedule key
- Therapeutic tumor-specific monoclonal antibodies
- Tyrosine kinase inhibitors
- Immune checkpoint modulators

CLINICAL TRIALS OF VACCINES AND TARGETED IMMUNOMODULATORS

Patient Population	Number of patients	Vaccine	Drug Regimen	Immunologic Outcome
metastatic melanoma	n=16	MART-1 pulsed autologous DC	Dose escalation tremelimumab (α-CTLA-4)	Low levels of MART-1 T cells
metastatic hormone-refractory prostate cancer	n=28	GM-CSF-secreting prostate tumor cells	Dose escalation ipilimumab (α-CTLA-4)	25% with ≥50% PSA decline; evidence of DC and T cell activation
refractory, unresectable melanoma	n=676	gp100	Ipilimumab (n=137) Ipilimumab+gp100 (n=403) gp100 (n=136)	Improved overall survival with ipilimumab

In early clinical development:
α-CD-40, α-PD-1, α-B7-H1

Ribas 2009 Clin Cancer Res 15: -6276.
van den Eertwegh 2012 Lancet Oncol 13: 509.
Hodi 2010 NEJM 363: 711.

“Hope is not a strategy—you have to follow the science”

THANK YOU!